ACCP Critical Care Medicine Board Review: 21st Edition

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Contents

Authors

Wissam B. Abouzgheib, MD, FCCP
Director of Interventional Pulmonary Program
Pulmonary and Critical Care Department
Cooper University Hospital
Camden, NJ

Nikhil R. Asher, MD
Clinical Fellow
Department of Critical Care Medicine
University of Pittsburgh Medical Center
Pittsburgh, PA

David L. Bowton, MD, FCCP
Professor and Head, Section on Critical Care
Department of Anesthesiology
Wake Forest University School of Medicine
Winston-Salem, NC

Bennett P. deBoisblanc, MD, FCCP
Professor of Medicine and Physiology
Director, Critical Care Services
Medical Center of Louisiana
New Orleans, LA

R. Phillip Dellinger, MD, MSc, FCCP
Professor of Medicine
Cooper Medical College of Rowan University
Vice Chief, Department of Medicine
Head, Division of Critical Care
Cooper University Hospital
Camden, NJ

Brian K. Gehlbach, MD
Associate Professor
Division of Pulmonary, Critical Care, and Occupational Medicine
Department of Internal Medicine
University of Iowa
Iowa City, IA

Hjalti Gudmundsson, MD
Fellow, Interventional Cardiology
Cardiovascular Division
University of Iowa Carver College of Medicine
Iowa City, IA

Jesse B. Hall, MD, FCCP
Professor of Medicine, Anesthesia, and Critical Care
The University of Chicago
Pritzker School of Medicine
Chicago, IL

Steven M. Hollenberg, MD, FCCP
Professor of Medicine
Robert Wood Johnson Medical School
University of Medicine and Dentistry of New Jersey
Director, Coronary Care Unit
Cooper University Hospital
Camden, NJ

Phillip A. Horwitz, MD
Associate Professor of Internal Medicine
University of Iowa Carver College of Medicine
University of Iowa
Iowa City, IA

Robert C. Hyzy, MD, FCCP
Associate Professor
Division of Pulmonary and Critical Care Medicine
University of Michigan School of Medicine
Ann Arbor, MI

Stephen P. Kantrow, MD
Associate Professor of Medicine
Section of Pulmonary and Critical Care Medicine
LSU Health Sciences Center
New Orleans, LA

George H. Karam, MD, FCCP
Paula Garvey Manship Professor of Medicine
Louisiana State University School of Medicine
New Orleans, LA
Head, Department of Internal Medicine
Earl Long Medical Center
Baton Rouge, LA

John P. Kress, MD, FCCP
Associate Professor of Medicine
Section of Pulmonary and Critical Care
University of Chicago
Chicago, IL

John F. McConville, MD
Assistant Professor of Medicine
Section of Pulmonary and Critical Care Medicine
Director, Internal Medicine Residency Program
University of Chicago
Chicago, IL

Kevin McGrath, MD
Associate Professor of Medicine
Director, GI Endoscopy Lab
University of Pittsburgh Medical Center
Pittsburgh, PA

Michael S. Niederman, MD, FCCP
Chairman, Department of Medicine
Winthrop University Hospital
Mineola, NY
Professor of Medicine
Vice Chairman, Department of Medicine
SUNY at Stony Brook
Stony Brook, NY

David Pitrak, MD
Professor of Medicine
Chief of Infectious Diseases
The University of Chicago
Chicago, IL

Jean-Sebastien Rachoin, MD
Assistant Professor of Medicine
Cooper Medical School of Rowan University
Department of Medicine, Division of Hospital Medicine
Cooper University Hospital
Camden, NJ

Gregory A. Schmidt, MD, FCCP
Professor, Division of Pulmonary, Critical Care, and Occupational Medicine
Department of Internal Medicine
University of Iowa
Iowa City, IA

Mary E. Strek, MD, FCCP
Professor of Medicine
Section of Pulmonary and Critical Care
The University of Chicago
Chicago, IL

Harold M. Szerlip, MD, MS, FCCP
Professor and Vice-Chairman
Department of Medicine, University of Arizona College of Medicine
Chief of Medical Service, UAMC-SC
University of Arizona/UPHH Consortium
Tucson, AZ

Karl W. Thomas, MD, FCCP
Clinical Professor
Division of Pulmonary Diseases, Critical Care, and Occupational Medicine
University of Iowa
Iowa City, IA

Arthur P. Wheeler, MD, FCCP
Professor of Medicine
Division of Allergy, Pulmonary, and Critical Care Medicine
Vanderbilt University School of Medicine
Nashville, TN

Douglas B. White, MD, MAS
Associate Professor
Director, Program on Ethics and Decision Making in Critical Illness
Department of Critical Care Medicine
University of Pittsburgh Medical Center
Pittsburgh, PA

Frank Zimmerman, MD
Assistant Professor of Pediatrics
The University of Chicago Children's Hospital
Chicago, IL

Janice L. Zimmerman, MD, FCCP
Professor of Clinical Medicine
Weill Cornell Medical College
Division Head, Critical Care
Department of Medicine
Director, Medical ICU
The Methodist Hospital
Houston, TX

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Steven M. Hollenberg, MD, FCCP	Speakers bureau: Novartis-Makers of Valsartan
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Harold M. Szerlip, MD, MS, FCCP	Grant monies (from industry related sources): Spectral Diagnostics research grant CytoPherx research grant
Janice L. Zimmerman, MD, FCCP	Product/procedure/technique that is considered research and is NOT yet approved for any purpose: glucagon, insulin for beta-blocker and calcium channel blocker overdose; lipid emulsion for overdose

The following authors of the ACCP Critical Care Medicine Board Review: 21st Edition have indicated to the ACCP that no potential conflict of interest exists with any respective company/organization, and this should be communicated to the participants of this educational activity:

Wissam B. Abouzgheib, MD, FCCP
Nikhil R. Asher, MD
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Bennett P. deBoisblanc, MD, FCCP
R. Phillip Dellinger, MD, MS, FCCP
Brian K. Gehlbach, MD
Hjalti Gudmundsson, MD
Jesse B. Hall, MD, FCCP
Robert C. Hyzy, MD, FCCP
Stephen P. Kantrow, MD
George H. Karam, MD, FCCP
John F. McConville, MD
Kevin McGrath, MD
Jean-Sebastien Rachoin, MD
Gregory A. Schmidt, MD, FCCP
Mary E. Strek, MD, FCCP
Karl W. Thomas, MD, FCCP
Arthur P. Wheeler, MD, FCCP
Douglas B. White, MD, MAS
Frank Zimmerman, MD

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Rely on the ACCP Critical Care Medicine Board Review 2012 to review the type of information you should know for the Critical Care Subspecialty Board Examination of the American Board of Internal Medicine (ABIM). Designed as the best preparation for anyone taking the exam, this comprehensive, exam-focused review will cover current critical care literature and management strategies for critically ill patients.

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Chapter 1. Endocrine Emergencies

Robert C. Hyzy, MD, FCCP

Objectives:

- Recognize the clinical presentations of endocrine emergencies involving the pancreas, thyroid, adrenal, and pituitary glands.
- Learn the approach to laboratory testing necessary for the diagnosis and management of these conditions in the ICU.
- Understand the treatment for each endocrine emergency.

Key words: adrenal failure; diabetes insipidus; diabetic ketoacidosis; hyperosmolar hyperglycemic state; hypoglycemia; myxedema coma; pheochromocytoma; thyroid storm

Synopsis:

Many endocrine emergencies require admission to the ICU. Although not necessarily common as a primary diagnosis requiring ICU admission, many endocrine emergencies occur in the context of ongoing illness and comorbidities, where the stress of intercurrent illness serves to exacerbate and unmask the underlying condition. Hence, the practicing intensivist needs not only to be able to diagnose and manage these conditions as presenting diagnoses but also to recognize endocrine emergencies in the context of critical care more generally.

Diabetic Ketoacidosis

Clinically significant hyperglycemic syndromes consist of diabetic ketoacidosis (DKA) and the hyperglycemic hyperosmotic state (HHS), frequently also referred to as hyperosmotic nonketotic syndrome. The American Diabetes Association definitions for these conditions are given in Table 1. Serum glucose level is usually below 800 mg/dL in DKA, whereas in HHS a glucose level in excess of 1,000 mg/dL is not uncommon. DKA is characterized by a syndrome of hyperglycemia, ketonemia, and an anion gap metabolic acidosis, usually in excess of 20.

$$\text{Anion gap} = \text{serum sodium} - (\text{serum chloride} + \text{serum bicarbonate})$$

The degree of acidosis and magnitude of the increase in anion gap are contingent on the rate of ketoacid production and urinary excretion. Hyperglycemia produces glycosuria and an osmotic diuresis, resulting in extracellular fluid volume depletion, which can be profound and result in hypotension. Many of the symptoms of DKA result in large measure from this: polyuria, polydipsia, tachycardia, and lethargy. The degree of acidosis is the primary determinant of depressed sensorium. In addition, other symptoms such as nausea, vomiting, abdominal pain, and Kussmaul respirations with a characteristic fruity breath may be present.

DKA is usually diagnosed in known diabetics who present to the emergency room with either noncompliance or with a concomitant stressful illness, especially infection, which has resulted in progressively worsened glycemic control and the onset of ketogenesis. Occasionally, a patient, usually an adolescent or young adult, will present with DKA as the initial presentation of their diabetes. Other causes of ketoacidosis include alcohol and starvation, which should be in the differential diagnosis in patients without a known history of diabetes.

Besides elevations in serum glucose and the presence of ketones in serum in urine, laboratory abnormalities seen at presentation in DKA include: a low serum bicarbonate, elevated anion gap, leukocytosis, hyperkalemia, elevated BUN and creatinine (suggesting prerenal azotemia), and elevated amylase and lipase. Leukocytosis is proportionate to the degree of acidemia and can confuse the clinical picture as regards the presence of infection. Hyperkalemia, due to extracellular osmotic shifting and insulin deficiency, is common despite a deficit in total body potassium, largely from urinary losses. Serum sodium is variable in DKA and reflects a balance between osmotic dilution in the serum from hyperglycemia and urinary losses due to osmotic diuresis. Pseudohyponatremia may be seen in patients with concomitant hyperlipidemia. Although pancreatitis is uncommon, patients with

Table 1—*Diagnostic Criteria for Diabetic Ketoacidosis (DKA) and Hyperglycemic Hyperosmolar Syndrome (HHS)*

Diagnostic Criteria and Classification	DKA			HHS
	Mild	Moderate	Severe	
Plasma glucose, mg/dL	>250 mg/dL	>250 mg/dL	>250 mg/dL	>600 mg/dL
Arterial pH	7.25–7.30	7.00 to <7.25	<7.00	>7.30
Serum bicarbonate, mg/dL	15–18	10 to <15	<10	>15
Urine ketone	Positive	Positive	Positive	Small
Serum ketone	Positive	Positive	Positive	Small
Effective serum osmolality	Variable	Variable	Variable	>320 mOsm/kg
Anion gap	>10	>12	>12	<12
Mental status	Alert	Alert/drowsy	Stupor/coma	Stupor/coma

Adapted from Kitabchi AE. Hyperglycemic crises in adult patients with diabetes: a consensus statement from the American Diabetes Association. *Diabetes Care*. 2006;29(12):2739–2748.

elevations of amylase and lipase should have pancreatitis ruled out. Arterial blood gas shows acidosis with a compensatory respiratory alkalosis and hypocapnia. Acidemia is usually present.

Treatment of DKA is centered on expanding intravascular volume and is best performed utilizing normal saline solution. As patients are usually several liters down, there is little risk in administering normal saline solution in large quantity. Regular insulin is administered as an IV bolus of 0.10 to 0.15 U/kg/h, followed by a continuous IV infusion at 0.10 U/kg/h. Blood glucose should be lowered by about 50 mg/dL/h and assessed hourly, with downward adjustments made in the insulin drip as blood glucose lowers. Clinicians should recognize that fingerstick capillary blood glucose measurements can be inaccurate in critically ill patients. Fingerstick glucose measurements are lower than glucose measured from venous blood in hypotensive patients but at other times may be found to be higher than venous blood. Serum electrolytes should be assessed q2-4h.

IV fluid resuscitation aimed at expanding intravascular volume is essential, and several liters may be required. Although hypernatremia is frequently present, normal saline solution should be administered IV until the intravascular volume deficit is corrected, as normal saline solution is hypotonic relative to the patient's serum and is more effective at expanding plasma volume than the administration of hypotonic saline solution such as 0.45 NaCl. Once intravascular volume has been restored and the patient's glucose has lowered to the 200 range, glucose and hypotonic saline solution, in the form of dextrose 5 in 0.45 NaCl, should be administered until the DKA has resolved. This serves to avoid hypoglycemia in the context of not as yet resolved DKA and permits the continued administration of IV insulin. IV insulin should be continued until ketogenesis has resolved, as reflected in normalization of the anion gap.

The routine treatment of metabolic acidosis with IV sodium bicarbonate has been largely abandoned, in recognition that vigorous volume expansion alone is generally sufficient. Nevertheless, patients presenting with a pH <7.00 can be considered for this if tissue perfusion is compromised or life-threatening hyperkalemia is present. The management of serum potassium levels in DKA requires careful attention, with frequent monitoring necessary. Despite initial hyperkalemia, with the administration of insulin and the correction of metabolic acidosis, hypokalemia develops and should be treated with IV potassium supplementation. Usually 20 to 30 mEq/L is added to 0.45 saline solution, as the addition of potassium to normal saline solution would result in the administration of hypertonic fluids. Hypophosphatemia often develops during treatment of DKA, but it seldom requires supplementation, which should be administered only if clinically significant or severe (<1.0 mg/dL).

Clinical resolution of DKA can be monitored via venous pH and serum anion gap. Repeat arterial blood gases are not required. After the normalization of the anion gap has occurred, the patient should receive subcutaneous regular insulin. The administration of IV dextrose is

stopped, and IV insulin is discontinued 30 min later. These changes are best made once the patient has resumed oral nutrition, otherwise ketogenesis may resume.

Cerebral edema can occur as a complication of DKA treatment in patients under 20 years of age, but the risk is mitigated if rapid correction of sodium and water deficits are avoided and glucose is added to IV fluids once serum glucose level has dropped to the low 200 range.

Hyperosmolar Nonketotic Dehydration Syndrome

HHS, also often referred to as the hyperosmolar nonketotic syndrome, occurs when hyperglycemia occurs with little or no ketoacidosis. HHS occurs in patients who are only partially insulin deficient, and hence HHS is more common among older, type 2 diabetics. While the usual symptoms of hyperglycemia such polyuria, polydipsia, dehydration, and tachycardia are present, an anion gap metabolic acidosis from ketogenesis is not. The severity of hyperglycemia is often quite significant (>1,000 mg/dL). The resultant hyperosmolality produces depression of the CNS, which, when severe, can cause coma. HHS is contrasted with varying degrees of DKA in Table 1.

Serum sodium is often low in HHS due to osmotic shifting of water from the intracellular compartment. That is, water enters the extracellular compartment, following the gradient created by the osmotically active glucose molecules. As serum glucose levels tend to be higher in HHS than in DKA, this effect can be quite profound. In addition, just as in DKA, plasma volume is contracted at the same time, owing to osmotic diuresis from glucosuria. If, however, the glucosuria effect predominates, hypernatremia may be observed. In either circumstance, the serum sodium level is fictitiously altered by hyperglycemia. A common correction factor to determine the actual serum sodium is:

$$\text{Na corrected} = \text{Na measured} + [0.016 \times (\text{Glucose in mg/dL} - 100)]$$

The corrected sodium is used to determine free water deficit, which can serve as a guide to the amount of volume resuscitation required:

$$\text{Free water deficit (men)} = (\text{Weight in kg} \times 0.6) - (\text{Na}/140 - 1)$$

$$\text{Free water deficit (women)} = (\text{Weight in kg} \times 0.5) - (\text{Na}/140 - 1)$$

The treatment of HHS involves the same management principles as DKA: vigorous volume replacement and an IV insulin drip. The amount of normal saline solution required to restore extracellular fluid tends to be greater in HHS than in DKA. Half normal saline solution is administered once this has been achieved.

Glucose Control in the ICU

Reports of significant benefit to patients with stress-induced hyperglycemia in the ICU treated with IV insulin to achieve blood glucose levels between 80 and 100 mg/dL were followed by others that suggested that the risk of hypoglycemia was significant, particularly among patients with sepsis. The large Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial demonstrated an increase in 90-day mortality in patients treated with this approach, sometimes called "tight glycemic control," compared with a less aggressive approach. Only the subset of patients with trauma or those being treated with corticosteroids demonstrated a trend toward benefit with tight control. However, it should be recognized that the control group in NICE-SUGAR had a mean glucose level around 140 mg/dL; this suggests that, while practices have changed over the last decade and tight control is not warranted, patients with stress-induced hyperglycemia should still be treated with IV insulin, albeit at a more modest target of less than 150 mg/dL.

Hypoglycemia

Hypoglycemia (blood glucose level <60 mg/dL) is seldom a cause of admission to the ICU but is seen as a consequence of other conditions, the ingestion of oral hypoglycemic agents or an overdose of long-acting insulin being exceptions. Common causes of hypoglycemia in the ICU

include hepatic failure, renal failure, sepsis, adrenal insufficiency, leukemia, lymphoma, tumors including hepatoma or pancreatic islet β-cell tumor, or additional drugs such as β-blockers or pentamidine. Symptoms of hypoglycemia include nervousness, tremulousness, tachycardia, and diaphoresis, all of which are triggered by a compensatory adrenergic response to the hypoglycemia. If severe hypoglycemia is present, coma or seizures can ensue.

When clinically suspected, hypoglycemia should be promptly treated with an ampule of dextrose, containing 50 mL of 50% dextrose solution, IV push. Blood glucose should be monitored hourly via fingerstick measurements, enabling a timely therapeutic response. A second ampule may be required within an hour of treatment. Patients should also receive a dextrose drip of either 5% or 10% solution, at a rate appropriate to the clinical circumstances encountered.

Glucagon, hydrocortisone, or octreotide can be administered if hypoglycemia is profound and refractory to the above measures, but it is seldom required.

Myxedema Coma

Myxedema coma is a severe form of hypothyroidism characterized by CNS depression and hypothermia from a low basal metabolic rate. Women are more commonly affected than men. The other manifestations common to less severe hypothyroidism may also be present. These include: lethargy, cold intolerance, delayed deep tendon reflexes, hypothermia, bradycardia, alopecia, dry, doughy skin, hoarseness, and hyperglossia. A pericardial effusion may be present, although significant cardiac compromise is uncommon. Laboratory abnormalities that are diagnostic include an elevated TSH and a low free T4. In addition, several other laboratory abnormalities can occur. These include hyponatremia, hypercapnia, a normocytic normochromic anemia, hyperlipidemia, hypoglycemia, and an elevation in creatine phosphokinase. Hyponatremia is due to an impairment in free water excretion and can result in seizure activity. Hypoglycemia can occur from hypothyroidism alone or may be due to concomitant adrenal insufficiency.

Myxedema coma is often the result of prolonged noncompliance with thyroid supplementation in the face of absent thyroid function, such as following I^{131} ablation. Drugs that can cause underlying hypothyroidism include amiodarone, propylthiouracil, lithium, and sulfonamides. Myxedema coma can be precipitated by cold exposure, the concomitant administration of sedative drugs, especially opioids, or stress such as infection and myocardial infarction. Infection may be masked by an inability to mount a temperature spike. Myxedema has a significant attributable mortality of almost 40%, particularly among elderly and septic patients or patients with prolonged hypothermia, cardiac compromise, or coma.

Once clinically suspected, a serum TSH, free T4, and cortisol should be drawn. A cosyntropin stimulation test should also be performed whenever possible. However, treatment of myxedema coma should begin based on clinical suspicion and should not wait for laboratory confirmation. The treatment of myxedema coma is IV administration of thyroxine, starting with a loading dose of 300 μg of thyroxine followed by daily administration of doses ranging from 50 to 100 μg. As unsuspected adrenal insufficiency is frequently also in evidence, all patients with myxedema coma should be empirically treated for possible adrenal insufficiency. This can be accomplished either through the daily administration of hydrocortisone at a dose of 300 mg. Patients with myxedema coma are frequently intubated for airway protection or hypercapnia. Other supportive measures include the use of passive warming and supplemental nutrition.

Euthyroid Sick Syndrome

Patients who are critically ill frequently manifest abnormalities in thyroid function tests, suggesting the possibility of hypothyroidism. Owing to an increased conversion of T3 to reverse T3, these patients demonstrate a low serum T3 level, a condition called euthyroid sick syndrome. T4 levels may also be low, particularly in the setting of protracted critical illness, and the TSH level can also vary, being either slightly elevated or decreased. Free T4 levels are normal, indicating

the absence of clinical hypothyroidism. Hence, no thyroid supplementation is required.

Thyroid Storm

Thyroid storm is hyperthyroidism in the presence of significant cardiac or CNS manifestations. These include cardiac dysrhythmias, such as new onset atrial fibrillation, atrial flutter, and supraventricular tachycardia, or CNS manifestations, such as tremor, delirium, stupor, or even coma. The patient may be hypertensive and tachycardic. Apathetic affect may also be present, particularly among the elderly. Other manifestations of hyperthyroidism may be present, such as exophthalmos, hyperreflexia, heat intolerance, anxiety, nausea, vomiting, diarrhea, abdominal pain, and the presence of fine hair or pretibial edema.

Graves disease, an autoimmune condition, is the most common cause of hyperthyroidism. Importantly, thyroid storm can be triggered by physiologic stress in the setting of underlying hyperthyroidism, which may have been unsuspected until that time. These can include surgery, pregnancy, trauma, or significant acute illness of any kind.

As with myxedema, the diagnosis of thyroid storm is made clinically, with treatment undertaken in anticipation of confirmatory laboratory tests. Laboratory findings in hyperthyroidism and thyroid storm include elevations in T3 and T4, with a low TSH. In an uncommon variant of thyroid storm called T3 thyrotoxicosis, T3 levels are elevated but T4 levels remain normal. Less commonly, in central hyperthyroidism, TSH, T3, and T4 are all elevated.

Treatment of thyroid storm is multifaceted and attempts to affect thyroid hormone production, release, and peripheral conversion to the physiologically more active T3 and to block the effect of thyroid hormone on the body. Thyroid hormone synthesis is inhibited by administering either propylthiouracil, 200 mg q4h, or methimazole, 20 mg q4-6h. Iodine, either saturated solution potassium iodide or Lugol solution, is administered to block thyroid hormone release from the thyroid gland. Importantly, iodine must only be administered after thyroid hormone synthesis has been blocked, in order to avoid exacerbating the problem by enhanced thyroid hormone production. Decreasing conversion of T4 into T3 is accomplished through the administration of propylthiouracil, hydrocortisone, 100 mg q8h, and propranolol. Propranolol, 60 to 80 mg q4-6h, is also administered to block the hyperadrenergic manifestations of thyrotoxicosis and to control tachyarrhythmias. IV esmolol can be used instead of propranolol.

Other adjuncts to care of the patient with thyroid storm include passive cooling if hyperpyrexia is present. Acetaminophen is preferred, as acetylsalicylate increases free thyroid hormone in the serum through displacement on plasma proteins. Thyroidectomy may be required if a patient develops life-threatening agranulocytosis from propylthiouracil or methimazole. Finally, as with myxedema, the patient should be evaluated and treated for the possibility of concomitant hypoadrenalism.

Iodine therapy is discontinued and corticosteroids may be tapered once hyperpyrexia, CNS, and cardiac manifestations have resolved. Patients with Graves disease should ultimately undergo thyroid ablation. This can be accomplished either surgically or with I^{131}.

Adrenal Crisis

Adrenal insufficiency can be seen in a variety of conditions and may be either primary, that is, due to insufficient production of adrenocorticotropic hormone, or secondary, usually resultant from underproduction of glucocorticoids and mineralocorticoids. Causes of primary adrenal insufficiency include autoimmune, that is, Addison's disease; bilateral adrenal hemorrhage; abrupt withdrawal of exogenously administered corticosteroids, TB; septic shock; meningococcemia; metastatic malignancy; amyloidosis; and drugs such as etomidate and ketoconazole. Causes of secondary adrenal insufficiency include pituitary tumors; craniopharyngioma; as a postoperative complication; postpartum hypopituitarism (Sheehan's syndrome); infiltrative diseases such as hemochromatosis, sarcoidosis, histiocytosis, or histoplasmosis; TB; or withdrawal of exogenously administered corticosteroids. Patients with secondary adrenal insufficiency lack hyperpigmentation, dehydration, and hyperkale-

mia. Hypotension is less prominent, whereas hypoglycemia is more common than in primary adrenal insufficiency.

Adrenal crisis occurs in patients with adrenal insufficiency who have hypotension and volume depletion from the absence of mineralocorticoids. Like thyroid storm, adrenal crisis is often triggered by physiologic stress such as trauma, surgery, or acute medical illness. Clinically, patients may manifest hypotension, nausea, vomiting, fatigue, anorexia, depression, and amenorrhea and may lack hyperpigmentation and/or vitiligo. Abdominal, flank, lower back, or chest pain are common in patients with bilateral adrenal hemorrhage or infarction, the main risk factors for which are anticoagulation and postoperative state. Laboratory abnormalities can include hypoglycemia, hyponatremia, hyperkalemia, and eosinophilia.

In individuals who are not stressed, a total cortisol level of >15 μg/dL is sufficient to rule out adrenal insufficiency. A level <5 μg/dL constitutes absolute adrenal insufficiency with 100% specificity but low sensitivity (36%). A cut-off level of 10 μg/dL is 62% sensitive but only 77% specific. The appropriate response of the adrenal glands in the setting of critical illness is unknown. Some authors suggest that a level <25 μg/dL may be insufficient in critical illness such as sepsis. Cortisol is protein bound, and total cortisol levels bear a variable relationship to free cortisol levels. Patients who are hypoproteinemic may have a normal total free cortisol level despite a seemingly insufficient total cortisol level. In patients who are not septic, a cosyntropin stimulation test may be useful in order to determine whether adrenal reserve is lacking and relative adrenal insufficiency is present. Thirty or 60 min after the administration of 250 μg of cosyntropin, a form of synthetic adrenocorticotropic hormone, a rise in total cortisol level <9 μg/dL or an absolute level <20 μg/dL may be indicative of relative adrenal insufficiency.

Dexamethasone, 10 mg may be administered as a single dose while a cosyntropin stimulation test is being performed as therapy for adrenal insufficiency so that the laboratory analysis is not altered, as is the case with hydrocortisone.

In a recent randomized, placebo-controlled trial of corticosteroids in septic patients, CORTICUS, the cosyntropin stimulation test was found to be unreliable when correlated with free cortisol levels. In addition, contrary to earlier studies, a mortality benefit was not observed in the corticosteroid group. Patients receiving corticosteroids were able to be weaned off vasopressor medications an average of 2 days sooner than the placebo group but also were found to have a threefold risk of subsequent sepsis while in the ICU. In contrast, meta-analyses suggest that a mortality benefit might be expected only among patients who are at a high risk of death. Whether or not to administer corticosteroids to patients with vasopressor-dependent shock remains an area of great controversy in critical care. The standard dose is hydrocortisone, 50 mg IV q6h for 5 days. Concomitant mineralocorticoid administration has also been advocated in this setting, but a beneficial effect may only occur if given prophylactically.

Adrenal crisis is treated with an initial dose of 200 mg of IV hydrocortisone followed by 100 mg q6h. IV administration of normal saline solution is important to correct volume contraction. Hypotonic fluids should not be administered, as they can worsen hyponatremia. Mineralocorticoid administration is not required in adrenal crisis, with the possible exception of patients with sepsis.

Pheochromocytoma

A pheochromocytoma is a catecholamine-secreting tumor of chromaffin cells; most common in the adrenal glands, it may occur elsewhere in the body. It is an uncommon cause of secondary hypertension that may present in an accelerated form in the ICU. Symptoms, which are due to the release of catecholamines such as epinephrine, norepinephrine, and/or dopamine, include tachycardia, palpitations, diaphoresis, headache, chest pain, tremor, and flushing. The classic triad of episodic headache, sweating, and tachycardia is seldom in evidence. Episodes of catecholamine release and resultant symptoms tend to be episodic and seldom last more than a few hours at time. Other conditions resulting in increased sympathetic activity can result in BP elevations suggestive of pheochromocytoma, including autonomic dysfunction such as may be the case with spinal injury or Guillain-Barré syndrome; the use of sympathomimetic drugs such as cocaine,

phencyclidine, or amphetamines; and the ingestion of tyramine-containing foods in patients taking monoamine oxidase inhibitors.

The diagnosis, once suspected, is best confirmed by obtaining plasma levels of metanephrine and normetanephrine or 24-h urine levels of metanephrines and catecholamines when the patient is stable and not critically ill, as the stress of critical illness can produce misleading values that may be false positives. The administration of tricyclic antidepressants can also result in falsely elevated results. Subsequent to a chemical diagnosis, imaging studies such as CT scan or I^{123}-metaiodobenzylguanidine scan are performed to localize the tumor and determine resectability.

As with some other endocrinopathies, the stress of surgery can precipitate a hypertensive crisis due to catecholamine release in these patients. Patients with undiagnosed pheochromocytoma presenting with a hypertensive crisis following surgery have a high mortality. Patients with known pheochromocytoma who are scheduled to undergo surgery should receive preoperative management well in advance of surgery with an α-agent, such as phenoxybenzamine. β-Blocker administration is contraindicated unless prior α- blockade has been accomplished in order to avoid unopposed α-tone. The calcium channel blocker nicardipine can be a useful adjunct to management of these patients. Metyrosine, an inhibitor of catecholamine synthesis, may also be used.

As opposed to patients with essential hypertension who have a hypertensive crisis, the drug of choice for a patient with pheochromocytoma who develops a hypertensive crisis is phentolamine. This is administered intravenously in doses ranging from 2 to 5 mg every 5 min until the target BP is achieved. Sodium nitroprusside and nicardipine may also be considered.

Diabetes Insipidus (DI)

DI is a condition in which water adsorption by the collecting tubules of the kidney is impaired, either from a lack of the antidiuretic hormone (ADH) arginine vasopressin (AVP), as in central DI, or due to the lack of responsiveness of the collecting tubules, as is the case in nephrogenic DI. Symptoms are driven by the loss of free water and include polyuria, polydipsia, hypernatremia, volume contraction, and hyperosmolality. Most ICU patients have intake medically determined and, as a result, cannot respond to an increased thirst drive, resulting in hypernatremia. Diagnosis is made by measuring urine specific gravity, which reveals dilute urine. In primary polydipsia a low plasma sodium concentration (<137 mEq/L) is seen with a low urine osmolality (<one-half the plasma osmolality), whereas in DI a high-normal plasma sodium concentration (>142 mEq/L, due to water loss) is seen. Urine osmolality should be less than the plasma osmolality.

ADH is produced in the hypothalamus and released by the anterior pituitary gland. Causes of central DI include causes of panhypopituitarism, such as Sheehan's syndrome, anoxia, trauma, and tumors. In addition, infiltrative conditions including sarcoidosis and lymphoma as well as infectious diseases such as neurosyphilis or tuberculosis can result in central DI. Nephrogenic DI occurs in the setting of adequate AVP and is caused by disorders of the kidney that involve damage to the collecting tubules, where AVP would ordinarily act to promote water adsorption. Nephrogenic DI can be caused by several drugs, including lithium, demeclocycline, amphotericin B, and antiretroviral drugs such as tenofovir and indinavir. Hence, ADH levels are elevated in nephrogenic DI but are diminished or absent in central DI.

Central DI can be clinically distinguished from nephrogenic DI by administering the ADH analog desmopressin in conjunction with water restriction: administration of 1 μg desmopressin subcutaneously will cause the urine osmolality to increase by at least 50% if there is complete DI on a central basis. In partial central DI, the urine osmolality will increase by 10% to 50%. In nephrogenic DI, the urine osmolality will generally not increase after AVP administration. Water restriction is useful to determine if primary polydipsia is present. With water restriction, patients with primary polydipsia will exhibit a rise in urine osmolality, usually to above 500 mOsm/kg, but will not respond to desmopressin since endogenous release is intact.

Treatment of central DI entails correcting the free water deficit as well as prevention of ongoing polyuria through the administration of desmopressin 1 or 2 μg subcutaneously q12h. Free water deficit is calculated in the following manner:

$$0.6 \times \text{patient's weight in kg} \times (\text{patient's sodium}/140 - 1),$$

where $0.6 \times$ weight equals estimated body water, and 140 is the desired sodium. This represents total body water for young males; for females and elderly males multiply the weight in kg by 0.5. Because the urinary fluid losses in DI are hypotonic, the IV fluid is also hypotonic. Patients who are hypotensive due to hypovolemia should receive normal saline solution until intravascular volume has been replenished. Otherwise, hypotonic fluids may be administered. Careful monitoring of intake and output as well as serial electrolyte measurements are required to successfully manage these patients.

Management of nephrogenic DI is similar, although desmopression is not administered. The discontinuation of any drugs that may be causing nephrogenic DI is an important component of management. A thiazide diuretic is administered to induce mild extracellular fluid volume depletion, which causes increased water reabsorption at the proximal tubule. As a result, there is less water delivered to the distal nephron and, therefore, less urine is produced.

Nothing to Disclose

The author has disclosed that no relationships exist with any companies/organizations whose products or services may be discussed in this chapter.

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Notes

Chapter 2. Postoperative Crises

David L. Bowton, MD, FCCP, FCCM

Objectives:

- Differentiate between and describe the early and late causes of postoperative fever.
- List common causes of postoperative hyponatremia in the neurosurgical patient and discuss management and therapeutic options.
- Describe the common causes of hypotension following cardiac surgery and discuss their treatment options.

Key words: cardiac surgery; fever; hypotension; neurosurgery; postoperative complications

Synopsis:

This short review will summarize the presentation and management of selected postoperative complications, including postoperative fever and shock after general surgery; postoperative neurosurgical crises, including hyponatremia; hypotension after cardiac surgery; and perioperative management of antithrombotic therapy for cardiac stents. Malignant hyperthermia is characterized by hypercarbia, fever, and metabolic acidosis intraoperatively but may continue or recur postoperatively. Treatment is the discontinuation of anesthetic agents and administration of dantrolene. Fever in the first 2 to 3 days postoperatively is often due to surgical inflammation, while after 48 to 72 h it is more likely infectious. While the initial management of hypotension postoperatively is usually volume resuscitation, the consequences of volume resuscitation include abdominal compartment syndrome defined as a bladder pressure >20 to 25 mm Hg and organ failure. Its treatment is prompt recognition and surgical decompression. Hyponatremia in the postoperative neurosurgical patient is usually due to the syndrome of inappropriate diuretic hormone secretion, but cerebral salt wasting must be in the differential diagnosis. In the symptomatic patient, both are treated with 3% saline solution. Hypotension after cardiothoracic surgery is most commonly due to vasoplegia but can represent myocardial dysfunction or cardiac tamponade. Atrial fibrillation after cardiac surgery is common and is associated with prolonged length of stay. The unstable patient should be cardioverted, while more stable patients can be treated with calcium antagonists, amiodarone, or β-blockers. The perioperative management of antiplatelet therapy in patients with cardiac stents is challenging. These patients should generally have dual antiplatelet therapy continued throughout the perioperative period, with exceptions being cardiac and intracranial surgery.

General

Postoperative Fever

Postoperative fever is common. A temperature above 100.4°F within 72 h of surgery was noted in more than 20% of patients in a recent observational study of over 1,000 patients.[1] In this discussion of postoperative fever, a temporal classification will be used: immediately postoperative, acute (within the first week), and subacute (after the first week).

Immediately postoperatively, malignant hyperthermia (MH) is the most serious, potentially fatal cause of fever and one requiring immediate intervention. While MH is not strictly a postoperative phenomenon, it usually requires management and monitoring in the intensive care unit. MH occurs in approximately 1 in 30,000 general anesthetics. It typically requires both a genetic predisposition and a triggering agent. Triggering agents include all of the inhalational anesthetics and succinylcholine. Nitrous oxide (NO) and IV anesthetics are not triggers. While there is a genetic basis for MH and the inheritance pattern appears to be autosomal dominant in about 50% of identified cases, a family history of MH is elicited in fewer than 10% of MH patients.[2] There is a 2:1 male:female predominance and the majority of patients present in adulthood (median age 22 years).[2] Mutations in the ryanodine receptors (RYR1) in the sarcoplasmic reticulum are far and away most commonly associated with MH, though other mutations are known to be associated with MH, such as within the dihydropyridine receptors (DHP) in the striated muscle t-tubule membrane.

MH usually occurs within 90 min of induction and presents with respiratory acidosis and rapidly increasing temperature. Respiratory acidosis is seen in more than 90% of patients and rapidly rising temperature in nearly two-thirds of patients. Metabolic acidosis, muscle rigidity, and elevations in creatine kinase (usually >10,000 IU/L), while also observed commonly, are each reported in fewer than half of patients. The initial treatment is to stop all inhalational anesthetics (except NO), switch to an IV anesthetic agent, (eg propofol), and immediately increase minute ventilation and F_{IO_2}. Pharmacologic therapy with dantrolene is a cornerstone of therapy. Prior to

the introduction of dantrolene, mortality was as high as 60%, while the current mortality rate in the MH registry is 2%. Dantrolene is initiated as a bolus of 2.5 mg/kg IV, then 1 mg/kg boluses are given until fever decreases, $Paco_2$ decreases, or muscle rigidity abates (up to a total dose of 10 mg/kg). It is continued at 1 mg/kg every 6 h for 48 h. Electrolytes, especially serum potassium, and serum creatine kinase levels should be monitored. MH patients are predisposed to hyperkalemia due to potassium release from muscle contraction and rhabdomyolysis. The administration of calcium channel blockers should be avoided as they can precipitate marked elevations in serum potassium.

The patient and their family should receive counseling regarding MH and consider undergoing MH susceptibility testing. The patient should also wear a wristband alerting medical providers to their history of MH.

In the first postoperative week, tissue injury (without infection), dead bowel, anastomotic leak, and abscess should lead the differential diagnosis of elevated temperature. Tissue injury releases fever-associated cytokines, including IL-6, IL-1, TNF-α, and IFN-γ.[3] Their release is determined both by the amount of tissue injury and by genetically determined responses to tissue injury. This cytokine release is transient and is the likely etiology of the majority of postoperative fever within the first 72 h of surgery or trauma. In a recent prospective examination of more than 1,000 inpatients undergoing surgery,[1] nearly 25% developed a temperature $>100.4^\circ$ F within the first 72 h postoperatively. In most of these patients, there were no other signs or symptoms of an infectious etiology and an evaluation for an infectious etiology was performed in only 100 patients. In these 100 patients, an infection was identified in only 18 patients. There were no parameters identified, including the maximal temperature and the degree of elevation of the WBC count, which differentiated between those with an infection and those without infection. Of the 18 patients with confirmed infection, the source was clinically evident (symptoms and findings on abdominal examination) in nine: three with anastomotic leaks and one with an accidental unrecognized enterotomy, all requiring return to the operating room. Four of the remaining patients sustained superficial surgical site infections. Thus, the clinical examination can suggest or confirm the cause of early postoperative fever in a large percentage of patients. The causes of infectious fever that most commonly required laboratory or radiographic investigation to ascertain were pneumonia, *Clostridium difficile* enterocolitis, and urinary tract infections. Surgical site infections often present after the first week and frequently after the patient has been discharged from hospital.

An unusual cause of fever after surgical intervention is the postimplantation syndrome seen in 30% to 60% of patients after placement of an aortic stent graft. It is characterized by fever and leukocytosis and perigraft air (within the native aorta and around the stent graft) on CT scan, without demonstrable infection.[4,5]

Atelectasis is often cited as a cause of postoperative fever. However, there are few data to endorse this belief. A recent systematic review[6] concluded that there was insufficient evidence to support an association between atelectasis and postoperative fever or even that atelectasis caused fever.

Postoperative Hypotension

Hypotension in the immediate postoperative period is common. In the patient with a major intraabdominal catastrophe (eg, necrotic bowel, anastomotic leak), this usually is due to hypovolemia caused by large fluid shifts to the extravascular space and blood loss. The magnitude of hypovolemia is often underappreciated. In this setting, volume resuscitation is the cornerstone of therapy. The end points of resuscitation remain a topic of controversy. While central venous pressure (CVP) goals are often stated, CVP correlates poorly with volume responsiveness, and its application to bedside management is uncertain.[7] While some authors[8,9] suggest that supranormal values for cardiac index and oxygen delivery are appropriate goals, the evidence is contradictory and generally not supportive of such targets.

Bleeding is a specific case of hypovolemia in the immediate postoperative period. In the setting of massive blood loss, balanced transfusion is now widely recommended based on data

accumulated in the treatment of war-related traumatic injury. Thus, in patients who are massively bleeding and require more than 4 units of packed red blood cells, a strategy of using blood and plasma in ratios of 2:1 or 1:1 is now commonly employed.[10]

Regional anesthesia, specifically epidural or spinal anesthesia, is a relatively common cause of hypotension as a consequence of vasodilation due to loss of sympathetic tone. It usually responds to decreasing the dosage of anesthetic or narcotic and modest volume administration. Adrenal insufficiency is an uncommon cause of hypotension in the immediate postoperative period. Preoperative glucocorticoid therapy is a major risk factor. Small doses of corticosteroids or steroid administration for a short period of time are generally not risks; patients who receive less than 5 mg of prednisone daily or steroids for less than 2 weeks do not appear to be at increased risk for adrenal insufficiency.[11,12] While etomidate suppresses 11β-hydroxylase for 24 to 72 h, thus reducing cortisol synthesis, it does not appear to result in an increased need for cortisol replacement therapy.[13] The diagnosis of adrenal insufficiency in critically ill patients is difficult because of variability in the cortisol assay and the response to ACTH stimulation.[14,15] However, a random serum cortisol level $\leq$10 μg/dL is highly predictive of adrenal insufficiency using the metyrapone stimulation test as the criterion standard.[14]

From 25 to 48 h postoperatively, the etiology of hypotension and fever is more often related to intraabdominal sepsis caused by abscess, necrotic bowel, or an anastomotic leak. Patients usually present with fever, tachycardia, tachypnea, and elevated WBC, along with abdominal pain or tenderness and abdominal distension. Elderly, chronically ill, or immunocompromised patients may present atypically without one or more of these findings. Abdominal CT scans, while often useful, may not be able to differentiate blood from abscess or benign fluid collections. Reexploration is often needed to ascertain the diagnosis and for appropriate treatment, but it is too often delayed.[16] *Clostridium difficile* enterocolitis has become an increasingly common cause of fever with diarrhea and should always be considered in the differential diagnosis.

Abdominal Compartment Syndrome

Abdominal compartment syndrome (ACS) is the syndrome of elevated intraabdominal pressure in the setting of organ failure due to compression of abdominal structures. It was originally described in patients following severe abdominal trauma but is now increasingly recognized as potentially complicating any clinical setting where accumulation of ascitic and interstitial fluid within the abdominal compartment occurs. Thus, in addition to primary intraabdominal processes, medical or surgical patients following large-volume fluid resuscitation (as for septic shock) are also at risk for ACS. Intraabdominal pressure is most often measured as intravesical pressure and is normally less than 12 mm Hg. Pressures above 12 mm Hg define intraabdominal hypertension, while pressures above 20 mm Hg with organ dysfunction define ACS.[17] Commonly seen organ failures include renal failure due primarily to renal vein compression, pulmonary failure due to severe reduction of thoracic compliance, gut failure due to reduced mesenteric and mucosal blood flow, hypotension (cardiovascular failure) due to impaired venous return and ventricular filling, hepatic failure due to reduced blood flow and consequent impaired lactate clearance, and CNS failure due to elevation of intracranial pressure resulting from impaired venous drainage. The definitive treatment of ACS is usually surgical decompression, though in the setting of large volumes of ascites, large-volume paracentesis (>1,500 mL) has been successfully employed.[18] Other measures to reduce intraabdominal volume or increase abdominal compliance, including NG suction, sedation, and paralysis, may be employed as temporizing measures until definitive therapy can be undertaken.

Postoperative Neurosurgic Crises

Altered Mental Status

A rapid decline in level of consciousness or new deficits on neurologic examination is almost always related to compromised brain blood flow, either focal or global. These alterations can be due to space-occupying lesions (edema, blood) compro-

mising blood flow, hydrocephalus increasing intracranial pressure (ICP) and reducing cerebral perfusion pressure (CPP), or a primary vascular process (thrombosis or vasospasm). Because acute reductions in brain blood flow must be treated promptly to minimize the volume of infarcted tissue, acute alteration in mental status or function is almost always an indication for emergent cranial CT scan to evaluate treatment options. Epidural hematomas, subdural hematomas, and large superficial intraparenchymal hemorrhages resulting in acute compression are usually considered good candidates for operative treatment. Importantly, hemorrhage within the posterior fossa, because of the very limited room for expansion and the proximity of the brainstem, is a neurosurgical emergency, and surgical evacuation of posterior fossa hemorrhages should routinely be considered.[19,20] Acute hydrocephalus results from obstruction of the lateral, third, or fourth ventricles due to tumor, edema, parenchymal hemorrhage, or intraventricular blood. It occurs in over 20% of patients with subarachnoid hemorrhage. If a CT scan reveals acute hydrocephalus in the patient with an altered level of consciousness, consideration should be given to placement of an external ventricular drain, which permits both the measurement of ICP and the drainage of CSF to reduce ICP.

When cerebral edema is seen on the CT scan in the patient with an acute alteration in consciousness, ICP should generally be monitored and consideration given to the initiation of osmotherapy. Monitoring the ICP permits knowing and maintaining CPP. Generally, the CPP target is greater than 50 mm Hg, although as noted below, higher levels are sometimes required in patients with acute brain ischemia due to cerebral vasospasm or thrombosis. ICP can be effectively lowered with mannitol or hypertonic saline solution. Hypertonic saline solution is available as 3%, 7.5%, and 23.4% concentrations. A recent metaanalysis[21] suggests that hypertonic saline solution is probably more effective than mannitol, though mannitol remains first-line therapy in most ICUs. Corticosteroids are often used in patients with cerebral edema due to tumors or inflammation (vasogenic edema). Dexamethasone is most often used. There is no role, however, for steroids in the treatment of cerebral edema due to trauma or stroke.[22,23] In patients with focal symptomatic brain ischemia such as in the setting of vasospasm after subarachnoid hemorrhage, elevation of perfusion pressure can be associated with improvement in the neurologic deficits. A trial of therapeutic hypertension may be warranted in this setting, with systolic blood pressures above 200 mm Hg sometimes required to achieve reversal of the neurological deficit. This clearly must be balanced against the risk of adverse cardiac effects, and there are no prospective trials to guide decision making with respect to improving long-term outcomes or balancing risks and benefits.

When the decline in mental status develops more gradually, over many hours or a day or more, hypoventilation and hyponatremia are prominent causes. Hypoventilation can be easily confirmed with blood gas analysis, followed by appropriate steps to increase minute ventilation. These include the initiation of noninvasive positive pressure ventilation in patients who are cooperative, reduction in dosage or careful reversal of sedative and/or narcotic medications, or intubation and mechanical ventilation.

Hyponatremia

Hyponatremia frequently complicates neurological diseases. The most common cause is the syndrome of inappropriate antidiuretic hormone secretion (SIADH), while cerebral salt wasting is much less common and is most often seen in patients with subarachnoid hemorrhage (SAH). Both present with an inappropriately high urine sodium concentration and urine osmolarity in the setting of a low serum sodium and low serum osmolarity. In SIADH, intravascular volume is normal or high, while in cerebral salt wasting, intravascular volume is low. In patients with low intravascular volume, a high urine sodium concentration helps to distinguish cerebral salt wasting from volume depletion (which will result in low urinary sodium) but with elevated antidiuretic hormone (ADH) levels (appropriate ADH secretion) to minimize urinary volume loss and restore intravascular volume. The treatment of mild to moderate hyponatremia due to SIADH (serum sodium value greater than 120 mEq) is usually fluid restriction. In patients with SAH, volume restriction is not usually employed for

fear of causing hypovolemia and worsening vasospasm or precipitating cerebral ischemia. In patients with SAH and symptomatic patients with a serum sodium value less than 120 mEq, hypertonic saline solution is the mainstay of therapy. Three percent saline solution is most commonly used because in patients with SIADH, 0.9% saline solution will not usually raise the serum sodium concentration because of obligate excretion of the administered sodium in the inappropriately concentrated urine (urine osmolarity greater than serum osmolarity), resulting in a net increase in retention of free water. In patients who are severely symptomatic (eg, seizures), the goal is to raise the serum sodium level by 1 mEq/h for the first 2 to 4 h but by no more than 10 mEq in the first 24 h; 100 mL of 3% saline solution will raise the serum sodium (Na) by 1.0 to 2 mEq. Too-rapid correction of hyponatremia is associated with central pontine myelinolysis, or the more general osmotic demyelination syndrome (describing extra-pontine demyelination). The increase in serum Na can be approximated by the following formula:

$$\text{Increase in serum Na} = (\text{Infusate [Na]} - \text{Serum [Na]}) \times \text{Liters infused}/(\text{TBW} + 1)$$

where TBW = total body water (approximately 0.5 × lean body weight in women; 0.6 in men).

The role of vasopressin-2 receptor antagonists (tolvaptan and conivaptan) remains uncertain because of the paucity of evidence demonstrating clinical benefit in critically ill patients and the inability to control the rate of rise of sodium.

Diabetes Insipidus

Diabetes insipidus (DI) is characterized by excretion of large volumes of urine with low specific gravity despite low intravascular volume and is due to decreased excretion of ADH, central DI or loss of effect of ADH, nephrogenic DI. Central DI is observed in 10% to 60% of patients following transsphenoidal hypophysectomy. The range in incidence is largely a function of tumor size, with resection of larger tumors more often associated with DI. A triphasic response following transsphenoidal hypophysectomy has been described. This consists of early DI immediately after and up to 5 days postoperatively due to suppression of ADH release because of hypothalamic dysfunction, followed within 5 to 10 days by SIADH due to ADH release from degenerating posterior pituitary, followed by delayed or permanent DI due to depletion of ADH. Early DI is seen in approximately 40% of patients, delayed SIADH in 8%, and delayed or permanent DI in about 5%. Fewer than 5% of patients undergoing transsphenoidal hypophysectomy will manifest all components of the triphasic response. High urine output (often 400–800 mL/h) immediately following surgery must be differentiated from postoperative fluid diuresis or excretion of an osmotic load (radiographic contrast or mannitol). A very low urine-specific gravity (<1.005) or low urine osmolarity (<200 mOsm/L) is highly suggestive that the high urine output is due to DI and that volume status and serum sodium must be carefully monitored to avoid the development of hypotension due to volume loss and hypernatremia. Normal saline solution is used to maintain intravascular volume; using urine output to gauge the amount required. Desmopressin acetate can be used to reverse the DI, but care must be used to avoid hyponatremia, which is common in this patient population in the postoperative period.[24]

Airway Emergencies

Airway emergencies are an infrequent but highly morbid postoperative crisis. In a patient undergoing surgery in the neck (eg, anterior cervical spine surgery or carotid endarterectomy), complaints of difficulty swallowing or breathing or the presence of stridor should prompt an immediate evaluation of the patient and consideration of airway compromise in the differential diagnosis. In patients undergoing cervical spine surgery, 25% to 6% will develop an airway complication, and one third or more of these will require reintubation.[25] In patients undergoing carotid endarterectomy (CEA), the reintubation rate is 1% to 2%.[26] Hematoma is the cause of airway compromise in almost all patients following CEA, in contrast to edema and consequent airway narrowing and compression after anterior cervical spine surgery. Hemato-

ma formation typically occurs within the first 6 h of CEA, while airway compromise after anterior cervical spine surgery occurs later but usually within the first 36 h. Following cervical spine surgery or CEA, it should be presumed that the patient will have a difficult airway and that the most skilled airway provider available should be present to assist with securing the airway. There is no clear consensus regarding the relative merits of fiber-optic intubation versus direct laryngoscopy to secure the airway, but both should be available with clinical circumstances and operator expertise dictating the choice. While the need for an emergent surgical airway is rare, its very rarity should dictate that each hospital have a process in place to effect this without delay when needed.

Postoperative Cardiothoracic Surgical Crises

Hypotension

Hypotension after cardiothoracic surgery is common and can be due to vasodilation, blood loss, cardiac tamponade, myocardial dysfunction, or dysrhythmias. Vasodilation is the most common cause of hypotension and is seen immediately postoperatively; it can persist for hours to days. The etiology of the vasodilation is multifactorial. A low preoperative ejection fraction is associated with relatively depressed levels of arginine vasopressin and with postoperative vasodilation. IL-1 is increased following cardiopulmonary bypass and, by generation of cyclic guanine monophosphate, is associated with vasodilation and hypotension. Use of ACE inhibitors preoperatively is also associated with depressed levels of arginine vasopressin and hypotension. Treatment of hypotension, after ensuring adequate intravascular volume repletion, is vasopressor infusion, most commonly neosynephrine or norepinephrine. Recently, in light of the relative depression of arginine vasopressin levels, the use of vasopressin in low fixed doses (0.03 U/min) to restore vasopressin levels to more appropriate levels has been suggested.[27]

Bleeding resulting in hypotension occurs in approximately 5% of patients following coronary artery bypass grafting (CABG). Reoperation for bleeding is required in approximately 2.4% of patients following CABG.[28] Patients who require reoperation for bleeding have about four times the mortality rate of patients who do not require reoperation (8% vs 2%), but whether this is due to reoperation or that many of the risk factors for bleeding are also risk factors for mortality is unclear. There are numerous risk factors for bleeding, the most important of which are age >70 years, reoperation (eg, prior CABG), renal replacement therapy or elevated serum creatinine, emergency surgery, and the use of preoperative adenosine diphosphate receptor inhibitors (eg thienopyridines) or glycoprotein IIb/IIIa receptor antagonists. Bleeding is usually manifested by excess drainage from mediastinal and/or pleural drains (> 200 mL/h). In the patient with excessive blood loss after CABG, reversible factors should be sought beginning with a prolonged activated clotting time due to residual heparin effect, which should be treated with protamine sulfate. Hypothermia inhibits coagulation, and the patient should be rewarmed if hypothermic. Thrombocytopenia is common after cardiopulmonary bypass (CPB) and, coupled with platelet dysfunction due to preoperative antiplatelet agents, often argues for platelet transfusion in the bleeding patient. Platelets are suspended in plasma, so platelet transfusions will provide some clotting factors as well. Less commonly, prolongation of the aPTT or PT will suggest clotting factor depletion and the need for repletion with prothrombin complex concentrate. Recombinant factor VII concentrate is usually avoided in this population because of the risk of precipitating bypass graft thrombosis. Inadequate surgical hemostasis is usually a diagnosis of exclusion, but chest drainage exceeding 400 mL/h that does not rapidly slow should precipitate consideration of reoperation. Patients who receive anticoagulants after CABG have a three-fold increased risk for bleeding,[29] and recent ACCP guidelines suggest that DVT prophylaxis in patients undergoing CABG with an uncomplicated postoperative course be limited to pneumatic compression hose.[30]

Myocardial Dysfunction

Myocardial dysfunction is another frequent cause of hypotension following cardiac surgery.

It may be consequent to myocardial injury or edema consequent to cardiopulmonary bypass (CPB), cardiac tamponade with inadequate ventricular filling, left ventricular myocardial ischemia, or right ventricular dysfunction due to pulmonary hypertension or right ventricular ischemia. Postoperative cardiac tamponade may occur even with an open pericardium due to focal collection of blood and compression of cardiac chambers, most often the right atrium and/or right ventricle. The risk of tamponade is increased by the use of anticoagulants in the immediate perioperative period. While atypical presentations are common, cardiac tamponade should be suspected in the patient with tachycardia, a low cardiac index, and a high CVP. Hypotension and elevated pulmonary artery occlusion pressure (equal to the CVP) are frequently seen. If cardiac tamponade is suspected, echocardiography should be performed to confirm the diagnosis. After median sternotomy, it is often difficult to obtain good sonographic windows, and transesophageal echocardiography is usually needed to detect right atrial compression as opposed to pericardial fluid surrounding the heart, as might be seen with a closed pericardium. Pericardial tamponade is almost always an indication for reoperation to remove the compressing fluid.

Ischemic myocardial dysfunction can be due to graft occlusion, coronary embolization, or inadequate intraoperative myocardial protection. Graft occlusion occurs in 5% to 10% of CABGs and is more often due to graft kinking or other technical problem (eg, occluding stitch) than to thrombosis or spasm. Correction of a correctable mechanical cause of ischemia should be undertaken when feasible. When not possible or unsuccessful, inotropic support is the mainstay of therapy. Epinephrine and milrinone are the current mainstays of inotropic support. Epinephrine acts at β and α receptors, providing inotropy (β_1-receptor agonism) and support of blood pressure. Milrinone inhibits phosphodiesterase 3 and results in both increased inotropy and reduced afterload through vasodilation. Consequently, its impact on blood pressure can be difficult to predict (increased flow vs reduced resistance) but usually results in a fall in blood pressure and thus is usually used with a vasopressor, often phenylephrine, or a balanced inotrope/vasopressor, such as epinephrine.

Right ventricular dysfunction can cause left ventricular dysfunction due to forward flow failure with reduced left ventricular filling and by shifting of the ventricular septum toward the left ventricle, impairing both left ventricular filling and optimally coordinated left ventricular contraction. Right ventricular dysfunction can be due to ischemia or acutely worsening pulmonary hypertension. As with left ventricular ischemia, maintenance of coronary perfusion pressure is important to maintain coronary blood flow to the right ventricle. Milrinone can often reduce pulmonary vascular resistance and improve right ventricular systolic function. If inotropes alone are ineffective, pulmonary vasodilators, such as inhaled nitric oxide and inhaled epoprostenol, may be useful to reduce right ventricular afterload and increase cardiac output. Inhaled epoprostenol is less expensive than nitric oxide and has replaced nitric oxide for this indication in many centers.

Dysrhythmias

Dysrhythmias are a frequent cause of hypotension after cardiac surgery. Bradycardia due to edema or damage of the cardiac conduction system or secondary to ischemia (eg, from nodal arterial interruption) is common, and most patients will have temporary epicardial pacemaker leads inserted intraoperatively. Following CPB, the stroke volume is often small and fixed, necessitating a more rapid heart rate to maintain cardiac index. Thus it is common to pace these patients at heart rates of 95 to 100 beats/min if the initial cardiac index is low. The bradycardia and small stroke volume are most often transient and the need for pacing resolves within 24 h.

The most common tachyarrhythmia after CABG or valve replacement surgery is atrial fibrillation; it occurs in 25% to 35% of patients and is an independent predictor of prolonged hospital stay and increased costs.[31] With the onset of atrial fibrillation, ventricular filling is often inadequate because of both the loss of coordinated atrial contraction and the shortening of the filling time. This can result in loss of cardiac output and in hypotension. In patients

who are hemodynamically unstable, D/C cardioversion is the preferred treatment. However, because patients are susceptible to recurrence and are predisposed to atrial fibrillation for several weeks following surgery, additional treatment directed at rate control or rhythm control should be provided. No large prospective trial has been performed to determine the relative merits of rate control vs rhythm control in postoperative atrial fibrillation, though a rate control approach has the merit of not exposing the patient to the risks of class I or class III antiarrhythmic drugs. Further, the noncardiac adverse effects of amiodarone are significant and in a patient without markedly impaired ventricular function, hypotension, or severe asthma, β-blockers are probably the treatment of choice. However, in patients who are hypotensive or who have significantly depressed myocardial function, the administration of either β-blockers or nondihydropyridine calcium antagonists has a higher incidence of myocardial depression and hypotension than amiodarone.

Because of the frequency of postoperative atrial fibrillation and its impact on cost and length of stay, considerable attention has been given to the prevention of atrial fibrillation. The most effective prophylactic agents appear to be β-blockers and amiodarone, though magnesium and biatrial pacing have also been proposed.[31] There is insufficient evidence for definitive recommendations; however, prophylactic β-blockers and amiodarone appear to provide the greatest benefit. β-Blockers appear somewhat more effective than amiodarone when begun preoperatively but if begun postoperatively, β-blockers and amiodarone appear equally, if incompletely, effective in reducing the incidence of atrial fibrillation. Discontinuation of β-blocker therapy in patients receiving preoperative β-blockers significantly increases the risk of postoperative atrial fibrillation; thus, β-blockers should be continued in these patients whenever possible.

Surgery and Cardiac Stents

Over 500,000 patients undergo percutaneous coronary intervention with stent placement annually in the United States. Virtually all these patients require continuous antiplatelet therapy after stent placement. However, antiplatelet therapy poses an increased risk for perioperative bleeding, and thus the challenge of perioperative management of patients with intracoronary stents is a common one. Stent thrombosis, while uncommon with appropriate patient management, can be catastrophic. Case fatality rates of stent thrombosis in the perioperative period have been reported to be 50% or greater.[32] There are no prospective trials of management strategies focused on the perioperative period; thus, recommendations are based on evidence gleaned from studies of discontinuation of antiplatelet agents for various reasons. Discontinuation of dual antiplatelet therapy within 6 weeks of placement of a bare metal stent or 3 to 6 months of placement of a drug-eluting stent is associated with an increased risk stent thrombosis. Conversely, dual antiplatelet therapy increases the risk of perioperative bleeding and morbidity in patients undergoing CABG, but whether this increased risk of bleeding extends to patients undergoing other types of surgery is not clearly defined. A recent systematic review of published studies examining the risk of discontinuation of antiplatelet agents and stent thrombosis 30 days or more after placement of a drug-eluting stent found that the median time to ischemic event with cessation of thienopyridine or thienopyridine plus aspirin was 7 days, while if aspirin was continued, the median time to event was 122 days.[33] On the basis of these and other data, the ninth edition of the ACCP Evidence-Based Clinical Practice Guidelines recommends deferring surgery for 6 weeks following placement of a bare metal stent and at least 6 months following placement of a drug-eluting stent.[32] In patients in whom non-CABG or intracranial surgery cannot be deferred for these time periods, the current recommendation is to continue dual antiplatelet therapy. In patients undergoing CABG within this early time frame, the recommendation is to discontinue clopidogrel or prasugrel 5 days before CABG, continue aspirin through the perioperative period, and reload the thienopyridine (eg, 300 mg clopidogrel) postoperatively. For urgent intracranial surgery, thienopyridines should probably be discontinued even earlier if feasible and aspirin discontinued prior to surgery

and restarted as early as possible postoperatively (depending on the specific surgery and perceived bleeding risk).

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Chapter 3. Mechanical Ventilation

Gregory A. Schmidt, MD, FCCP

Objectives:

- Review modes.
- Examine physiology of ventilation.
- Discuss the types of respiratory failure.
- Introduce key ventilation concepts.
- Review equation of motion.
- Discuss VILI and VIDD.
- Review autoPEEP.
- Examine permissive hypercapnia.
- Discuss the ventilator bundle.

Key words: acute lung injury; airway pressure release ventilation; ARDS; assist-control ventilation; autoPEEP; COPD; equation of motion; high-frequency oscillatory ventilation; inverse ratio ventilation; lung-protective ventilation; mechanical ventilation; noninvasive ventilation; permissive hypercapnia; pressure assist-control ventilation; pressure control; pressure-regulated volume control; pressure support; status asthmaticus; synchronized intermittent mandatory ventilation; tidal volume; ventilator bundle ventilator-induced diaphragm dysfunction; ventilator-induced lung injury; volume assist-control ventilation

Synopsis:

This chapter offers an approach in which two aspects of mechanical ventilation, oxygenation (largely determined by F_{IO_2} and positive end-expiratory pressure [PEEP]) and ventilation (depending mostly on mode, rate, and tidal volume or set inspiratory pressure) are considered separately. Then the ventilator is used as a probe of the patient's respiratory system mechanical derangements, and ventilator settings are tailored to the patient's mechanical and gas exchange abnormalities. Modes of ventilation are analyzed and key ventilation concepts of ventilator-induced lung injury; ventilator-induced diaphragm dysfunction; autoPEEP; permissive hypercapnia; and the ventilator bundle are covered.

The fundamental purpose of mechanical ventilation is to assist in elimination of carbon dioxide and the uptake of adequate oxygen while the patient is unable to do so or should not be allowed to do so. Such patients fall into two main groups: (1) those in whom full rest of the respiratory muscles is indicated (such as during shock; severe, acute pulmonary derangement; or deep sedation or anesthesia), and (2) those in whom some degree of respiratory muscle use is desired (eg, to strengthen or improve the coordination of the respiratory muscles; to assess the ability of the patient to sustain the work of breathing; or to begin spontaneous ventilation). It is important for the intensivist to be explicit about whether the respiratory muscles should be rested or exercised because the details of ventilation (mode, settings) usually follow logically from this fundamental point. For example, in a patient in profound shock, the ventilator should be set to fully take over the work of breathing (eg, using volume assist-control) while the flow and pressure waveforms are examined to determine whether this goal has been met.

Using the Ventilator to Control Oxygenation

The ventilator settings most concerned with oxygenation are the fractional inspired oxygen (F_{IO_2}) and positive end-expiratory pressure (PEEP). Generally, mode, tidal volume, rate, and other settings have only very modest effects on arterial partial pressure for oxygen (Pa_{O_2}). For example, in the ARDS Network tidal volume trial, use of 6 vs 12 mL/kg predicted body weight was associated with a small but real decrement in the ratio of Pa_{O_2} to F_{IO_2} (P/F ratio 156 vs 178).[1]

Oxygen

Oxygen is clearly toxic in high concentration, likely because of reactive oxygen species' effects on many biological systems. The threshold for toxicity is uncertain, especially in the injured lung. Generally, F_{IO_2} less than 0.6 is considered nontoxic while higher fractions are avoided when possible. There is some experimental evidence that the injured lung may be more resistant to oxygen-induced injury. Given the uncertainties in this area, most clinicians strive to limit exposure to concentrations in excess of 0.6 to less than 24 h, using PEEP, diuresis, positional maneuvers, or inhaled vasodilators.

PEEP

Nearly 40 years ago, PEEP was linked to protection against gross and histologic lung injury.[2] It has been postulated that PEEP limits tidal recruitment and derecruitment, thereby reducing lung inflammation.[3,4] Yet PEEP may provoke deleterious effects so that choosing the appropriate level requires balancing benefits and costs. One widely used approach is that devised by the ARDS Network, in which PEEP and F_{IO_2} combinations are chosen from a table to achieve oxygenation goals.[1] Three clinical trials addressed the potential role of higher levels of PEEP than required for acceptable oxygenation. Although each failed to demonstrate that higher PEEP enhances survival, all showed a trend in that direction (after adjustment for differences in baseline covariates),[5–7] and meta-analyses have shown this benefit to be statistically significant.[8,9]

In patients with acute lung injury (ALI) and ARDS, lung units collapse largely because of compressive forces, especially in dependent lung zones. One would anticipate PEEP to be effective in keeping the lung open when it produces a positive transpulmonary pressure. Surprisingly, when patients are managed according to the ARDS Network low PEEP recommendations, transpulmonary pressure is often negative, despite PEEP.[10] Raising PEEP to produce a positive transpulmonary pressure raised oxygenation and compliance and produced a trend toward higher survival. Alternative approaches to indivualizing the level of PEEP include analyzing the pressure-volume curve for evidence of the inflation limb lower inflection point (Pflex), deflation limb upper Pflex, maximal compliance, true inflection point of the deflation limb, the degree of hysteresis, or the stress index.[11,12] Normally the airway opening pressure rises linearly during constant flow, volume-controlled ventilation because respiratory system mechanical properties (compliance and resistance) do not vary much over the tidal range. If compliance increases during tidal inflation (suggesting that lung is being recruited), the pressure-time display will be convex upward (stress index <1): more PEEP is likely to be helpful. If the pressure-time display is concave upward, compliance is falling as the lung inflates, possibly signaling overdistention: tidal volume or PEEP should be lowered.

Mean Airway Pressure

In addition to F_{IO_2} and PEEP, the mean airway pressure affects recruitment and oxygenation. High-frequency oscillatory ventilation (HFOV), inverse ratio ventilation (IRV), and airway pressure release ventilation (APRV) are various ways to raise mean airway pressure and, thereby, oxygen partial pressures.

Using the Ventilator to Effect Carbon Dioxide Elimination

The arterial partial pressure for carbon dioxide (Pa_{CO_2}) depends on total body carbon dioxide production and alveolar ventilation. The ventilator can be used to set minute ventilation, the sum of alveolar ventilation and dead space ventilation. Various ventilatory modes control minute ventilation by delivering a tidal volume (directly, as in volume-preset modes, or indirectly, as in pressure-preset modes). Carbon dioxide is also eliminated during HFOV through various incompletely understood mechanisms.

Modes of Mechanical Ventilation

Technologic innovations have provided a plethora of differing modes by which a patient can be mechanically ventilated. Various modes have been developed with the hope of improving gas exchange, patient comfort, or speed of return to spontaneous ventilation. Aside from minor subtleties, however, nearly all modes allow full rest of the patient, on the one hand, or substantial exercise on the other. Thus, in the great majority of patients, choice of mode is mostly a matter of patient or physician preference. Noninvasive ventilation should be considered before intubation and ventilation in many patients who are hemodynamically stable and do not require an artificial airway, especially those with acute-on-chronic respiratory failure, postoperative respiratory failure, cardiogenic pulmonary edema, or acute respiratory failure complicating severe immunosuppression.

The equation of motion relates the pressure at the airway opening (Pao) to volumes, flows, respiratory system mechanics, and patient effort:

$$Pao = \frac{V}{Crs} + \dot{V}R + \ddot{V}I - Pmus$$

Where V is volume above functional residual capacity; Crs is static compliance of the respiratory system; $\dot{V}$ is inspiratory flow rate; R is inspiratory resistance; the $\ddot{V}$ I term relates to acceleration and inertia and is relevant only during HFOV; and Pmus is the pressure produced by patient muscular effort.

During volume-preset ventilation (and assuming a passive patient, where Pmus = 0), the plateau airway pressure (Pplat) is determined by the tidal volume (V_T) and the static compliance of the respiratory system (Crs):

$$Pplat = V_T/Crs + PEEP$$

where PEEP also includes autoPEEP.

Conversely, in pressure-preset modes, a fixed inspiratory pressure (Pinsp) is applied to the respiratory system, whatever the resulting V_T. However, the V_T is predictable (again, assuming a passive patient) when the Crs is known:

$$V_T = (Pinsp - PEEP) \times Crs$$

assuming time for equilibration between Pinsp and alveolar pressure. Thus, a patient with static Crs of 50 mL/cm H_2O ventilated on volume assist-control ventilation (VACV) at a V_T of 500 mL with no PEEP (or autoPEEP) will have a Pplat of about 10 cm H_2O while the same patient ventilated on pressure assist-control ventilation (PACV) at 10 cm H_2O will have a V_T of about 500 mL. Thus, although physicians' comfort level with volume-preset and pressure-preset modes may be very different, the modes can be similar as they are tied to each other through the patient's Crs.

A potential advantage of pressure-preset ventilation is greater physician control over the Ppeak (since Ppeak = Pinsp) and the peak alveolar pressure, which could lessen the incidence of ventilator-induced lung injury. However, this same reduction in volutrauma risk should be attainable during volume-preset ventilation if a V_T appropriate to the lung derangement is chosen. Indeed, the ARDS Network ARMA trial, which demonstrated a mortality reduction in the low-V_T group, used VACV and a V_T of 6 mL/kg predicted body weight.[1] Pressure-preset modes could make such a lung-protection strategy easier to carry out by dispensing with the need to repeatedly determine Pplat and periodically adjust the V_T. During use of pressure-preset modes, the patient also has greater control over inspiratory flow rate, and, therefore, potentially increased comfort. Several features of pressure-preset modes have raised concern that lung protection cannot be assured. Most importantly, a safe level of maximal alveolar pressure is not known. Moreover, unless the patient is fully passive, the transpulmonary pressure cannot be controlled using pressure-preset modes and is not even known. A final limitation is that pressure-preset modes do not allow ready determination of the respiratory system mechanical properties.

In the following descriptions, each mode is first illustrated for a passive patient, such as following muscle paralysis, then for the more common situation in which the patient plays an active role in ventilation. On some ventilators, V_T can be selected by the physician or respiratory therapist, while on others a minute ventilation and respiratory rate (f) are chosen, secondarily determining the V_T. Similarly, on some machines an inspiratory flow rate is selected while on others flow depends on the ratio of inspiratory time (T_I) to total respiratory cycle time and f, or an inspiratory to expiratory (I:E) ratio and f.

Conventional Modes of Ventilation

Volume Assist-Control Ventilation

Volume assist-control was found to be the most commonly used mode in an international survey of mechanical ventilation. Among its advantages are that it was the mode used in the ARMA trial demonstrating reduced mortality in patients with ALI and ARDS and that respiratory mechanics can be measured readily.

Passive Patient: The set parameters of the assist-control mode are the inspiratory flow rate, frequency (f), and V_T. The ventilator delivers f equal breaths per minute, each of V_T volume. V_T and flow determine the T_I, T_E, and the I:E ratio.

Pplat is related to V_T, the compliance of the respiratory system, and PEEP, while the difference between Ppeak and Pplat includes contributions from flow and inspiratory resistance.

Active Patient: The patient has the ability to trigger extra breaths by exerting an inspiratory effort exceeding the preset trigger sensitivity, each at the set V_T and flow, and to thereby change T_I, T_E, and I:E ratio, and to potentially create or increase autoPEEP. Typically, each patient will display a preferred rate for a given V_T and will trigger all breaths when the controlled ventilator frequency is set a few breaths/min below the patient's rate; in this way, the control rate serves as an adequate support should the patient stop initiating breaths. When high inspiratory effort continues during the ventilator-delivered breath, the patient may trigger a second, superimposed ("stacked") breath (rarely a third, as well). Patient effort can be increased (if the goal is to exercise the patient) by increasing the magnitude of the trigger or by lowering V_T (which increases the rate of assisting). Lowering f at the same V_T generally has no effect on work of breathing when the patient is initiating all breaths.

Synchronized Intermittent Mandatory Ventilation

In the passive patient, SIMV cannot be distinguished from controlled ventilation in the ACV mode. Ventilation is determined by the mandatory f and V_T. However, if the patient is not truly passive, he may perform respiratory work during the mandatory breaths. More to the point of the SIMV mode, he can trigger additional breaths by lowering the airway opening pressure below the trigger threshold. If this triggering effort comes in a brief, defined interval before the next mandatory breath is due, the ventilator will deliver the mandatory breath ahead of schedule to synchronize with the patient's inspiratory effort. If a breath is initiated outside of the synchronization window, V_T, flow, and I:E ratio are determined by patient effort and respiratory system mechanics, not by ventilator settings. The spontaneous breaths tend to be of small volume and are highly variable from breath to breath. The SIMV mode has historically been used to gradually augment the patient's work of breathing by lowering the mandatory breath f, but SIMV has been shown to prolong weaning.[13,14] Although this mode continues to be used widely, there is little rationale for it, and SIMV is falling out of favor.

PACV

In the passive patient, ventilation is determined by f, the inspiratory pressure increment (Pinsp − PEEP), I:E ratio, and the time constant of the patient's respiratory system. In patients without severe obstruction (ie, time constant not elevated) given a sufficiently long T_I, there is equilibration between the ventilator-determined Pinsp and alveolar pressure (Palv) so that inspiratory flow ceases. In this situation, V_T is highly predictable, based on Pinsp (= Palv) and the mechanical properties of the respiratory system (Crs). In the presence of severe obstruction or if T_I is too short to allow equilibration between ventilator and alveoli, V_T will fall below that predicted based on Pinsp and Crs. It is typically the case during PACV that alveolar and ventilator pressures do not equilibrate either at end-inspiration or at end-expiration. Thus the maximal inspiratory alveolar pressure is generally less than the set inspiratory pressure on the ventilator and the end-expiratory pressure exceeds the set expiratory pressure (ie, there is autoPEEP).

The active patient can trigger additional breaths by reducing the airway opening pressure (Pao) below the triggering threshold, raising the I:E ratio. The inspiratory reduction in pleural pressure combines with the ventilator Pinsp to augment the transpulmonary pressure and the V_T. This point leads many intensivists to be skeptical regarding the ability of PACV to ensure lung-protective tidal volumes in patients with ALI and ARDS. Because T_I is generally set by the physician, care must be taken to discern the patient's neural T_I (from the waveforms display) and adjust the ventilator accordingly; otherwise, additional sedation might be necessary.

Pressure-Support Ventilation (PSV)

The patient must trigger the ventilator in order to activate this mode, so pressure support is not applied to passive patients. Ventilation is

determined by Pinsp, patient-determined f, patient effort, and the respiratory mechanics. Once a breath is triggered, the ventilator attempts to maintain Pao at the physician-determined Pinsp, using whatever flow is necessary to achieve this. Eventually flow begins to fall as a result of either cessation of the patient's inspiratory effort or increasing elastic recoil of the respiratory system as V_T rises. The ventilator will maintain a constant Pinsp until inspiratory flow falls an arbitrary amount (eg, to 25% of initial flow) or below an absolute flow rate. Because patients' respiratory system time-constants vary widely (so that the time for flow to fall to 25% varies widely), many patients have to work actively to turn off the inspiratory pressure, raising the work of breathing. Some ventilators allow the intensivist to adjust the threshold for turning off the expiratory flow, allowing the ventilator to be tailored to the respiratory mechanics. Especially in patients with exacerbations of COPD, a threshold well above 50% is often necessary to minimize this unintended expiratory work. During PSV, the work of breathing can be increased by lowering Pinsp or making the trigger less sensitive, and can inadvertently increase if respiratory system mechanics change, despite no change in ventilator settings. Respiratory system mechanical parameters cannot be determined readily on this mode because the ventilator and patient contributions to V_T and flow are not represented by Pao; accordingly, these important measurements of Pplat, Ppeak – Pplat, and autoPEEP are measured during a brief, daily switch from PSV to volume-preset ventilation. A potential advantage of PSV is improved patient comfort and, for patients with very high drive, reduced work of breathing compared with volume-preset modes.

Mixed Modes

Some ventilators allow combinations of modes, most commonly SIMV plus PSV. There is little reason to use such a hybrid mode, although some physicians use the SIMV as a means to add sighs to PSV, an option not otherwise generally available. Because SIMV plus PSV guarantees some backup minute ventilation (which PSV does not), this mode combination may have value in occasional patients at high risk for abrupt deterioration in central drive.

Dual-Control Modes

The sophisticated microprocessors included with modern ventilators allow remarkably complex modes of ventilation. These modes typically try to meld the best features of volume-preset and pressure-preset modes. Some cause a switch of modes between breaths (eg, pressure-regulated volume control [PRVC]; volume support [VSV]) or within a breath (eg, volume-assured pressure support [VAPS]). In general, these modes are complex, and their effects may vary greatly depending on the details of the patient's effort. None has been shown to be safer or more useful than more conventional modes. The greatest problem with such newer modes is that they are very complex, the algorithm describing their function is not usually understood by practitioners, and they change during a breath, or from breath to breath, depending on patient effort, sometimes in ways that can provoke unanticipated effects.

PRVC

This is a pressure-preset mode with a set T_I (ie, it is time-cycled) in which the ventilator compares the V_T with a physician-set tidal volume and automatically and gradually adjusts P_I of subsequent breaths to deliver the desired V_T. A downside of PRVC is that as patient effort increases, the ventilator reduces support. Proponents argue that this mode provides the benefits of pressure-preset modes while at the same time guaranteeing V_T. Whether this guarantee makes the mode better or worse for the patient is debated, but this is one way to provide a lung-protective tidal volume using a pressure-preset mode.

VSV

Volume support is a pressure-preset mode in which P_I is automatically varied to gradually bring V_T in line with the desired V_T over several

breaths, differing from PRVC in that T_I is not set but, rather, depends on patient effort as in PSV. It is unknown whether this mode speeds or impedes weaning.

VAPS

This mode begins as PSV but, if a desired V_T is not met, the ventilator switches to VACV within the same breath in order to guarantee V_T. As with many dual-control modes, the physician delegates decision-making to the ventilator. Complex adjustments and their potentially detrimental effects on the patient may come into play at any time of day or night, depending on changes in mechanical properties of the respiratory system or changes in the patient's level of consciousness, comfort, or neuromuscular competence.

Choosing Mode and Settings

If full rest of the respiratory muscles is desired, it is incumbent on the physician to ensure that this is indeed achieved (although see ventilator-induced diaphragm dysfunction below). Although some patients are fully passive while being ventilated (those with deep sedation or therapeutic paralysis, some forms of coma, metabolic alkalosis, sleep-disordered breathing), most patients will make active respiratory efforts, even on volume assist-control ventilation (VACV), at times performing extraordinary amounts of work. Unintended patient effort can be difficult to recognize but, aside from obvious patient effort, may be signaled by an inspiratory fall in intrathoracic pressure (as noted on a central venous or pulmonary artery pressure tracing, or with an esophageal balloon) or by triggering of the ventilator. Recognizing patient effort has been greatly aided by the provision of real-time displays of flow and pressure waveforms. Using waveforms, it is easiest to gather information regarding the patient-ventilator interaction when patients are ventilated with a volume-preset mode [VACV or synchronized intermittent mandatory ventilation (SIMV)]. Still, some useful information can be gleaned from waveforms during pressure-preset ventilation (PSV and PACV).

The first step is to seek signs of inspiratory effort in the pressure tracing. In volume-preset modes, the signs of persistent effort include the presence of triggering, concavity during inspiration, and a variable peak airway opening pressure (Ppeak). When the goal of ventilation is to rest the respiratory muscles, ventilator adjustments, psychological measures, and pharmacologic sedation all may be effective. Ventilator strategies to reduce the patient's work of breathing include increasing the minute ventilation to reduce P_{CO_2} (although this may run counter to other goals of ventilation, especially in patients with ARDS or severe obstruction), increasing the inspiratory flow rate, and changing the mode to pressure-preset ventilation (PSV or PACV). Therapeutic paralysis is required to achieve ventilatory goals only occasionally, but it is interesting that 48 h of cisatracurium for the sickest patients with ARDS ($P/F < 150$) reduces lung inflammation, overt barotrauma, and mortality.[15]

The next step is to determine whether the patient has significant airflow obstruction. This can be inferred by inserting a brief end-inspiratory pause, then determining the difference between Ppeak and plateau airway pressure (Pplat), as long as a constant inspiratory flow (square wave) is used. Alternatively, one can examine the expiratory flow waveform, seeking low flow and prolonged expiration, signs that are present regardless of the mode of ventilation (VACV, SIMV, PSV, PACV). Bronchodilator therapy can be assessed by noting whether expiratory flow increases, the expiratory time (T_E) shortens, or there is a reduction in Ppeak, Pplat, or autoPEEP.

Finally, one should ensure that the patient and ventilator are synchronized, that is, that each attempt by the patient to trigger the ventilator generates a breath. The most common situation in which the patient fails to trigger breaths occurs in severe obstruction when autoPEEP is present. This is recognized at the bedside when the patient makes obvious efforts that fail to produce a breath. Using waveforms, these ineffective efforts cause a temporary slowing of expiratory flow, sometimes halting it completely.

Full rest of the respiratory muscles has an adverse consequence: active disuse atrophy, termed ventilator-induced diaphragm dysfunction (VIDD). Within hours of full respiratory

muscle rest, enhanced muscle proteolysis can be detected and diaphragm muscle fibers atrophy.[16] Active diaphragm contraction is able to reduce the risk of VIDD, suggesting that most patients should be ventilated in a way to preserve some active effort. VIDD can be sufficiently severe as to impede extubation as the patient recovers from critical illness.

Triggered Sensitivity

In the assist-control, SIMV, and pressure-support modes, the patient must lower the Pao below a preset threshold in order to "trigger" the ventilator, or divert some flow from the ventilator circuit (flow-triggering). There is no significant difference in the work required to trigger between pressure-triggered and flow-triggered settings. When autoPEEP is present the patient must lower Palv by the autoPEEP amount to have any impact on Pao or divert flow. This can dramatically increase the required effort for breath initiation, a problem that cannot be solved by adjusting the sensitivity or type of triggering.

Unconventional Ventilatory Modes

IRV

IRV is defined as a mode in which the I:E ratio is >1. Compared with conventional modes of ventilation, lung oxygen exchange is often improved with IRV, owing to increased mean alveolar pressure and volume consequent to the longer time above functional residual capacity or as a result of creation of autoPEEP. Delivering IRV using PACV and VACV generally requires heavy sedation with or without muscle paralysis, leading most practitioners to use APRV when selecting IRV.

APRV

APRV consists of CPAP, which is intermittently released to allow a brief expiratory interval. Conceptually, this mode is pressure-controlled IRV during which the patient is allowed to initiate spontaneous breaths. An advantage over IRV is that patients are more comfortable, requiring less sedation. It is not known whether APRV can deliver lung-protective ventilation, so this mode is not a good choice in patients with ALI or ARDS, although it is often selected as a rescue mode when oxygenation cannot be maintained with usual therapy. Whether this mode provides any benefit over modern low-V_T ventilation remains to be shown.

PAV

PAV is intended only for spontaneously breathing patients. The goal of this novel mode is to attempt to normalize the relationship between patient effort and the resulting ventilatory consequences.[17] The ventilator adjusts Pinsp in proportion to patient effort both throughout any given breath and from breath to breath. This allows the patient to modulate his breathing pattern and total ventilation. This is implemented by monitoring instantaneous flow and volume (V) of gas from the ventilator to the patient and varying the Pinsp as follows:

$$\text{Pinsp} = \text{f1} \times \text{V} + \text{f2} \times \text{flow}$$

where f1 and f2 are selectable functions of volume (elastic assist) and flow (resistive assist), values for which can be estimated from the patient's respiratory mechanics. Potential advantages of this method are greater patient comfort, lower Ppeak, and enhancement of the patient's reflex and behavioral respiratory control mechanisms.

HFOV

Several modes of ventilation have in common the use of V_T smaller than the dead space volume. Gas exchange does not occur through convection as during conventional ventilation, but through bulk flow, Taylor diffusion, molecular diffusion, nonconvective mixing, and possibly other mechanisms. Theoretical benefits of HFOV include the possibility to keep the lung open (recruited) while limiting overdistention, since tidal excursions are small. A substantial risk is that dynamic hyperinflation is the rule and alveolar pressure is greatly underestimated by monitoring pressure at the airway opening. HFOV holds promise as the natural extension of lowering the V_T as a means to prevent volutrauma, and there is renewed interest in this

old technique. In a controlled trial in patients with ARDS, HFOV showed no advantage in terms of gas exchange or of short-term or long-term mortality but did appear to be safe, at least during the performance of a clinical trial.[18] A nonsignificant trend toward a short-term mortality benefit for HFOV has been interpreted as a reason to pursue additional clinical studies. It is worth mentioning, however, that the control arm ventilation strategy was not lung-protective, potentially biasing the study in favor of HFOV.

Noninvasive Ventilation

Mechanical ventilation for acute respiratory failure carries a high morbidity and mortality caused, in part, by violation of the glottis by the endotracheal tube. In patients with acute-on-chronic respiratory failure, numerous studies have demonstrated that noninvasive ventilation (NIV) effectively relieves symptoms, improves gas exchange, reduces the work of breathing, lessens complications, shortens the ICU length of stay, and improves survival.[19,20]

Nasal, oronasal, and full facial masks, as well as full-head helmets, have been used successfully. Nasal masks are especially difficult to use in edentulous patients who are unable to control mouth leak. Careful attention to mask leaks and adjusting air flow and pressure-support levels are important considerations. Inflatable cuffs, nasal bridge protection, and the availability of a range of mask sizes to ensure proper fit can minimize mask complications. The author finds it useful to initiate ventilation by briefly holding the mask (already connected to the ventilator) onto the patient's face, rather than first strapping the mask on and then initiating ventilatory assistance. Sedative medications are occasionally appropriate and can improve tolerance of NIV, but they carry some risk of respiratory depression and aspiration.

Patient-ventilator asynchrony (PVA) describes a patient's breathing efforts that are not coupled to machine output. During NIV, two mechanisms of PVA are common. The first is failure of the patient to lower sufficiently the proximal airway pressure (mask pressure) because of the presence of autoPEEP. As during invasive ventilation, counterbalancing the autoPEEP with externally applied PEEP provides a means by which to lower the work of triggering. The second common mechanism for PVA is failure of the ventilator to detect end inspiration because the patient's subsiding effort is cloaked by a mask leak. Most pressure-support ventilators terminate inspiration when inspiratory flow falls to a preset threshold, often at an arbitrary low value of flow or at a fixed percent of the peak inspiratory flow. Mask leaks prevent the flow from falling to this threshold, so the ventilator fails to switch off the inspiratory pressure even while the patient is making active expiratory efforts. This serves to increase patient discomfort and the work of breathing. Ventilators designed for NIV are very "leak tolerant" as are some newer ICU ventilators redesigned with NIV in mind. Using other methods for terminating inspiration, such as time-cycled pressure-support or volume assist-control, can minimize this problem.

Either conventional ICU ventilators or one of many portable bilevel pressure-targeted ventilators, initially designed for home ventilation, can be used. Limitations of portable pressure-targeted ventilators include the lack of waveform displays, the inability to deliver a high F_{IO_2} (greater than about 40%; some new machines allow an F_{IO_2} as high as 1.0), and the potential for rebreathing of exhaled gas. Whether volume-preset ventilation (such as assist-control) or pressure-preset ventilation is superior for NIV remains debated, but nearly all practitioners now use pressure-support. Both modes have been used successfully, but direct comparisons between modes are few.

The author believes the following points will minimize the chances that NIV will fail:

1. Develop an individual and institutional commitment to NIV.
2. Select patients carefully, excluding those with hemodynamic instability, inadequate airway protective reflexes, or little prospect of improvement within the next several days.
3. Have available a selection of masks to increase the probability of a good fit.
4. Use the pressure-support mode, beginning with modest settings, such as PEEP = 3 cm H_2O, PSV 3 = 8 cm H_2O, and the most

sensitive trigger, periodically removing the mask to allow the patient to sense its effect.
5. Education, reassurance, and modest sedation (when required) may improve tolerance to the mask and ventilator.
6. Increase the PEEP to ease the work of triggering with a goal of (typically) 4 to 6 cm H_2O; raise the level of PSV until the patient is subjectively improved, the V_T is sufficient, and the rate begins to fall, with a goal of 10 to 15 cm H_2O.
7. Detect and correct mask leaks by repositioning, achieving a better fit, changing the type of mask, removing nasogastric tubes (gastric decompression is not recommended during NIV), or adjusting the ventilator to reduce peak airway pressure.
8. Pay particular attention in the first hour to patient-ventilator synchrony, using waveform displays as a guide.

Management of the Patient's Initial Ventilator Settings

Initial ventilator settings depend on the goals of ventilation (eg, full respiratory muscle rest vs partial exercise), the patient's respiratory system mechanics, and minute ventilation needs. Although each critically ill patient presents myriad challenges, it is possible to identify five subsets of ventilated patients: (1) the patient with normal lung mechanics and gas exchange; (2) the patient with severe airflow obstruction; (3) the patient with acute-on-chronic respiratory failure; (4) the patient with acute hypoxemic respiratory failure, and (5) the patient with restrictive lung or chest wall disease.

In all patients, the initial F_{IO_2} should usually be 0.5 to 1.0 to ensure adequate oxygenation although it can usually be lowered within minutes when guided by pulse oximetry and, in the appropriate setting, applying PEEP. In the first minutes following institution of mechanical ventilation, the physician should remain alert for several common problems. These include, most notably, airway malposition, aspiration, and hypotension. Positive-pressure ventilation may reduce venous return and so cardiac output, especially in patients with a low mean systemic pressure (eg, hypovolemia, venodilating drugs, decreased sympathetic tone from sedating drugs, neuromuscular disease) or a very high ventilation-related pleural pressure (eg, chest wall restriction, large amounts of PEEP, or obstruction causing autoPEEP). If hypotension occurs, intravascular volume should be rapidly expanded while steps are taken to lower the pleural pressure (smaller V_T, less minute ventilation).

Patients With Normal Respiratory Mechanics and Gas Exchange

Patients with normal lung mechanics and gas exchange can require mechanical ventilation for several reasons: (1) because of loss of central drive to breathe (eg, drug overdose or structural injury to the brainstem); (2) because of neuromuscular weakness (eg, high cervical cord injury, acute idiopathic myelitis, myasthenia gravis); (3) as an adjunctive therapy in the treatment of shock; or (4) to achieve hyperventilation (eg, in the treatment of elevated intracranial pressure following head trauma). In patients who do not have acute lung injury, data are accumulating that using low tidal volumes (6–8 mL/kg of predicted body weight) reduces the risk of developing lung injury.[21]

Soon after the initiation of ventilation, airway pressure and flow waveforms should be inspected for evidence of patient-ventilator dyssynchrony or undesired patient effort. If the goal of ventilation is full rest, the patient's drive can often be suppressed by increasing the inspiratory flow rate, frequency, or V_T; of course, the latter two changes may induce respiratory alkalemia. If such adjustments do not diminish breathing effort (despite normal blood gases) to an undetectable level, sedation may be necessary. If this does not abolish inspiratory efforts and full rest is essential (as in shock), muscle paralysis should be considered. A small amount of PEEP (5–7.5 cm H_2O) is used to prevent atelectasis.

Patients With Severe Airflow Obstruction

Severe obstruction is seen most commonly in patients with status asthmaticus but also rarely in those with inhalation injury or central airway lesions, such as tumor or foreign body, that are not bypassed with the endotracheal tube. Some

of these patients may benefit from NIV, but most will require invasive ventilation. These patients are usually extremely anxious and distressed. Deep sedation should be provided in such instances, supplemented in some patients by therapeutic paralysis. These interventions help to reduce oxygen consumption (and hence carbon dioxide production) to lower airway pressures and to reduce the risk of self-extubation.

Because the gas exchange abnormalities of airflow obstruction are largely limited to ventilation-perfusion mismatch, an F_{IO_2} of 0.5 suffices in the vast majority of patients. The primary principle behind ventilation settings is to limit minute ventilation to reduce the consequences of dynamic hyperinflation.[22] An inspiratory flow of 60 L/min is recommended, and higher flow rates do little to increase T_E. For example, if the V_T is 500, the respiratory rate is 15, and the flow is 60 L/min, the T_E is 3.5 s. Raising flow (dramatically) to 120 L/min increases the expiratory time to only 3.75 s, a trivial improvement. In contrast, a small reduction in respiratory rate to 14/min increases the T_E to 3.8 s. This example serves to emphasize not only the relative lack of benefit of raising the flow rate but also the importance of minimizing minute ventilation when the goal is to reduce autoPEEP. Some patients who remain agitated during ACV can be made more comfortable by using PSV (or PACV) with a total inspiratory pressure of around 30 cm H_2O. Finally, if the patient is triggering the ventilator, some PEEP should be added to reduce the work of triggering.[23] Although this occasionally compounds the dynamic hyperinflation, potentially compromising cardiac output, usually autoPEEP increases little as long as PEEP is not set higher than about 85% of the autoPEEP. The goals are (1) to minimize alveolar overdistention (Pplat < 30) and (2) to minimize dynamic hyperinflation (autoPEEP < 15 cm H_2O or end-inspiratory lung volume < 20 mL/kg), a strategy that largely prevents barotrauma. Reducing minute ventilation to achieve these goals generally causes the P_{CO_2} to rise above 40 mm Hg, often to 70 mm Hg or higher. Although this requires sedation, such permissive hypercapnia is tolerated quite well, except in patients with increased intracranial pressure and perhaps in those with ventricular dysfunction or critical pulmonary hypertension.[24]

Patients With Acute-on-Chronic Respiratory Failure

Acute-on-chronic respiratory failure is a term used to describe the exacerbations of chronic ventilatory failure, often requiring ICU admission, usually occurring in patients with COPD. Unlike patients with status asthmaticus, patients in this population tend to have relatively smaller increases in inspiratory resistance, their expiratory flow limitation arising in equal amount from loss of elastic recoil. As a consequence, in the patient with COPD and minimally reversible airway disease, peak airway pressures on the ventilator tend not to be extraordinarily high, yet autoPEEP and its consequences are common. At the time of intubation, hypoperfusion is common, as manifested by tachycardia and relative hypotension, and typically responds to briefly ceasing ventilation combined with fluid loading.

Many such patients can be ventilated effectively with NIV as described above. For those who require intubation, the goals of rest and appropriate hypoventilation can usually be achieved with initial ventilator settings of a V_T of 5 to 7 mL/kg and a respiratory rate of 20 to 24 breaths/min, with a VACV mode set on minimal sensitivity. Because gas exchange abnormalities are primarily those of ventilation-perfusion mismatch, supplemental oxygen in the range of an F_{IO_2} of 0.4 should achieve better than 90% saturation of arterial hemoglobin. Daily spontaneous breathing trials (SBT) help identify the earliest opportunity to extubate. Also, there may be advantage in extubating to NIV, even after failing an SBT.

Patients With Acute Hypoxemic Respiratory Failure

Acute hypoxemic respiratory failure is caused by alveolar filling with blood, pus, or edema, the end results of which are impaired lung mechanics and gas exchange. The gas exchange impairment results from intrapulmonary shunt that is largely refractory to oxygen therapy. In ARDS, the significantly reduced functional residual capacity arising from alveolar flooding and collapse leaves many fewer alveoli to accept the V_T, making the lung appear stiff and

dramatically increasing the work of breathing. The ARDS lung should be viewed as a small lung, however, rather than a stiff lung. In line with this current conception of ARDS, it is now clearly established that excessive distention of the ARDS lung compounds lung injury (ventilator-induced lung injury) and may induce systemic inflammation.[1,25] Ventilatory strategies have evolved markedly in the past decade, changing clinical practice and generating tremendous excitement.

The goals of ventilation are to reduce shunt, avoid toxic concentrations of oxygen, and choose ventilator settings that do not amplify lung damage. The initial F_{IO_2} should be 1.0 in view of the typically extreme hypoxemia. PEEP is indicated in patients with diffuse lung lesions but may not be helpful in patients with focal infiltrates, such as lobar pneumonia. In patients with ARDS, higher levels of PEEP than required for oxygenation may reduce the degree of recruitment-derecruitment, potentially improving outcomes as discussed above. Recruitment maneuvers have generally applied a sustained inflation pressure while the patient is therapeutically paralyzed. For example, CPAP of 40 cmH_2O for 40 s has often been chosen. Although these maneuvers have shown some ability to transiently raise the P_{O_2}, they have not been shown to change clinically meaningful outcomes. The V_T should be 6 mL/kg on ACV; a higher V_T is associated with higher mortality. Potentially, PACV could be used as well, but the parameters that ensure lung-protective ventilation are not known. In either mode, the respiratory rate should be set at 24 to 36/min. An occasional consequence of lung-protective ventilation is hypercapnia. This approach of preferring hypercapnia to alveolar overdistention, termed "permissive hypercapnia," is very well tolerated.

Patients With Restriction of the Lungs or Chest Wall

A small V_T (5–7 mL/kg) and rapid rate (18–24/min) are especially important to minimize the hemodynamic consequences of positive-pressure ventilation and to reduce the likelihood of barotrauma. The F_{IO_2} is usually determined by the degree of alveolar filling or collapse, if any. When the restrictive abnormality involves the chest wall (including the abdomen), the large ventilation-induced rise in pleural pressure has the potential to compromise cardiac output. This in turn will lower the mixed venous P_{O_2} and, in the setting of ventilation/perfusion mismatch or shunt, the Pa_{O_2} as well. If the physician responds to this falling Pa_{O_2} by augmenting PEEP or increasing the minute ventilation, further circulatory compromise ensues. A potentially catastrophic cycle of worsening gas exchange, increasing ventilator settings, and progressive shock is begun. This circumstance must be recognized because the treatment is to reduce dead space (eg, by lowering minute ventilation or correcting hypovolemia).

The Airway During Split-Lung Ventilation

The lungs may be separated for purposes of differential ventilation by two major means: (1) blocking the bronchus of a lobe or whole lung while ventilating with a standard endotracheal tube, or (2) passing a double-lumen tube (DLT). A number of different devices have been used to obstruct a bronchus, but experience is largest with the Fogarty embolectomy catheter. DLTs carry the advantages of allowing each lung to be ventilated, collapsed, re-expanded, or inspected independently.

Split-lung ventilation is only rarely useful in the critical care unit, but occasionally its benefits are dramatic. Large bronchopleural fistulas severely compromise ventilation and may not respond to HFOV. A DLT will maintain ventilation of the healthy lung while facilitating closure of the bronchopleural fistula. During massive hemoptysis, lung separation may be lifesaving by minimizing blood aspiration, maintaining airway patency, and tamponading the bleeding site while awaiting definitive therapy. Finally, patients with focal causes of acute hypoxemic respiratory failure, such as lobar pneumonia or acute total atelectasis, may benefit from differential ventilation and application of PEEP.

Ventilator Bundle

Ventilator-associated pneumonia (VAP) is costly, may contribute to mortality, and is often

preventable. Several tactics have been shown to reduce the risk of VAP and, when joined together, this group is called the "ventilator bundle." The components include elevation of the head of the bed to 30° or greater; daily sedative interruption; daily spontaneous breathing trials; deep venous thrombosis prophylaxis; and preventive measures to reduce the risk of GI hemorrhage.

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Notes

Chapter 4. Hypertensive Emergencies and Urgencies

R. Phillip Dellinger, MD, MSc, FCCP; and Jean-Sebastien Rachoin, MD

Objectives:

- Be able to recognize a hypertensive emergency.
- Have insight into characteristics of antihypertensive medications that allow matching them to specific types of hypertensive emergencies.
- Know toxicities and side effects of antihypertensive drugs.

Key words: aortic dissection; hypertensive emergency; hypertensive encephalopathy; postoperative hypertension; stroke

Synopsis:

A hypertensive emergency is defined as hypertension associated with acute organ dysfunction. In the presence of a hypertensive emergency, the goal BP over the first hour should be a reduction in mean arterial pressure no greater than 20% to 25% (in consideration of the effects of BP lowering on the cerebrovascular blood flow autoregulation curve, which is likely to be shifted to the right in these patients). Exceptions to the 20% to 25% rule include unclipped or uncoiled aneurismal hemorrhage associated with hypertension and aortic dissection. There are many drugs used to treat hypertensive emergencies. Intravenous nicardipine acts primarily as an arterial vasodilator and has a quick onset of action but a slower offset. Clevidipine is a newer agent similar to nicardipine but with a quicker offset. Intravenous labetalol is a combined αβ-blocker, and esmolol is an IV β-blocker, both of potential utility. Sodium nitroprusside has stood the test of time as a reliable agent for effective treatment for hypertensive emergencies, although there should be some caution as to cyanide toxicity when exceeding US Food and Drug Administration labeling instructions or in patients with renal insufficiency. Specific clinical situations that require special considerations for therapy include hypertensive encephalopathy, acute aortic dissection, acute ischemic stroke, and intracerebral/subarachnoid hemorrhage. Treatment of catecholamine-induced hypertension is best managed with benzodiazepines along with nicardipine or verapamil. postoperative hypertension is associated with wound hemorrhage and other complications.

Definitions

Hypertension is one of the most common chronic medical conditions affecting almost one-third of adults in the United States.[1] The course of this disease can be complicated by abrupt and severe elevation in BP resulting in end-organ damage with dire consequences.

The nomenclature pertaining to hypertensive crises has undergone many revisions and the term malignant hypertension has been replaced by two more explicit appellations, hypertensive emergency and hypertensive urgency (based on the presence or absence of end-organ damage).[2] Distinguishing between those two syndromes has substantial clinical implications and impacts the goal of BP treatment as to both timing and mode of administration of medications.

Hypertensive urgency is defined as an elevation of BP greater than 179/109 mm Hg. When accompanied with end-organ dysfunction, it is called hypertensive emergency.[2]

Frequency, Risk Factors, and Impact on Mortality

The exact incidence of hypertensive emergency is unclear, ranging from 1% to 15% in most studies.[3–5] There does not seem to be any decline in its occurrence over the last 40 years.[3] On the other hand, however, the mortality attributable to hypertensive emergencies has steadily declined over the same time period from more than 70% to less than 10% currently.[6,7]

The most frequent risk factors for hypertensive emergency include lack of access to a primary care physician, poor compliance with medications, drug abuse, and obesity.[8] Secondary causes of hypertension are not commonly seen but can be considered in young nonobese patients.

Pathogenesis

Two parallel processes synergistically interact and result in hypertensive emergency. The *primum mauvens* seems to be the rapid elevation in BP from various mechanisms (eg, illicit drug use) that induces both volume contraction (from

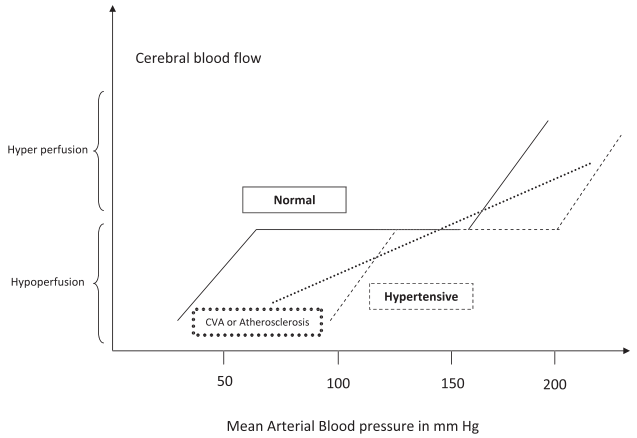

Figure 1. Cerebral blood flow autoregulation. Reprinted with permission from *ACCP Critical Care Medicine Board Review*. 20th ed. Northbrook, IL: American College of Chest Physicians; 2009.

pressure natriuresis) with subsequent generation of vasoconstrictive substances and endothelial damage with free oxygen species formation and thrombotic microangiopathy.

Identification of End-Organ Damage

A complete history, thorough physical examination, and pertinent laboratory and imaging need to be obtained to differentiate between hypertensive urgency and emergency.

Headache, confusion, seizures, or visual disturbances can indicate hypertensive encephalopathy,[9] whereas chest pain and shortness of breath can point toward cardiac ischemia or aortic dissection.

The initial evaluation needs to include at least a complete blood count (rule out hemolysis), chemistry basic panel (acute renal insufficiency), urine analysis, chest radiograph (congestive heart failure or aortic dissection), and ECG (cardiac ischemia). Appropriate ordering of CT scan of the head or chest can be considered as well as cardiac echocardiography, depending on the circumstances.[10] In pregnant patients, tests for values of a urine protein and creatinine and blood uric acid need to be ordered. Furthermore, we typically order a urinary drug screen on all patients.

Plasma renin activity, aldosterone, and metanephrines can also be obtained if a secondary cause is suspected. Of note, hypokalemia is not an infrequent finding and should not by itself trigger a workup for a secondary cause (cause other than essential hypertension).[11]

Once the clinical picture of the patient is classified as emergency vs urgency, appropriate therapy can be instituted.

Principles of Treatment of Hypertensive Urgencies and Emergencies

In normotensive patients, cerebral blood flow is maintained constant despite variation in systemic BP by changing the caliber of lumen or arterioles. This process of autoregulation can be sustained between 50 and 150 mm Hg for normal patients. Beyond the upper limit, the increased BP overcomes the protective abilities of vessels that vasodilate, leading to brain hyperperfusion, cerebral edema, and hypertensive encephalopathy.[12]

In chronic hypertensive patients, the same autoregulation curve is shifted to the right, and brain blood perfusion occurs at higher pressure.[13] Additionally, the curve can become a straight line in patients with acute CNS events (such as ischemic stroke) or significant atherosclerosis (Fig 1).

Overzealous lowering of BP can lead to organ hypoperfusion.[14,15] Therefore, cautious lowering of BP should be performed, and patients with hypertensive emergency are best managed in an intensive care setting.

The issues that need to be addressed to guide optimal therapy are the BP goal, the timing of attainment, mode of administration, and type of antihypertensive.

For hypertensive urgencies, the clinician should aim for a progressive lowering of the BP over 1 to 2 days. In some cases, an even longer time period may be appropriate. In the absence of end-organ damage, a rapid decrease in BP may cause more harm than good. Oral medications should be used, and the clinician should restart the patient's regular medications. Additional oral medications can be used to lower as needed to treat spikes in BP (see section on oral medications).

For hypertensive emergencies, the goal BP should be a reduction of the mean arterial pressure of 20% to 25% within 1 h.[16] Afterward,

Table 1—*Treatment of Hypertensive Emergencies*

Clinical Setting	Goal Blood Pressure	Timing	Preferred Agents	Comment
Aortic dissection	Systolic BP <120 or normalizing BP	<20 min	Esmolol followed by nicardipine or nitroprusside or labetalol	Adequate β-blockade *should* precede initiation of vasodilators
Acute ischemic cerebrovascular accident	Systolic BP <220	Within 1 h	Labetalol, nicardipine	Goal systolic BP <185 in patients eligible for thrombolytic therapy
Acute hemorrhagic stroke	Systolic BP <140	Within 1 h	Labetalol, nicardipine	Reduces hematoma growth
Hypertensive encephalopathy	MAP lower by 20% to 25%	Within 1 h	Labetalol, nicardipine, or nitroprusside	Avoid sodium nitroprusside
Pregnancy	Diastolic BP <110	Within 1 h if preeclampsia	IV hydralazine or labetalol, nicardipine	Addition of magnesium for preeclampsia (ultimate treatment is delivery)
Postoperative hypertension	Systolic BP <180	Within 1 h	Nicardipine or labetalol	Treat reversible factors first

a more progressive and much slower lowering can be done. Patient should be treated in a controlled setting with IV antihypertensive with close monitoring of BP using an arterial line. Oral medications should be started in conjunction with the parenteral infusion as soon as possible.

Unfortunately, there is a paucity of head-to-head trials and a strong lack of good-quality studies about superiority of one agent over another in regard to morbidity and mortality outcomes.[17] When choosing an IV antihypertensive, physicians should take into account the clinical presentation, patient's demographics, side effects, and route of elimination of the medication.

IV Agents

Nicardipine

IV nicardipine is a second-generation calcium channel blocker that acts primarily by arterial vasodilation and crosses the blood-brain barrier. Since it acts mainly on arterioles with small resistance, it does not increase intracranial pressure and maintains cerebral blood flow.[18] It increases cardiac index and coronary blood flow and is unlikely to induce cardiac ischemia.[19]

The parenteral form of nicardipine has an acidic pH (between 3.7 and 4.7) thus should preferentially be administered via a central line. If a peripheral line is used, it should be rotated every 12 h. This medication is contraindicated in patients with advanced aortic stenosis.[19]

The initial infusion rate is 5 mg/h with an onset of action less than 20 min. It can be titrated by increments of 2.5 mg/h up to 30 mg/h.

One study[20] of patients admitted through the ED with hypertensive crisis (of which 64% had end-organ damage) randomized subjects to either IV nicardipine or IV labetalol. The authors found that at 30 min, patients who received nicardipine had a higher likelihood of achieving their goal BP compared with those who received labetalol.

Clevidipine

Clevidipine is a third-generation calcium channel blocker that was recently approved for use in the United States. It is metabolized by ester hydrolysis, thus is not affected by hepatic or renal dysfunction.[21] Similar to nicardipine, it does not decrease cardiac index.

Its main drawback is that it is prepared as a 20% phospholipid emulsion. Therefore, it should not be administered to patients with abnormal lipid metabolism, and clinicians need to account for the infused calories. Because of the risk for infection, the vial should be changed 4 h after puncturing.

The initial infusion rate is 1 to 2 mg/h with a very rapid onset of action (less than 5 min) and short half-life (1 min). It can be titrated by doubling the rate every 90 s, but caution is advised since there are limited data for high doses (>21 mg/h) or when used for a prolonged period (72 h).

Aronson et al[22] analyzed the results from three prospective open-label parallel studies that included 1,512 patient after cardiac surgery. The authors found a similar impact of clevidipine compared with nicardipine on BP control but better than nitroglycerine or sodium nitroprusside. In addition, clevidipine had a mortality benefit compared with sodium nitroprusside but not to the other drugs.

Clevidipine was also shown to be effective for treating patients who presented to the ED or the ICU with hypertensive crises.[23]

Overall, clevidipine is an attractive but more expensive option for rapid, tight, and short-term BP control, especially in the postoperative setting.

Labetalol

IV labetalol is a combined α- and β-blocker with a 1:7 ratio.[24] Because of this dual property, it reduces heart rate without decreasing cardiac output. It also does not decrease cerebral or renal blood flow and does not increase intracranial pressure.[25]

It can be administered as intermittent IV doses starting at 20 mg followed by increments of 20 to 80 mg every 10 min or by a constant infusion starting at 1 mg/minute to a total dose of 300 mg.[26–28] If the desired BP effect in not achieved with a total dose of 300 mg, then an alternate medication should be initiated. The anticipated duration of BP control after labetalol loading is 6 to 8 h.

It can be used in most hypertensive emergency cases.

Esmolol

Esmolol is an IV β-blocker, being fairly selective with a short half-life (less than 10 min) and quick onset of action (1 min).[29] In our experience, it does not constitute a potent antihypertensive agent and is more useful for chronotropic control. It has, however, substantial importance in the treatment of aortic dissection, where decreased inotrophy and avoidance of tachycardia are important features of treatment. It is administered as an infusion with a loading dose 1 mg/kg followed by a drip at 50 μg/kg/min.

Enalaprilat

Enalaprilat is an IV ACE inhibitor that exhibits vasodilatory properties by reducing the production of angiotensin II. It is administered as intermittent IV doses with similar effect at doses of 0.625 mg or greater.[30]

It does not reliably reduce BP within 60 min and can have a peak effect up to 4 h after administration that may last up to 24 h. Thus, compared with other medications, it constitutes a less attractive option.

It is contraindicated in the third trimester of pregnancy. It may be particularly useful in severe hypertension associated with scleroderma and high levels of circulating angiotensin II.

Sodium Nitroprusside

Sodium nitroprusside (NTP) is a nitric oxide donor that induces a potent arteriolar and venous vasodilation. Although it quickly lowers BP, some of its systemic effects are potentially problematic.

Sodium nitroprusside has been reported to induce coronary and cerebral steal syndromes as well as increase intracranial pressure, although these are unlikely to be of clinical issue.[31–33] When combining several studies comparing clevidipine (CLV) with nitroglycerin, sodium nitroprusside, or nicardipine in patients after cardiac surgery. there was no difference in the incidence of myocardial infarction, stroke, or renal dysfunction for CLV-treated patients compared with the other treatment groups. There was also no difference in mortality rates between the CLV and nitroglycerine or CLV and nicardipine. However, mortality was slightly greater with NTP compared with CLV ($P = .04$).[22] Sodium nitroprusside also has the potential to induce cyanide and thiocyanate toxicity, although neither is likely to occur when following US Food and Drug Administration-recommended dosing. Despite these concerns,

NTP has been used in thousands of patients with clinical success, including a vast number of patients with hypertensive encephalopathy with effective treatment of cerebral edema. In a controlled study comparing NTP with fenodopam, a dopamine-1 antagonist with similar vasodilator characteristics as NTP, NTP was shown to be equally effective and safe.

The use of IV NTP requires hemodynamic monitoring with an arterial line in place. Sodium nitoprusside has the shortest half-life of all the effective arteriolar vasodilators used to treat hypertensive emergencies, offering a distinct advantage in that regard.

Hydralazine

IV hydralazine is a peripheral vasodilator with less predictable onset of action and magnitude of effect.[34] It may induce reflex tachycardia, which could be detrimental in the presence of myocardial ischemia or aortic dissection. It is thought to be a very effective drug for the treatment of preeclampsia and eclampsia. It also has utility in the immediate postop period, as patient's bridge from nil per os to capability for oral intake (as does IV bolus metoprolol in this circumstance).

Other

Diuretics and nitroglycerin can be considered for patients with acute pulmonary edema or decompensated congestive heart failure with very high filling pressures. Nitroglycerin is a predominantly venous dilator that can decrease both preload and cardiac index.

Diuretic administration should be confined to these cases since most other patients with hypertensive crises are volume depleted.

Fenoldopam is a peripheral dopamine-1 agonist with similar BP-lowering effects as nitroprusside but without any concerns as to cyanide toxicity in the presence of renal insufficiency.[35]

Oral Medications

Captopril

Captopril is the fastest-acting angiotensin-converting enzyme inhibitor with an onset of action of 15 min. It can induce a reliable drop in the BP that lasts for 4 to 6 h.[36,37] The starting dose is 6.25 mg.

Clonidine

Clonidine is a central-acting α_2 agonist. It induces a decrease in the sympathetic tone with a significant reduction in BP.[38,39] It can also cause sedation and is most useful in patients with drug or alcohol withdrawal. Doses start at 0.1 mg/h.[39]

A rebound effect has been reported on discontinuation. This side effect is worsened with concomitant β-blockade therapy.[40]

Labetalol

The oral form of labetalol has an α- to β-blocker ratio 1:4 and can be used at doses starting at 100 to 200 mg/h with good results.[41]

Nifedipine

Nifepidine can result in significant hypotension shortly after administration with risk for major morbidity and mortality. Its use in a short-acting form for treatment of hypertensive urgency should be avoided in most circumstances.[42] It does have characteristics that may offer advantages in severe preeclampsia associated hypertension.

Specific Clinical Situations

Hypertensive Encephalopathy

A 52-year-old man had generalized seizures and a BP of 244/160 mm Hg. The patient received lorazepam IV with the cessation of seizures. He was intubated and mechanically ventilated. A fundus examination revealed papilledema, supporting the diagnosis of hypertensive encephalopathy. Clinical manifestations of a hypertensive encephalopathy-induced increase in intracranial pressure include headache, nausea, vomiting, confusion, lethargy, generalized seizures, and coma. A differential diagnosis of hypertensive encephalopathy includes severe hypertension in association with subarachnoid

hemorrhage, intracerebral hematoma, or stroke. A CT scan may be required to ensure that these entities are absent. In hypertensive encephalopathy, as well as in most hypertensive emergencies and urgencies, the initial BP therapeutic target is to decrease the mean arterial pressure by 15% to 25%.

Acute Aortic Dissection

Aortic dissection is caused by a tear in the intima of the aorta and is propagated by pulse wave. It is diagnosed usually by CT scan imaging of the aorta with IV contrast or by transesophageal echocardiography. It is classified into types A or B, depending on whether it involves the ascending aorta (type A involves the ascending aorta). The mainstay of management of type A aortic dissection is surgery coupled with BP control. For type B, however, aggressive BP control is considered equivalent to surgical intervention if vital organ perfusion is not compromised by dissection-induced obstruction of major vessels coming off the aorta.[43]

Since propagation of the arterial tear is dependent mainly on the cardiac pulse wave, therapy is aimed at decreasing shear forces while avoiding tachycardia (but also avoiding bradycardia). Thus, a combined approach using effective β-blockade followed by a vasodilator is considered the most effective treatment.[44] The goal of treatment is to achieve a systolic BP of less than 120 mm Hg using parenteral agents in less than 20 min.[45]

Although it is only approved for use in the perioperative settings, esmolol is considered the β-blocker agent of choice for treatment of aortic dissection.[26,46] After adequate β-blockade, we usually add IV NTP or nicardipine. Alternatively, IV labetalol can also be used as a single drug.[47]

Acute Ischemic Stroke

Soon after an acute ischemic cerebral-vascular event, blood vessels surrounding the affected area lose their capacity to autoregulate and maintain a constant blood flow. Perfusion of the affected and surrounding area will depend mainly on pressure gradient. BP elevation should therefore be viewed as a physiologic response aimed at overcoming changes in vessel autoregulation.[48,49] Precipitous changes in BP can aggravate or induce ischemic events.

The impact of BP on outcomes in stroke has a U-shaped curve effect with worse outcomes present at both low and high pressures.[50,51]

In an observational study of 304 patients, Castillo et al[52] found that the use of antihypertensive medications and a drop of greater >20mm Hg of BP in the first 24 h were significantly associated with adverse outcomes (death, neurologic deterioration).

If a patient is not considered candidate for thrombolytic therapy, recent guidelines recommend initiation of antihypertensive treatment only when the systolic BP is greater than 220 mm Hg or diastolic >120 mm Hg. A lower threshold (systolic of 185 and diastolic of 110) is recommended for patients eligible for reperfusion therapy.[53]

Nicardipine and labetalol are considered drugs of choice. Sodium nitroprusside is recommended as a second-line treatment

Intracerebral and Subarachnoid Hemorrhage

In the setting of an intracerebral hemorrhage, marked elevation in BP is thought to put the patient at risk for hematoma expansion.[54] This occurs mainly in the first 24 h, may occur in the absence of significant BP elevation, and is associated with increased mortality.[55]

A recent prospective controlled study randomized 404 patients into an aggressive BP treatment goal of 140 mm Hg within 1 h and subsequently to maintain this target level for the next 7 days or a systolic BP of 180 mm Hg. This study showed that intensive BP control was associated with less hematoma growth over the 72 h following admission.[56,57]

Thus, indirect evidence suggests that early intensive BP control (systolic BP <140 mm Hg within 1 h) could improve outcomes in patient with intracranial hemorrhage.

Hypertension is seen in about one-third of patients with subarachnoid hemorrhage.[58] There is a general agreement that BP should be lowered to normal prior to the coiling or clipping of the aneurysm and that afterward a higher BP not

only is more tolerated but also can potentially have beneficial effects.[59]

Pregnancy

Hypertension can precede, occur, or complicate pregnancy and is defined as an elevation of BP >140/90 mm Hg.[60]

The treatment of hypertension in the pregnant patient needs to balance the potential adverse effects of BP in the mother with the decrease in placental perfusion. The threshold for treatment is not clear, and tight BP control has been shown to decrease only the need for emergent hospitalization, not the incidence of either preeclampsia or eclampsia.[61]

There was no BP difference between nicardipine and labetalol and no hypotensive episodes in a study that randomized 60 pregnant patients with hypertensive crises to one of the two treatments.[62]

Guidelines recommend treatment at a diastolic >105 mm Hg or in the presence of end-organ damage, and IV hydralazine is considered the drug of choice for hypertensive crisis.[60] Patients with preeclampsia also need to receive intravenous magnesium sulfate.

Catecholamine-Induced Hypertension

Most of the time, this is seen in the setting of cocaine abuse or clonidine withdrawal. In patients taking cocaine, β-blockers and even combined α- and β-blockers (labetalol) should likely be avoided because of a concern of an unopposed α effect on BP.[63] Elevated BP should be managed with benzodiazepines along with nicardipine or verapamil.[64,65]

Postoperative Hypertension

The incidence of postoperative hypertension is hard to quantify since there is a lack of a consensual definition.[66] Abrupt elevation of systemic pressure is not unusual after surgery and can be due to pain, increased sympathetic tone,[67] or rapid fluid shifts and may be a short-lived event that will not lead to adverse consequences.

Treatment threshold should be individualized to patient characteristics (risk of bleeding, comorbid conditions) and types of procedure (vascular or intracranial). In some situations, maintaining adequate pressure can be crucial for organ perfusion (such as in thoracic aneurysm repair). In the specific setting of cardiothoracic surgery, treatment should be initiated when BP reaches 140/90 mm Hg or with a mean arterial pressure of 105.[66]

When facing significant elevations of BP in the postoperative setting, we usually start by identifying and correcting reversible factors and then discuss goals and timing of BP control with the operating surgeon.

Most postoperative blood hypertension lasts less than 6 h,[68] and good pressure control can be performed using nicardipine or labetalol, depending on the clinical setting.[47]

Hypertensive Crisis With High-Pressure Pulmonary Edema

Clinical features of a severe hypertension-induced rise in left ventricular (LV) end-diastolic pressure with associated high pulmonary capillary pressure and pulmonary edema include severe hypoxemia, CO_2 retention, pink frothy sputum, and pulmonary edema seen on a chest radiograph. The typical patient will have chronic LV hypertrophy with diastolic function and normal or increased ejection fraction. Initial therapy targets any intervention that lowers the LV end-diastolic pressure. This includes an increase in venous capacitance, a decrease in arteriolar resistance, and increasing compliance (softening) of the LV. Diuresis is an effective therapy, although studies have demonstrated that most patients with this diagnosis do not have increased intravascular blood volume; therefore, vasodilatation is the most effective therapy. The use of diuretics, although effective in abating pulmonary edema, may leave the patient's intravascular volume depleted with prerenal azotemia. Since diastolic function is often present, therapy with β-blockers is also very effective. Labetalol may also be useful as a combination α-/β-blocker. Acute ischemia, associated with hypertension, may occur during weaning from mechanical ventilation and also may produce an increase in BP, an associated rise in LV end-diastolic pressure, and pulmonary

edema as a cause of weaning failure. This presentation is likely to be more insidious than the presentation of the patient presenting to the emergency department with acute hypertension-induced pulmonary edema since lower ranges of BP elevation may be present with a contribution of myocardial ischemia-induced wall stiffness playing a prominent role in the rise in pulmonary capillary pressure.

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Notes

Chapter 5. Pregnancy and Critical Illness

Mary E. Strek, MD, FCCP

Objectives:

- Review normal maternal physiologic adaptations to pregnancy.
- Understand oxygen delivery to and the effects of critical illness on the fetus.
- Recognize and treat acute cardiovascular disorders and shock in pregnancy.
- Diagnose and manage acute pulmonary disease and causes of acute hypoxemic respiratory failure in pregnancy.
- Review pregnancy-specific disorders such as preeclampsia, amniotic fluid embolism and acute fatty liver.

Key words: critical illness; preeclampsia; pregnancy; shock; venous thromboembolism

Synopsis:

Critical illness in pregnancy can be a devastating occurrence. The physiologic changes of pregnancy may both mask and worsen the underlying critical illness, and all interventions must take into account the well-being of the fetus as well as the mother. While it is fortunate that critical illness in pregnancy is infrequent, most intensivists will have little experience to draw on when caring for these patients. This chapter will review the physiologic changes of pregnancy with an emphasis on those organ systems most affected by critical illness. Cardiac disorders will be reviewed with a focus on the diagnosis and treatment of hypoperfused states such as cardiogenic, hemorrhagic, and septic shock. Preeclampsia, a disease characterized by widespread vascular endothelial dysfunction, has a variable presentation, as it affects many organ systems. For optimal maternal and fetal outcomes, early diagnosis and treatment of preeclampsia is essential. Pulmonary disorders such as acute asthma exacerbations and venous thromboembolism are more common in pregnancy and have guidelines to direct management. In some cases, critical illness results from a worsening of underlying disease or the onset of a pregnancy related illness. In all cases, understanding the physiologic changes of pregnancy, knowledge of the most advanced approach to diagnosis and treatment, and inclusion of the obstetric team in care will result in the optimal outcome for both mother and fetus.

Critical illness in pregnancy is infrequent; therefore, most intensivists have little experience in caring for these patients. This chapter will review the physiologic changes of pregnancy with an emphasis on those organ systems most affected by critical illness. Acute cardiovascular disorders will be reviewed with a focus on the diagnosis and treatment of hypoperfused states such as cardiogenic, hemorrhagic and septic shock, and preeclampsia. Common pulmonary disorders such as asthma and venous thromboembolism will be reviewed with an emphasis on guideline-based care. For all the disorders reviewed in this chapter, the emphasis is on the changes to diagnosis and treatment necessitated by pregnancy.

Epidemiology

Causes of maternal mortality and admission to the ICU during pregnancy vary, depending on the time period and location of data collection. A study using data from the Centers for Disease Control and Prevention shows that in the United States from 1998 to 2005, medical and cardiovascular conditions accounted for a quarter of maternal deaths.[1] Pregnancy-related complications such as hemorrhage, hypertensive disorders, and venous thromboembolism were no longer the leading causes of maternal death. Mortality was increased in older and African American patients. Perhaps the most important finding was that pregnancy-related mortality is higher now (14.5 pregnancy related deaths per 100,000 live births) than in the past 20 years. It is unclear whether this reflects changes in reporting and coding, an older and more obese maternal population with chronic cardiopulmonary conditions, or a failure of medical care. In a small study from a university hospital in Argentina,[2] the majority of admissions to the ICU were of obstetric cause (74%) from hypertensive disease (40%), hemorrhage (16%), and infection (12%).

Physiologic Adaptations and General Approach

Throughout pregnancy, physiologic changes occur in multiple organ systems to meet the

Table 1—*Cardiopulmonary Adaptations in Normal Pregnancy*

Parameter	Change	Time Course
Blood volume	Increases 40%	Peaks 34 weeks
Stroke volume	Increases	Throughout
Heart rate	Increases 15 to 20 bpm	Peaks 32 to 36 weeks
Cardiac output	Increases 30% to 50%	Peaks 25 to 32 weeks
Blood pressure	Decreases 10% to 20%	Nadir 28 weeks
Oxygen consumption	Increases 20% to 35%	Peaks term
Minute ventilation	Increases 20% to 40%	Peaks term
Tidal volume	Increases 30% to 35%	Peaks term
Respiratory rate	No change	

metabolic demands of the fetus, placenta, and mother and to prepare the mother for delivery. An understanding of these adaptations, especially in regard to the cardiac and pulmonary systems, is essential when evaluating a critically ill gravid patient in order to distinguish normal adaptation from signs of critical illness in pregnancy (Table 1).

Maternal and Fetal Adaptations

Numerous cardiovascular changes occur that may result from maternal blood flow through the low resistance uteroplacental unit and increased production of hormones such as aldosterone and progesterone.[3,4] This decreases systemic vascular resistance and blood pressure. An increase in circulating blood volume results from both increased red blood cell production and plasma volume. The greater increase in plasma volume causes a fall in colloid osmotic pressure and hemoglobin. Heart rate, stroke volume, and cardiac output all increase early in pregnancy. These cardiac parameters are affected by the gravid uterus; a significant fall in cardiac output occurs in the supine position in the third trimester. This awareness allows the clinician to turn the hypotensive patient to the left side, which moves the gravid uterus off the inferior vena cava and aorta, thereby augmenting venous return and decreasing systemic vascular resistance. Right ventricular, pulmonary artery, and pulmonary artery wedge pressures are generally unchanged from prepartum values.

Pulmonary adaptations result from increased progesterone, which increases oxygen consumption.[5] Minute ventilation rises in excess of the increased carbon dioxide production that occurs. Tidal volume increases, but respiratory rate remains unchanged. This hyperventilation is offset by renal compensation, which results in a mild respiratory alkalosis. The typical blood gas values of pregnancy are as follows: P_{O_2}, 105 mm Hg in the first trimester and >95 mm Hg in the third trimester; P_{CO_2}, 28 to 32 mm Hg; bicarbonate, 18 to 21 mEq/L; and pH, 7.45. Decreased chest wall compliance decreases functional residual capacity by 20%. A compensatory increase in the transverse and anterior-posterior diameter of the chest increases the inspiratory capacity so that only a modest decrease in TLC occurs. No change is noted in FVC, FEV_1, or measures of respiratory muscle strength.

Renal adaptation is directed at both the increased excretory load from the fetus and increased maternal metabolism. The glomerular filtration rate and urinary volume increase, resulting in a fall in levels of serum creatinine (<0.09 mg/mL) and blood urea nitrogen (<15 mg/dL). Displacement of Gl organs cephalad, lateral, and posterior occurs. Progesterone related alteration in smooth muscle relaxation causes a decreased lower esophageal sphincter tone and hypomotility of the GI tract. Alkaline phosphatase value increases and albumin level decreases with no change in hepatic enzyme levels.

In caring for the critically ill gravid patient, it is important to understand how oxygen is delivered and then transferred to the fetus.[6] Oxygen delivery depends on uterine artery blood flow and maternal oxygen content. Uterine artery blood flow is maximally dilated at baseline and unable to adapt to stress by local vascular adjustment. Conditions that decrease maternal

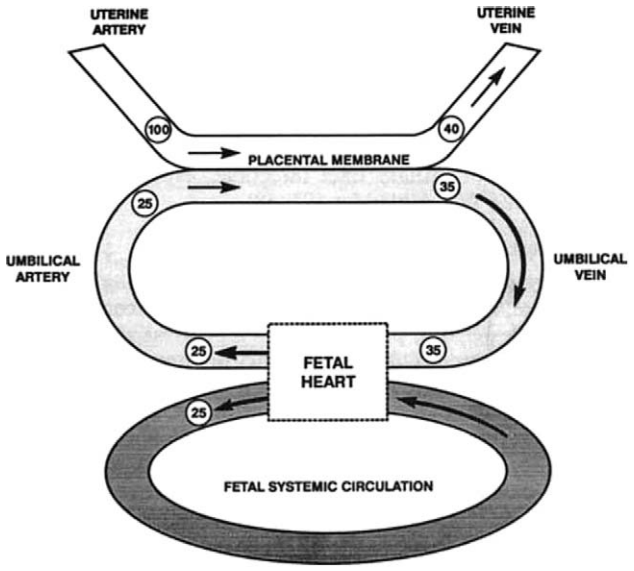

Figure 1. Maternal-fetal oxygen transfer. Numbers in circles are partial pressure of oxygen (mm Hg). Reproduced with permission from Lapinsky et al.[6]

cardiac output or uterine artery blood flow will adversely affect oxygen delivery to the fetus. Uterine artery vasoconstriction with decreased flow results from maternal hypotension, exogenous or endogenous catecholamines, and maternal alkalosis. Uterine contractions also decrease uteroplacental perfusion. Once oxygenated blood is delivered by the uterine artery to the placenta, oxygen transfer occurs by an elegant concurrent exchange mechanism (Fig 1). The difference in oxygen tension between the maternal and fetal circuits results in transfer of oxygen from the maternal to the fetal circulation. Equilibration is incomplete with umbilical venous blood going to the fetus having a lower oxygen tension (P_{O_2}, 30 to 40 mm Hg) than in the uterine vein. After combining with deoxygenated blood in the fetal inferior vena cava, fetal arterial P_{O_2} is 20 to 25 mm Hg.

Despite the hypoxic fetal environment, compensatory mechanisms maintain a relatively high fetal oxygen content and oxygen delivery and protect the fetus against hypoxic insult. Fetal hemoglobin concentration is high (15 g/dL) and has increased affinity for oxygen. Fetal cardiac output is increased with both ventricles pumping blood to the systemic circulation. In times of stress, the fetal circulation preferentially directs blood flow to fetal heart, brain, and adrenals. There is evidence that these mechanisms protect against hypoxemia that would be catastrophic by adult criteria. Fetal oxygenation is maintained until fetal oxygen content is reduced by more than 75%. Irreversible fetal brain damage begins only after 10 min without oxygen.

General Approach to Evaluation and Treatment

As noted above, numerous physiologic adaptations occur during pregnancy (Table 1). These are important to remember in order to distinguish normal adaptation from signs of critical illness and suggest general principles of ICU management. On examination during pregnancy, heart rate is increased, blood pressure decreased, a third heart sound may be physiologic, and pedal edema is common. Normal laboratory values include a mild dilutional anemia and decreased serum albumin value. An enlarged cardiac silhouette is seen as pregnancy progresses. Assessing the adequacy of blood flow may be difficult on examination and may require a bedside echocardiogram. The initial approach to the critically ill gravid patient is directed at maximizing oxygen delivery by placing the patient in the left lateral decubitus position and supplying supplemental oxygen. Noninvasive positive pressure ventilation for acute respiratory failure has not been studied in pregnancy. In the awake patient needing temporary assistance, noninvasive positive pressure ventilation is a reasonable first step, but the patient must be monitored closely. Theoretical limitations include pregnancy-related upper airway edema and aspiration. Early intubation and mechanical ventilation is appropriate to maintain oxygen delivery to the fetus. The decrease in functional residual capacity, combined with increased oxygen consumption, makes the pregnant woman and fetus more vulnerable to hypoxia. This is an important consideration during endotracheal intubation. Fetal well-being is best assessed by monitoring the fetal heart rate in conjunction with obstetrics.

The placenta is not a barrier for most medications, and it must be assumed that drugs given to the mother cross the placenta. The exceptions are medications with high molecular weight, such as insulin and heparin. Drug absorption and metabolism are affected by

Table 2—*US Food and Drug Administration Pregnancy Risk Classification*

Category	Definition	Comments
A	Well-controlled studies fail to demonstrate fetal risk in the first trimester. No evidence of risk in later trimesters.	Few medications in this category.
B	Animal reproduction studies fail to demonstrate fetal risk. No well-controlled studies in pregnant women.	
C	Animal reproduction studies show adverse fetal effect. No well-controlled studies in humans. Potential benefits may warrant use in pregnant women despite potential risks.	Most medications are in this category. Obtain additional information from literature to decide on use.
D	Evidence of human fetal risk from investigational data, marketing experience or studies in humans. Potential benefits may warrant use in pregnant women despite potential risks.	Use only if no other option in life-threatening situations.
X	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk. Risks in pregnant women clearly outweigh potential benefits.	*Never* use these medications in pregnancy!

increased plasma volume and glomerular filtration rate and decreased albumin and gastric motility.[7] These pharmacokinetic changes suggest that medications with multiple daily doses may be preferred over once-daily administration. While it is imperative to know the US Food and Drug Administration pregnancy risk classification for medications used in the ICU, these guidelines do not supplant clinical judgment (Table 2). Most drugs are category C with varying quality of data to support this classification. Large long-term prospective trials have not been performed for most medications, thus; these guidelines are inadequate as the sole source of information.

Cardiac Disorders and Hypoperfused States

Cardiovascular disease is the leading cause of maternal mortality in the United States.[1] The physiologic changes of pregnancy, advanced maternal age, and obesity increase the risk of a cardiovascular complication. The tremendous increase in blood volume delivered to the uterus and placenta increases the risk of hemorrhage, especially postpartum. The physiologic and immunologic changes of pregnancy may predispose to certain infections and alter their presentation and severity. The focus below is on the diagnosis and treatment of these hypoperfused states in pregnancy (Table 3). Cardiac dysfunction, hemorrhage, and sepsis may result in shock. Should a cardiopulmonary arrest occur, guidelines suggest alterations to the performance of cardiopulmonary resuscitation (Table 4). Preeclampsia is a common pregnancy related complication that results from endothelial dysfunction with end-organ hypoperfusion. It has a variable and sometimes subtle presentation given the many organs affected.

Cardiovascular Disease and Cardiogenic Shock

A wider spectrum of cardiac disease now results in critical illness in pregnancy. Advanced maternal age; an increasing number of gravidas with risk factors for ischemic heart disease such as obesity, hypertension and diabetes mellitus; and women with congenital heart disease surviving into adulthood likely explain this observation.[8] Antecedent subclinical heart disease may manifest for the first time as a result of the increased cardiovascular demands of pregnancy. Preexisting cardiovascular conditions with high adverse event rates for both mother (mortality >10%) and child include severe pulmonary arterial hypertension (risk of maternal death 25% to 40%), Eisenmenger's syndrome, severe aortic stenosis and other left-sided obstructive lesions, severe, symptomatic mitral stenosis and regurgitation, and pulmonic stenosis and dilated cardiomyopathy or aortopathy.[9] Fetal complications are also increased and include prematurity,

Table 3—*Causes of Hypotension in Pregnancy*

Clinical Syndrome	Common Etiologies
Acute myocardial infarction	Coronary artery disease
	Coronary artery dissection, vasospasm or thrombosis
Aortic dissection	Hormonal and hemodynamic changes of pregnancy
Cardiogenic shock	Congenital heart disease
	Valvular heart disease
	Peripartum cardiomyopathy
Hemorrhagic shock	Uterine atony
	Retained placenta
	Trauma
Right-heart dysfunction	Pulmonary hypertension
	Amniotic fluid embolism
	Pulmonary embolism
	Venous air embolism
Septic shock	Abortion
	Chorioamnionitis
	Endometritis
	Pyelonephritis
	Pneumonia

intrauterine growth retardation, and fetal demise. The incidence of acute myocardial infarction (AMI) increases three- to fourfold because of the hyperdynamic and hypercoagulable state noted in pregnancy. The diagnosis is often missed. Coronary artery dissection, spasm, and thrombosis are all causes of AMI in pregnancy.[10] AMI may occur in all stages of pregnancy and has been noted in patients as young as 19 years old. Aortic dissection also occurs most commonly during the third trimester and should be in the differential diagnosis of chest or interscapular pain during pregnancy.

Peripartum cardiomyopathy develops in the last month of pregnancy up to 5 months postpartum.[11] Risk factors include African American race, advanced maternal age, twin gestations, anemia, preeclampsia, and gestational hypertension. The typical patient is over the age of 30 years old and peripartum. Patients report dyspnea, orthopnea, and pedal edema that may initially be attributed to the physiologic changes of pregnancy. Echocardiography demonstrates systolic dysfunction. The majority of patients have a gradual recovery of ventricular function. The use of implantable defibrillators may have decreased mortality. Pulmonary embolism is noted with increased frequency in these patients.

The diagnosis of cardiovascular disease is most often made by a chest radiograph, electro-

Table 4—*Modifications to Advanced Cardiovascular Life Support in Pregnancy*

ABCs	Modifications
Airway	Insert early to prevent aspiration
	Use smaller tracheal tube
	Preoxygenation essential
	Rapid sequence intubation with cricoid pressure
Breathing	Clinical assessment of tracheal tube placement
	Less oxygen reserve
Circulation	Manual leftward displacement uterus
	Chest compressions higher on the sternum
	Avoid femoral vein for venous access
Defibrillation	Remove fetal or uterine monitors
Decisions	Consider pregnancy related causes of arrest
	Perform emergency cesarean section within 5 min of arrest if fetus viable

cardiogram, and echocardiogram. Transesophageal echocardiography and magnetic resonance imaging are the most sensitive and specific tests for aortic dissection, although computed tomography is more readily available. The diagnosis of an AMI may be complicated by the fact that ST-segment changes can be seen during cesarean section and an increase in creatinine kinase may occur for 24 h after delivery. Troponin levels increase marginally and remain below normal except in patients with preeclampsia therefore may be more reliable for diagnosis of AMI.[10] Cardiac catheterization with percutaneous coronary intervention with bare metal stents is preferred over thrombolytic therapy given the increased incidence of coronary artery dissection.

Cardiac drugs best avoided in pregnancy include angiotensin converting enzyme inhibitors and receptor antagonists, amiodarone, warfarin, and spironolactone. Dobutamine is the preferred vasoactive medication for the treatment of cardiogenic shock. In severe pulmonary hypertension, intravenous prostacyclin has been given without fetal harm. Preliminary studies suggest that prolactin inhibitors, such as bromocriptine, may be of benefit in treating peripartum cardiomyopathy.[12] Labor and delivery are high risk for women with cardiac disease. The optimal delivery method is assisted vaginal delivery with epidural anesthesia to control pain. Indications for cesarean section include obstetric complications, fetal distress, or inability to tolerate labor and delivery. General anesthesia and surgical delivery may be preferred for hypertrophic cardiomyopathy, aortic stenosis, or pulmonary hypertension, conditions that place the patient at risk of decompensation during the increased cardiac demand and large fluid shifts of labor and delivery.

Acute Hemorrhage and Hemorrhagic Shock

Hemorrhagic shock is a major cause of both maternal death and ICU admission (Table 3). When it occurs, the bleeding can be both massive and swift with major blood loss having occurred before it is clinically apparent at the bedside. In a setting of increased risk, a mild increase in heart rate or fall in blood pressure should prompt consideration of hemorrhage. Lack of overt bleeding does not rule out hemorrhage. Postpartum hemorrhage is most common and results primarily from uterine atony (60% to 70%) followed by retained placental products (20% to 30%) and obstetric trauma (10%).[12] Causes of antepartum hemorrhage include ectopic pregnancy, abortion, placenta previa (placenta implanted below the fetus), or abruption (separation of placenta before delivery) and trauma from motor vehicle accidents, falls, and assaults. Rare causes of hemorrhage include uterine rupture or inversion and disseminated intravascular coagulation (DIC) from sepsis, amniotic fluid embolism, preeclampsia, and fetal demise.[13]

Suspected obstetrical hemorrhage requires a coordinated and fast-acting multidisciplinary approach to care. Ultrasound and careful bedside obstetrical examination are helpful in diagnosis. Resuscitation includes identification and control of the bleeding source and rapid administration of blood products through large-bore IV access. This is one situation where unmatched type specific rather than fully cross-matched packed red blood cells may need to be given. Fresh frozen plasma, cryoprecipitate, and platelets are transfused as needed to prevent a dilutional coagulopathy and thrombocytopenia. Laboratory studies should be sent and reviewed to look for a coagulation disorder (DIC). Once DIC is established, factor replacement and fresh frozen plasma are given based on laboratory findings and bleeding. Obstetrics should be called immediately to evaluate for lacerations, ensure complete removal of the placenta, and assist with compression and contraction of the uterus. Uterine atony is treated with bimanual uterine massage, bladder drainage, uterotonic medication, and removal of retained placental products.[14] IV oxytocin is given first followed by methylergonovine (contraindicated in hypertensive states) or prostaglandin therapy if bleeding persists.[15] There may be a role for administration of human recombinant activated factor VII; such use is off label at present. Case reports attest to its effectiveness in controlling life-threatening obstetrical hemorrhage after other measures have failed. Interventions that may be required to control bleeding include uterine balloon tamponade, arterial embolization of uterine vessels by

interventional radiology, and surgical uterine compression sutures or ligation of pelvic arteries. Hysterectomy is performed if the above measures fail.

Infection and Septic Shock

Infections account for 10% of maternal mortality in the United States and up to 25% of ICU admissions in a small study from Argentina.[1,2] Decreased cell-mediated immunity predisposes to disseminated infections with *Listeria monocytogenes*, herpes virus, and varicella. Many infections result directly from the pregnant state. These include septic abortions, chorioamnionitis, endometritis, septic pelvic thrombophlebitis, and incisional infection (Table 3). The increased incidence of urinary tract infections and pyelonephritis may result from ureteral stasis as pregnancy progresses. Pneumonia in pregnancy is reviewed below. Infections are often polymicrobial, caused by gram-positive, gram-negative, and anaerobic organisms that normally colonize the lower genital tract. Infection with toxin-producing strains of *Clostridium*, *Streptococcus*, and *Staphylococcus* may be rapidly fatal. Toxic shock syndrome should be considered when severe or quickly evolving sepsis follows a medical abortion (*Clostridium sordellii*) or is noted postpartum (*Streptococcus*).[16] Cholecystitis and appendicitis are not more common, but their clinical presentations may be altered in pregnancy. Sepsis may be complicated by ARDS, multiorgan system failure, cardiac dysfunction, and DIC, as well as adverse fetal outcomes.

Diagnosis is complicated by the normal physiologic changes of pregnancy, which include a mildly decreased blood pressure and a mildly elevated heart rate and white blood cell count. A thorough abdominal and pelvic examination and ultrasound evaluation are essential to look for occult sites of infection. Blood, urine, and pelvic sites should be cultured. Chorioamnionitis is suggested by fever, maternal or fetal tachycardia, abdominal tenderness, and foul-smelling amniotic fluid; however, the presentation may be occult.[17] As in the nonpregnant population, early goal-directed therapy is recommended to prevent the development of severe sepsis and shock.[18] This includes fluid resuscitation and measurement of central venous pressure as an indicator of circulating volume, which is generally unchanged in pregnancy. Bedside echocardiography may aid in assessment of volume status. Computed tomography scan or magnetic resonance imaging of the pelvis may aid in the diagnosis of septic pelvic thrombophlebitis. Broad-spectrum antibiotics are given, directed at likely polymicrobial infection. Aminoglycosides are toxic to the fetus and should be avoided antepartum. If chorioamnionitis is present, the fetus must be delivered. Heparin, in addition to antibiotics, is recommended to treat septic thrombophlebitis. Source control is crucial to a good outcome, with surgical drainage or hysterectomy required in some cases.

Cardiopulmonary Resuscitation

Pregnancy requires modifications to advanced cardiovascular life support, as shown in Table 4.[19,20] If magnesium overdose is possible, calcium chloride should be given. A recent systematic review suggests that chest compressions with a left lateral tilt are less forceful than in the supine position.[21] They recommend manual leftward displacement of the gravid uterus. An emergency cesarean section should be considered if the resuscitation is unsuccessful since maternal circulation may dramatically improve with uterine evacuation. This should occur within 5 min of initiating resuscitation.[21,22] Although fetal survival has been reported in cases where it was performed later, 93% of surviving infants were delivered within 15 min in one review of the literature.

Preeclampsia

Preeclampsia is a unique disorder of pregnancy with serious adverse consequences both for the mother and the fetus. Abnormal placental implantation may cause altered production of angiogenic factors that disrupt the maternal vascular endothelium in multiple organ systems. Although the classic triad of hypertension, generalized edema, and proteinuria after 20 weeks of gestation suggests the diagnosis, the presentation is often subtle and may even occur postpartum, so a high index of suspicion is necessary to recognize this life-threatening dis-

Table 5—*Multisystem Organ Involvement in Preeclampsia*

Organ	Clinical Syndrome
Central nervous system	Eclamptic seizure
	Posterior reversible encephalopathy
	Cerebral vascular accident
	Cerebral hemorrhage or edema
Lungs	ARDS
Cardiac	Pulmonary edema
Renal	Acute kidney injury
Liver	Hepatocellular damage, hepatic infarction, subcapsular hemorrhage or rupture
Systemic vasculature	Vasoconstriction
Coagulation	HELLP syndrome, DIC, placental abruption

HELLP = hemolysis, elevated liver enzymes, low platelets.

order. Management depends on severity, with delivery of the placenta the only curative therapy. Blood pressure control is essential to prevent end-organ damage but does not affect progression of the underlying disease process. Numerous clinical trials have demonstrated the benefit of magnesium sulfate in preventing and treating eclamptic seizures.

Pathophysiology: Preeclampsia occurs in 2% to 8% of pregnant women.[23] Risk factors besides the primigravid state include chronic hypertension, renal disease, diabetes mellitus, obesity, age $\geq$40 years, autoimmune disease, and the presence of antiphospholipid antibodies.[24] Multiple gestation and hydatidiform mole are also risk factors, as is preeclampsia in a prior pregnancy or a family history of preeclampsia. Preeclampsia may progress to a convulsive and potentially deadly phase, termed eclampsia, without warning or overt preeclampsia. Eclampsia may occur up to 1 month postpartum and greatly increases the risk of poor outcome for mother and fetus. An especially fulminant complication of preeclampsia is *h*emolysis, *e*levated *l*iver *e*nzymes, *l*ow *p*latelets (HELLP) syndrome, which complicates 10% to 20% of cases of severe preeclampsia.[25]

The exact etiology of preeclampsia is unknown, but a genetic predisposition and host factors favor its development. Failed or abnormal development of blood vessels supplying the placenta causes placental ischemia and oxidative stress followed by the altered production of angiogenic factors that enter the maternal circulation and cause vascular endothelial dysfunction. This results in increased loss of fluids from the intravascular compartment, increased sensitivity to endogenous and exogenous pressor agents, and activation of the coagulation cascade.

The reduction in placental perfusion and increased circulating concentrations of markers of endothelial activation and intravascular coagulation occurs before the onset of clinical disease and may affect many organ systems (Table 5). Cerebral vasospasm, ischemia, or edema and hypertensive encephalopathy may contribute to eclamptic seizures. Glomeruloendotheliosis is the characteristic finding in the kidney on histopathologic study, but renal dysfunction may also result from renal ischemia and intravascular volume depletion. Pulmonary edema may result from increased left ventricular afterload, myocardial dysfunction, decreased colloid osmotic pressure, vigorous fluid therapy, and increased capillary permeability. While it most commonly occurs after parturition, in a subgroup of obese and chronically hypertensive patients with left ventricular hypertrophy and diastolic dysfunction, antepartum pulmonary edema develops. The HELLP syndrome is characterized by more extreme multiorgan dysfunction from secondary fibrin deposition and organ hypoperfusion. A microangiopathic hemolytic anemia and consumptive coagulopathy may lead to DIC. In HELLP, the liver involvement is characterized by periportal or focal parenchymal necrosis with elevated liver function test results.

Diagnosis: The diagnosis of preeclampsia may be difficult since the hypertension may be subtle and proteinuria minimal or absent. The majority of normal pregnancies are complicated by edema, so this nonspecific finding is no longer necessary for diagnosis. Diagnostic criteria vary

Table 6—*Management of Severe Preeclampsia*

Intervention	Comment
Delivery	Immediately if >36 weeks' gestation
Corticosteroids	If between 24 and 34 weeks' gestation
Magnesium sulfate	Loading dose 4 g over 15 to 20 min Continuous infusion 1 g/h
Hydralizine	5 mg IV, then 5 to 10 mg every 20 to 40 min (max 20 mg)
Labetalol	10 to 20 mg IV, then 20 to 80 mg at 20- to 30-min intervals until target blood pressure (maximum 300 mg), or Infusion starting at 1 to 2 mg/min and titrated up until the target blood pressure achieved
Surveillance	Measure blood pressure at least every 2 h Frequent measurement of values for serum creatinine, magnesium, hemoglobin, platelet count, and transaminase

but include new onset hypertension with a systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg on two or more occasions and ≥300 mg protein in a 24-h urine collection. There has been considerable interest in the development of a reliable biomarker. Elevated levels of antiangiogenic factors, such as fms-like tyrosine kinase 1 and endoglin, and decreased levels of the proangiogenic protein placental growth factor have been useful in suggesting the diagnosis in research settings but are not yet recommended for general use.[24]

Since preeclampsia may involve the central nervous system, lungs, liver, kidneys, systemic vasculature, coagulation, and the heart, it may have a varied presentation (Table 5). Signs and symptoms of preeclampsia may be mild or nonspecific with malaise, headache, visual changes, nausea, vomiting, and epigastric or right upper quadrant pain being reported. Hemolysis on a peripheral blood smear, increased serum bilirubin level, increased serum transaminase levels, and thrombocytopenia suggest the diagnosis of the HELLP syndrome. The differential includes acute fatty liver of pregnancy and, when renal dysfunction is also present, hemolytic uremic syndrome (HUS) or thrombotic thrombocytopenic purpura (TTP).

Maternal complications of severe preeclampsia are shown in Table 5. Posterior reversible encephalopathy syndrome, a recently described acute cerebral condition characterized by transient headache, altered mental status, seizures, and loss of vision with findings of posterior leukoencephalopathy on imaging studies, is seen in preeclampsia.[26] Acute renal failure is uncommon and seen most often in patients with the HELLP syndrome, placental abruption, massive hemorrhage, or coagulopathy.

Management: The principles of management include early diagnosis, close medical observation, and a well-timed delivery in order to maximize both maternal and fetal well-being (Table 6). Preeclampsia may be mild or severe with the aggressiveness of therapy based on disease severity and fetal maturity. Markers of disease severity that should alert the physician to an increased risk of complications include systolic or diastolic blood pressures of ≥160 and ≥110 mm Hg, respectively; proteinuria ≥2 g/24 h or ≥100 mg/dL in a random specimen; oliguria; pulmonary edema; and early onset disease (<34–35 w). Elevation in systolic rather than diastolic blood pressure may correlate with risk of stroke.

Patients who are ≥36 weeks' gestation should undergo delivery since removal of the placenta is the only curative therapy. Earlier in gestation, delivery is recommended for patients with severe preeclampsia, eclampsia, HELLP, multiorgan involvement, or fetal distress, while conservative management with close monitoring to improve neonatal survival and morbidity may be appropriate in select cases at tertiary perinatal centers.

Blood pressure is controlled with either labetalol or hydralazine. The objective of antihypertensive therapy is to prevent end-organ complications. While hydralazine has been the traditional treatment, in the ICU setting, IV labetalol is now the drug of choice.[27] Diuretics should be used with caution, as they may aggravate the reduction in intravascular volume that is often seen in preeclampsia.

Table 7—*Causes of Hypoxmic Respiratory Failure in Pregnancy*

Etiology	Time of Presentation
Asthma	Risk greatest second trimester Unusual in labor and delivery
Aspiration	Labor and delivery
Amniotic fluid embolism	Up to 48 h after labor and delivery First- and second-trimester abortion
Pulmonary embolism	Any trimester After cesarean section Risk greatest peripartum
Venous air embolism	Instrumentation Labor and delivery
Preeclampsia	After 20 weeks Up to 2 weeks postpartum
Pneumonia	Severity in certain infections increased third trimester
Tocolytic pulmonary edema	Preterm labor

Magnesium sulfate has been shown in numerous well-conducted studies summarized in a Cochrane review to prevent eclamptic seizures and is superior to phenytoin and nimodipine.[28] Magnesium halves eclampsia risk in patients with preeclampsia and likely reduces the risk of maternal death. The two trials comparing magnesium with diazepam were too small for reliable conclusions about their effects. Magnesium sulfate has been shown to be better than diazepam and phenytoin in preventing recurrent seizures in patients with eclampsia. Toxicity is decreased if after the traditional loading dose of 4 g IV, an infusion of 1 g/h is given. Monitoring serum magnesium levels is not required at this dose. Magnesium sulfate should be given to all women with either preeclampsia or eclampsia for 24 h.

Patients with persistent thrombocytopenia, hemolysis, or organ dysfunction may actually have TTP or HUS and may benefit from plasmapheresis with fresh frozen plasma. Management of intrahepatic hemorrhage with subcapsular hematoma includes administration of blood products, delivery, and control of liver hemorrhage. Embolization of the hepatic artery is often successful, but evacuation of the hematoma and packing of the liver may be required.

Respiratory Disorders and Acute Hypoxemic Respiratory Failure

Respiratory disorders are a less frequent cause of admission to the ICU and maternal mortality (Table 7). Asthma is the most common disease to complicate pregnancy, affecting 4% to 8% of all gravidas. Amniotic fluid or venous air embolism, tocolytic-associated pulmonary edema, pneumonia, and aspiration may result in acute lung injury or ARDS.[29] The institution of mechanical ventilation in the pregnant patient requires careful attention to the special needs of both mother and fetus. Venous thromboembolic disease is a major cause of maternal mortality in the United States.

Asthma

Asthma remains a high-risk condition for both mother and fetus.[30] Active treatment to control asthma improves both maternal and fetal outcomes. The course of asthma during pregnancy is variable. Patients with more severe asthma are more likely to experience worsening asthma during pregnancy. Asthma is most severe during the second and third trimesters of pregnancy, with improvement the last month of pregnancy. Adverse maternal outcomes in pregnant woman with asthma include pregnancy-related hypertension, preeclampsia, and cesarean delivery. Adverse fetal outcomes include preterm birth and infants small for gestational age.

The management of the pregnant patient with status asthmaticus is similar to that of the nonpregnant patient, with a few exceptions.[31] Mild hypoxemia should be treated aggressively because it may be detrimental to the fetus. An arterial blood gas with a $Paco_2$ of >35 mm Hg

may be a sign of impending ventilatory failure given the baseline respiratory alkalosis in normal pregnancy. Most asthma medications are safe for use during pregnancy. Inhaled albuterol may be mixed with ipratropium bromide. Guidelines recommend systemic corticosteroids, such as methylprednisolone, 120 to 180 mg/d in three or four divided doses for 48 h. An IV infusion of magnesium sulfate can be considered for its potential bronchodilator effect in refractory cases. Heliox, a low-density mixture of helium and oxygen, may decrease the work of breathing and preclude intubation and mechanical ventilation. Noninvasive positive pressure ventilation can be considered for the hemodynamically stable patient without impending respiratory failure. Any pregnant patient with impending respiratory failure should be intubated for mechanical ventilation. Ventilation strategies are similar to the nonpregnant patient but include a lower tolerance of permissive hypercapnia as maternal academia impairs fetal oxygen extraction. The use of a lower tidal volume, a lower respiratory rate, and an increased inspiratory flow minimizes intrinsic positive end-expiratory pressure (PEEP).

Respiratory Infections

The incidence of pneumonia during pregnancy may be increasing.[32] It is the most common cause of fatal nonobstetric infection in pregnancy. The decreased cell mediated immunity of pregnancy may increase the severity of infection with varicella, coccidioidomycoses, and influenza A (H1N1). Primary infection with varicella virus progresses to pneumonia more often in adults than children. Coccidioidomycosis is the fungal infection associated with increased risk of dissemination during pregnancy, especially if it is contracted in the third trimester. Obstetric complications of pneumonia include preterm labor and delivery, respiratory failure, and maternal and fetal mortality.

A number of studies during the influenza A (H1N1) epidemic demonstrated increased disease severity and mortality.[33] Sixty percent of the deaths during the 2009 influenza season occurred in the third trimester, when influenza morbidity and mortality are known to be higher. Pregnant patients presented similarly to nonpregnant patients, but they experienced greater delay in receiving antiviral treatment. Rapid antigen tests for influenza are less sensitive than culture, so pregnant patients should be treated empirically with antiviral medications as soon as infection is suspected even if the rapid influenza test is negative. Documented bacterial coinfection was rare in H1N1-infected pregnant women.

In the pregnant woman, HIV infection is complicated by the risk of perinatal transmission to the fetus, preterm delivery, and opportunistic infection, especially pneumonia. *Pneumocystis jiroveci* pneumonia may complicate pregnancy and be especially virulent. It is the most common cause of AIDS-related death in pregnant woman in the United States with respiratory failure requiring mechanical ventilation common. Both maternal and fetal mortality are high. The clinical presentation is not altered by pregnancy.

The choice of antibacterial agents must take into account potential fetal toxicity. Penicillins, cephalosprins, and second-generation macrolides are safe. Tetracycline and chloramphenicol are contraindicated; sulfa-containing regimens should be avoided near term except for the treatment of *Pneumocystis*. Oseltamavir is the drug of choice to treat influenza during pregnancy and when given within the first 4 days of symptom onset has been associated with decreased rates of complications and death. Favorable results have been obtained using acyclovir to treat pregnant women with varicella pneumonia, especially when used early. Amphotericin B should be used to treat disseminated coccidioidal infections in pregnancy. No adverse effects on the fetus have been reported with amphotericin. Fluconazole and other azole antifungals are potentially teratogenic. *Pneumocystis* is treated with trimethoprim-sulfamethoxazole, which results in an improved outcome compared with other therapies. Corticosteroids are added as for the nonpregnant patient.

Amniotic Fluid Embolism

Amniotic fluid embolism is uncommon but likely underrecognized. Maternal mortality is much lower (13% to 30%) than previously estimated (80% to 90%), but most survivors

develop permanent neurologic deficits from cerebral hypoxia. Risk factors include advanced maternal age, cesarean or assisted vaginal delivery and eclampsia.[34] Most cases occur during labor and delivery, but it has been reported during abortions and following trauma.

The classic presentation is characterized by the abrupt onset of severe dyspnea, tachypnea, and hypoxemia, followed by cardiovascular collapse and altered mental status or seizures. Shock, cardiogenic pulmonary edema, ARDS, and DIC are seen and may be the presenting manifestation. There is great debate regarding the mechanism by which these clinical findings occur. While amniotic fluid and particulate matter may enter the maternal circulation, pulmonary vascular obstruction is thought to be a minor factor in the pathogenesis. An anaphylactoid reaction to circulating fetal material has been suggested but remains unproven. Vasoconstrictor arachidonic acid metabolites present in the amniotic fluid may contribute to pulmonary hypertension and associated acute right-sided heart failure. Pulmonary edema is also noted due to both capillary leak and left-sided heart failure. Bleeding secondary to DIC occurs in up to 50% of patients who survive the first 30 to 60 min. Cytologic examination of pulmonary artery catheter blood may show fetal cells but is not sufficient to make the diagnosis because this has been observed in patients without clinical evidence of amniotic fluid embolism.

Treatment is supportive and aimed at ensuring adequate oxygenation, stabilizing the circulation, and controlling bleeding. Initial management includes intubation and mechanical ventilation with lung-protective ventilation. PEEP is titrated to achieve a Pa_{O_2} of >90 mm Hg and a F_{IO_2} <0.6. An echocardiogram may help determine the degree of left-sided and right-sided heart failure. Case reports attest to successful use of inhaled nitric oxide and extracorporeal membrane oxygenation (ECMO) and antraaortic balloon bump therapies for right-sided and left-sided heart failure, respectively.

ARDS

Pregnancy-specific causes of ARDS include placental abruption, chorioamnionitis, endometritis, septic abortion, and eclampsia, while ARDS may also result from aspiration, sepsis, transfusion, and trauma (Table 7). Acute lung injury is more likely to result in pulmonary edema given the increased plasma volume and decreased plasma oncotic pressure noted in pregnancy. Fetal distress and premature labor are common. The management of ARDS is directed at treatment of the underlying cause, supportive care, and close monitoring of the fetus. Intubation and mechanical ventilation are usually necessary.

Airway and Ventilator Management

The indications for intubation and mechanical ventilation are not significantly changed by pregnancy. Since securing an airway in an obstetrical patient may be challenging, this should be achieved by a skilled individual (Table 8). Mallempati scale score increases as pregnancy progresses and predicts difficulty of obtaining an airway.[35] Preintubation airway inspection and proper positioning is key. Airway edema is common, and the highly vascular upper airway may bleed from minor intubation-related trauma. Use of cricoid pressure to minimize the risk of pulmonary aspiration is recommended.

Tidal volume should be determined using nonpregnant predicted ideal body weight.[36] There are no studies to guide whether the initial ventilator settings should maintain the mild respiratory alkalosis of pregnancy (P_{CO_2}, 27 to 34 mm Hg). Marked respiratory alkalosis should be avoided because animal models suggest that hyperventilation can decrease uteroplacental blood flow. The patient with ARDS should be ventilated with a small tidal volume (4–6 mL/kg) and high respiratory rate to avoid ventilator-induced lung injury, although the safety of permissive hypercapnia in pregnancy has not been studied. In case reports of lung-protective ventilation in pregnancy, no adverse effects were noted when P_{CO_2} was maintained at or below 60 mm Hg. Close monitoring of the fetal heart should occur during ventilatory changes, avoiding settings that are associated with fetal distress. During the third trimester of pregnancy, chest wall stiffness from the gravid uterus may cause

Table 8—*Risks of Intubation*

Risk	Response
Low oxygen reserve	Preoxygenate
Airway highly vascular	Avoid nasotracheal intubation
Airway edema	Use smaller tracheal tube (6 to 7 mm)
Weight gain obscures anatomy	Proper positioning
Aspiration risk	Sodium citrate and citric acid (Bicitra), rapid sequence induction

high airway pressures unrelated to lung stiffness or overdistension.

When ARDS from a diffuse lung lesion is present requiring high levels of oxygen, sufficient PEEP should be used to correct arterial hypoxemia at a nontoxic F_{IO_2} (<0.6). In the pregnant patient, oxygen tension is monitored rather than saturation because the difference in Pa_{O_2} between maternal and fetal circulations drives oxygen transfer. The aim is to keep the Pa_{O_2} >90 mm Hg, a value higher than that used in the nonpregnant patient, to prevent fetal distress.[37] To minimize the decrease in venous return that occurs with positive pressure ventilation, it is important that the pregnant patient be managed in a left lateral position when possible.

In patients with ARDS requiring high levels of PEEP or with hemodynamic instability, muscle relaxation and sedation may decrease oxygen consumption. Nondepolarizing neuromuscular blocking agents, such as cisatracurium, pancuronium, vecuronium, and atracurium, produce no adverse fetal effects with short-term use. Cisatracurium is preferred because it does not depend on renal or hepatic function for elimination. Most patients require sedation during intubation and mechanical ventilation. If benzodiazepines are used early in pregnancy, the lowest dose and shortest possible duration are recommended, as there is theoretical risk of cleft palate. Propofol is a pregnancy category B hypnotic agent and has been used safely in pregnancy. Morphine and fentanyl are generally safe during pregnancy. These agents cross the placenta, and if given near the time of delivery, immediate intubation of the neonate may be required. If life-threatening respiratory failure persists despite maximizing ventilatory strategies, ECMO may be considered. Data on the use of ECMO during pregnancy are limited, but several case reports support its use as a salvage intervention.

Venous Thromboembolic Disease

DVT and pulmonary embolism (PE) remain a significant cause of maternal mortality occurring in all three trimesters and postpartum.[38] The risk of VTE is increased fourfold during pregnancy and is highest during the postpartum period.[39] Hypercoagulability, venous stasis, and endothelial damage to pelvic vessels during delivery occur in normal pregnancies; thus, all pregnant women are at increased risk of VTE. Additional risk factors include age >35 years, cesarean section, obesity, heart disease, diabetes, sickle cell disease, African American race, smoking, and multiple pregnancy. Thrombophilia increases the risk even further and is noted in approximately 50% of woman with VTE during pregnancy. More DVTs in pregnancy are ileofemoral and more likely to embolize than in the nonpregnant individual. There is a 70% to 90% incidence of left leg DVT thought due to increased compression of the left iliac vein, where it is crossed by the right iliac artery as the gravid uterus enlarges.

Diagnosis and treatment of both DVT and PE are more complicated in pregnancy. The diagnosis of VTE requires a high index of suspicion because dyspnea, tachycardia, and mild lower extremity edema are often noted in normal pregnancy. Pregnant women with pelvic vein DVT occasionally present with lower abdominal pain, fever, and an elevated white blood count mimicking acute appendicitis. If clinical features suggest DVT or PE, some authorities recommend treatment with low-molecular-weight heparin (LMWH) while diagnostic testing is pursued.[38] Bilateral venous compression ultrasound is the diagnostic test of choice for DVT, although it is less accurate for isolated calf and iliac vein thrombosis. A positive study result is considered sufficient to justify continued treatment with anticoagulation. A negative study result mandates further testing, which, depending on the clinical suspicion, might involve repeat compression ultrasonography in 5 to 7 days or further

imaging of proximal veins with magnetic resonance imaging or computed tomography. Since the D-dimer increases as pregnancy progresses, it is not a useful diagnostic test.[39,40]

While some experts have recommended bilateral venous compression ultrasound as the initial diagnostic test in the setting of suspected PE, a recent American Thoracic Society clinical practice guideline recommends chest radiograph followed by lung scintigraphy ($\dot{V}/\dot{Q}$ scan) if the chest radiograph is normal.[40] If the $\dot{V}/\dot{Q}$ scan is nondiagnostic, a CT pulmonary angiogram is performed, which has the advantage of providing additional imaging of the chest. Radiation exposure to the fetus from either test is low and within the amount considered safe in pregnancy. Lung scintigraphy compared with CT, angiography has a lower risk of maternal breast and lung cancer. Echocardiography may be useful to document right-sided clot or right-heart strain. It is important to make a definitive diagnosis, and the clinical presentation alone cannot be relied on to diagnose or exclude VTE.

Adjusted-dose subcutaneous LMWH is recommended for treatment of acute VTE in pregnancy.[41] Heparin should be continued for at least 6 weeks postpartum for a minimum duration of therapy of 3 months. Current guidelines recommend LMWH because the risks of bleeding, heparin-related thrombocytopenia, and osteoporosis are all decreased with this agent. The half-life of LMWH is shorter in pregnancy as the volume of distribution changes and glomerular filtration rate increases as pregnancy progresses. Despite this, recent guidelines suggest that once-daily dosing may be used. Routine dose adjustment based on weight gain during pregnancy and periodic antifactor Xa LMWH levels is not necessary for most patients. For patients with heparin-induced thrombocytopenia, danaparoid (a LMWH) is recommended. Warfarin crosses the placenta and is absolutely contraindicated (category X) because of the high incidence of embryopathy in the first trimester, small incidence of fetal CNS abnormalities throughout pregnancy, and possible fetal hemorrhage. Life-threatening VTE should prompt consideration of thrombolytic therapy. Thrombolysis can be performed safely in pregnancy, although there is the potential risk of maternal or fetal hemorrhage and fetal loss. Recombinant tissue plasminogen activator does not cross the placenta and is the preferred thrombolytic agent.

Other Disorders of Pregnancy

Acute Renal Failure

The incidence of acute kidney injury (AKI) leading to renal failure in pregnancy has fallen significantly.[42] AKI may complicate preeclampsia, amniotic fluid embolism, and acute fatty liver of pregnancy. Idiopathic acute renal failure is an unusual complication of pregnancy and may occur days to weeks after a normal pregnancy and delivery. The disorder may be a variant of HUS or TTP. Sepsis may cause AKI, especially in the setting of pyelonephritis. There are case reports of acute renal failure from genitourinary compression from the gravid uterus, which may be more likely to occur in the setting of increased uterine distention from polyhydramnios, multiple gestation, or uterine fibroids.

In general, the treatment of AKI in pregnancy is similar to that in the nonpregnant patient, with supportive care and dialysis as necessary. Renal dysfunction associated with preeclampsia and the HELLP syndrome should respond to delivery of the fetus, while TTP and HUS require plasmapheresis with fresh frozen plasma. An evaluation for occult sepsis should be performed when the etiology of acute renal failure is unclear.

Acute Liver Failure

Acute liver failure is an uncommon complication of pregnancy and rarely complicates preeclampsia and the HELLP syndrome.[43] Acute fatty liver of pregnancy may result in acute liver failure if not recognized and treated. Risk factors include twin gestations and first pregnancy. Evidence suggests it results from deficiencies of the enzymes of mitochondrial fatty acid β-oxidation. When a woman heterozygous for these enzyme defects is pregnant with a homozygous fetus, fetal fatty acids accumulate and are detected in maternal circulation. This accumulation leads to hepatic fat deposition and impaired hepatic function. The mean onset is at 36 weeks of gestation, although the disorder can be seen as

early as 26 weeks and postpartum. Patients present with headache, nausea and vomiting, right upper quadrant or epigastric pain, malaise, and anorexia. This may mimic the clinical presentation of preeclampsia. Jaundice may follow 1 to 2 weeks later. Cholestasis with mild to moderate elevations in serum aminotransferases is the rule. Abdominal CT scans may demonstrate decreased attenuation, although this imaging exposes the fetus to significant radiation. Acute fatty liver of pregnancy progresses to fulminant hepatic failure complicated by encephalopathy, renal failure, pancreatitis, hemorrhage, DIC, seizures, coma, and death. Because deterioration may occur rapidly, expectant management is not advised. The treatment is delivery of the fetus. Jaundice, liver dysfunction, and DIC may worsen for a few days after delivery but then should improve. Maternal and fetal mortality has improved with early delivery. Full maternal recovery is to be expected. Because long-chain 3-hydroxyacyl-coenzyme dehydrogenase deficiency in the fetus is associated with acute fatty liver of pregnancy, infants may have hypoglycemia, hypotonia, acute or chronic skeletal and cardiac muscle dysfunction, and sudden infant death syndrome.

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Chapter 6. Venous Thromboembolic Disease

R. Phillip Dellinger, MD, MSc, FCCP; and Wissam Abouzgheib, MD, FCCP

Objectives:

- Know the risk factors for pulmonary embolism.
- Understand the importance of pretest probability for the diagnostic approach to pulmonary embolism.
- Be able to contrast sensitivity versus specificity of CT angiogram and leg ultrasound in the diagnostic approach to pulmonary embolism.
- Know the indications and contraindications for thrombotic therapy of pulmonary embolism.

Key words: CT pulmonary angiogram; deep vein thrombosis; massive pulmonary embolism; pulmonary embolism; thrombolytic therapy

Synopsis:

Venous thromboembolic disease is a pathologic formation of a thrombus within the venous system of the lower extremities or the pulmonary arteries. Pulmonary embolism (thromboembolism) is responsible for 200,000 to 300,000 hospital admissions per year. Risk factors include those that are inherited or acquired and affect Virchow's triad: vascular endothelial injury, hypercoagulable state, and venous stasis. Clinical findings are nonspecific and include signs and symptoms suggestive of either deep vein thrombosis or pulmonary embolism. A chest radiograph may be normal in up to 25% of patients. Arterial blood gasses may also be normal. A nonelevated D-dimer is a useful test to make pulmonary embolism unlikely. B-type natriuretic peptide and troponin may be elevated. CT pulmonary angiography is the best diagnostic test as to sensitivity and specificity other than digital subtraction dye angiogram that, although remaining the gold standard, is much more invasive and less often used. Ventilation perfusion lung scan, venous compression ultrasonography, and echocardiography may also be very useful adjuncts for diagnosis or exclusion of pulmonary embolism. Anticoagulation is initially with unfractionated or low-molecular-weight heparin. Thrombolytic therapy, if not contraindicated, is used in patients with pulmonary embolism–induced hemodynamic instability. Inferior vena cava filters are used in patients with contraindication to anticoagulation or with hemodynamic instability and contraindication to thrombolytic therapy. Surgical thrombectomy may be considered in situations of severe hemodynamic instability with contraindication to thrombolytic therapy and close proximity to the operating room and cardiopulmonary bypass.

VTE is defined as pathologic formation of a thrombus within the venous system; it includes DVT and pulmonary embolism (PE). Rudolph Virchow first described the term "embolism" in the 19th century,[1] and from this Virchow's triad is derived: vascular endothelial injury, hypercoagulability, and venous stasis. Those three states represent the combination of host factors that predispose to VTE. Embolization of blood clots into the pulmonary arterial circulation often leads to significant cardiopulmonary dysfunction. Diagnosis, treatment, and prevention of PE are of particular interest to critical care practitioners and will be the focus of this chapter.

Incidence

VTE is a common disorder and associated with significant mortality, morbidity, and significant socioeconomic costs. VTE is the third most common cardiovascular disease after myocardial infarction and stroke.[2] The estimated incidence ranges between 1 to 2 per 1,000 person-years. The incidence is expected to increase with the current aging population.[2,3] In the United States alone, the incidence of new or recurrent cases of VTE exceed 900,000 cases.[4] PE, a substantial subset of these cases, is responsible for 200,000 to 300,000 hospital admissions per year.

Risk Factors

VTE has genetic (inherited thrombophilia) and acquired risk factors. Knowledge of the latter is important for prevention measures (Table 1). More than 50% of patients with VTE have combined risk factors, acquired and inherited. It is generally accepted that patients with provoked VTE do not require screening for inherited thrombophilia.

Inherited Thrombophilia

Inherited thrombophilia occurs from increased levels or function of coagulation factors, defects of coagulation factor inhibitors, defects of fibrolysis, hyper homocysteinemia or altered platelet function.

Table 1—*Risk Factors for DVT/PE*

Inherited Thrombophilia
Increased levels or function of coagulation factors
Activated protein C resistance
Factor V Leiden mutation
Prothrombin gene mutation
Elevated factor VII levels
Defects of coagulation factor inhibitors
Antithombin
Protein C
Protein S
Defects in fibrolysis
Hyperhomocysteinemia
Altered platelet function
Acquired risk factors
Advancing age
Prolonged bed rest
Postoperative period
Trauma
Advanced malignancy
Previous DVT
Right-side heart failure
Prolonged travel
Pregnancy
Birth control pills

Acquired Risk Factors

Acquired risk factors are more prevalent than inherited thrombophilia and account for the majority of cases of VTE.[4] Advancing age is the most significant acquired risk factor followed by recent surgery, venous stasis, trauma, advanced malignancy, pregnancy, postpartum state, birth control pills, and previous DVT.

The frequency of VTE increases exponentially between the ages of 20 and 80 years old.[5] Although an age of >40 years has often been used as a break point for age-related increase in VTE, increasing age increases risk beginning with adulthood and continues to increase after the age of 40 years, nearly doubling with each decade. Stein et al. demonstrated a 0.23% incidence of PE with linear relation to age in a tertiary care general hospital. The incidence of women was higher in individuals greater than 50 years old but not in those less than 50 years old.[5]

Abdominal operation requiring general anesthesia >30 min increases the risk for VTE. Orthopedic surgery of the lower extremity has been recognized as one of greatest risk factors. DVT occurs in >50% of patients who do not receive prophylactic therapy when undergoing elective total hip and knee replacement surgery.[6]

Venous stasis is also a major risk factor. Long-distance air travel has been linked to PE. There is an estimated 40% risk of VTE and a 5% incidence of PE in patients with traumatic spinal cord injury and associated paralysis of lower extremities. The period of greatest risk is during the first 2 weeks after the initial injury; death occurs rarely in this patient group after 3 months. Although precise estimates of risk increase in malignancy are difficult to ascertain, advanced cancer is associated with a high risk of VTE. With other factors considered equal, surgery for malignant disease results in a twofold to threefold increase in thromboembolism compared with surgery for nonmalignant conditions. Patients with a history of VTE who undergo major surgery, period of immobility, or who are hospitalized for serious medical illnesses must be aggressively targeted for prophylaxis therapy.[6]

Clinical Findings

The clinical presentations of pulmonary embolism are diverse and often difficult to recognize. Many patients will experience only a subset of the characteristic symptoms, sometimes exhibit atypical symptoms, or may even be asymptomatic.

Signs and Symptoms

The most common symptoms/signs of dyspnea, tachypnea, and tachycardia are seen with myriad other disorders and are often transient. Clinical judgment, however, is a critical first step in the evaluation and suspicion of PE as highlighted in the PIOPED study.[7]

Physical examination is not typically helpful, with the exception of findings of increased right-sided pressure such as increased jugular venous distension, or widely split-second heart sound, murmur of tricuspid regurgitation, or an accentuated pulmonary closure sound. Examination of the lower extremity is unreliable for predicting the presence or absence of DVT. Nevertheless, new findings supportive of acute deep-vein obstruction, particularly unilateral leg swelling in the setting of pulmonary symptoms compatible with thromboembolism, should strengthen the possibility of PE. Fever (temperature of

≥100.0° F) has been demonstrated in 14% of angiographically documented PE with no other cause of fever.[8] Only 2 of 228 had temperatures ≥103.0° F.

ECG and Chest Radiography

ECG and chest radiographs are commonly used in the initial evaluation of patients with chest pain or dyspnea. However, both lack sensitivity and specificity in diagnosing or excluding pulmonary embolism. It is nevertheless important to appreciate ECG findings suggestive of increased right-sided pressure such as new right axis deviation, new right bundle branch block, sinus tachycardia, and atrial fibrillation. Chest radiograph is also insensitive but helpful in excluding other causes of chest pain such as pneumonia or pneumothorax. Typically described findings are as follows: ipsilateral elevation of the diaphragm on the affected side, wedge-shaped pleural based infiltrate (Hampton hump), focal oligemia (Westermark sign), or enlarged right descending pulmonary artery (Palla sign), atelectasis and cardiomegaly. Chest radiograph may be normal up to 25%.

Arterial Blood Gases

Respiratory alkalosis is a common finding in the tachypneic patient with PE. With massive pulmonary embolus, respiratory acidosis may be present because of increased dead space. The partial pressure of oxygen may be decreased, normal, or increased. Normal A-a gradient lacks negative predictive value to exclude PE[9] and is more likely to occur in the presence of previous normal cardiopulmonary status. Nonmassive PE produces hypoxemia by release of bronchoconstrictors, production of atelectasis, and reperfusion injury to the endothelial-epithelial barrier. Massive PE is almost always associated with hypoxemia and frequently with CO_2 retention. Other potential causes of hypoxemia in massive PE include low mixed venous oxygen caused by low cardiac output as well as the potential for opening of a probe-patent foramen ovale caused by high right-sided pressures. A probe-patent foramen ovale is present in a small but significant percentage of the general population. In the presence of very high right-heart pressures, this right-to-left shunt produces hypoxemia unresponsive to oxygen therapy and also places patients at risks for embolic cerebral vascular events.

D-Dimer

Plasmin-derived degradation product is commonly included in the initial evaluation of patients with suspected PE. Although extremely sensitive, D-dimer lacks specificity for PE (30%-75%).[10] Many other conditions (surgery, trauma, inflammation, infection) may elevate plasma D-dimer levels. The strength of D-dimer is its high sensitivity and ability, with a normal test able to rule out VTE in low-risk patients.

B-Type Natriuretic Peptide (BNP)

BNP is released by ventricular myocardial cells in response to wall distension and overload. It is a prognostic and not diagnostic biomarker for PE. When measured within 4 h of admission for PE, elevated BNP levels (>90 pg/mL) have a sensitivity of 85% and a specificity of 75% in predicting PE-related worse clinical outcomes such as need for emergent thrombolysis, mechanical ventilation, need for vasopressor therapy, emergent surgical embolectomy, cardiopulmonary resuscitation, or death.[11]

Troponin

Similar to BNP, elevated troponin levels indicate high incidence of complications while normal troponin levels have a 97% to 100% negative predictive value for in-hospital deaths.[12,13]

Growth Differentiation Factor 15 (GDF-15)

GDF-15 is a distant member of the transforming growth factor β family of cytokines. It is overproduced in cardiomyocytes in response to stress such as pressure overload or ischemia. It also may be elevated because of cancer, diabetes, congestive heart failure, or renal failure. GDF-15 has been shown to be an independent predictor of PE-related complications such as need for vasopressors, mechanical ventilation, cardiopulmonary resuscitation, or death.[14]

Diagnosis

The treatment of PE or DVT is essentially the same; therefore, either diagnosis is sufficient for decision making.

CT Angiography (CTA)

CTA is of significant value in detecting pulmonary emboli. Several practical advantages have made CTA the favored diagnostic study for suspected PE, including availability, rapid interpretation, and evaluation of the chest for alternative diagnoses. The PIOPED II trial was designed to study the ability of the CTA to predict presence or absence of PE.[15] All patients who were evaluated for possible PE underwent a ventilation/perfusion scan and leg ultrasound. CTA also was performed but was not used to make or exclude the diagnosis of PE, and PE was considered present in the presence of a high-probability ventilation/perfusion scan or a positive leg ultrasound. PE was considered absent in the presence of a normal perfusion scan. All other subjects, for research question purpose, received digital subtraction angiography for definitive diagnosis of presence or absence of PE. Sensitivity and specificity were ascertained. Pretest probability of PE was ascertained for all subjects. It is apparent that, like perfusion scanning, CTA loses diagnostic yield in circumstances of extreme discordance (high clinical probability/negative CTA and low clinical probability/positive CTA).

Recently, multidetector scanners have significantly improved the sensitivity as well as the positive and negative predictive value of CTA. Recent studies have found the sensitivity and specificity of CTA to be greater than 95%, and a negative CTA carries a 3-month risk of VTE of 1% to 2%, similar to a negative pulmonary angiogram.[15–17] One sensitivity issue with the CTA diagnosis of PE was the decreased ability to detect vessels beyond the segmental arteries. Current multidetector scanners allow resolution and evaluation of filling defects down to the sixth-order branches of the pulmonary arteries. Considering all advantages mentioned above, CTA is now the predominant imaging modality used in diagnostic algorithms for the evaluation of PE.

Ventilation/Perfusion ($\dot{V}/\dot{Q}$) Lung Scan

Perfusion lung scanning (usually done in combination with ventilation scanning) is typically classified into high probability, intermediate probability, low probability, and normal. Probability of PE increases with size of perfusion defect, number of moderate to large size defects, and perfusion defects that are significantly larger than ventilation defects or present in the absence of ventilation defects. Although ventilation scanning is usually performed in combination with perfusion scanning to quantify ventilation defects, chest radiographs can be used in place of ventilation scanning in patients without chronic pulmonary disease or acute bronchospasm. The Pioped I study[7] supported the following findings: (1) normal lung scans make PE very unlikely; (2) a high-probability scan can usually be used to confer the diagnosis of PE; (3) a minority of patients have high-probability perfusion scans; (4) a clinical impression of low likelihood of PE when combined with a low-probability scan increases the predictive value of the low-probability scan; (5) intermediate-probability scans cannot be used for definitive decision making; (6) the great majority of patients with suspected PE cannot have PE excluded with perfusion scanning; and (7) it is best to call low-probability and intermediate-probability scans "nondiagnostic," with the classification system then becoming high-probability, nondiagnostic, and normal. Nondiagnostic scans require additional testing because they do not allow a decision as the presence or absence of PE. In recent years, CT angiography has replaced the $\dot{V}/\dot{Q}$ scan as the favored diagnostic test. However, $\dot{V}/\dot{Q}$ scan remains an important alternative diagnostic modality to CT scan in patients with pregnancy, contrast allergy, or renal insufficiency or as additive testing when CT angiogram is negative and risk is high. $\dot{V}/\dot{Q}$ may be the modality of choice to evaluate patients for chronic thromboembolic pulmonary hypertension.

Venous Compression Ultrasonography

Compression ultrasound (CUS) combines Doppler venous flow detection with venous imaging and has become the leg imaging

procedure of choice in most medical centers in the United States. The diagnostic utility of CUS is related to imaging of a venous filling defect associated with noncompressible vein in that location. When initial diagnostic tests are inconclusive, ultrasonography of the deep venous system is a useful adjunctive test in the diagnosis and treatment of PE. Practically, the approach to treatment of both DVT and submassive PE is the same, and thus a positive ultrasonogram for DVT obviates the immediate need for further diagnostic studied to demonstrate PE. A negative ultrasonogram is somewhat more challenging and requires consideration of several clinical factors. DVT is detectable by ultrasonography in only 50% of patients with an acute PE. Thus, a negative ultrasonogram does not rule out PE. Conversely, absence of DVT by CUS, in combination with some combination of low-probability perfusion scan or failure to detect PE on helical CT scan and the absence of high clinical suspicion, usually allow withholding treatment.[18,19]

Echocardiography

Transthoracic or transesophageal echocardiography has limited diagnostic value for ruling out PE in the absence of hemodynamic instability. It is very useful for critically ill and unstable patients who are unable to be moved to have conclusive testing where it may diagnose alternative etiologies of hypotension or support PE as the cause of hypotension by demonstrating right ventricular hypokinesis, dysfunction, or dilatation. Rarely, thrombus within the pulmonary arteries or right ventricle can be visualized. However, it carries prognostic value when the diagnosis of PE is known. Several studies have shown that RV dysfunction or dilatation is associated with worse outcomes, including increased mortality.[20–22]

Pulmonary Angiography (PA)

PA remains the "gold standard" for diagnosis of PE; morbidity and mortality rates from PA are low and usually acceptable. Angiography is considered positive when a persistent filling defect or cut-off sign is noted. Risk is increased if angiography is followed by thrombolytic therapy. It is nowadays rarely performed for practical and medical reasons. It is more expensive than CTA and often unavailable in small centers. In addition, studies have shown comparable results between PA and CTA.[19] The death rate from PA in the PIOPED study[7] was 0.5% with a low incidence (0.8%) of major nonfatal complications (respiratory failure, renal failure, or hematoma necessitating transfusion). Major nonfatal complications were four times more likely to occur in ICU patients. Despite early studies that suggested a higher incidence of mortality caused by pulmonary angiography in patients with high pulmonary artery pressures, this was not found to be true in the PIOPED I study.[7] Pulmonary angiography done within 1 week of acute symptoms should reliably detect pulmonary emboli even in the presence of anticoagulation. In patients with angiographically proven PE, perfusion defects persist for at least 7 days without resolution and in the majority for 14 days. This is an important consideration since patients may be referred to a tertiary-care center with uncertain diagnosis of PE, having received therapy for a considerable period of time.

Diagnosis of PE in Pregnancy

The diagnosis of PE in pregnant patients can be challenging. Ventilation/perfusion scan carries a low risk in this specific patient group. In pregnant patients with negative ultrasound findings, identifying the location of perfusion defects on an indeterminate diagnosis perfusion scan and following with selective pulmonary angiography targeting those defects is likely the best approach because it potentially minimizes dye load if PE is present. Warfarin is an absolute contraindication in the first trimester and a relative contraindication in the second and third trimesters. Long-term heparin administration in the pregnant woman is a significant risk for osteoporosis.

Treatment

Early recognition and diagnosis of VTE lead to early initiation of anticoagulation, which remains the cornerstone of VTE treatment. Early anticoagulation is very effective and often life

saving. Several pharmacological changes have been recently added to the treatment of VTE along with significant interventional procedures. A number of new anticoagulants have been introduced, with some providing the ability of outpatient treatment.

Anticoagulation

Anticoagulation is highly effective in patients with VTE. It reduces the incidence of recurrent disease from 25% to 3% during the first 6 to 12 months of therapy.[23] Blocking further clotting, stabilizing the clot, and allowing the endogenous thrombolytic system to break down the clot are the main pathophysiological benefits of anticoagulation.

Unfractionated Heparin (UFH)

For many years, the initiation of UFH in a hospital setting along with oral vitamin K antagonist has been the standard of care. UFH therapy is continued for 4 to 5 days. The activated partial thromboplastin time (aPTT) should be maintained at 1.5 to 2.0 times control. Although subtherapeutic, aPTT is strongly correlated with thromboembolic recurrence, a supratherapeutic aPTT does not appear to correlate with important bleeding complications.[24] Based on this information, targeting a PTT of 2.0 times normal rather than 1.5 times normal may be ideal. In patients without contraindication for anticoagulation, UFH should be started as soon as VTE is considered. A loading dose of 5,000 to 10,000 U of heparin is indicated for PE. It is important to remember that warfarin is contraindicated in pregnancy, and anticoagulation should be maintained with heparin. In addition, heparin dosage requirements are increased in pregnancy. Decreases in platelet count or heparin-induced thrombocytopenia (HIT) may occur with heparin therapy. A nonimmunologically mediated decrease in heparin (HIT-1) may occur and is usually without dramatic drops in platelet count. It occurs early in treatment and does not usually require discontinuation of heparin. A more dramatic and clinically significant decrease in platelet count (HIT-2) may rarely occur with heparin therapy (days 3 to 4 or earlier with previous heparin exposure), is immunologically mediated, and does require immediate discontinuation of heparin. Arterial thrombosis (white clot) and worsening venous thrombosis may be part of this more severe syndrome. When the platelet count drops more than 50% and HIT-2 is suspected, heparin therapy should be stopped. The addition of a direct thrombin inhibitor to prevent or treat heparin-induced thrombosis is indicated. There is also a chance for cross-reactivity with low-molecular-weight heparin (LMWH), and that is not advisable as a therapeutic option. With HIT-2, warfarin should not be instituted for 2 days because of the possibility of increased clot formation.

LMWH

LMWH was first studied and approved for the prevention of DVT, then was subsequently demonstrated to have similar mortality and morbidity outcomes to UFH in the treatment of VTE.[25] Several advantages make LMWH preferable over UFH, including more predictable and reliable anticoagulation, increased patient satisfaction, ability to self-administer, possibility of home-based treatment, decreased administration costs, and no need for monitoring anticoagulation. Thrombocytopenia is uncommon enough that no more than one platelet count is recommended during a treatment period of 5 to 7 days. If therapy is prolonged more than 7 days, subsequent platelet count is recommended. A disadvantage in the critically ill patient is the longer half-life if bleeding occurs if urgent procedures are required. LMWH does not prolong aPTT. Antifactor Xa levels reflect LMWH activity but are not routinely necessary in most treated patients. LMWH dose adjustment is required in patients with renal insufficiency (creatinine clearance of 30 mL/min) and in obese (>150 kg) or thin (<50 kg) patients. Antifactor Xa levels may be needed to optimize dosing if LMWH is used in these groups. When bleeding occurs after recent administration of LMWH, protamine is may be of utility for reversal, but the degree of effectiveness is difficult to judge.

Factor Xa Inhibitors

Factor Xa is a common factor for both intrinsic and extrinsic coagulation pathways, making it an

ideal target for anticoagulation. The first available Factor Xa inhibitor was fondaparinux, administered subcutaneously and once daily with a long half-life of 17 h. It has been shown to be equally efficacious to UFH in the initial treatment of pulmonary embolism.[26] Idrabiotaparinux is another agent that is currently under evaluation and has an even longer half-life of 80 h. If approved, it will be administered subcutaneously once a week for the treatment of VTE. Recently, a new oral factor Xa (rivaroxaban) has been introduced. Dose-finding studies in patients undergoing orthopedic procedures suggested that an oral dose of 10 mg/day was suitable for prevention of VTE. Also, a recent study showed "noninferiority" in the treatment of VTE compared with LMWH.[27]

Direct Thrombin Inhibitors

Several direct thrombin inhibitors (DTIs) have been approved and are available for the treatment of VTE, including hirudin, bivalrudin, dabigatran, and argatroban. The main indications for use of DTIs are contraindication to heparin or HIT2, mainly because their lack of interaction with platelets and their inability to potentiate heparin-induced thrombocytopenia. Their main drawbacks are unpredictable anticoagulation, need for frequent monitoring, potential drug interactions, and continuous infusion.

Thrombolytic Therapy

Several clinical trials using thrombolytic therapy have showed improved hemodynamic and radiologic findings with faster clot resolution but were unable to show improved mortality.

Streptokinase, urokinase, and recombinant plasminogen activator (rTPA) are all thrombolytic agents studied in the treatment of PE. rTPA is almost exclusively use in the United States. FDA-approved dosing is 100 mg over 2 h; more rapid administration may be appropriate in imminent death such as 40 mg over minutes followed by 60 mg over the remainder of the 2-h period.

Traditional absolute contraindications are history of hemorrhagic stroke, active internal bleeding, active intracranial neoplasm, recent acute cerebrovascular event (2 months), or recent cerebrovascular procedure (2 months). One report noted, however, the successful use of urokinase therapy of PE in nine neurosurgical patients (mean, 19 days after surgery) with no intracranial hemorrhage. Intracranial bleeding, a primary concern, occurs in about 3% of patients with massive PE who are treated with thrombolytic therapy.[28] Retroperitoneal hemorrhage can also be life threatening and most frequently occurs as a sequela of previous femoral vein access for pulmonary angiography or other associated femoral lines. Relative contraindications include any history of cerebrovascular event; a <10-day postpartum period; recent organ biopsy or puncture of a noncompressible vessel; recent serious internal trauma; surgery within the last 7 days; uncontrolled coagulation defects; pregnancy; cardiopulmonary resuscitation with rib fracture; thoracentesis; paracentesis; lumbar puncture; and any other conditions that place the patient at risk for bleeding. In general, angiographic or CTA documentation of PE should be obtained before thrombolytic therapy because of the potential serious complications. Occasionally, thrombolytic therapy may be considered in hemodynamically unstable patients at high risk for PE who cannot be moved to receive additional testing. Bedside echocardiography, if immediately available, offers support for diagnosis in this circumstance since right ventricular dilation must be present if the shock is caused by PE. When angiography, CTA, or perfusion scanning are possible, the patient is at risk for death, and the clinical scenario is strongly suggestive, echocardiography supporting PE should be adequate for initiating therapy. Heparin should not be administered during thrombolysis, but heparin therapy should be resumed without a bolus when the aPTT is 1.5 to 2 times control. No coagulation tests are necessary during thrombolytic infusion. If bleeding occurs during thrombolytic therapy, drug should be discontinued (short half-life). If bleeding should persist, cryoprecipitate or fresh frozen plasma infusion should be considered. The use of thrombolytic therapy has been advocated in the presence of large clot burden or echocardiographic evidence of right ventricular dysfunction. The use of thrombolytic therapy in free-floating RV thrombi also remains controversial.

The American College of Chest Physicians consensus statement on thrombolytic agents continues to recommend that decisions be highly individualized for that patient, and clinicians should have latitude in using or not using. They are, however, recommended in general for hemodynamic instability and massive ileofemoral thrombosis.[29]

Pulmonary Embolectomy

Embolectomy can be performed using catheters or surgically. It is usually indicated in patients with massive pulmonary embolism and shock who have failed thrombolytic therapy or have absolute contraindications. Pulmonary embolectomy is usually performed in selected centers depending on the operators' expertise and availability. It carries a high reported mortality (up to 30%) considering that eligible patients usually have significant comorbidities (recent surgery, bleeding diathesis, recent cerebrovascular events).[30]

Inferior Vena Cava Filters (IVC Filters)

An IVC filter serves as a trap in the inferior vena cava. While allowing the passage of flowing blood, it prevents large blood clots traveling from the pelvis or the lower extremities to embolize into the pulmonary circulation. Traditional indications for IVC filter placement include contraindication to anticoagulation, onset of bleeding with anticoagulation, and failure of anticoagulation to prevent recurrent thromboembolic events. Other indications for filter placement include hemodynamic instability in patients with contraindications to thrombolytic therapy and patients with HIT as bridge to therapeutic warfarin therapy. The empiric use of IVC filter in patients with a large pulmonary clot burden or borderline cardiopulmonary reserve is more controversial. IVC filter placement may also be considered in patients with high risk for DVT and contraindications for anticoagulation prophylaxis, such as trauma patients with lower extremity or pelvic fractures, or patients with severe neurologic deficits or severe brain trauma. The decision to anticoagulate patients who have had an IVC filter placed remains controversial, but the use of anticoagulation may prevent further clot formation and increase the patency rate of the filter overtime. In patients with a transient increased risk of VTE, retrievable filters are available. They theoretically protect against PE in the short term while avoiding the long-term complications of IVC filters. These retrievable filters are usually removed 2 to 6 weeks after deployment. Complications of filter placement include vessel injury during deployment, subsequent venous thrombosis at the insertion site, filter migration and embolization into the heart or the pulmonary arteries, filter erosion through the IVC, and IVC obstruction. A decrease of recurrent PE has been documented, but a decrease in mortality has not been conclusively demonstrated.[31]

Hemodynamics of Massive PE

Hemodynamic instability and shock are the most important factors contributing to PE-related death. The hemodynamic response to acute occlusion of the pulmonary vessels depends on several factors that increase pulmonary vascular resistance (PVR) and pressure overload, including clot size and the degree to which the clot is centrally positioned. Hypoxemia further elevates PVR, and pulmonary artery (PA) pressures as do mediators that include serotonin, platelet-activating factor, thrombin, vasoactive peptides (C3, C5a), and histamine. The increase in PVR translates into an elevated PA pressure as long as cardiac output is sustained. As pressure loading worsens, RV stroke volume may drop. Initial compensation by catecholamine-mediated tachycardia may delay the drop in cardiac output. Right ventricular dilation maintains cardiac output by preserving stroke volume, even if the ejection fraction falls. However, in the most severe cases, a combination of RV pressure overload, dilation, and ischemia eventually leads to a drop in stroke volume and cardiac output. Increased RV size increases wall stress and tension. Wall stress reduces RV oxygen uptake and, combined with increased oxygen demand, sets the stage for ischemia. Perfusion of the RV depends on the gradient between mean arterial pressure and subendocardial pressure in the RV. Elevated RV end-diastolic pressures impair subendocardial perfusion and oxygen

supply. The loss of subendocardial perfusion, increased RV wall tension, and increased oxygen demand result in RV ischemia and infarction. Studies of hemodynamic profiles in patients with acute PE have demonstrated mean pulmonary artery pressures >40 mm Hg only in patients with pre-existing cardiopulmonary disease, suggesting that the normal right ventricle is incapable of generating mean pulmonary artery pressures >40 mm Hg in the setting of acute pulmonary vascular bed obstruction. Based on the above, volume therapy is typically ineffective and may be deleterious, with resultant overdistension of the right ventricle. Therapy should be targeted toward reducing RV afterload by reducing pulmonary clot burden, avoiding volume-induced RV overdistension (right atrial pressure >20 mm Hg), and maintaining adequate aortic diastolic pressure (upstream filling pressure for the left and right ventricles) Vasopressors may be beneficial by increasing aortic diastolic pressure when it is critically low. Combination inotrope/vasoconstrictor therapy such as dopamine or norepinephrine plus dobutamine is recommended in the hypotensive patient. Vasoconstriction of systemic vascular bed with selective vasodilation of pulmonary vascular be would be ideal. Inhaled nitric oxide has anecdotally been demonstrated to improve thermodynamics in PE by this mechanism. Surgical thrombectomy may be considered in situations of severe hemodynamic instability with a contraindication to thrombolytic therapy and close proximity to the operating room. Bypass capability is necessary and the clinical scenario should indicate a certain or almost certain clinical diagnosis of massive PE. Interventional radiology use of mechanical fragmentation may be an alternative to surgery in patients with severe hemodynamic instability and contraindication to thrombolytic therapy.

Prevention of PE

Despite significant advances in the prevention and treatment of VTE, pulmonary embolism remains the most common preventable cause of hospital death.[32] It is in fact responsible for 150,000 to 200,000 deaths per year in the United States.[33] When death occurs, usually it is within 30 min of the event, which is not long enough for most forms of treatment to be effective.[34] Without prophylaxis, the frequency of fatal PE is approximately 7% for emergency hip surgery, 2% after elective hip surgery, and 1% after elective surgery. Autopsy findings suggest that PE causes 5% of deaths in patients receiving mechanical ventilation.[34] The great majority of patients in the ICU should receive heparin prophylaxis for thromboembolic disease. The dose for general surgical patients or in medical patients is typically 5,000 U twice or three times daily of unfractionated heparin subcutaneously or LMWH daily. Low-dose LMWH is the heparin of choice in knee surgery patients, hip surgery patients, and CNS trauma patients. It also offers the advantage of one injection vs three in all patients.

Hemorrhagic side effects of low-dose heparin are rare (<2%) in patients without hemorrhagic diathesis. High-risk patients or those who have contraindications for heparin should receive intermittent pneumatic venous compression (IPVC) additively or as a replacement. IPVC is contraindicated in the face of arterial compromise of extremity. Clinically significant DVT develops in many trauma cases. Risk factors include advanced age, prolonged immobilization, severe head trauma, paralysis, pelvic and lower extremity fractures, direct venous trauma, shock, and multiple transfusions. Low-dose heparin and/or IPVC may not be effective in the highest risk patient. In trauma patients at high risk for bleeding and those at high risk for pulmonary emboli, some investigators have recommended prophylactic IVC filter placement, especially if leg injury prevents application of pneumatic compression devices. Similar rationale has been offered when PE is diagnosed in advanced malignancy. Neither of these uses has been validated. Despite the availability of numerous prophylactic agents and numerous guidelines for the prevention of VTE, there is strong evidence that appropriate prophylaxis is not offered to a large number of patients, particularly those hospitalized with medical conditions.[35]

Summary

VTE is common and often associated with significant morbidity and mortality. Factors that

promote the development of DVT also increase the risk of PE. Clinical presentation is often nonspecific, hindering fast and accurate diagnosis. PE is associated with high mortality rate without treatment; however, rapid recognition and effective treatment significantly reduce morbidity and mortality. CT angiography has become the primary diagnostic test. Predictive capability of negative CT findings in high-risk patients is enhanced by additional studies (normal D-dimer level, negative leg ultrasound, and low-probability perfusion scan). Thromboembolic therapy is primarily recommended in patients with hemodynamic instability and no contraindications.

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Notes

Chapter 7. Acute Coronary Syndromes

Phillip A. Horwitz, MD; and Hjalti Gudmundsson, MD

Objectives:

- Understand the common pathophysiology in acute coronary syndrome subtypes.
- Understand the role of early risk stratification and choice of management strategy in non-ST-elevation acute coronary syndromes.
- Understand the indications and options for emergent reperfusion in ST-elevation myocardial infarction.
- Review the mechanical complications of myocardial infarction.
- Review the pharmacologic and lifestyle modifications to improve the long-term prognosis in acute coronary syndrome patients.

Key words: acute coronary syndrome; anticoagulation; cardiogenic shock; coronary artery disease; coronary intervention; fibrinolysis; myocardial infarction; unstable angina

Synopsis:

Acute coronary syndrome (ACS) represents a spectrum of acute cardiac ischemic syndromes that include unstable angina (UA), non-ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI). They share the common pathophysiology of "vulnerable" atherosclerotic plaque rupture and subsequent thrombus formation. The management of STEMI centers on emergent coronary artery reperfusion with either fibrinolytic therapy or primary percutaneous coronary intervention. Anticoagulation strategies and risk stratification followed by appropriate use of coronary revascularization are the focus of management in UA and NSTEMI. All ACS patients need to have preventative treatments and lifestyle modifications instituted to prevent future adverse events.

Acute coronary syndrome (ACS) represents a spectrum of acute myocardial ischemic syndromes that include unstable angina (UA), non-ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI). All of these clinical syndromes share a common pathophysiology related to the rupture of unstable coronary atherosclerotic plaques. UA and NSTEMI are differentiated primarily by their severity; in NSTEMI, thrombus formation and ischemia is severe and prolonged enough to cause myocardial cell necrosis. Essentially all STEMI syndromes are characterized by myocardial cell death and cardiac biomarker release.

Approximately 1.4 million Americans are hospitalized for ACS yearly; 800,000 of those patients will have an acute myocardial infarction (MI), and the remainder will have a troponin-negative syndrome. Costs associated with ACS hospitalization in the United States have been estimated at 150 billion dollars annually.[1]

Pathophysiology of ACS

Coronary risk factors such as smoking, hypertension, dyslipidemia, and diabetes influence the risk of atherosclerotic plaque formation. These risk factors result in endothelial damage. Circulating inflammatory cells bind to areas of damaged endothelium and, along with low density lipoprotein particles, migrate into the vascular intima. Macrophages take up oxidized low density lipoprotein, initiate an inflammatory response, and become foam cells that make up an initial vascular "fatty streak." These macrophages, in combination with activated smooth muscle cells and other inflammatory cells, lead to development of the fibrous cap that characterizes the mature atherosclerotic plaque.

The stability of atherosclerotic plaques is variable. The risk of developing ACS appears more related to composition of individual plaques than to the degree of coronary artery stenosis. ACS is caused by thrombus formation at the site of a ruptured culprit atherosclerotic plaque. Characteristics of these so-called "vulnerable plaques" consist of a large lipid core (occupying >50% of plaque volume), inflammatory infiltrate with increased density of macrophages and T lymphocytes, low density of smooth muscle cells (thin fibrous cap), increased content of tissue factor, and a cap with a disorganized collagen structure.[2] Elevated levels of C-reactive protein have been associated with the presence of plaques at increased risk of rupture.[3]

Table 1—*Signs and Symptoms Suggesting the Diagnosis of Acute Coronary Syndrome*

	High Likelihood of ACS	Intermediate Likelihood of ACS	Low Likelihood of ACS
History	Syndrome similar to previously documented angina Known history of CAD	Chest pain/arm pain Age ≥70 Diabetes Male	Atypical symptoms Cocaine use
Physical exam	CHF Diaphoresis Hypotension Transient MR murmur	Peripheral vascular disease	Pain reproducible by palpation
ECG	New ST-segment deviation (≥1 mm) T-wave inversion in multiple precordial leads	Q waves ST depression 0.5-1.0 mm T-wave inversion >1 mm	Normal
Cardiac biomarkers	Elevated	Normal	Normal

ACS = acute coronary syndrome; CAD = coronary artery disease; CHF = congestive heart failure; MR = mitral regurgitation. Adapted with permission from Braunwald et al.[4]

Thrombin and platelet activation/aggregation play a central role in the pathogenesis of ACS. Rupture of a plaque exposes thrombogenic contents, such as tissue factor, which activate the extrinsic clotting cascade. This leads to thrombin generation and fibrin deposition. Collagen and von Willebrand factor lead to platelet activation, aggregation, and crosslinking. Ultimately, coronary artery thrombus is formed. This can progress to occlusion and transmural infarction or can limit flow and embolize, causing ischemic symptoms and more limited cell necrosis.

Clinical Findings in ACS

History, physical exam, assessment of cardiac biomarkers, and examination of the ECG are used to establish the diagnosis, severity, and prognosis of patients presenting with ACS. Table 1 summarizes clinical signs, symptoms, and initial testing used to determine the likelihood that an ACS is the cause of a patient's acute syndrome.[4]

Signs and Symptoms

Patients with ACS will have signs or symptoms of myocardial ischemia either at rest or with minimal activity. Symptoms can include substernal chest pain or pressure that radiates to the arm or jaw. Chest pain syndromes are frequently accompanied by shortness of breath, diaphoresis, or nausea. Some patients may only present with "atypical" symptoms in the absence of a chest pain syndrome. These findings are similar to those of chronic angina, but they can occur either at rest or with minimal activity or can increase in frequency or severity (crescendo angina). A significant proportion of ACS patients will have no symptoms. Up to one-third of patients with MI will be asymptomatic; so-called "silent MIs" are more likely to occur in the elderly, women, and in patients with diabetes.

Patients with ACS can present with signs and symptoms of left ventricular failure due to ischemia, hypotension, a new murmur of mitral regurgitation, pulmonary edema, or an S3 gallop. The presence of these signs may be markers for higher-risk patient subsets.

Cardiac Markers

Markers of myocardial cell necrosis, such as myoglobin, CK, CK-MB, and troponin I and T, are used to identify acute MI. Most institutions rely on the measurement of cardiac-specific troponins (I or T), given their high sensitivity and specificity for myocardial cell necrosis. Because troponin levels usually do not rise until 6 h after symptom onset, these biomarkers might be normal early in the course of both ST-elevation and non-ST-elevation syndromes. The long half-life of troponins limits their utility in diagnosing reinfarction, as they remain elevated in the circulation for 6 to 14 days postinfarct.

ECG

Patients presenting with a suspect ACS should have an ECG performed within 10 min of arrival. Diagnostic ST-segment elevation on ECG has a high specificity for STEMI and is used to guide decisions about emergent reperfusion therapies. The presence of ST-segment depression or diffuse T-wave inversion can identify higher-risk subsets of patients presenting with UA/NSTEMI. Dynamic ST-segment changes are utilized in risk algorithms to guide initial therapies, as discussed below.

Early Hospital Care and Treatment Pathways

All patients with a suspected ACS should be admitted to an acute care hospital. Patients should be kept on bed rest and have continuous telemetry monitoring. Pulse oximetry should be utilized to ensure adequate arterial oxygen saturations, and supplemental oxygen should be used to correct any hypoxemia.

History, exam, and ECG findings are used to triage patients presenting with possible ACS syndromes to potential diagnostic categories:

1. Noncardiac/nonischemic syndromes;
2. Stable coronary ischemic syndromes;
3. UA/NSTEMI; and
4. STEMI.

Patients without coronary ischemia should be managed according to their suspected diagnosis. Stable angina patients can often be managed on an outpatient basis with optimization of anti-ischemic regimens and noninvasive evaluations.

True ACS patients (UA/NSTEMI or STEMI) are managed according to their specific diagnostic and treatment guidelines, as discussed in the following sections.

UA and NSTEMI

Risk Stratification in UA/NSTEMI

Treatment goals for non-ST-elevation ACS (NSTE-ACS) include rapid relief of ischemic symptoms and prevention of recurrent coronary events. Symptom relief includes treatment with anti-ischemic therapies. Early risk stratification is critical for patients presenting with UA or NSTEMI and helps guide the choice of anticoagulant therapies as well as treatment pathways.

Patients can be stratified into "high-risk" and "low-risk" subsets by their clinical characteristics, cardiac enzyme profiles, and ECG. Patients with an increased risk of adverse outcomes include those with older age, decompensated congestive heart failure (CHF), diabetes, malignant arrhythmias, and peripheral vascular disease. ECG is a strong predictor of risk with NSTE-ACS. The presence of dynamic ECG changes, most specifically ST-segment changes, is a strong predictor of adverse outcomes. Transient ST-segment elevation, or, more commonly, ST-segment depression on ECG, portends a worse prognosis. T-wave changes tend to have less specificity for recurrent events. Cardiac troponin elevation is highly predictive of prognosis for patients presenting with ACS. Troponin elevations identify patient subsets that may benefit from more aggressive/invasive treatment strategies and more aggressive antithrombotic therapies such as glycoprotein IIb/IIIa receptor antagonists.

A number of scoring systems have been developed from large trials with the purpose of risk stratifying patients presenting with ACS. The Thrombolysis In Myocardial Infarction (TIMI) risk score is one such algorithm that was developed and validated to guide prognostication and treatment strategy in patients with NSTE-ACS (Table 2). The TIMI risk score uses clinical variables to determine a 0 to 7 point score that is predictive of a 14-day combination endpoint of death, recurrent MI, and urgent

Table 2—*TIMI Risk Score for NSTE-ACS*

Patient Characteristic
Age >65 y
≥3 CAD risk factors[a]
Previous coronary stenosis ≥50%
ST-segment deviation
Severe symptoms (eg, ≥2 anginal episodes in the past 24 h)
Aspirin use within 1 wk
Elevated cardiac biomarkers

NSTE-ACS = non-ST-elevation acute coronary syndrome.
[a] Includes family history, dyslipidemia, diabetes, active smoking.

Table 3—*TIMI Risk Score for Unstable Angina/Non-ST Elevation MI: All-Cause Mortality, MI, and Severe Ischemia at 14 Days*

TIMI Score	Rate Composite Endpoint, %
0/1	4.7
2	8.3
3	13.2
4	19.9
5	26.2
6/7	40.9

revascularization (Table 3).[5] Stratifying UA/NSTEMI patients into high-risk and low-risk subsets with this algorithm aids in directing subsequent inpatient management.

Early Invasive vs Conservative Management Strategy

For patients presenting with UA/NSTEMI, an initial treatment strategy needs to be determined. Two major treatment options are employed in the management of these patients:

An early invasive strategy includes coronary angiography within the first 4 to 48 h after presentation with a UA/NSTEMI. Angiography is performed with the intent to revascularize a culprit coronary stenosis with either percutaneous coronary intervention (PCI) or coronary artery bypass surgery dependent on coronary artery anatomy and individual patient characteristics.

A conservative management strategy employs an initial period of medical stabilization with anticoagulation and anti-ischemic therapies. This is typically followed by risk stratification with noninvasive cardiac stress testing. Invasive coronary angiography is deferred unless the patient has recurrent ischemic symptoms or they have high-risk findings on noninvasive testing.

Multiple randomized trials have been performed to determine the optimal treatment strategy for patients with UA/NSTEMI. The Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS) TIMI-18 trial randomized 2,220 high-risk UA/NSTEMI subjects treated with aspirin, heparin, and a glycoprotein IIb/IIIa inhibitor to either an early invasive (<48 h after presentation) or a conservative management strategy. The rate of the composite endpoint of death, MI, and rehospitalization for ACS was reduced in the early invasive arm (15.9% vs 19.4%; $P = .025$) at 6 months.[6] In a meta-analysis of seven trials of management strategy in UA/NSTEMI, an early invasive strategy was shown to have a 25% reduction in mortality compared with conservative treatment in high-risk ACS patients.[7] Data from other trials of early vs delayed intervention appear to favor performing coronary intervention in the first 12 to 24 h after presentation with "high-risk" UA/NSTEMI, particularly in those who have positive cardiac biomarkers.[8] All studies showing a benefit of an early invasive strategy do so in the setting of intensive antithrombotic therapy.

These findings guide the American Heart Association/American College of Cardiology (AHA/ACC) guidelines in choosing management strategy in these patients. Table 4 summarizes recommendations for treatment strategy decisions in UA/NSTEMI.[9]

Early Hospital Care in UA/NSTEMI

Initial management of patients presenting with suspected NSTE-ACS includes observation in a facility with cardiac monitoring (eg, chest pain unit, telemetry unit) where serial cardiac biomarkers and 12-lead ECGs can be performed.

Table 4—*Selection of Initial Treatment Strategy in UA/NSTEMI*

Invasive Strategy	Conservative Strategy
Recurrent or refractory ischemia	Low TIMI risk score (≤3)
Positive cardiac markers	Patient preference
New ST-segment deviation	Physician preference
Hemodynamic instability	Poor revascularization candidate
Acute CHF	Patients with extensive comorbidities
Ischemic mitral regurgitation	
Recent PCI (within 6 mo)	
Prior CABG	
Reduced left ventricular function (<40%)	
Elevated TIMI risk score (≥4)	

CHF = congestive heart failure; CABG = coronary artery bypass graft.

Anti-ischemic and analgesic therapies are instituted. Antithrombotic treatment should be initiated and include aspirin and antithrombin therapy. Early risk stratification then guides the initial management strategy and additional antithrombotic treatment.

Anti-ischemic/Analgesic Treatment

Nitroglycerin: Nitrates are first-line therapies for patients presenting with symptomatic ACS and reduce ischemia by decreasing ventricular preload through venodilation. Sublingual nitroglycerin (0.4 mg) is recommended for patients with ongoing chest pain in the absence of contraindications. IV nitroglycerin can be considered for patients with ongoing or recurrent symptoms after multiple doses of sublingual nitrates. Initial dose is 10 mcg/min and can be uptitrated to a maximum of 200 mcg/min. Therapeutic goals include resolution of chest pain or a decrease in arterial pressure.

β-Blockers: AHA/ACC guidelines recommend that oral β-blocker therapy be instituted in the first 24 h for patients who do not have contraindications for use.[9] These agents reduce myocardial oxygen demands by direct effects on heart rate and BP. Oral medication is adequate in most patients, but IV dosing such as IV metoprolol in 5-mg doses can achieve more rapid effects. β-Blockade should be avoided or used cautiously in UA/NSTEMI patients with signs of heart failure, low cardiac output, bradycardia, and active asthma. β-Blockers may also be contraindicated in patients at increased risk of cardiogenic shock. Oral β-blocker can be uptitrated as heart rate and BP permit.

Calcium Channel Blockers: These agents are not clearly beneficial in the treatment of ACS. Their use should be reserved for patients who cannot be safely treated with nitrates or β-blockade. Calcium blockers such as verapamil and diltiazem have more anti-ischemic effects than the dihydropyridine agents.

Morphine: Morphine acts as an analgesic and anxiolytic as well as having ventricular preload reducing actions. Morphine sulphate (2 to 4 mg IV) can be administered to ACS patients who have continued ischemic symptoms despite treatment with nitrates.

Angiotensin-Converting Enzyme (ACE) Inhibitors: Treatment guidelines recommend treatment with an oral ACE inhibitor (or an angiotensin II receptor blocker in the ACE inhibitor intolerant) for those patients with signs of CHF or depressed ejection fraction ($\leq$40%). Therapy should be instituted in first 24 h in patients without contraindications such as relative hypotension. IV ACE inhibitors should not be used early in ACS patients due to an increased risk of precipitating hypotension.[9]

Antithrombotic Therapy in UA/NSTEMI

The pathophysiology of ACS centers on culprit plaque rupture and subsequent coronary thrombus formation. Antithrombotic therapy is the mainstay of treatment in patients who present with UA/NSTEMI. Antithrombotic treatment has two components: (1) anticoagulant therapy directed against components of the coagulation cascade, and (2) antiplatelet therapy designed to limit platelet activation and aggregation. AHA/ACC guidelines for use of antithrombotic therapy are summarized in Figure 1.[9]

Anticoagulant Therapy

Guidelines recommend institution of anticoagulant therapy in all patients presenting with ACS. IV heparin, both the unfractionated and low-molecular-weight formulation, is the most widely used agent. Two other agents are approved for use in ACS, the direct thrombin inhibitor bivalirudin and the factor X inhibitor fondaparinux.

Heparin: Heparins, in conjunction with antithrombin III, bind and inactivate thrombin, leading to its anticoagulant effects. Trials of unfractionated heparin have demonstrated reduced rates of death and MI in ACS patients. Limitations of unfractionated heparin include unpredictable dosing patterns, need for frequent monitoring, and the risk of developing heparin-induced thrombocytopenia.

Low-molecular-weight heparins (LMWH) inhibit both factor Xa and thrombin. They have more predictable anticoagulant effects and do not require anticoagulant monitoring. The risk of developing heparin-induced thrombocytopenia

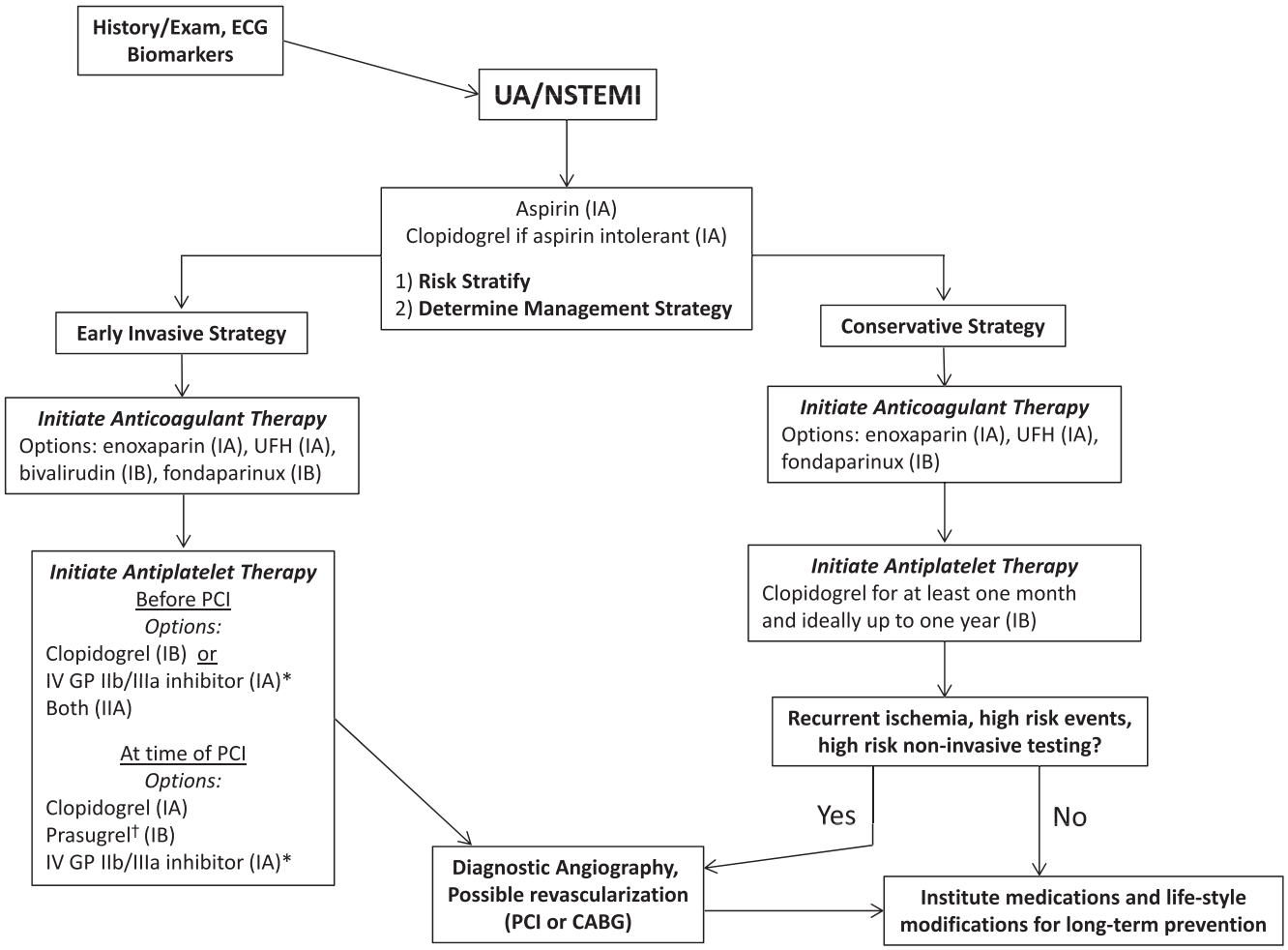

Figure 1. Summary of AHA/ACC guidelines for the treatment of UA/NSTEMI emphasizing antithrombotic strategies (recommendation class, level of evidence).
*Tirofiban or eptifibatide
†Prasugrel not recommended in patients ≤60 kg, history of TIA or stroke, >75 years of age, propensity to bleed.

is reduced but not eliminated with the use of LMWH. Clinical trials of LMWH compared with unfractionated heparin have shown mixed results. In the Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial, enoxaparin was not superior to unfractionated heparin in preventing ischemic events in high-risk ACS patients.[10] Some studies have suggested the superiority of LMWH in patients managed conservatively. AHA/ACC guidelines state that enoxaparin is preferable to unfractionated heparin for UA/NSTEMI being managed with a conservative strategy unless coronary artery bypass graft surgery within 24 h is planned.

Direct Thrombin Inhibitors: Direct thrombin inhibitors bind directly to thrombin in the absence of a cofactor (like antithrombin III) and have the advantage of being able to inhibit clot bound thrombin. They do not cause heparin-induced thrombocytopenia and can be used in heparin-allergic patients. The Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial tested the direct thrombin inhibitor bivalirudin against the combination of heparin plus a glycoprotein (GP) IIb/IIIa inhibitor for moderate- to high-risk ACS patients being managed with an early invasive strategy. Bivalirudin alone was shown to have a non-inferior effect on ischemic endpoints and had reduced rates of major bleeding (3.0% vs 5.7%, $P < .001$) compared with the combination of heparin and GP IIb/IIa inhibitor.[11]

Guidelines have given bivalirudin a class I recommendation for use in UA/NSTEMI patients being managed with an early invasive

strategy.[9] A second direct thrombin inhibitor, argatroban, is approved for management of ACS patients with a history of heparin-induced thrombocytopenia.

Factor X Inhibitors: Fondaparinux is a synthetic pentasaccharide that binds to antithrombin and inhibits factor Xa. It has predictable bioavailability and anticoagulant effects that obviate the need for anticoagulant monitoring. In the Organization to Assess Strategies for Ischemic Syndromes (OASIS-5) trial of fondaparinux vs enoxaparin in ACS patients, fondaparinux was shown to have similar ischemic endpoint outcomes with a reduction in major bleeding events.[12] However, an unexpected complication of increased catheter clot formation during PCI was noted, which has led to limited use of this agent. Despite this issue, the guidelines have incorporated fondaparinux as an option for anticoagulant treatment of ACS patients managed with both conservative and invasive strategies.

Antiplatelet Therapy

Acetylsalicylic Acid (Aspirin): Aspirin is an irreversible cyclooxygenase inhibitor leading to a decreased production of thromboxane. Aspirin treatment reduces thromboxane mediated platelet activation and aggregation. Aspirin should be administered to all patients with ACS as soon as possible after hospital presentation. At least 162 mg is required in the aspirin-naïve patient to achieve rapid and maximal antiplatelet effects. Typical initial dosing would be 325 mg of aspirin followed by a daily 81-mg maintenance dose continued indefinitely. Treatment with clopidogrel is indicated in the aspirin-allergic patient.

Clopidogrel: The thienopyridine agent, clopidogrel, is an irreversible inhibitor of the platelet $P2Y_{12}$ adenosine diphosphate (ADP) receptor. This receptor is central to mechanisms of platelet activation and aggregation.

The CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial randomized 12,500 aspirin-treated UA/NSTEMI patients to either clopidogrel (300-mg load/75-mg daily dose) or placebo. CURE demonstrated a 20% reduction in the primary endpoint of cardiovascular death, nonfatal MI, or stroke. This benefit was seen in patients treated medically, with coronary intervention and with CABG.[13] Other trials and analyses have demonstrated a 30% to 40% decrease in major adverse cardiovascular events in patients pretreated with clopidogrel prior to PCI.[14,15]

Clopidogrel has a prolonged half-life after discontinuation. In patients undergoing major surgery (including coronary artery bypass graft), clopidogrel and other ADP receptor antagonists should be stopped for 5 to 7 days prior to the procedure if possible. Based on the CURE trial results, CABG patients should have their clopidogrel restarted postoperatively and continued for 30 days to 1 year.

Other ADP Receptor Antagonists: Prasugrel is a potent thienopyridine ADP receptor antagonist with more rapid and higher levels of platelet inhibition than clopidogrel. The TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet inhibitioN with prasugrel (TRITON) TIMI-38 studied 13,600 moderate- to high-risk UA/NSTEMI patients scheduled for PCI. Patients were randomized to prasugrel (60-mg load, 10 mg daily) or clopidogrel. A 2.2% absolute risk reduction in the primary endpoint of cardiovascular death, nonfatal MI, or stroke was seen in the prasugrel group ($P < .001$). There was an increase in life-threatening bleeding (1.4% vs 0.9%) seen with prasugrel.[16] AHA/ACC guidelines have included prasugrel as an alternative to clopidogrel in this patient population.[8] Prasugrel is contraindicated in patients with an increased risk of bleeding including: age $\geq$75 years, body weight $\leq$60 kg, and history of stroke or transient ischemic attacks. In addition, prasugrel is a reasonable choice for patients that have developed thrombotic complications such as stent thrombosis despite clopidogrel therapy.

Ticagrelor is an oral, reversible, nonthienopyridine antagonist of the $P2Y_{12}$ receptor and provides more rapid and predictable levels of antiplatelet activity than clopidogrel. In a large randomized trial of ACS patients, subjects on ticagrelor had a 16% reduction in vascular death, MI, and stroke ($P < .001$) at 1 year and a 1.1% absolute reduction in cardiovascular death ($P = .01$) compared with those treated with clopidogrel. There were no significant increases in major bleeding.[17] Ticagrelor has recently been approved by the US Food and Drug Administration for the treatment of patients with ACS. Loading dose is 180

mg followed by 90-mg dose bid. Like clopidogrel, this drug should be stopped 5 days prior to major surgery. Due to a potential interaction with higher doses, patients receiving ticagrelor should take $\leq$100 mg of daily aspirin.

Glycoprotein IIb/IIIa Inhibitors: The platelet glycoprotein (GP) IIb/IIIa receptor regulates the "final common pathway" for platelet aggregation in response to various stimuli. Platelet aggregation is mediated by binding to fibrinogen and the von Willebrand factor leading to platelet cross-linking. GP IIb/IIIa antagonists have been shown to reduce ischemic cardiac complications after extensive evaluation in a large series of randomized clinical trials. Clinical efficacy with these agents has been demonstrated during PCI in patients with stable and unstable coronary syndromes, as adjunctive therapy for the medical management of ACS, and in combination therapy for patients with acute ST-elevation infarctions.[18–22]

Three IV agents are currently available in the United States. The two small molecule GP IIb/IIa inhibitors, tirofiban and eptifibatide, are approved for the upfront management of patients presenting with ACS. The monoclonal antibody, abciximab, should not be administered to ACS patients unless PCI is already planned.

Revascularization in UA/NSTEMI

Coronary revascularization options in patients with UA/NSTEMI include PCI or coronary bypass surgery. Deciding between these two options requires accounting for individual patients' clinical characteristics (age, presence of diabetes, left ventricular dysfunction, etc.), their comorbidities, technical features of their specific coronary anatomy, and patient preference. In general, AHA/ACC guidelines[9] recommend CABG surgery in ACS patients with:

1. Presence of significant left main coronary disease.
2. Patients with three-vessel coronary disease, especially if left ventricular dysfunction is present.
3. Patients with two-vessel disease including significant proximal left anterior coronary artery disease with left ventricular dysfunction or demonstrable ischemia on noninvasive testing.
4. Patients in whom PCI is not optimal or possible.

PCI, if technically feasible, can be appropriate for UA/NSTEMI patients with one- to two-vessel coronary artery disease, in nondiabetics with multivessel disease and intact left ventricular function, and in patients at high risk for CABG surgery.

Management of STEMI

STEMI is a medical emergency most often caused by a rupture of a plaque in a coronary artery resulting in a complete occlusion of the vessel. Patients with STEMI present with similar symptoms as patients with other ACS, such as UA and NSTEMI, although the symptoms are often greater in intensity and duration. Typical symptoms are severe, with crushing substernal chest pain described as pressure or squeezing sensation. The chest pain often radiates to the jaw, neck, epigastrium, left shoulder, and down the left arm. This is often associated with dyspnea, diaphoresis, nausea, lightheadedness, and palpitations. Evidence of compromised left ventricular function and low cardiac output may be prominent with altered mental status, vasoconstriction, bibasilar crackles, and third and fourth heart sounds.

The presenting ECG is central to making the early diagnosis of STEMI and initiating decisions regarding emergent reperfusion. Candidates for emergent reperfusion therapies have all of the following:

1. A clinical syndrome consistent with acute myocardial ischemia/injury.
2. ST-segment elevation $\geq$1 mm in two or more contiguous leads or new left bundle branch block.
3. Symptom onset of $\leq$12 h.

Early reperfusion of an infarct-related artery limits infarct size, preserves left ventricular function, and improves patient survival. The term "time is muscle" is often used as there is overwhelming evidence that time to treatment is directly related to mortality reduction and

Table 5—*Common Fibrinolytic Regimens and Adjunctive Anticoagulation*

Drug	Dose	Adjunctive Therapy
Alteplase (tPA)	Front-loaded dosing: 15 mg bolus, then 0.75 mg/kg over 30 min, then 0.50 mg/kg over 60 min (total, 100 mg)	ASA 325 mg Heparin 60 U/kg bolus (max 4,000 U) then 12 U/kg/h (max 1,000 U/h) Clopidogrel 300-mg load
Tenecteplase (TNK)	30–50-mg single bolus based on weight	ASA 325 mg Enoxaparin 30 mg IV, then 1 mg/kg bid Clopidogrel 300-mg load
Reteplase (rPA)	10 U and repeat 10 U in 30 min	ASA 325 mg Heparin 60 U/kg bolus (max 4,000 U) then 12 U/kg/h (max 1,000 U/h) Clopidogrel 300-mg load

ASA = aspirin.

myocardial salvage. All patients who present within 12 h of symptom onset should be considered for immediate reperfusion therapy. Symptoms after 12 h may be an indication of a stuttering course of occlusion and spontaneous reperfusion and reocclusion, and the patient may benefit from aggressive early therapy (mainly primary PCI).

Treatment advances over the last few decades have dramatically lowered the mortality and morbidity from STEMI. Reperfusion of the infarct-related coronary artery in STEMI is central to optimal STEMI treatment, reducing infarct size, minimizing myocardial damage, preserving left ventricular function, and decreasing morbidity and mortality such as heart failure and electrical instability. Two strategies exist for restoring culprit coronary flow in STEMI patients: (1) pharmacological reperfusion with fibrinolytic agents and (2) mechanical, catheter-based, reperfusion (primary PCI).

Reperfusion Strategies

Fibrinolytic Therapy: Fibrinolytic therapy is one of the best and most rigorously studied treatments in cardiovascular medicine. Tens of thousands of STEMI patients have been randomized to fibrinolytics in a series of large clinical trials. The Fibrinolytic Therapy Trialists' Collaborative Group combined analysis of nine large trials including over 58,000 patients randomized to thrombolytic therapy vs medical management. This study showed an overall 18% reduction in mortality with the use of fibrinolytic therapy and even greater reduction (25%) in patients that presented with a new left bundle branch block. Overall there was a 1% risk of stroke and 0.7% risk of major, noncerebral bleeding.[23] In contrast to the treatment of STEMI, fibrinolytic agents have shown no benefit when used for the treatment of UA/NSTEMI.[24]

Streptokinase, a first-generation lytic agent that is not fibrin specific, is still widely used around the world. The more potent, third-generation, fibrin-specific agents are the agents of choice in the United States. Several newer fibrinolytic agents are available with similar efficacy and risk profiles but with slightly different administration protocols and adjunctive antithrombotic regimens (Table 5). There is no significant difference among different fibrinolytic agents or plasminogen activators in reduction in mortality or the incidence of stroke.[25] The benefit of the newer agents is easier dosing, which minimizes errors. Clinical trials of fibrinolytic agents have shown 90-min open artery and flow (normal perfusion) rates of about 60%.

Once a fibrinolytic agent has been administered as a treatment for STEMI, the patient is assessed for evidence of clinical reperfusion. This has been defined as resolution of chest pain, resolution of ST-segment elevation of more than 50%, and reperfusion arrhythmias. This is important in light of availability of rescue PCI discussed below.

Bleeding is the major risk of fibrinolytic agents. Table 6 summarizes the major absolute and relative contraindications for receiving these agents.[26] Hemorrhagic stroke is rare but may

result in catastrophic disability and mortality. Fibrinolytic therapy for STEMI is a proven and effective treatment in eligible patients. However, many eligible patients do not receive fibrinolytics due to a fear of treatment-related complications. Large registries of STEMI patients have reported that 25% to 50% of eligible patients presenting to US hospitals do not receive fibrinolytics, largely due to fear of bleeding.[27]

Primary PCI: Primary PCI has now become the preferred strategy for prompt early reperfusion if appropriate resources are available. Primary PCI offers several important potential advantages over fibrinolytic therapy, including: higher patent artery rates, less recurrent ischemia, less intracranial hemorrhage, and the ability to treat fibrinolytic-ineligible patients. The benefits from primary PCI are attributed to improved myocardial salvage resulting from achieving higher rates of normal coronary flow (90-min coronary patency in up to 90% of patients) and a lower risk of reocclusion and reinfarction. PCI minimizes the risk of intracranial hemorrhage and is preferable to alternative treatments in high-risk patients, such as those with cardiogenic shock, severe CHF, or hemodynamic or electrical instability.[28] A meta-analysis of clinical trials comparing primary PCI to fibrinolytic agents demonstrated a 22% relative reduction in mortality, 50% reduction in stroke, and a 57% reduction in recurrent MI in favor of primary PCI.[29]

The primary disadvantage of primary PCI is the potential for significant treatment delays. The majority of US STEMI patients present to hospitals that are not primary PCI capable. One potential management strategy for these patients is rapid transfer to a primary PCI hospital. This strategy was examined in the Danish DANAMI-2 trial, in which such patients were randomized between fibrinolytic therapy and immediate transfer to a primary PCI center. This study demonstrated a 5.7% absolute reduction in death, reinfarction, and disabling stroke in the primary PCI arm.[30] However, the vast majority of these patients were transferred rapidly (time from initial presentation to catheter reperfusion [door-to-balloon time] of less than 2 h). Registries of US STEMI patients have shown both large increases in mortality if door-to-balloon times are delayed and poor performance in achieving acceptable transfer times.[31] This even further emphasizes the importance of time to treatment in STEMI.

Table 6—*Contraindications for Thrombolytic Use*

Absolute Contraindications
Prior intracranial hemorrhage
Known structural cerebral vascular lesion
Known intracranial neoplasm
Recent ischemic stroke (≤3 mo)
Suspected aortic dissection
Active bleeding or bleeding dyscrasia
Significant recent head trauma (≤3 mo)
Relative Contraindications
History of chronic, severe, poorly controlled hypertension
Severe hypertension on presentation (SBP >180 mm Hg or DBP >110 mm Hg)
Traumatic CPR (>10 min)
Recent major surgery (≤3 wk)
Recent internal bleeding or active peptic ulcer disease
Pregnancy
Current use of anticoagulant

SBP = systolic BP; DBP = diastolic BP.

Rescue PCI: A subset of STEMI patients treated with fibrinolytic drugs fails to reperfuse as evidenced by persistent symptoms and ST-segment elevation. So called "rescue PCI" has been performed in such patients. Fibrinolytic failure patients are at higher risk for subsequent morbidity and mortality with their infarctions. They are also at higher risk of complications during rescue PCI, particularly with bleeding complications and stroke. Fibrinolytics have been shown to activate platelets, and concerns about bleeding have limited the use of combinations of full-dose thrombolytics and potent antiplatelet agents such as GP IIb/IIIa inhibitors. A meta-analysis of trials of rescue PCI revealed no improvements in mortality but significant reductions in heart failure and reinfarction compared with conservative treatment.[32] Rescue PCI was also associated with increased risk of stroke and minor bleeding. Repeat fibrinolytic administration had no effect on mortality or reinfarction but led to increased bleeding. Guidelines recommend a strategy of rescue PCI for patients in whom fibrinolytic therapy has failed (ST-segment elevation <50% resolved 90 min following fibrinolytic) and a moderate or large area of myocardium is at risk (anterior infarcts and inferior

infarcts with right ventricle or posterior involvement).[28]

AHA/ACC guidelines emphasize treatment times in recommending choice of reperfusion therapy for STEMI.[28]

- Patients presenting to a hospital with PCI capability should be treated with primary PCI (goal: ≤90 min door-to-balloon time).
- Patients presenting to a hospital without PCI capability and who cannot be transferred to a PCI center and undergo primary PCI within 90 min of first medical contact should be treated with fibrinolytic therapy (goal: ≤30 min to time of fibrinolytic administration).

Adjunctive Treatments in STEMI

Thienopyridine: Clopidogrel reduces vessel thrombosis in patients treated with coronary stents during primary PCI. Clopidogrel has also been shown to increase culprit vessel patency and reduce rates of major adverse cardiac events when utilized in conjunction with fibrinolytic therapy for STEMI.[33] Guidelines recommend clopidogrel loading (300 mg) and maintenance therapy in patients under the age of 75 who receive fibrinolytic therapy. Early treatment with clopidogrel or prasugrel therapy is also reasonable in patients referred for primary PCI.[16,28]

β-Blockers: The use of early β-blocker therapy in STEMI reduces the risks of reinfarction and ventricular fibrillation but increases the risk of cardiogenic shock.[34] Oral β-blocker therapy should be instituted in the first 24 h after STEMI in patients who do not have signs of heart failure, evidence of low cardiac output, or other contraindications to treatment. IV β-blockers can be administered at the time of presentation in hypertensive STEMI patients without an increased risk of cardiogenic shock or other contraindications.

ACE Inhibitors: ACE inhibitors have been shown to reduce mortality and the development of clinical heart failure in patients following MI.[35] ACE inhibitors should be started in all patients without a contraindication who have a depressed ejection fraction (<40%) after STEMI. The benefits are greatest in those who have a history of previous infarction or clinical heart failure, but other groups appear to benefit. Oral agents should be given to all STEMI patients who tolerate them and should be continued long term. IV ACE inhibitors are contraindicated due to a high risk of hypotension.[36] Angiotensin receptor blockers should be used in the ACE inhibitor-intolerant patient.

Aldosterone Antagonists: The Eplerenone Post-acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) trial demonstrated a 17% reduction in cardiovascular death in post-STEMI patients with left ventricular dysfunction and heart failure treated with the oral aldosterone antagonist eplerenone.[37] Guidelines recommend use of aldosterone blockade in postinfarction patients with depressed ejection fraction and clinical heart failure who are already on therapeutic doses of β-blockers and ACE inhibitors.[28] Care must be taken to avoid the development of hyperkalemia with these agents.

Complications of MI

Cardiogenic Shock: Acute MI is the most common cause of cardiogenic shock. Shock complicates approximately 6% to 8% of infarcts.[38] Shock patients typically manifest hypotension (systolic pressure <80 to 90 mm Hg), elevated pulmonary artery wedge pressures, and depressed cardiac index (<1.8 to 2.0 L/min/m^2). The most common cause of cardiogenic shock is pump failure (>40% of myocardium involved) following infarction, typically STEMI. Other causes of shock include acute mitral regurgitation, acute ventricular septal defect, and right ventricular infarction (discussed below). When shock due to pump failure complicates infarction, the mortality is as high as 60% to 80%.

The majority of patients in large registries do not undergo revascularization. The SHould we emergently revascularize Occluded Coronaries for cardiogenic shocK (SHOCK) trial examined the role of early revascularization by randomizing cardiogenic shock patients to early revascularization vs a strategy of aggressive initial medical stabilization. Six-month survival was improved in the patients who had coronary revascularization as compared to conservative management (56.0% vs 46.7%), although overall mortality was still very high.[39]

Initial management of cardiogenic shock complicating acute infarction includes, in addition to emergent revascularization, correction of hypovolemia, avoidance of negative inotropes (eg, β-blockers), and vasopressor support. Echocardiography can identify mechanical complications of infarction that may precipitate shock. Patients may require ventilatory support and invasive hemodynamic monitoring. Finally, many patients may benefit from mechanical support devices such as the intraaortic balloon pump. While there is no definitive randomized data showing reduced mortality, intraaortic balloon pump support remains standard care for patients with shock that is refractory to medical therapy.[40] Newer mechanical support devices have recently become available that provide even greater hemodynamic support than the intraaortic balloon pump and may prove efficacious in treating cardiogenic shock patients.

Ventricular Septal Rupture: The incidence of interventricular septal rupture has dramatically fallen with reperfusion therapy and was reported to be around 0.2% in early thrombolytic trials.[41] Ventricular septal rupture may occur within the first 24 h after infarction but more commonly is seen between days 3 and 7. There appears to be an increased risk of rupture in patients with single-vessel disease, particularly of large left anterior descending arteries, and there is a higher prevalence of this complication during first MIs. This diagnosis should be suspected in a patient with a recent infarction that appears stable, who suddenly deteriorates with hypotension, shock, and pulmonary edema. Rupture is often accompanied by heart block, signs of biventricular failure, and a new, harsh holosystolic murmur. This condition is best diagnosed with echocardiography with color flow imaging. Diagnosis can also be made by documentation of a large left-to-right shunt at the time of right heart catheterization. The treatment of choice is surgical closure, although, more recently, techniques and devices have been developed allowing percutaneous closure. Survival is grim in both treatment strategies, with overall survival of $<30\%$ in some series. Ventricular septal rupture patients who can be initially stabilized allowing delayed repair have improved survival.

Acute Mitral Regurgitation (MR): There are several mechanisms for the development of MR in the setting of an acute infarction, including: left ventricular dilatation leading to enlargement of the mitral annulus, papillary muscle dysfunction from ongoing ischemia, and papillary muscle rupture. The Global Utilization of Streptokinase and Tissue Plasminogen Activator to Treat Occluded Arteries (GUSTO-1) trial demonstrated that new MR is a predictor of poor prognosis.[42] While mild MR is more common, severe MR occurs in only 2% to 4% of patients postinfarct and is associated with a mortality of 25%. MR typically occurs 7 to 10 days after an acute infarction, though this onset may vary according to the mechanism. Papillary muscle rupture with resultant severe MR is a life-threatening condition and typically occurs within 2 to 7 days postinfarct. This diagnosis should be considered in a patient with a new pansystolic murmur and sudden pulmonary edema. Rupture is more common after inferior or posterior infarction because the vascular supply to the posteromedial papillary muscle is less robust than supply to the anterolateral papillary. Transthoracic echocardiography with color flow mapping is the diagnostic tool of choice, although the transesophageal approach often is helpful to further quantify the severity of the MR and to plan surgical repair. Initial treatment is afterload reduction with drugs such as nitroprusside and intra-aortic balloon pump support, but the definitive therapy is surgical.

Cardiac Free-Wall Rupture: Free-wall rupture is a recognized cause of mortality in patients with acute MI and was reported to be the cause of cardiogenic shock in 3% of patients presenting with shock after an acute MI. This is a devastating complication of STEMI or NSTEMI and in most cases leads to tamponade and death. However, a subacute course has also been described in patients with a contained rupture or pseudoaneurysm that have a more benign course. Survival is poor even with surgical intervention.

Right Ventricular Infarction: Of patients with inferior or inferoposterior infarct, 10% to 20% develop hemodynamically significant right ventricular dysfunction. Right ventricular infarction can also complicate some anterior infarctions. The treatment for right ventricular infarct is

different compared to other complications of myocardial infarcts, and, therefore, timely diagnosis is important. The clinical manifestation of right ventricular dysfunction is the triad of hypotension, elevated jugular venous pressure with clear lung auscultation, and the absence of dyspnea. Frequently these patients have a positive Kussmaul's sign with the failure of the jugular venous pressure to drop with inspiration. The ECG typically shows an inferior infarct with ≥1-mm ST elevations in right-sided leads (V4R), and the chest radiograph is usually without pulmonary vascular congestion. An echocardiogram shows right ventricular dysfunction and is a critical test to differentiate this condition from cardiac tamponade. Pulmonary wedge pressure is normal, but right atrial pressure is elevated. Left ventricular filling is decreased with resulting low cardiac output, and fluid loading is therefore important in the initial management of right ventricular infarctions. Fluid resuscitation with isotonic saline and avoidance of drugs that reduce preload is first-line therapy. However, temporary inotropic therapy may be required if a fluid challenge fails to improve the cardiac output. Long-term survival is most related to the extent of left ventricular infarction as the right ventricle typically recovers most of its function.[38]

Post-ACS Treatment Recommendations

Post-ACS preventive medications and lifestyle modifications are critical in prevention of recurrent events as ACS patients transition from the acute illness to chronic coronary artery disease. Table 7 summarizes the guideline-recommended therapies after a hospitalization for ACS.

Conclusion

Major advances in the treatment of ACS patients have been made in the last 2 decades. The central role of the activated platelet in the pathogenesis of ACS has been recognized. The development of novel anticoagulants that target this abnormal physiology in ACS has been an important breakthrough. Improvements in reperfusion therapies, specifically in catheter-based revascularization, have revolutionized the treatment of ST-elevation infarction. After a thorough patient history, exam, and appropriate use of ECG and cardiac biomarkers, ACS patients can be efficiently risk stratified and directed into management pathways that have been shown to improve outcomes. Medical, mechanical, and behavioral therapies implemented can effectively enhance both short-term and long-term survival, reduce symptoms, and improve quality of life.

Table 7—*Post-ACS Preventive Medications and Lifestyle Modification*

Aspirin	75 to 160 mg daily, indefinitely
Clopidogrel[a]	75 mg daily for 30 d to 1 y Indicated for at least 1 y after drug-eluting stent PCI
β-blockade	Indicated for all post-MI patients
ACE inhibitor	Indicated for all post-MI patients, especially if EF <40%
Statin therapy	Target LDL-C <100 mg/dL; consider <70 mg/dL
Smoking cessation	Counseling, referral to cessation program
Physical activity	30 min daily physical activity, ≥5 d/wk
Cardiac rehabilitation	Risk factor assessment and modification, education, prescribed exercise
Weight loss	In overweight patients

EF = ejection fraction; LDL-C = low-density lipoprotein cholesterol.
[a] Treatment with prasugrel or ticagrelor an option.

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Notes

Chapter 8. Heart Failure and Cardiac Pulmonary Edema

Steven M. Hollenberg, MD, FCCP

Objectives:

- Review the definition, demographics, and etiology of congestive heart failure diagnosis.
- Understand the pathophysiology of the heart failure syndrome.
- Review general treatment goals and medical therapy for heart failure, with an emphasis on acute heart failure in the ICU.

Key words: aldosterone antagonism; angiotensin-converting enzyme inhibition; angiotensin receptor blockers; cardiogenic shock; congestive heart failure; remodeling; vasodilators

Synopsis:

Congestive heart failure (CHF) can be defined as the inability of the heart to provide an adequate cardiac output without invoking maladaptive compensatory mechanisms. This chapter will review the definition, demographics, and etiology of CHF diagnosis and will present the general treatment goals and medical therapy. Additionally, the pathophysiology of the heart failure syndrome will be explored.

Definition and Epidemiology

Congestive heart failure (CHF) can be defined as the inability of the heart to provide an adequate cardiac output without invoking maladaptive compensatory mechanisms. CHF affects >5 million patients in the United States, which is an estimated 2.5% of the adult population.[1] Heart failure develops in 550,000 patients for the first time every year, and CHF results in >280,000 cardiovascular deaths and about 1.1 million hospital admissions per year in the United States. CHF is now the most common reason for hospitalization in the elderly, and annual costs are estimated at more than $33 billion.[1] The incidence of heart failure has been increasing, not only because of the aging of the population but also because improved treatment of hypertension and coronary disease is allowing patients to avoid early mortality only to have heart failure develop later.

The causes of heart failure are protean and are listed in Table 1. The predominant causes, however, are ischemia, hypertension, alcoholic cardiomyopathy, myocarditis, and idiopathic cardiomyopathy. Coronary artery disease is also increasing, both as a primary cause and as a complicating factor of CHF.

Heart failure can be broken down into several different classifications, as follows: acute versus chronic; left-sided versus right-sided; and systolic versus diastolic dysfunction. It is important for the clinician to distinguish between systolic and diastolic dysfunction, as both the diagnostic workup and therapeutic sequence differ. Although CHF results most commonly from decreased systolic performance, diastolic dysfunction, which is defined clinically as cardiogenic pulmonary congestion in the presence of normal systolic performance, is becoming more common as a cause of CHF, particularly in the elderly. The estimated prevalence of diastolic heart failure is 30% to 35% overall, and >50% in patients >70 years old.[2,3]

The severity of chronic heart failure is most commonly delineated using the classification developed by the New York Heart Association (NYHA). This classification divides patients into functional classes depending on the degree of effort needed to elicit symptoms (Table 2). More recently, stages in the evolution of heart failure have been proposed by an American College of Cardiology/American Heart Association task force to emphasize its progressive nature and to focus on preventive measures and early intervention (Table 3). These stages have been linked to therapeutic approaches.

Pathophysiology

Heart failure is a syndrome caused not only by the low cardiac output resulting from compromised systolic performance but also by the effects of compensatory mechanisms. Myocardial

Table 1—*Etiologies of CHF*

Ischemic
Hypertensive
Idiopathic
Valvular
Peripartum
Familial
Toxic
Alcoholic
Radiation
Drug-related (anthracyclines)
Heavy metals (cobalt, lead, or arsenic)
Metabolic/nutritional
Systemic diseases
Hypothyroidism
Connective tissue disease
Diabetes
Sarcoidosis
Infiltrative
Amyloidosis
Hemochromatosis
Tachycardia induced
Autoimmune

damage from any cause can produce myocardial failure. To compensate for the reduced cardiac output of a failing heart, ventricular filling pressure rises in an attempt to maintain output via the Frank-Starling law. These elevated diastolic filling pressures can compromise subendocardial blood flow and cause or worsen ischemia. With continued low cardiac output, additional compensatory mechanisms come into play, including sympathetic nervous system stimulation, activation of the renin-angiotensin system, and vasopressin secretion. All of these mechanisms lead to sodium and water retention and venoconstriction, increasing both preload and afterload. These increases in preload and afterload, although initially compensatory, can exacerbate the heart failure because elevated preload increases pulmonary congestion, and elevated afterload impedes cardiac output.

Recent attention has focused on cardiac remodeling, the process by which ventricular size, shape, and function are regulated by mechanical, neurohormonal, and genetic factors, as a pathophysiologic mechanism in heart failure. Remodeling may be physiologic and adaptive during normal growth, but excessive remodeling after myocardial infarction (MI), cardiomyopathy, hypertension, or valvular heart disease can be maladaptive.[4] Early local remodeling after MI may expand the infarct zone, but late remodeling, which likely involves neurohormonal mechanisms initiated by hemodynamic stress, involves the left ventricle (LV) globally and is associated with dilation that increases over time, distortion of ventricular shape, and hypertrophy of the walls. The failure to normalize increased wall stresses results in progressive dilatation and deterioration in contractile function. Similar processes are operative in other sorts of cardiomyopathy as well. Ventricular remodeling can be considered a primary target for treatment and a reliable surrogate for long-term outcomes.[3]

Table 2—*NYHA Functional Classification of Heart Failure*

Class	Description
I	Symptoms of heart failure only at levels that would limit healthy people
II	Symptoms of heart failure with ordinary exertion
III	Symptoms of heart failure on less than ordinary exertion
IV	Symptoms of heart failure at rest

Diagnosis

The symptoms and signs of CHF relate to low cardiac output and elevated ventricular filling pressures. Low output produces the symptoms of weakness and fatigue and an ashen appearance, sometimes with mottling. Increased left-sided filling pressures result in symptoms of pulmonary congestion, such as dyspnea, cough, orthopnea, and paroxysmal nocturnal dyspnea as well as signs that may include tachycardia; pulmonary rales; a diffuse, enlarged, and laterally displaced point of maximal impulse; an S3 and S4 gallop; and a murmur of mitral regurgitation. Elevated

Table 3—*Stages of Heart Failure*

Stage	Description
A	High risk for heart failure; no structural disease or symptoms
B	Heart disease with asymptomatic left ventricle dysfunction
C	Prior or current symptoms of heart failure
D	Advanced heart disease and severely symptomatic or refractory heart failure

right-sided preload can lead to such symptoms as anorexia, nausea, and abdominal pain, along with signs of systemic congestion, such as jugular venous distention, right-sided S3 gallop, murmur of tricuspid regurgitation, hepatomegaly, ascites, and peripheral edema.

The presentation of acute heart failure and pulmonary edema can be dramatic—the sudden onset of shortness of breath and tachypnea with use of accessory muscles. Crackles and, often, wheezing can be heard throughout the lung fields, at times obscuring some of the cardiac auscultatory findings. Hypotension and evidence of peripheral vasoconstriction and hypoperfusion may be present if cardiac output is decreased. The differential diagnosis of cardiac pulmonary edema includes other causes of acute dyspnea, such as pulmonary embolism, pneumothorax, and bronchial asthma as well as causes of noncardiac pulmonary edema, such as aspiration, infection, toxins, or trauma.

The initial evaluation of a patient with pulmonary edema should include an ECG and chest radiograph. The ECG may show evidence of myocardial ischemia and can also detect arrhythmias; conduction abnormalities, such as AV block and bundle branch block, may be diagnosed. In addition, Q waves indicative of previous infarction or criteria diagnostic of ventricular hypertrophy may provide clues about the substrate for heart failure; atrial enlargement speaks to the chronicity of elevated filling pressures. The chest radiograph can demonstrate pulmonary vascular redistribution, with or without bilateral hazy pulmonary infiltrates, classically perihilar, as well as cardiomegaly. Pleural effusions may be identified but are neither sensitive nor specific.

Laboratory evaluation should include baseline measurement of serum electrolytes, creatinine, and blood glucose; liver function tests; and a CBC count. Measurement of plasma B-type natriuretic peptide (BNP) has also been introduced[5] into the diagnostic algorithm for CHF. BNP is produced by ventricular myocytes in response to increased wall stress (ie, increased filling pressures and stretch).[5] Plasma BNP levels are increased in patients with heart failure, and the plasma concentration of BNP has been shown to correlate with NYHA functional class. The measurement of BNP has been used to distinguish between heart failure and pulmonary causes of dyspnea. In the Breathing Not Properly study of 1,586 patients presenting to the emergency department with a chief complaint of dyspnea, a plasma BNP level >400 pg/mL accurately predicted CHF, whereas levels <100 pg/mL indicated noncardiac dyspnea; values between 100 and 400 pg/mL were less useful.[6] Such intermediate values may be caused by CHF but may also represent preexisting LV dysfunction or right-sided heart failure. The addition of echocardiography in the acute setting may be especially valuable in patients with intermediate BNP levels.[7]

Echocardiography can provide important information about cardiac size and function, and it should be performed in all patients with new-onset heart failure. Echocardiography is simple and safe, and it permits the systemic interrogation of cardiac chamber size, LV and right ventricle function, valvular structure and motion, atrial size, and pericardial anatomy. Regional wall motion abnormalities are compatible with coronary heart disease but are not specific for ischemia as they are also seen in 50% to 60% of patients with idiopathic dilated cardiomyopathy. Fibrotic and thinned akinetic areas, however, indicate previous infarction. Doppler echocardiography can be used to evaluate the severity of mitral and tricuspid regurgitation, and tricuspid regurgitation velocity can be used to estimate pulmonary artery pressure. In addition, Doppler echocardiography is increasingly used in the diagnosis of diastolic dysfunction.[8]

Therapy

Treatment Goals

The goals of CHF therapy are to control symptoms, improve exercise tolerance, prolong life, and, where possible, correct the underlying cause. Different therapies can have disparate effects on these goals.

Therapeutic agents can be viewed in the light of the pathophysiologic mechanisms of CHF development. Traditionally, these have been considered in hemodynamic terms. Fluid restriction and diuretic and venodilator agents decrease cardiac preload. Angiotensin-converting enzyme

Table 4—*Remodeling and Survival by Drug Class*

Established Therapy	Remodeling Effects	Survival Effects
ACE-I	Benefit	Benefit
ARB	Benefit (+ACE better)	Benefit (+ACE better)
Aldosterone antagonists	Benefit	Benefit
β-blocker	Benefit	Benefit
Diuretic	No benefit	No benefit
Digoxin	No benefit	No benefit
Other therapies		
Endothelin antagonists	No benefit	No benefit
TNF-α	No benefit	No benefit
Inotropes	Adverse	Adverse

TNF = tumor necrosis factor.

Table 5—*Precipitating Causes of CHF*

Myocardial ischemia or infarction
Excess salt or fluid intake
Noncompliance or inadequate drug regimen
Renal failure
Arrhythmias
Anemia
Infection
Fever
Thyrotoxicosis
Pregnancy
Pulmonary embolism

(ACE) inhibitors, angiotensin receptor blockers (ARBs), and aldosterone antagonists counteract the activation of the renin-angiotensin-aldosterone system and reduce afterload. Arterial dilators can also reduce afterload. Inotropic agents can improve cardiac pump function and increase output. More recently, attention has been given to the way therapy affects counterproductive neurohormonal activation. β-Blockers can counteract sympathetic activation and are being used more commonly in heart failure management. The most current approaches, however, take into account the effects of different therapies on ventricular remodeling. Agents used for therapy that have been shown to have a beneficial effect on remodeling, such as ACE inhibitors, ARBs, aldosterone antagonists, and β-blockers, reduce mortality and are effective across the whole spectrum of heart failure severity (Table 4). Mechanical approaches to remodeling, most notably cardiac resynchronization therapy (CRT), also appear to be effective.

General Measures

The first order of business in the therapy for patients with new or decompensated CHF is to address the precipitating causes, the most prominent of which are listed in Table 5. Bypass surgery or percutaneous intervention for cardiac ischemia can improve symptoms and ventricular performance. Registry data consistently support the notion that in the presence of significant amounts of ischemic yet viable myocardium, revascularization confers a survival benefit.[9] For patients with arrhythmias, either cardioversion or rate control can produce marked improvement.

Patients with acute heart failure should be put on bed rest (which by itself can produce diuresis), with sodium restriction to <2 g/d and fluid restriction in severe cases. Attention should be paid to prophylaxis for deep venous thrombosis.

Pharmacologic Therapy

Diuretics

Diuretics cause renal sodium and water loss, decreasing preload, and thus pulmonary and systemic congestion. For inpatient treatment of decompensated heart failure, loop diuretics such as furosemide are usually chosen initially because of their rapid onset and are administered in IV bolus doses. When used for patients who present with pulmonary edema, most of the rapid effect of furosemide is attributable to venodilation.

If there is no response to a bolus dose of a loop diuretic, the dose is titrated to achieve the desired effect, usually by doubling the dose. Loop diuretics enter the glomerulus primarily by tubular secretion into the proximal tubule and so exhibit a threshold effect. Once the effective dose has been determined, the degree of diuresis is usually adjusted by changing the frequency of diuretic administration. If intermittent bolus doses of loop diuretics are ineffective or are

poorly tolerated because of large fluid shifts and consequent hypotension, continuous infusion may be preferable.[10] Alternatively, another diuretic with a different mechanism of action, such as metolazone or chlorothiazide, may be added.

The use of diuretics can lead to significant hypokalemia or hypomagnesemia, which can predispose the patient to arrhythmias. Careful addition of a potassium-sparing diuretic can be considered in some settings.

Nitrates

Nitrates are still the first-line agents for the symptomatic relief of angina pectoris and in cases when MI is complicated by CHF. Given the high incidence of coronary artery disease in patients with CHF, the use of nitrates to reduce preload is often desirable. In patients with severely decompensated CHF, therapy with IV nitroglycerin is preferred because of the questionable absorption of oral and transdermal preparations and for the ease of titration; IV nitroglycerin should be started at 5 μg/min and increased in increments of 5 μg/min every 3 to 5 min as needed for symptomatic relief. The major adverse effects of nitrates are hypotension and headache.

Long-term therapy with oral nitrates alone does not affect ventricular remodeling and, thus, in the absence of ongoing ischemia, is not usually a first-line choice. When combined with hydralazine, however, salutary effects on outcome have been demonstrated, first in the V-Heft,[11] and more recently in the A-HeFT trial.[12] These trials are described in the "Hydralazine" section.

ACE Inhibitors

ACE inhibitors inhibit the conversion of angiotensin I to angiotensin II and the breakdown of bradykinin. Both of these actions produce vasodilation, the latter through bradykinin-induced nitric oxide production; however, the increased inhibition of ventricular remodeling seen with ACE inhibitors, compared to that seen with other vasodilators, speaks to the potential for involvement of other mechanisms. Local renin-angiotensin systems, both intracardiac and intravascular, contribute to myocardial hypertrophy and remodeling, and their inhibition by ACE inhibitors may explain part of their beneficial effects.[13] ACE inhibitors also modulate sympathetic nervous system activity, and increased nitric oxide production may exert direct beneficial effects on cardiac myocytes.

ACE inhibitors improve hemodynamics, functional capacity, and survival in patients across the spectrum of severity of chronic CHF and after MI. The CONSENSUS group[14] compared therapy with enalapril to placebo in 253 patients with advanced heart failure (NYHA class III or IV) and showed a 40% reduction in 6-month mortality; this benefit was sustained, and the risk reduction averaged over the 10-year duration of the trial was 30%. The SOLVD treatment trial[15] compared therapy with enalapril to placebo in 2,569 patients with symptomatic heart failure (NYHA class II to III) and showed a 16% mortality reduction. Moreover, therapy with ACE inhibitors also prevented the development of CHF in patients with asymptomatic LV dysfunction in the SOLVD prevention trial.[16]

ACE inhibitors also improve the outcome in patients with asymptomatic LV dysfunction or overt heart failure after an acute MI. In the Survival and Ventricular Enlargement Trial (or SAVE trial),[17] 2,231 asymptomatic patients with an ejection fraction (EF) $<40\%$ were randomly assigned to receive either captopril or placebo. Captopril therapy decreased mortality by 19% at 42 months; it also decreased hospitalization for heart failure and, interestingly, recurrent MI.[17] The latter effect may have been due to an improvement in endothelial function. The Acute Infarction Ramipril Efficacy (or AIRE) trial[18] compared therapy with ramipril to placebo in 2,006 patients with clinical heart failure and showed a 27% reduction in mortality at 15 months. The survival benefit was maintained over the long term in both trials.

Patients should be started on therapy with low doses and titrated upward to the range demonstrated to be beneficial in clinical trials (ie, captopril, 50 mg three times daily; enalapril, 20 mg twice daily; or lisinopril, 40 mg once daily). Side effects of ACE inhibitors include cough, renal failure (usually occurring in the setting of renal artery stenosis), hyperkalemia, and angioedema.

ARBs

An alternative approach to inhibiting the effects of angiotensin II is the use of agents that block the angiotensin II receptor (ie, ARBs). Because these agents do not increase bradykinin levels, the incidence of some side effects, such as cough and angioedema, is greatly reduced. In a number of trials, the hemodynamic effects of ARBs have been shown to be similar to those of ACE inhibitors. Trials comparing ACE inhibitors to ARBs in patients with heart failure have suggested similar mortality reductions.[19] Nonetheless, the number of patients with heart failure treated with ARBs and followed up for mortality is still relatively small compared with those treated with ACE inhibitors, and so therapy with ARBs is usually reserved for patients who cannot tolerate ACE inhibitors; however, ARBs are a good alternative.

The recognition that angiotensin II is produced by pathways other than ACEs has provided a rationale for using ACE inhibitors and ARBs in combination therapy. This approach was tested in the 2001 V-Heft,[20] in which valsartan or placebo was added to usual therapy in patients with heart failure. Although mortality was unchanged, a combined end point of mortality and hospital admission for CHF was reduced with valsartan therapy. A subset analysis of this trial yielded the provocative finding that although valsartan therapy improved mortality in patients who were receiving ACE inhibitors but not β-blockers, and in those receiving β-blockers but not ACE inhibitors, when valsartan was added as triple therapy on top of ACE inhibitors and β-blockers, mortality was increased.[20] Other trials, however, have not shown adverse effects of triple combination therapy. In the VALIANT trial,[21] which compared therapy with valsartan, captopril, and the combination of the two agents in patients with acute MI and CHF, an adverse effect of the combination of ARBs, ACE inhibitors, and β-blockers was not seen. Increased mortality was also not observed when the ARB candesartan was added to therapy with ACE inhibitors and β-blockers in patients with heart failure in the CHARM-Added trial.[22]

Aldosterone Antagonists

Although aldosterone is predominantly known for its role in the regulation of renal sodium and potassium excretion, its neurohumoral effects are gaining increased recognition. Aldosterone inhibition also affects ventricular remodeling. The RALES trial[23] randomized 1,653 patients with NYHA class III and IV heart failure to receive spironolactone or placebo, and found a reduction in the 24-month mortality rate from 46 to 35% (relative risk, 30%; $P < .001$). Hyperkalemia was uncommon, and the main side effect was gynecomastia. The recently reported EPHESUS trial[24] randomized 6,632 patients with LV dysfunction after MI to receive eplerenone or placebo and found a 15% reduction in mortality (relative risk, 0.85; 95% confidence interval, 0.75 to 0.96; $P < .01$). In this trial, hyperkalemia was noted in 5.5% of the eplerenone group compared to 3.9% of the placebo group ($P < .01$), but, interestingly, the incidence of hypokalemia was reduced from 13.1% to 8.4%.

It should be noted that the doses of aldosterone antagonists used in these heart failure trials were well below those used for diuresis. Nonetheless, careful attention to serum potassium levels is warranted when using these agents for any indication.

β-Blockers

Symptomatic heart failure results in the activation of neurohumoral mechanisms, including the sympathetic nervous system, which initially support the performance of the failing heart. Long-term activation of the sympathetic nervous system, however, exerts deleterious effects. Circulating catecholamine levels correlate with survival in these patients.[25] Sympathetic activation can increase ventricular volumes and pressure by causing peripheral vasoconstriction and impairing sodium excretion by the kidneys; it can also provoke arrhythmias. The long-term stimulation of β-receptors reduces the responsiveness to β-adrenergic agonists because of the downregulation and desensitization of the β-receptor and its coupled signaling pathways; β-blockade can upregulate adrenergic receptor density, restoring inotropic and chronotropic

responsiveness.[26] Catecholamines induce oxidative stress in cardiac myocytes, potentially leading to programmed cell death, which is a process counteracted by β-blockers.[27] β-Blockers also reduce the circulating level of vasoconstrictors and mitigate their effects, decreasing afterload. Perhaps most importantly, catecholamines promote deleterious ventricular remodeling, and β-blockers can decrease LV end-systolic and end-diastolic volume.[26] Thus, although it is perhaps counterintuitive on hemodynamic grounds, there is now compelling evidence that β-blockers are beneficial not only for patients with acute MI complicated by heart failure but also with chronic heart failure from all causes.[26]

β-Blockers have now been evaluated in >10,000 patients with heart failure and systolic dysfunction. This collective experience indicates that long-term treatment with β-blockers can relieve symptoms, improve ventricular performance, and reduce mortality and the need for hospitalization. The following three agents have been shown to decrease mortality in patients with NYHA class II and III heart failure: metoprolol XL[28], bisoprolol[29], and carvedilol.[30] Studies[31] with carvedilol have suggested that the benefits extend to patients with NYHA class IV heart failure. These benefits of β-blockers are seen in patients with or without coronary artery disease, patients with or without diabetes, and patients who are already receiving ACE inhibitors.

Initiation of therapy with β-blockers, however, can be problematic during the acute phase of heart failure, as they can depress contractility. When administered for the treatment of heart failure indications per se, β-blockers should be introduced when the patient is in a well-compensated and euvolemic state, typically in the ambulatory setting and at low doses. Patients who experience an exacerbation of heart failure while receiving maintenance β-blocker therapy, particularly at a higher dose, present a previously rare dilemma that is becoming more common. No controlled observations are available to guide therapy, so current practice remains largely at the discretion of individual clinicians. Discontinuing therapy with β-blockers, or decreasing their dose, may expose myocardial β-receptors to endogenous catecholamines and may result in a brief increase in contractility. On the other hand, the slow titration of β-blockers will need to begin anew after the resolution of acute CHF. It is usually best to attempt to resolve acute episodes of heart failure by diuresis and the adjustment of other medications while holding β-blocker doses constant, and to halve the dose if heart failure persists.

Hydralazine

Hydralazine reduces afterload by directly relaxing smooth muscle. Its effects are almost exclusively confined to the arterial bed. In healthy subjects, the hypotensive actions of hydralazine provoke a marked reflex tachycardia, but this response is often blunted in patients with heart failure.

Hydralazine therapy is effective in increasing cardiac output in patients with heart failure. Therapy with hydralazine in combination with oral nitrates was the first therapy shown to improve mortality in CHF patients, reducing mortality in patients with NYHA class III and IV heart failure in the V-Heft trial.[11] Enalapril was shown to be superior to this combination.[32] In addition, oral hydralazine must be administered four times a day, and prolonged administration is attended by the development of a lupus-like syndrome in up to 20% of patients; thus, hydralazine has usually been reserved for ACE-intolerant patients.

In 2004, a fixed dose of both isosorbide dinitrate and hydralazine administered twice daily was tested in black patients with NYHA class III and IV heart failure, a subgroup that was previously noted to have a favorable response to this therapy and that may not respond as well to ACE inhibition.[12] Therapy with hydralazine and nitrates improved mortality, hospitalization for heart failure, and quality of life.[12]

Nesiritide

Nesiritide is a recombinant form of human BNP. Assays of circulating BNP levels have been used in the diagnosis of heart failure and have some prognostic value, but the therapeutic use of BNP differs. When infused intravenously, nesiritide is a balanced arterial and venous vasodilator that may also have a modest natriuretic effect.

In patients with heart failure, IV nesiritide has been shown to increase stroke volume and cardiac output and to decrease right atrial and pulmonary capillary wedge pressure.[33] Its effects, compared with those of IV nitroglycerin, in patients with acute heart failure were tested in the randomized VMAC trial.[34] In this trial, 489 patients, including 246 who underwent pulmonary artery catheterization, were randomly assigned to receive nesiritide, IV nitroglycerin, or placebo for 3 h. After this initial placebo-controlled period, the placebo-treated patients were randomly reassigned to receive either nesiritide or IV nitroglycerin, and all patients were observed for 24 h (ie, the active-treatment phase).[34] Therapy with nesiritide decreased the mean pulmonary capillary wedge pressure significantly more than therapy with either IV nitroglycerin or placebo at 3 h (5.8 vs 3.8 and 2.0 mm Hg, respectively) and significantly more than therapy with nitroglycerin at 24 h (8.2 vs 6.3 mm Hg, respectively). Symptoms of dyspnea were decreased and global clinical status was improved with nesiritide therapy compared with placebo, but there was no significant difference in these parameters compared to therapy with IV nitroglycerin. There was no significant difference in the 30-day rehospitalization rate or the 6-month mortality rate.[34]

Nesiritide is given as an initial IV bolus of 2 μg/kg followed by a continuous infusion of 0.01 μg/kg/min; the dose can be increased every 3 h by 0.005 μg/kg/min up to a maximum of 0.03 μg/kg/min. Hypotension is the most common side effect.

Although nesiritide has natriuretic properties, it has not been shown to improve the glomerular filtration rate or renal plasma flow.[35] In addition, meta-analyses of data from the VMAC trial[33] and other trials have suggested that nesiritide may worsen renal function[36] and decrease survival at 30 days compared with conventional therapies.[37] The degree to which these issues are applicable for use in patients with acute heart failure and hemodynamic decompensation is controversial, but the potential adverse effect on long-term outcome is a significant concern, the resolution of which awaits the completion of appropriately powered prospective clinical trials.

Digoxin

Digitalis, which has been used to treat heart failure for >200 years, works by inhibiting Na-K-dependent adenosine triphosphatase activity, causing intracellular sodium accumulation and increasing intracellular calcium via the sodium–calcium exchange system. Digoxin improves myocardial contractility and increases cardiac output, but its inotropic effects are mild compared with those of catecholamines. The effect of digoxin on patient survival was definitively addressed in the Digoxin Investigators' Group (or DIG) trial,[38] a study of 6,800 patients with symptomatic CHF and systolic dysfunction. There was no difference in survival between the digoxin and placebo groups, but survival did significantly decrease during hospitalization for patients with heart failure.[38] Thus, apart from its use as an antiarrhythmic agent, digoxin is recommended for therapy in patients with systolic dysfunction and symptomatic heart failure despite therapy with diuretics, ACE inhibitors, and β-blockers.

Inotropic Agents

In severe decompensated heart failure, inotropic support may be initiated. Dobutamine is a selective β_1-adrenergic receptor agonist that can improve myocardial contractility and increase cardiac output. Dobutamine is the initial inotropic agent of choice in patients with decompensated acute heart failure and adequate systolic BP. Dobutamine has a rapid onset of action and a plasma half-life of 2 to 3 min; infusion is usually initiated at 5 μg/kg/min and then titrated. Tolerance of the effects of dobutamine may develop after 48 to 72 h, possibly because of the downregulation of adrenergic receptors. Dobutamine has the potential to exacerbate hypotension in some patients and can precipitate tachyarrhythmias.

Milrinone is a phosphodiesterase inhibitor with positive inotropic and vasodilatory actions. Because milrinone does not stimulate adrenergic receptors directly, it may be effective when added to therapy with catecholamines or when β-adrenergic receptors have been downregulated. Compared to catecholamines, phosphodies-

terase inhibitors have fewer chronotropic and arrhythmogenic effects.

Although they are clearly useful in improving hemodynamics in the acute setting, controversy has arisen regarding the use of inotropic agents (other than digoxin) as outpatient maintenance therapy for chronic heart failure. Concerns have included exacerbation of arrhythmic complications by induction of myocardial ischemia or by independent pathways and the perpetuation of neurohumoral activation that might accelerate the progression of myocardial damage. Milrinone has been examined in a prospective manner in the OPTIME-CHF trial[39] in order to determine whether its use could reduce hospitalization time after an exacerbation of acute heart failure. Although these observations did not demonstrate any advantage for patients who were treated with milrinone, patients whom the investigators thought "needed" acute inotropic support were not included in the trial, thereby biasing the enrollment toward a less severely afflicted cohort.[39] Therefore, the utilization of such agents today remains at the discretion of the clinician. The proof that these agents have beneficial effects on hard clinical end points remains elusive, but their hemodynamic effects are attractive for treating patients with decompensation.

Inotropic infusions need to be titrated carefully in patients with ischemic heart disease to maximize coronary perfusion pressure with the least possible increase in myocardial oxygen demand. Invasive hemodynamic monitoring can be extremely useful for the optimization of therapy in these unstable patients, because clinical estimates of filling pressure can be unreliable, and because changes in myocardial performance and compliance and therapeutic interventions can change cardiac output and filling pressures precipitously. The optimization of filling pressures and serial measurements of cardiac output (and other parameters, such as mixed venous oxygen saturation) allow for the titration of inotropes and vasopressors to the minimum dosage required to achieve the chosen therapeutic goals, thus minimizing the increases in myocardial oxygen demand and arrhythmogenic potential.

Arrhythmias

Arrhythmias are common in patients with heart failure. Nonsustained ventricular tachycardia may occur in as many as 50% of patients, and complex ventricular depolarizations in as many as 80%. Forty to 50% of these deaths are sudden, and many are attributable to arrhythmias.

The mortality benefits of some of the standard therapies for heart failure, particularly β-blockers, may be attributable in part to antiarrhythmic properties. Specific antiarrhythmic agents, however, have not proven to be very effective for preventing sudden death in patients with heart failure,[40] and so attention has focused on identifying patients who would benefit from the placement of an implantable cardiac defibrillator (ICD).

The insertion of an ICD as secondary prevention in survivors of sudden cardiac death or patients with hemodynamically significant sustained ventricular tachycardias has been well demonstrated to improve survival in clinical trials.[40] Virtually all of the patients enrolled in the study had LV dysfunction, and about half had clinical heart failure.

ICDs are also effective as primary prevention in selected patients with heart failure. The MADIT I trial[41] and MUSST[42] showed a mortality benefit with ICD therapy in patients with LV dysfunction (EF, <35% to 40%) and nonsustained ventricular tachycardia in whom sustained ventricular tachycardia was inducible in an electrophysiologic study.[41,42] The MADIT II trial[43] showed a mortality benefit with ICD therapy in a trial in which the entry criterion was simply an EF <30%. Most of the patients in these trials had ischemic cardiomyopathy. More recently, the SCD-HeFT[44] compared ICD implantation to amiodarone therapy in patients with heart failure due either to ischemic or nonischemic cardiomyopathy (EF, <35%) and found a mortality benefit with ICD in both groups.

Cardiac Resynchronization

Left bundle-branch block or other conduction system abnormalities can cause dyssynchronous ventricular contraction. Such dyssynchrony

causes abnormal septal motion, decreasing contractile performance and myocardial efficiency. It also reduces diastolic filling times and can increase the duration and degree of mitral regurgitation. The goal of CRT is to pace the LV and right ventricle to restore physiologic atrioventricular timing and contraction synchrony. This is accomplished by placing the standard leads in the right atrium and right ventricle and by placing a special lead through the coronary sinus to enable pacing of the lateral aspect of the LV.

CRT, by optimizing the coordination of contraction, improves LV contractile function, stroke volume, and cardiac output, with decreased pulmonary capillary wedge pressures. This improved performance is associated with a decrease or no increase in myocardial oxygen consumption, thus increasing myocardial efficiency. Most importantly, biventricular pacing is associated with reverse ventricular remodeling. In the MIRACLE trial,[45] biventricular pacing produced significant decreases in LV end-systolic and end-diastolic dimensions, a significant reduction in mitral regurgitation jet area, and a reduction in LV mass, all of which are signs of reverse remodeling. Cardiac resynchronization also improved exercise capacity, functional class, and quality of life in patients in this trial.[45]

Studies of outcomes after CRT are beginning to emerge.[45] The COMPANION trial[46] compared optimal medical therapy with CRT with and without an ICD in 1,520 patients with NYHA class III to IV heart failure and an LV EF <35%. The primary end point, a combination of all-cause mortality and hospitalization, was reduced in both the CRT-alone arm and the CRT-plus-ICD arm compared with medical therapy[46] The reduction in the secondary end point of all-cause mortality alone was significant only in the CRT-plus-ICD arm compared with medical therapy. In the recently reported Cardiac Resynchronization-Heart Failure (or CARE-HF) trial,[47] cardiac resynchronization reduced the interventricular mechanical delay, ventricular volume, and mitral regurgitation; increased EF; improved symptoms and quality of life and reduced both death and the combined end point of death and hospitalization compared with medical therapy.

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Chapter 9. Acute and Chronic Liver Failure in the ICU

Jesse B. Hall, MD, FCCP

Objectives:

- Review the causes of acute liver failure and the management of patients with acute liver failure who may require liver transplantation.
- Explain the pathophysiology of CNS dysfunction in both acute and chronic liver failure and the justification for invasive intracranial pressure monitoring.
- Describe complications seen in the early postoperative period after liver transplantation.
- Describe the causes of acute deterioration in patients with cirrhosis and how stabilization can be achieved early in the ICU course.

Key words: acetaminophen overdose; cirrhosis; hepatorenal syndrome; liver failure; liver transplantation; portosystemic encephalopathy; spontaneous bacterial peritonitis; variceal hemorrhage

Synopsis:

Patients with acute liver failure (ALF) or chronic liver failure (CLF) may require care in the ICU. Patients with ALF often require ICU care because of associated encephalopathy and cerebral edema, and they may require invasive monitoring of intracranial pressure to guide therapies to reverse elevated intracranial pressure and determine prognosis. In addition to supportive treatment and guided therapy to reverse causes of liver injury, the most severely ill patients with ALF often require simultaneous evaluation for liver transplantation. Accordingly, the critical care physician must be familiar with pretransplantation evaluation and transplant complications that may be encountered in the ICU. Patients with CLF, which is invariably related to underlying cirrhosis, often require ICU care for acute deteriorations related most often to infection, portosystemic encephalopathy (PSE), or GI hemorrhage. These patients may also be under consideration for liver transplantation but most frequently the goals of ICU care are to reverse their acute condition so they may be optimized for transplantation at some point in the future, if appropriate. For a patient with ALF or CLF, the critical care physician functions within the nexus of colleagues from hepatology, GI endoscopy, transplant medicine, surgery, and interventional radiology and will often need to coordinate these subspecialists to optimize care of the patient.

Acute Liver Failure

Acute hepatitis is defined as acute damage to the liver parenchyma related to exposure to hepatotoxins or infectious agents; common agents of injury are viruses, alcohol, or medications. When the injury is sufficiently severe as to produce jaundice, coagulopathy, and encephalopathy, the patient is deemed to have acute liver failure (ALF). If the time from jaundice to the onset of encephalopathy is less than a week the ALF is termed hyperacute; longer than 7–28 days, acute; and longer than 5–26 weeks, subacute.

Etiology

In almost all registries of patients with ALF, which are dominated by patients referred to liver transplant centers, more than half of the cases are related to drug exposure and the great majority of these are exposure to acetaminophen. Accordingly, a thorough drug history is essential in evaluating these patients, and because of their frequent encephalopathy, this history may need to be obtained through collateral sources, including pharmacy records. Another notable cause is acute viral infection, although the incidence of acute viral hepatitis may be decreasing related to immunization.

Antidote Therapy for Acetaminophen Intoxication

Because intentional or accidental acetaminophen overdose is the most common cause of ALF and because an antidote—*N*-acetylcysteine (NAC)—is available, it is essential to consider this possible drug toxicity early in the course of patient evaluation and to treat appropriate patients. Acetaminophen metabolism is complex. This drug may be converted to a sulfated or glucuronidated form, and these metabolites and the parent compound are excreted in the urine. As urinary clearance becomes maximal, increasing amounts of drug are conjugated in the liver via a glutathione-dependent pathway, and these metabolites are also renally excreted. When glutathione stores are exhausted and all of these pathways are saturated, metabolism proceeds via

Table 1—*Grades of Encephalopathy*

Grade	Description
Grade 0	No alteration of mental status
Grade 1	Awake and responsive with mild confusion and disorientation
Grade 2	Awake but agitated; increasingly confused and disoriented; may exhibit hallucinations
Grade 3	Increasing suppression of mental status
Grade 4	Stuperous but arousable to vocal or tactile stimulation; essentially comatose but with intact pupillary responses

cytochrome P450 pathways with the production of hepatotoxic metabolites. NAC, as a glutathione donor, enhances metabolism of nontoxic metabolites.

If the exact time of a single large ingestion is known, a serum level can be applied to an established nomogram—the Rumack-Matthew nomogram—to predict the risk of toxicity. However, the timing of ingestion is often not known, or the patient may have more chronic exposure to drug or may have used a time-release preparation. These confounding conditions, coupled with the facts that NAC may confer benefits even in patients without detectable acetaminophen levels and is a fairly safe drug, should guide the clinician to a very low threshold for initiating NAC therapy.

NAC may be given enterally or intravenously, and the drug appears to be equally efficacious when administered by either route. Because there is a significant incidence of anaphylactoid reactions with IV therapy, the enteral route is preferred unless GI dysfunction precludes it.

Monitoring Intracranial Pressure and Treating Intracranial Hypertension

As noted earlier, encephalopathy is a hallmark and defining characteristic of ALF. Although the early phases of encephalopathy in ALF relate to metabolic failure of the liver with accumulation of metabolites that depress CNS function, patients with ALF are also at risk for rapid evolution of cerebral edema, creating elevated intracranial pressure and risk of ischemic injury of the brain. Accordingly, one of the goals of ICU care for ALF is careful and frequent neurologic assessment to determine when this evolution may be occurring.

Patients in the ICU with ALF should have frequent neurologic exams, and their level of encephalopathy should be formally assessed and recorded. A grading system is given in Table 1.

When patients progress to grade 3 encephalopathy, they usually require intubation to protect the airway and prevent aspiration. At this juncture consideration should be given to placement of a monitoring device to track intracranial pressure. This can be challenging in this group of patients, who invariably exhibit degrees of coagulopathy reflected by their reduced platelet counts and elevated international normalized ratio (INR), but with transient correction this procedure can be performed with acceptable risk and complications. Once monitoring is initiated, treatments, as suggested in Figure 1, can be instituted to avoid injury related to intracranial hypertension. Failure to control intracranial hypertension associated with an unacceptably low cerebral perfusion pressure should prompt assessment for irreversible brain injury, which would preclude the patient being considered for liver transplantation.

Acute Alcoholic Hepatitis

Given the widespread consumption of alcohol in excessive quantities and hepatic toxicity of ethanol, alcoholic hepatitis (AH) is a common cause of patients presenting with acute liver injury, but many will not exhibit all of the manifestations of ALF. AH usually presents after many years of alcohol use, although it is not unusual for a patient to have ceased alcohol consumption in the days to weeks before presentation. AH is characterized by a rapid onset of jaundice, often with fever, ascites, and proximal muscle loss. The liver is typically

enlarged and tender on examination. In more severe cases encephalopathy may develop, and hence, the patient may be determined to have ALF and require ICU admission. Laboratory testing often reveals elevation of serum aspartate aminotransferase levels more than twice the normal range but rarely above 300 IU/mL, while alanine aminotransferase levels are less elevated, and the ratio of aspartate aminotransferase to alanine aminotransferase is usually >2. Elevation of creatinine at the time of presentation often signals the development of hepatorenal syndrome (HRS) and is a laboratory marker for poor prognosis.

A number of scoring systems have been developed to prognosticate mortality in patients with AH, including the Maddrey discriminant function, Model for End-Stage Liver Disease (MELD) score, Glasgow score, and Lille score. These scores variably use age and a number of laboratory values—bilirubin, prothrombin time or INR, creatinine, WBC count, urea nitrogen, albumin, and bilirubin change over time—to predict outcome. The other major use of these scores is to identify the highest-risk patients in whom therapies beyond supportive treatment—in particular, corticosteroids and NAC—may be used to promote hepatic recovery, although the results of prospective trials evaluating these agents are mixed.

In the past, recent alcohol use has been considered an absolute contraindication to liver transplantation, and most transplant programs require patients to demonstrate abstinence from alcohol for 6 months before they would be considered for transplantation. This notion has been challenged, however, and one recent study reported results of patients with AH and a high risk of death during the acute phase of their liver disease who underwent transplantation and had a relatively low rate of documented posttransplant alcohol use.

Selecting Patients for Transplantation

A major challenge in the management of patients with ALF is to determine those who will recover with medical treatment, those for whom surgery is futile, and those in whom the risks of surgery and lifelong immunosuppression are justified. This judgment is best made by careful consideration by the transplant and critical care teams and occurs in the context of the knowledge that an estimated 17,000 patients are awaiting liver transplantation in the United States at any given time though only 5,000 transplants are performed per year.

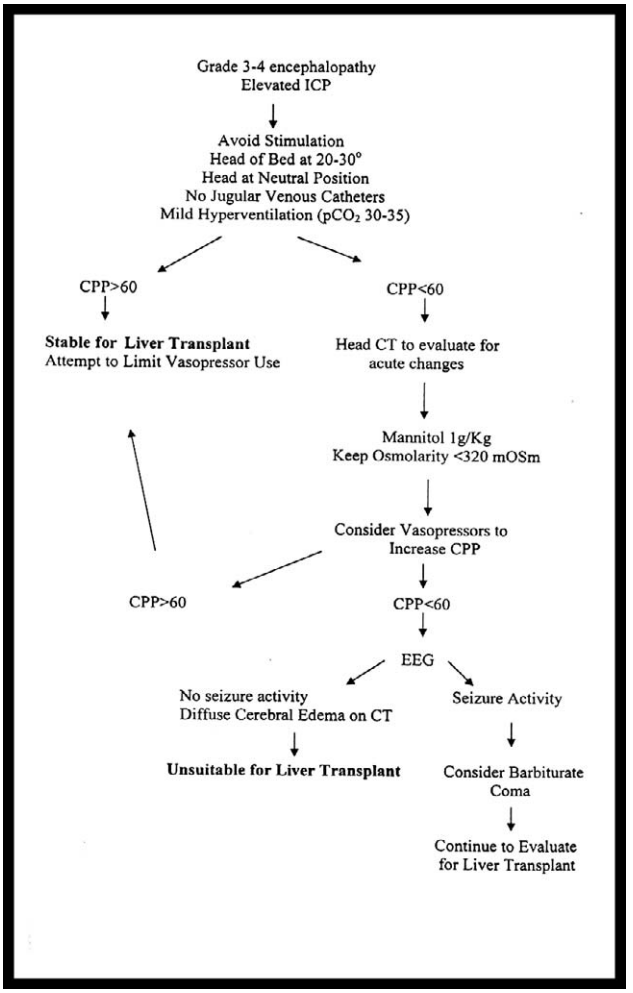

Figure 1. Algorithm for treating intracranial hypertension. CPP indicates cerebral perfusion pressure; ICP, intracranial pressure.

A number of different scoring systems have been used to achieve the best allocation of organs to patients. In the United States, perhaps the most widely used is the MELD score, given as

$$\text{MELD score} = 10(0.957 * \text{Creatinine} + 1.12 * \text{total bilirubin} + 1.12 * [\text{INR} + 0.643]).$$

The MELD score has the benefit of using simple laboratory tests that are readily available

for all patients, and it has been shown to achieve a more efficient distribution of available organs when implemented as a severity score that prioritizes patients for transplantation.

Complications of Transplantation

Complications of transplantation in the perioperative period are closely related to premorbid disease and condition, the particular transplant procedure undertaken, rejection of the graft or host, and consequences of immunosuppression. These complications may be divided into noninfectious and infectious processes.

Early noninfectious complications that may be seen when patients return to the ICU after liver transplantation include hemorrhage, primary graft failure, hepatic artery thrombosis, bile leaks, and acute rejection. Primary graft failure is estimated to occur in 1% to 5% of transplants and is of course catastrophic, requiring retransplantation on an emergent basis. It may be suggested by the appearance of the transplanted liver at the end of the surgical procedure and clinically continues as massive hepatic necrosis until retransplantation is accomplished. Hepatic artery thrombosis can also manifest as massive liver necrosis in the immediate postoperative period or may be more subacute in presentation with accompanying bile leak or the development of hepatic abscesses. An extremely low threshold should be applied to interrogation of the circulation to the transplanted organ by ultrasound, which has a high sensitivity and specificity for this complication and should guide early interventions to establish a patent arterial supply to the transplanted organ. Acute rejection tends to occur 4 to 14 days after transplant and is signaled by fever and modest elevation of serum transaminases. Excluding other processes should permit diagnosis of rejection, along with biopsy if necessary, and the immunosuppressive regimen can be increased when infection is excluded.

Infections in the immediate posttransplant period tend to result from bacterial agents typically infecting a critically ill patient in the ICU. The distribution of sites of infection are similar to those in most postoperative patients, including the lung, urinary tract, wound, and invasive IV catheters. Accordingly, when manifestations of sepsis emerge, empiric antibiotic coverage should be appropriate to hospital-acquired pathogens then narrowed by culture results. With longer exposure to immunosuppression, a wider range of potential infectious agents must be considered.

Chronic Liver Failure (CLF): Management of Patients With Cirrhosis in the ICU

Patients with CLF who are typically admitted to the ICU include those with previously stable liver disease and a new problem, such as variceal hemorrhage, encephalopathy, or spontaneous bacterial peritonitis or other cause of sepsis, or patients listed for liver transplantation who are suffering a similar acute insult. In the latter case a crucial decision needs to be made regarding the patient's stabilization for eventual transplantation. For all of these patients, the critical care team will be working within the nexus of liver transplant, hepatology, interventional radiology, and endoscopy to diagnose and manage problems in the context of advanced liver disease.

Pathophysiology of Portal Hypertension

In health, approximately two-thirds of hepatic blood flow is portal. This circulation exhibits an extremely low resistance, with a pressure gradient of about 2 to 3 mm Hg. With injury to the liver producing fibrosis and bridging—hallmark histologic signs of cirrhosis—this gradient rises, and eventually, portal flow is reduced as collateral channels develop. These channels may be visible on the abdominal wall or may be the source of bleeding, such as esophageal varices. With portal hypertension, there is typically splenomegaly with a tendency for sequestration of blood components in the spleen. Ascites develops and, at this juncture, the combination of diverted flow and diminished hepatic function results in the systemic circulation exhibiting a diminished resistance as well—a hyperdynamic state mimicking in cardiovascular terms the high output hypotension of early phases of sepsis.

Infection in Patients With Cirrhosis

Patients with CLF should be considered to be immunocompromised, apart from treatments they may be receiving. Fungal disease, including invasive aspergillosis, has been described in greater frequency in patients with cirrhosis who have no other risk factors. In addition, patients with cirrhosis often have extensive contact with the health-care system and may become infected with nosocomial organisms exhibiting significant antibiotic resistance. The adjusted risk ratio for hospitalization secondary to sepsis related to cirrhosis has been estimated to be 2.6, and the risk ratio for death at 2. The most common site for infection in patients with cirrhosis is the urine, followed by ascites, blood, and the respiratory tract.

Spontaneous bacterial peritonitis (SBP) should be considered in any patient with cirrhosis who has ascites and abdominal pain, systemic signs of sepsis, or deterioration of mental status consistent with PSE. The clinician should have an extremely low threshold for ultrasound-guided paracentesis for diagnosis. An ascetic fluid polymorphonuclear (PMN) WBC count >250 PMN/μL, visible organisms, or a positive culture are confirmatory. Extremely high PMN counts, particularly in association with multiple organisms on culture, protein levels >1 g/dL, high lactate dehydrogenase, and low glucose should prompt consideration of secondary peritonitis, implying a ruptured viscous, a catastrophic occurrence in patients with cirrhosis given their high risk for surgical intervention.

Most SBP infections are caused by gut flora, raising the possibility of gut translocation, but *Streptococcus* and *Staphylococcus* species may be seen. Cefotaxime is a reasonable empiric antibiotic choice, but if the patient has been received fluoroquinolone prophylaxis against SBP as an outpatient—an effective strategy in this setting—a wider-spectrum antibiotic may be needed. Because renal failure is a common complication in the setting of SBP with sepsis, many authors recommend colloid volume expansion at the time diagnosis is made. In one study, the incidence of acute renal failure and death was reduced by treatment with albumin (1.5 g/kg) at the time of diagnosis followed by 1 g/kg given on day three after diagnosis.

Table 2—*Causes of PSE*

Drugs
GI hemorrhage
Infection
Dehydration
Electrolyte disturbances
Hepatic decompensation
Increased protein intake
Uremia
Acidosis
Portosystemic shunts

PSE

Although deterioration of brain function in ALF may result from cerebral edema and elevation of intracranial pressure, this phenomenon is not very common in patients with cirrhosis, who more typically develop PSE related to accumulation of nitrogenous toxins that are normally cleared by the liver but have a variety of CNS effects. The plasma ammonia level is a rough guide to the accumulation of such toxins, and it is used to diagnose PSE and to gauge treatment. Causes of PSE or its worsening are given in Table 2.

Treatment of PSE entails careful serial neurologic examination of the patient to follow the course of the process and to determine the need for airway protection. Underlying causes, as given in Table 2, should be sought and corrected. Because cerebral edema is not typical of PSE, intracranial pressure monitoring is not usually needed. Treatment to reduce nitrogen load should be undertaken in most patients, and these treatments are usually directed to reduce the gut burden of nitrogenous material by promoting evacuation or reducing bacterial load. Lactulose can be given to promote diarrhea and as a nonspecific binder, and the antibiotics neomycin or rifaximin are often beneficial.

HRS

Renal failure is common in the critically ill patients with cirrhosis, and in addition to the usual causes, one must consider HRS, a form of renal dysfunction particular to advanced liver disease. Many of the characteristics of HRS are similar to those of severe prerenal azotemia—

increasing creatinine levels, oliguria, low urine sodium concentration, and a bland microscopic urinalysis—but they occur in the face of adequate circulation and absent hypovolemia. It is thought that dysregulation of intrarenal distribution of blood flow may contribute. Diagnosis is based on a serum creatinine concentration >1.5 mg/dL, which is not reduced with volume loading and assurance of resolution of hypovolemia, in the absence of treatment with nephrotoxic agents and absent evidence of renal parenchymal injury (eg, proteinuria, cellular casts).

HRS occurs in more than a third of patients with cirrhosis followed for more than 5 years and is a marker for poor outcome. Two types of HRS have been described. Type 1 is defined as rapid progression of renal failure over 2 weeks or less with a twofold increase in creatinine levels or a 50% reduction in creatinine clearance. Type 2 develops steadily over months, with creatinine clearance becoming <40 mL/min. Without transplantation, median survival is less than 2 weeks for type 1 and less than 6 months for type 2. Interestingly, if liver transplantation is performed before the patient progresses to a need for protracted dialytic therapy, renal function can often recover.

In the acute setting, HRS is best treated by therapies directed at the underlying liver failure or causes of acute deterioration. A variety of vasodilator therapies have been used, but the data supporting their benefit are not compelling. There may be a role for large-volume paracentesis coupled with intravascular volume loading. This strategy assumes a beneficial effect derived from lowering intra-abdominal pressure coupled with maximizing renal perfusion.

Massive Variceal Hemorrhage

Massive hemorrhage from esophageal varices is a life-threatening complication for patients with cirrhosis, and a highly orchestrated approach to their management is mandatory in the ICU. Early management requires large-bore catheter placement coupled with blood product replacement that includes red cells, clotting factors, and platelets. Because these patients often have baseline thrombocytopenia and factor deficits, very aggressive correction of coagulation status is necessary. It is also important to avoid cooling during the resuscitation because of the consequent adverse effects on coagulation. Given that massive volume loss is often coupled with worsening of encephalopathy in these patients, early attention to securing the airway is also warranted.

If early bleeding continues such that endoscopy is not feasible, consideration should be given to placing a balloon tamponade system in the stomach and esophagus. This is very much a temporizing measure but can stanch hemorrhage sufficiently to gain control of the situation in the early hours. Patients invariably require placement of an airway and immobilization with sedatives, if not paralytics, during placement of the balloons. A specialized large-bore catheter is placed through the mouth and into the stomach and position is confirmed. The gastric balloon portion of the tube is then inflated, and the tube is pulled back until the balloon stops at the gastroesophageal sphincter, tamponading varices here. Irrigation is conducted through channels in the tube terminating above and below the gastric balloon. At this juncture the distal port should be clear of blood, which would indicate bleeding above the level of the gastric balloon. If bleeding continues as monitored from the distal port, a source of bleeding in the stomach must be sought. If bleeding continues above the gastric balloon, a separate esophageal balloon is inflated to tamponade esophageal varices. This should resolve or greatly diminish hemorrhage, and continuous suction should be applied to a channel terminating above the esophageal balloon to avoid aspiration. At this point the next strategy is determined because this tube can produce necrosis if left in place for hours to days. Many recommend intermittent balloon deflation to minimize the risk of necrosis.

As early as feasible, endoscopy should be conducted to confirm the source of bleeding. If the bleeding is variceal, bands should be placed to establish hemostasis. Once variceal hemorrhage is confirmed, octreotide is begun as a continuous infusion to reduce portal blood flow.

The additional salvage therapy that may be used if these measures are unsuccessful is placement of a transjugular intrahepatic portosystemic shunt (TIPS). These devices very effectively reduce portal pressure and achieve

Table 3—*Complications of TIPS*

Misplacement
Portosystemic encephalopathy
Hemolytic anemia
Device stenosis
Vegetative infections (rare)
Cerebral edema (very rare)

hemostasis in more than 90% of patients. Although in the past use of a TIPS was reserved for patients in whom bleeding could not be controlled with endoscopic interventions, a recent trial demonstrated benefit when used early in the course of management of all patients with advanced cirrhosis (Child class B with continued bleeding or Child class C). Complications of the TIPS are shown in Table 3.

Nothing to Disclose

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Notes

Chapter 10. Hemodynamic Monitoring

John P. Kress, MD, FCCP

Objectives:

- Describe tools to assess adequacy of tissue perfusion.
- Describe etiologies of hypoperfusion.
- Describe ways to assess the response of the cardiopulmonary system to interventions for managing a hypoperfused state.

Key words: Echocardiogram; hemodynamic; perfusion; shock

Synopsis:

Hemodynamic monitoring may be defined as the collection and interpretation of various parameters that determine: (1) the adequacy of tissue perfusion; (2) the etiology of a hypoperfused state; and (3) the response of the cardiopulmonary system to interventions such as fluid therapy, vasoactive drugs, or adjustments in positive pressure ventilation. For many patients, adequate monitoring is achieved by routine vital signs along with collection of data such as history and physical examination, laboratory data (eg, BUN/creatinine, HCO_3^-, lactate, $ScvO_2$, SvO_2), input/output, and urine electrolytes. In other patients, invasive measurements are made, including use of arterial catheters, central venous catheters, and right heart catheters. These catheters provide for continuous transduction of pressure in either the arterial or venous circuit and sampling of blood for determination of oxygen saturation. Simultaneous determination of arterial and mixed venous blood gases also permits determination of oxygen content, oxygen delivery, oxygen consumption, arteriovenous oxygen content difference, and calculation of cardiac output by Fick determination.

The use of invasive methods for assessing hemodynamics—arterial and right heart catheters—grew during the evolution of critical care medicine despite a lack of prospective trials demonstrating efficacy and improved patient outcome. Indeed, one retrospective study suggested that use of the right heart catheter is associated with an independent negative effect on survival.[1] More recently, ultrasonographic assessment of hemodynamics has begun to move into the mainstream of monitoring in the ICU. Clearly no single test is perfect—all have limitations. Accordingly, it is important for the clinician to integrate multiple data points when interrogating a patient's hemodynamic status. This chapter will present the various tools available to assess the hemodynamic status of critically ill patients.

Urinary Studies

A urinary output of >0.5 mL/kg/h suggests that renal perfusion is adequate. This goal is frequently sought in the early stages of resuscitation of patients with hypovolemic and/or septic shock.[2] Another measure of renal perfusion that is frequently measured is the fractional excretion of sodium (FeNa) in the urine. The formula for this endpoint is the product of urinary sodium times serum creatinine divided by the product of serum sodium times urinary creatinine ([UNa × SCr]/[SNa × UCr] × 100). The cutoff of 1% is typically used to distinguish a prerenal condition from a state of acute tubular necrosis. Since loop diuretic therapy falsely raises the FeNa, one may use the fractional excretion of urea ([UUrea × SCr]/[SUrea × UCr] × 100) to assess renal perfusion in oliguric patients who have received loop diuretics. The FeNa may be falsely lowered in patients who have received IV contrast agents, cyclosporine, and tacrolimus.

Chest Imaging (Vascular Pedicle Width)

The intrathoracic veins become engorged when their volume and/or pressure is increased. The vascular pedicle width—defined by the horizontal distance between the lateral border of the superior vena cava and the left subclavian artery origin—has been shown to correlate with cardiac filling pressures, even in portable chest radiographs. Thomason and colleagues[3] reported that a vascular pedicle width greater than 63 mm on a portable chest radiographs was a reliable predictor of elevated cardiac filling pressures. The portable chest radiographs showing distension of

the azygous vein and widening of the vascular pedicle suggests that the great veins have increased volume and/or pressure.

Central Venous Catheterization

Static central venous pressures (CVPs) have been used traditionally as indicators of intravascular volume status; however, the use of atrial pressures as surrogate measures of intravascular volume is fraught with imprecision.[4] Atrial pressure is affected by many variables, which include intravascular volume, cardiac chamber compliance, and external (eg, pleural) pressures. Accordingly, increased CVPs and pulmonary capillary wedge pressures (PCWPs) can occur in many circumstances. As such, static CVPs and PCWPs are not reliable indicators of intravascular volume. For example, Osman and colleagues[5] reported on static measures of CVP and PCWP as predictors of responsiveness to a fluid challenge. The investigators found that neither CVP nor PCWP *at any level* reliably predicted whether or not a patient would respond to an IV fluid challenge.

The landmark paper on early goal-directed therapy by Rivers and colleagues[2] deserves comment in the context of the above statements. Some may suggest that the CVP is a useful endpoint to guide resuscitation in patients with septic shock since a target CVP of 8 to 12 mm Hg was used in this trial. However, there are a couple of important points to clarify about this study in the context of the topic of hemodynamic monitoring. First, *all* patients in the trial had a CVP target of 8 to 12 mm Hg; this was not a component of the intervention for the study group only. Accordingly, one cannot conclude from this trial that targeting a CVP of 8 to 12 mm Hg in the resuscitation of patients with septic shock is "evidence based." Rather, one can conclude that targeting a central venous oxygen saturation >70% using a multimodal approach to resuscitation (ie, IV fluids, vasoactive drug support, mechanical ventilation, packed RBC transfusion) leads to improved outcomes. Indeed, one could wonder if the CVP target was different (eg, 10–15 mm Hg or 6–10 mm Hg) whether the study outcomes would have differed. Administration of IV fluids typically increases the CVP, but whether this translates into an increase in blood flow to tissues is not clear (see above). Details on interpretation of atrial pressure waveforms are discussed later in this chapter.

Valvular Disease

The impact of valvular disease on hemodynamics can be substantial. In aortic stenosis, most patients suffer from a hypertrophied left ventricle. Accordingly, tachycardia is detrimental to hemodynamic stability since there is less time for diastole—when perfusion of the subendocardium occurs. Therefore, it is optimal to have a reduced heart rate. The hypertrophied left ventricle with its accompanying reduced compliance is also more dependent on atrial contraction for filling than is the normal ventricle. Accordingly, a sinus rhythm with a slow heart rate is optimal. Atrial fibrillation with a rapid ventricular response is often very poorly tolerated. The management of shock in this circumstance may include IV fluid administration, phenylephrine (no chronotropic effects), and urgent cardioversion. In aortic insufficiency, optimal hemodynamic management includes the use of chronotropic agents (eg, dobutamine, milrinone) to decrease regurgitant filling time and afterload-reducing agents (eg, nitroprusside, nicardipine, fenoldopam, angiotensin-converting-enzyme inhibitors) to facilitate forward flow. Mitral stenosis is managed optimally by negative chronotropic agents (eg, β-blockers), which seek to maximize diastolic filling time across the stenotic valve. The loss of atrial contraction is detrimental to left ventricular filling, though typically less so than in aortic stenosis, since the left ventricle is not usually hypertrophied. As left atrial size increases in the patient with mitral stenosis, the likelihood of maintaining a sinus rhythm is decreased. Accordingly, control of ventricular response rate is extremely important in these patients. Mitral regurgitation may occur acutely (eg, ischemic injury to papillary muscles) or present as a chronic condition in an ICU patient. Optimization of hemodynamic status occurs via attempts to establish and maintain sinus rhythm, as well as afterload reduction (eg nitroprusside, nicardipine, fenoldopam, angiotensin-converting-enzyme inhibitors) to decrease the percentage of regurgitant blood flow.

Pericardial Disease

The hemodynamic management of patients with pericardial tamponade is centered on definitive drainage of the pericardial space. IV fluid administration to increase venous return can be used as a temporizing measure while definitive treatment is being arranged. The classic physical findings of acute cardiac tamponade are a falling arterial pressure, a rising venous pressure, and distant muffled heart sounds ("a small quiet heart").[6] Kussmaul's sign (rising jugular venous pressure with inspiration) and pulsus paradoxus are other findings on physical examination. Echocardiographic features include abnormal inspiratory increase of right ventricular dimensions and abnormal inspiratory decrease of left ventricular dimensions, right atrial compression, right ventricular diastolic collapse, abnormal inspiratory increase of blood flow velocity through the tricuspid valve and abnormal inspiratory decrease of mitral valve flow velocity, dilated inferior cava with lack of inspiratory collapse, and a "swinging" heart.[7] Right ventricular filling is impaired throughout diastole; accordingly, the y-descent (ie, the right atrial pressure fall immediately after tricuspid opening as blood rushes into the right ventricle) on the right atrial pressure tracing is blunted. A rapid y-descent essentially rules out cardiac tamponade. The right atrial pressure tracing in pericardial constriction is different. In constrictive pericarditis, the earliest phase of diastolic right ventricular filling is not impaired; therefore, the y-descent is not blunted. Rather, the y-descent may be accentuated ("rapid y-descent") because the pressure is descending from higher right atrial pressure. Figure 1 illustrates the characteristic right atrial pressure findings in pericardial tamponade and constrictive pericarditis.

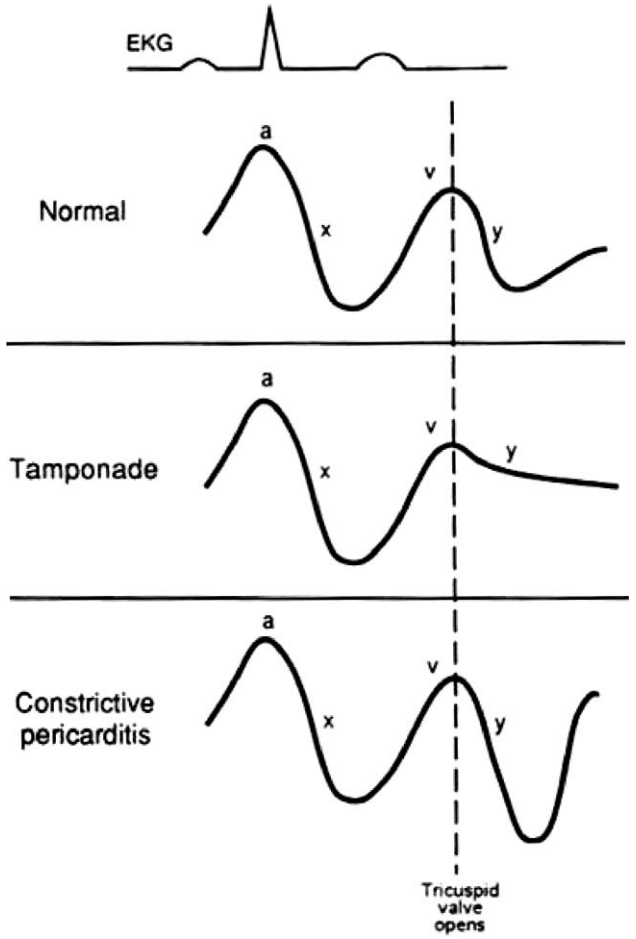

Figure 1. Atrial waveforms-normal, cardiac tamponade, constrictive pericarditis.

Dynamic Waveform Analysis in Hemodynamic Monitoring

The approach to hemodynamic monitoring in critical illness has undergone some relatively recent changes. As noted above, static measures of preload (eg, CVP, PCWP) are not helpful in predicting fluid responsiveness.[8] Terms such as "hypovolemic," "dehydrated," "hypervolemic," "volume overloaded" are being replaced with the more relevant question of whether or not a patient is volume responsive (ie, will the cardiac output increase if a discreet fluid challenge is administered?). Dynamic assessments of a patient's hemodynamic status challenge the circulation with a fluid bolus (IV fluid challenge or passive raising of the legs). The impact of such a fluid challenge on the cardiac output allows one to determine the patient's position on the Frank-Starling curve. One can also take advantage of the fact that the pleural pressure swings associated with breathing perturb the circulation by virtue of altering venous return. This relationship has been most extensively validated during positive pressure ventilation, which induces cyclic changes in the loading conditions of both ventricles. During a positive pressure breath, there is a decrease in right ventricular preload as well as an increase in right ventricular afterload, both of which lead to a decrease in right ventricular stroke volume. After

a delay of two or three (depending on the heart rate) heart beats, a decrease in left ventricular filling and stroke volume ensues (this is due to transit time of blood through the lungs and is typically seen during exhalation). These cyclic changes in right and left ventricular stroke volume are more notable on the steep portion of the Frank-Starling curve.

Since the pulse pressure (PP) (systolic blood pressure minus diastolic blood pressure) correlates well with the stroke volume, one can measure the variation in PP with positive pressure breathing. The PP variation can be measured easily with an indwelling arterial catheter. The formula is: $\Delta PP(\%) = 100 \times (PPmax - PPmin)/[(PPmax + PPmin)/2]$, where $\Delta PP(\%)$ indicates PP variation, PPmax indicates the maximal PP during the respiratory cycle and PPmin indicates the minimal PP during the respiratory cycle. A $\Delta PP(\%)$ threshold of 12.5% (range ~10%–15%) has been shown to predict fluid responsiveness across a broad domain of patients.[9] However, the use of PP variation as a measure of fluid responsiveness has limitations. The patient must have a regular cardiac rhythm (ie, stable R-R interval), and the tidal volume during positive pressure ventilation must be relatively large (eg, 8–10 mL/kg) in order to perturb the venous return enough to result in a detectable variation in stroke volume.[4,10]

Another endpoint worth mentioning is the change in CVP as a function of breathing. There is less certainty as to the value of this endpoint, since some studies have shown that a fall in CVP greater than 1 mm Hg predicts fluid responsiveness in spontaneously breathing patients,[11,12] while others have not.[13] From a practical perspective, a change in CVP of only 1 mm Hg magnitude can be difficult to detect; accordingly, caution should be used when targeting this endpoint to assess volume responsiveness.[14] Indeed, assessing fluid responsiveness in the spontaneously breathing patient is difficult,[15] since most studies have evaluated patients undergoing positive pressure ventilation.

Ultrasound/Echocardiography

The use of bedside ultrasound in critical care has increased substantially in recent years. Portable devices are now available in most ICUs. The benefits of ultrasound include its noninvasive nature, which lends itself to real-time assessment of pump function, ventricular cavity size, wall thickness, and regional wall motion abnormalities. In addition, one can perform real-time assessment of valve function and interrogate for the presence of pericardial disease. Echocardiography can also be used to measure cardiac output. Studies have demonstrated that fluid responsiveness can be established in hypotensive patients subjected to a passive leg raise whose cardiac output change was measured by echocardiography using aortic blood flow measurements.[16,17] Furthermore, the stroke area (SA) can be measured using transesophageal echocardiography. SA can be defined as the difference between the end-diastolic area and the end-systolic area using a transgastric, cross-sectional view of the left ventricle at the midpapillary muscle level. Using a calculation similar to that used for PP variation, respiratory variations in SA can be assessed. The ΔSA can be calculated as: $\{[SAmax - SAmin]/[(SAmax + SAmin)/2]\} \times 100\%$, where ΔSA is the SA variation as a function of breathing, SAmax is the maximal SA and SAmin is the minimal SA. Cannesson and colleagues[18] reported that a ΔSA cutoff value of 16% allowed fluid responsiveness prediction with a sensitivity of 92% and a specificity of 83%. Obviously, the skills necessary to use echocardiography in the ICU require training and practice.

Another useful endpoint is the measurement of inferior vena cava (IVC) diameter. An absolute IVC diameter less than 1 cm in hypotensive patients generally predicts fluid responsiveness.[19,20] Variation in IVC diameter as a function of respiration is also a useful endpoint to predict fluid responsiveness. One study of mechanically ventilated patients with septic shock noted that a *change* in IVC diameter greater than 18% was a reliable predictor of fluid responsiveness.[21] Likewise, variation in superior vena cava diameter as a function of respiration can be used to predict fluid responsiveness, with one study reporting a threshold of 36% diameter change with during positive pressure ventilation.[22] However, the superior vena cava can only be visualized with transesophageal echocardiography, limiting its widespread applicability.

Other Noninvasive Measures of Cardiac Output

The PiCCO™ system (Pulsion Medical Systems) uses transpulmonary thermodilution to calibrate stroke volume. This is done with an internal jugular vein catheter and a thermistor-tipped femoral arterial catheter, which measures cardiac index through transpulmonary thermodilution and pulse contour analysis. The device is able to report continuous cardiac output values.[23] Pulse-contour analysis (eg, FloTrac-Vigileo [Edward Lifesciences] device) provides continuous stroke volume measurements from the arterial pressure wave. It analyzes the pressure waveform 100 times per second over 20 s. The resulting 2,000 data points are analyzed to calculate stroke volume using a complex formula.[24] Discussion of this formula is beyond the scope of this chapter. Lastly, bioreactance is a tool that analyzes relative phase shifts of an oscillating current that occur when this current traverses the thoracic cavity. Commercially available devices placed on the chest can be used to generate such currents across the thorax in order to measure cardiac output. Discussion of the details of this technology is beyond the capacity of this chapter; however, the device has been validated as a noninvasive tool for measuring cardiac output.[25]

Blood Transport of Oxygen

Oxygen delivery (Qo_2) is the product of cardiac output (Qt) and the content of oxygen in the arterial blood (Cao_2) ($Qo_2 = Qt \times Cao_2$). The Cao_2 is determined by the hemoglobin concentration, the arterial hemoglobin saturation and dissolved oxygen not bound to hemoglobin. The formula for Cao_2 is 1.39 (constant) $\times$ hemoglobin (g/dL) $\times$ arterial oxygen saturation (Sao_2) + $0.0031 \times Pao_2$. In normal adults, the Qo_2 is approximately 50 dL/min (Qt) $\times$ [1.39 $\times$ 15 g/dL (hemoglobin concentration) $\times$ 1.0 (hemoglobin percent saturation) + 0.0031×100 (Pao_2)], or 50 dL/min (Qt) $\times$ 21.16 mL oxygen/dL blood (Cao_2). This formula calculates to 1,058 mL O_2 per minute. It is clear from this formula that most oxygen delivered to tissues is bound to hemoglobin. Dissolved oxygen (Pao_2) contributes minimally to the oxygen content in arterial blood. Normally, the content of oxygen in mixed venous blood (Cvo_2) is 15.95 mL O_2 per dL blood, since the mixed venous blood saturation is 75%. Accordingly, the normal tissue extraction ratio for oxygen is $Cao_2 - Cvo_2/Cao_2$ (21.16 − 15.95/21.16) or approximately 25%. Central venous oxygen saturation is not identical to mixed venous oxygen saturation; however, these two values are relatively close and tend to track in a similar direction. The differential diagnosis for a low venous oxygen saturation includes a reduced cardiac output (the most common reason), a reduced hemoglobin level with an inability to generate a compensatory increase in cardiac output, a reduced arterial oxygen saturation, and an increased tissue oxygen consumption rate.

Pulmonary Artery (PA) Catheterization

The use of PA catheterization in critical care has fallen out of favor in routine practice. This has occurred because numerous clinical investigations across a wide range of patient populations have failed to demonstrate a benefit with the use of this device.[26–31] Nonetheless, the device provides important information about cardiopulmonary physiology and is still used in many ICUs. Accordingly, it is important for the critical care physician to have an understanding of this device.

The PA catheter is capable of acquiring many data points. These are listed below with normal values in parentheses.

- Cardiac chamber pressures and waveforms
  - Right atrium (2–8 mm Hg), right ventricle (16–24/0–4 mm Hg), PA (16–24/5–12 mm Hg), PCWP (5–12 mm Hg)
- Cardiac output
  - Thermodilution (may be inaccurate with tricuspid regurgitation)
  - Fick equation [$Vo_2 = Qt \times (Cao_2 - Cvo_2)$]
  - Svo_2
  - Systemic vascular resistance = 80 $\times$ (mean arterial pressure − right atrial pressure/Qt) (dynes $\times$ s/cm^5)

Table 1—*Complications Related to Insertion and Use of the Pulmonary Artery (PA) Catheter*

A.	Complications related to central vein cannulation
B.	Tachyarrhythmias
C.	Right bundle branch block
D.	Complete heart block (preexisting left bundle branch block)
E.	Cardiac perforation
F.	Thrombosis and embolism
G.	Pulmonary infarction due to persistent wedging
H.	Catheter-related sepsis
I.	Pulmonary artery rupture
J.	Knotting of the catheter
K.	Endocarditis, bland and infective
L.	Pulmonic valve insufficiency
M.	Balloon fragmentation and embolization

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- Pulmonary vascular resistance = 80 × (mean PA pressure − PCWP/Qt) (dynes × s/cm^5)

Complications of PA catheterization are listed in Table 1.

Interpretation of Pressure Waveforms

Under most conditions, the waveforms obtained as the PA catheter is advanced through the right atrium, right ventricle, and into the PA to a wedged position are readily identified as characteristic of each segment of the circulation as it is traversed, as demonstrated in Figure 2. While waveform recognition is extremely helpful in positioning the catheter, and often makes the use of fluoroscopic techniques unnecessary, it is essential for the measurement and interpretation of waveforms displayed during PA catheterization to be correlated to the ECG tracing so that specific components of the waveform can be identified and various pitfalls in measurement of intravascular pressure can be avoided.

The Normal Atrial Pressure Waveform

In sinus rhythm, the atrial pressure waveform is characterized by two major positive deflections (A and V waves) and two negative deflections (x- and y-descents) (Fig 3). A third positive wave, the C wave, is sometimes seen. The A wave results from atrial systolic contraction and is followed by the x-descent as the atria relax following contraction. The C wave results from closure of the atrioventricular valves and interrupts the x-descent. After the x-descent, the V (ventricular) wave is generated by passive filling of the atria during ventricular systole. Lastly, the y-descent reflects the reduction in

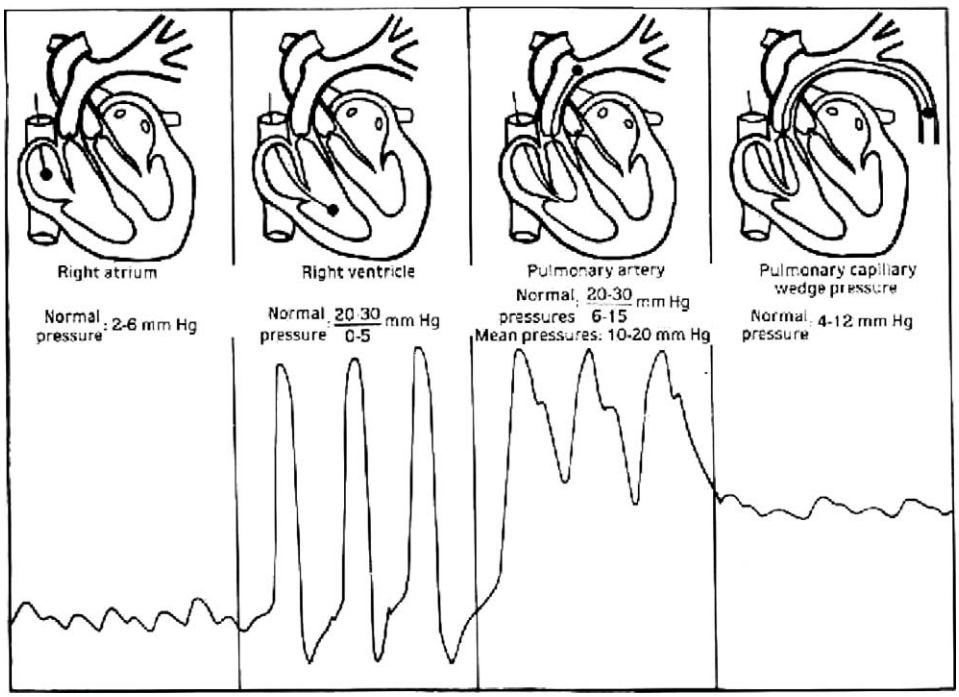

Figure 2. Normal waveform tracings during pulmonary artery catheter insertion.

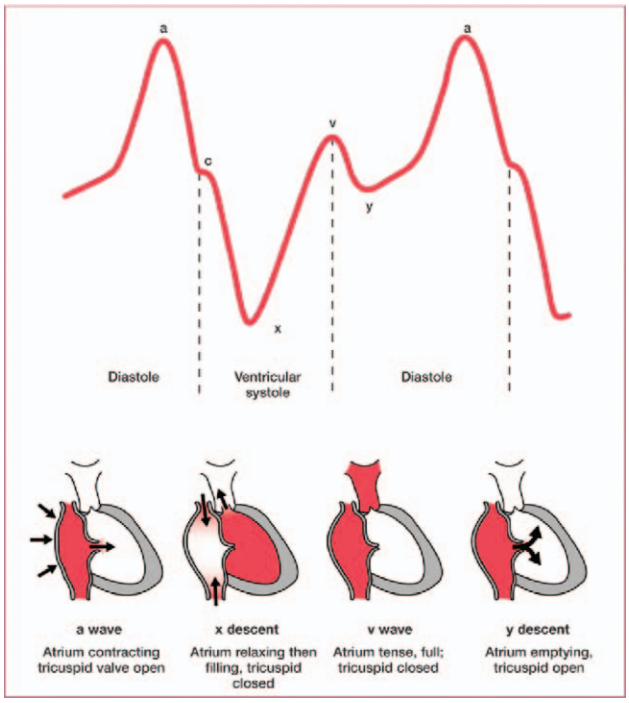

Figure 3. Atrial waveform.

atrial pressure as the atrioventricular valves open. In correlating these waveforms to the ECG, the first positive pressure wave to follow the P wave is the A wave. The right atrial A wave is usually seen at the beginning of the QRS complex, provided that atrioventricular conduction is normal. The peak of the right atrial V wave normally occurs simultaneously with the T wave of the ECG, provided that the Q-T interval is normal.

The PA waveform has a systolic pressure wave and a diastolic trough. A dicrotic notch due to closure of the pulmonic valve may be seen on the terminal portion of the systolic pressure wave. Like the right atrial V wave, the PA systolic wave typically coincides with the electrical T wave. The PA diastolic pressure (Ppad) is recorded as the pressure just before the beginning of the systolic pressure wave. The PCWP tracing contains the same sequence of waves and descents as the right atrial tracing. However, when the atrial waveform is referenced to the ECG, the mechanical events arising in the left atrium (PCWP) will be seen later than those of the right atrium, because the left atrial pressure waves must travel back through the pulmonary vasculature and a longer length of catheter. Therefore, in the PCWP tracing the A wave usually appears after the QRS complex and the V wave is seen after the T wave. As such, the systolic pressure wave in the PA tracing *precedes* the V wave of the PCWP tracing. An appreciation of the latter relationship is critical when tracings are being analyzed to ensure that balloon inflation has resulted in a transition from an arterial (PA) to atrial (PCWP) waveform, and to

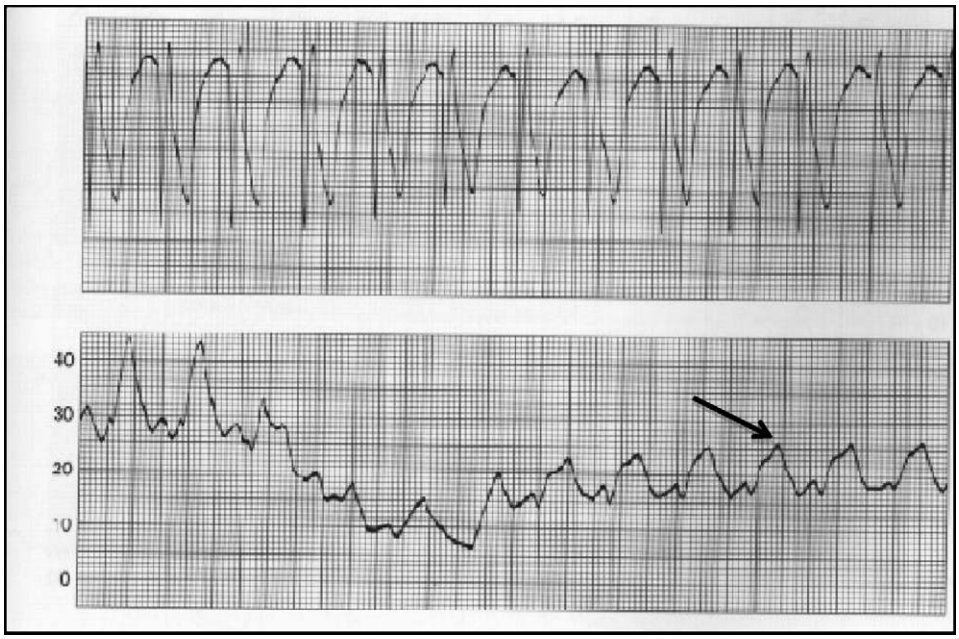

Figure 4. Transition from pulmonary artery tracing (right side of figure) to "wedged" position with mitral regurgitation and giant V wave (arrow).

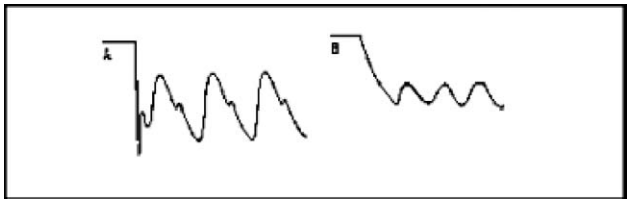

Figure 5. Rapid flush test: *A,* appropriately damped system; *B,* over damped system. Reprinted with permission from *ACCP Critical Care Medicine Board Review.* 20th ed. Northbrook, IL: American College of Chest Physicians; 2009.

detect the presence of a "giant" V wave in the PCWP tracing (Fig 4, see arrow).

Common Problems Producing Erroneous Pressure Waveforms: Of the many problems causing artifact or erroneous tracings, the most commonly encountered are overdamping, catheter whip, overwedging, incomplete wedging, and Zone I catheter conditions.

Overdamping results from air bubbles within the catheter system or kinking, clotting, and fibrin deposition along the catheter course; many times these problems can be resolved by catheter flushing.

The main effect of overdamping on the pressure waveform is to artifactually lower the systolic pressure and raise the diastolic pressure with consequent effects on interpretation (Fig 5).

Catheter whip arises from cardiac contractions causing shock transients transmitted to the catheter. The results on the right ventricular or pulmonary arterial waveforms are an exaggerated diastolic pressure in some cycles, highlighting the need to avoid readings obtained by electronic systems.

Overwedging (Fig 6) is signaled by a rise in recorded pressure with balloon inflation as the balloon herniates over the catheter tip or the tip is pushed into the vessel wall with continued fluid

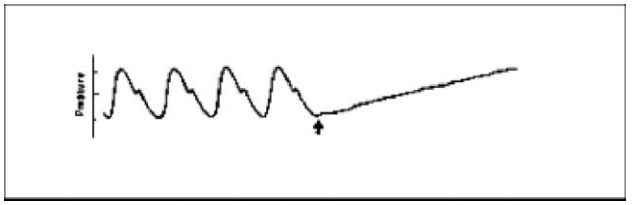

Figure 6. Overwedged catheter (see text). Reprinted with permission from *ACCP Critical Care Medicine Board Review.* 20th ed. Northbrook, IL: American College of Chest Physicians; 2009.

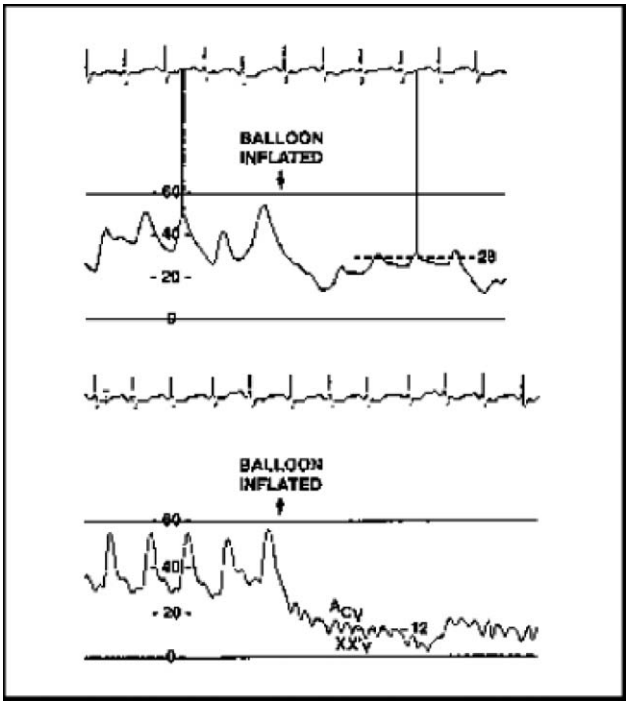

Figure 7. Incomplete wedge pressure (PCWP). *Top:* With balloon inflation, there is a decrease in pressure to a value that approximates pulmonary artery diastolic pressure (Ppad). The clinical setting (ARDS) is usually associated with a large Ppad-PCWP gradient. Review of the tracings indicates that there is a single positive wave coinciding with the electrocardiographic T wave after balloon inflation, a pattern inconsistent with a left atrial waveform. *Bottom:* Waveforms after the catheter had been retracted, the balloon inflated, and the catheter floated to a full wedge position. Now, there is a large Ppad-PCWP gradient and the tracing after balloon inflation is consistent with a left atrial waveform. The incomplete wedge tracing yielded an incorrect measurement of the wedge pressure as 28 mm Hg, substantially higher (in a very clinically relevant sense) than the true wedge pressure of approximately 12 mm Hg. Reprinted with permission from *ACCP Critical Care Medicine Board Review.* 20th ed. Northbrook, IL: American College of Chest Physicians; 2009.

ingress elevating the measured pressure. Overwedging requires repositioning of the catheter.

Incomplete wedging (Fig 7) and Zone I positioning of the catheter can be subtle but are important to identify since erroneous and often overestimation of PCWP occur.

Zone I conditions of the lung refer to those segments of the lung in which alveolar pressure exceeds pulmonary vascular pressure and hence there is no flow (Fig 8). This phenomenon is uncommon when the catheter is floated into position since this typically results in Zone II or III positioning. It would be more likely to result from forceful positioning of the catheter, hypo-

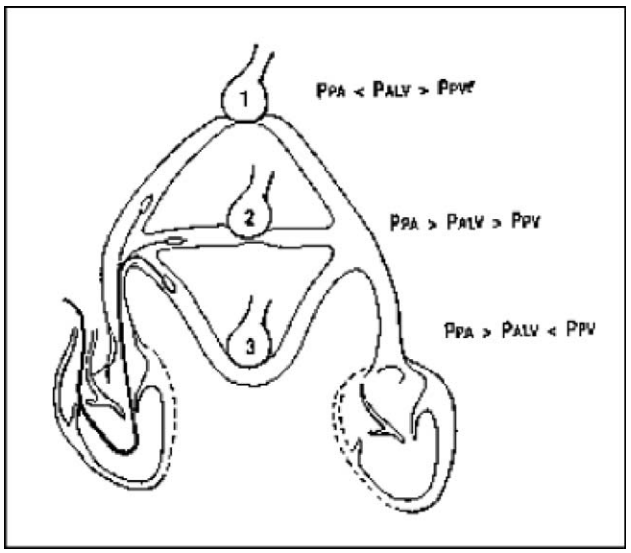

Figure 8. Lung zones. Reprinted with permission from *ACCP Critical Care Medicine Board Review.* 20th ed. Northbrook, IL: American College of Chest Physicians; 2009.

volemia emerging after placement, or with large increases in positive end-expiratory pressure (PEEP). This condition should be considered when changes in PCWP track PEEP changes exactly or when the respiratory excursion in PA systolic pressures exceeds the PCWP significantly (Fig 9).

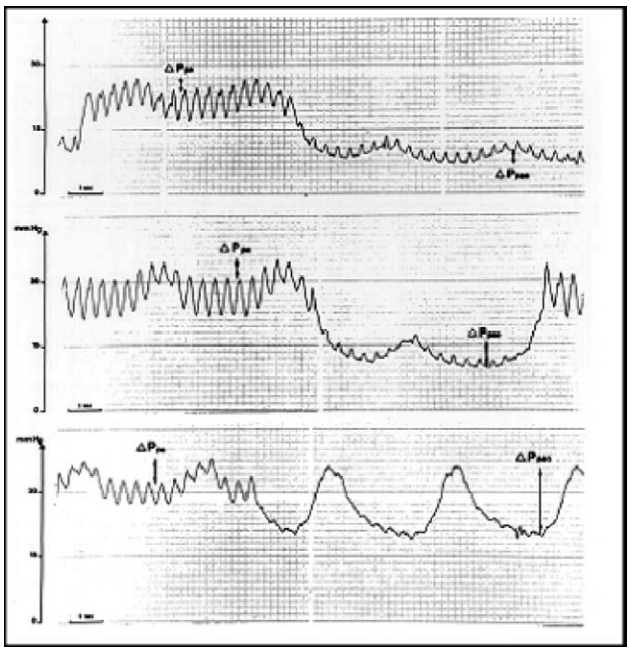

Figure 9. Pressure tracings recorded in the same patient at different levels of end-expiratory pressure zero on the *top panel,* 15 cm H_2O in the *center panel,* and 20 cm H_2O in the *bottom panel*. Reprinted with permission from *ACCP Critical Care Medicine Board Review.* 20th ed. Northbrook, IL: American College of Chest Physicians; 2009.

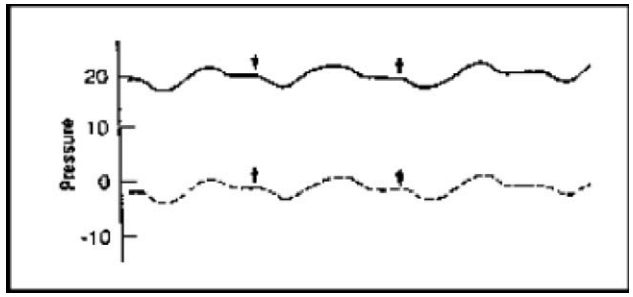

Figure 10. Respiratory effects on PCWP tracing. PCWP tracing is seen on the upper tracing, pleural pressure is seen on the lower tracing. Reprinted with permission from *ACCP Critical Care Medicine Board Review.* 20th ed. Northbrook, IL: American College of Chest Physicians; 2009.

The Correlation of Pressure to Ventricular Preload and Volume: The use of PCWP as a measure of left ventricular end-diastolic pressure and hence preload depends on the PCWP closely reflecting pulmonary venous, left atrial, and left ventricular pressures, that is, with minimal pressure gradient across the system. One potential confounder to interpretation of intravascular pressures is the fluctuation in intrathoracic pressure related to the respiratory cycle. The effect of varying intrathoracic pressure on the wedge (PCWP) pressure is seen in Figure 10. The top line is a PCWP tracing and the bottom is the intrapleural (Ppl) pressure. In this example the patient is receiving assisted ventilation. Arrows indicate end-expiratory pressures. Negative deflections in Ppl and PCWP pressures result from inspiratory muscle activity, and subsequent positive deflections represent lung inflation by the ventilator. At end expiration, the respiratory system has returned to its relaxed state and Ppl is back to baseline (–2 cm H_2O). Transmural wedge pressure remains approximately constant throughout the ventilating cycle. Since Ppl is not usually measured clinically, it is necessary that PCWP be recorded at a point where Ppl can be reliably estimated (ie, end-exhalation, assuming no expiratory muscle activity).

The correlation of pressure to volume is further complicated by a variety of conditions that cause the ventricle to be effectively stiff (diastolic dysfunction or pericardial disease) or conditions that cause juxtacardiac pressure to rise related to positive pressure ventilation (PEEP, intrinsic PEEP [PEEPi], active expiratory effort) (Fig 11).

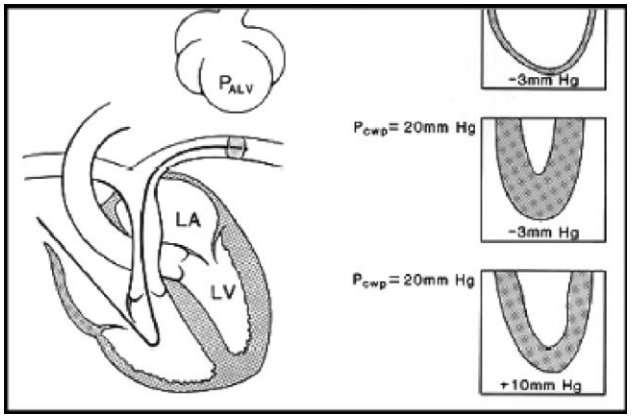

Figure 11. Elevated PCWP pressure (20 mm Hg) caused by three different physiological circumstances: high ventricular end diastolic pressure (LVEDP) in dilated cardiomyopathy with overfilled LV (upper figure on the right); high LVEDP in hypertrophied LV that is not overfilled (middle figure on the right); high LVEDP with a normal heart and increased pleural pressure due to intrinsic PEEP (lower figure on the right). Reprinted with permission from *ACCP Critical Care Medicine Board Review.* 20th ed. Northbrook, IL: American College of Chest Physicians; 2009.

The effects of PEEP in conditions such as ARDS are often blunted, since the stiff lungs of these patients do not distend greatly with high ventilator pressures, and hence minimal increases in juxtacardiac pressure are encountered. However, in cases in which PEEPi exists in COPD/asthma patients undergoing mechanical ventilation, or in agitated/obstructed patients with very

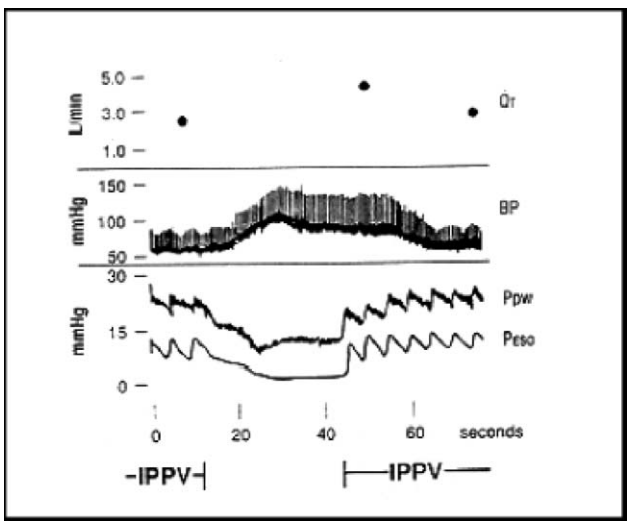

Figure 12. Effects of intrinsic PEEP on cardiac output (upper figure), blood pressure (middle figure), and PCWP/esophageal pressure (lower figure). See text. Reprinted with permission from *ACCP Critical Care Medicine Board Review.* 20th ed. Northbrook, IL: American College of Chest Physicians; 2009.

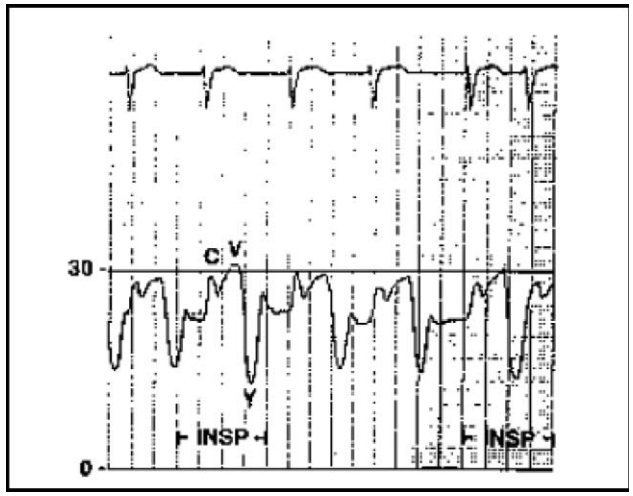

Figure 13. Giant V wave in right atrial waveform indicates tricuspid regurgitation. Reprinted with permission from *ACCP Critical Care Medicine Board Review.* 20th ed. Northbrook, IL: American College of Chest Physicians; 2009.

active expiratory muscle effort, cardiovascular effects may be large. This effect is shown in Figure 12, where the increase in blood pressure and cardiac output despite a fall in wedge pressure and esophageal pressure is shown during a brief interruption in positive pressure ventilation in a patient with COPD.

This constellation of problems is best avoided by:

- Awareness of their existence
- Reading pressure tracings at end expiration
- Considering measures (sedation, ventilator adjustment, paralysis) that diminish or eliminate PEEPi
- Considering a ventilator disconnect in patients with severe airflow obstruction and PEEPi to demonstrate limitation to venous return
- Using a fluid challenge when effective "diastolic" dysfunction may be present, to determine "preload reserve"

In determining the response to a fluid challenge, it is necessary to note that a minimum of 500 mL of crystalloid is required, and even then small effects on cardiac output and arterial blood pressure are typically seen.

Specific Disorders: Tricuspid regurgitation is encountered in conditions with direct valvular injury (eg, endocarditis) and generally in right heart failure. It is characterized by a prominent and broad V wave and a steep y-descent; the latter is often most useful for making this

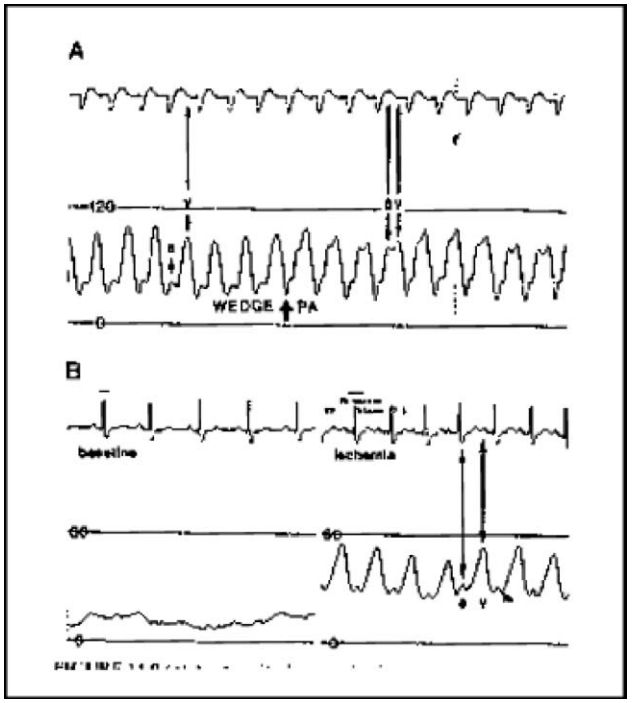

Figure 14. *A,* Acute mitral regurgitation with giant V wave in pulmonary wedge tracing. The pulmonary artery (PA) tracing has a characteristic bifid appearance due to both a PA systolic wave and the V wave. Note that the V wave occurs later in the cardiac cycle than the PA systolic wave, which is synchronous with the T wave of the electrocardiogram. *B,* Intermittent giant V wave due to ischemia of the papillary muscle. Wedge tracings are from same patient at baseline and during ischemia. Scale in mm Hg. Reprinted with permission from *ACCP Critical Care Medicine Board Review.* 20th ed. Northbrook, IL: American College of Chest Physicians; 2009.

diagnosis (Fig 13). It is useful to note tricuspid regurgitation not only for its implications for underlying disorders but also because it will confound thermal dilution cardiac output determination.

PA and PCWP tracings are shown in Figure 14. Significant mitral regurgitation may be present without a giant V wave (ascribed to enlarged and compliant left atrium that does not exhibit a large pressure excursion with the additional volume), and a number of conditions can cause a giant V wave in the absence of mitral regurgitation (hypervolemia, ventricular septal defect).

Right ventricular infarction is characterized by an elevated right ventricular end-diastolic pressure at initial passage of the catheter with narrow PPs when there is hemodynamic compromise. This same pattern can also be present in conditions causing acute right heart failure secondary to increases in pulmonary vascular resistance (eg, pulmonary embolus), but in these latter conditions there will be a large Ppad-PCWP gradient reflecting the increase in pulmonary vascular resistance.

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Chapter 11. Tachycardia and Bradycardia in the ICU

Frank Zimmerman, MD

Objectives:

- Understand basic electrophysiology and mechanisms of arrhythmias.
- Understand the incidence and management of common arrhythmias post-myocardial infarction.
- Understand the causes and management of bradycardia and heart block.
- Understand the differential diagnosis and acute management of tachycardias.
- Understand the diagnosis and management of ventricular arrhythmias.

Key words: antiarrhythmic medications; arrhythmias; bradycardia; supraventricular tachycardia; ventricular tachycardia

Synopsis:

Arrhythmias are common in the ICU setting and can be caused by a variety of reasons. The most common cause of arrhythmias in the ICU is metabolic disturbances. Tachyarrhythmias may occur in 12% to 78% of patients. Approximately 12% of patients develop sustained arrhythmias, and up to 78% have isolated premature atrial contractions or premature ventricular contractions. Both tachycardia and bradycardia may occur in the setting of acute myocardial infarction. Post-myocardial infarction tachycardias occur in 10% to 20%, with the most common being atrial fibrillation. Sustained ventricular tachycardia or ventricular fibrillation occur in <5% of patients usually in the first 4 h after ST-segment elevation myocardial infarction. The main principle in managing arrhythmias is to first evaluate the patient. This will help to determine the urgency and type of treatment based on the underlying cardiac status.

Basic Electrophysiology

Cellular Action Potential

The normal cardiac transmembrane potential is such that the inside of the cell is 50 to 95 mV negative relative to the outside of the cell. This resting potential of the cell is maintained by selective permeability of the membrane to sodium, potassium, and chloride ions and in large part to the sodium-potassium pump. If an external stimulus or a spontaneously generated current of sufficient amplitude occurs, the cell membrane becomes permeable to extracellular positively charged sodium ions that rush into the cell (depolarization) and result in an action potential to develop.

There are two distinct types of cell action potentials (Fig 1). The fast response or sodium channel action potential occurs in atrial muscle cells, His-Purkinje cells, ventricular muscle cells, and accessory pathways. Depolarization (phase 0) is caused by rapid influx of sodium ions into the cell. Repolarization (phase 1) is caused primarily by the transient outward potassium current. The plateau phase of repolarization (phase 2) is caused by a competition between inward movement of calcium ions and outward movement of potassium ions. The completion of repolarization (phase 3) is caused primarily by outward movement of potassium ions. The resting membrane potential (phase 4) occurs at around negative 80 mV to 90 mV and is relatively stable.

The second type of action potential is the slow response or calcium channel action potential. This is found in sinus node cells, atrioventricular (AV) node cells, or in damaged or ischemic cardiac cells. Depolarization (phase 0) is caused primarily by influx of calcium ions. Repolarization is caused by movement of potassium ions out of the cell. The resting membrane potential occurs at approximately –60 mV. There is gradual spontaneous depolarization during the resting membrane potential (phase 4), accounting for the property of automaticity in these types of cells. This is caused by an inward current (pacemaker current) carried by sodium and potassium ions.

Cell-to-Cell Conduction

Conduction throughout the heart occurs if a single cell action potential is able to stimulate its neighboring tissue. This is facilitated by cell-cell connections known as gap junctions. These

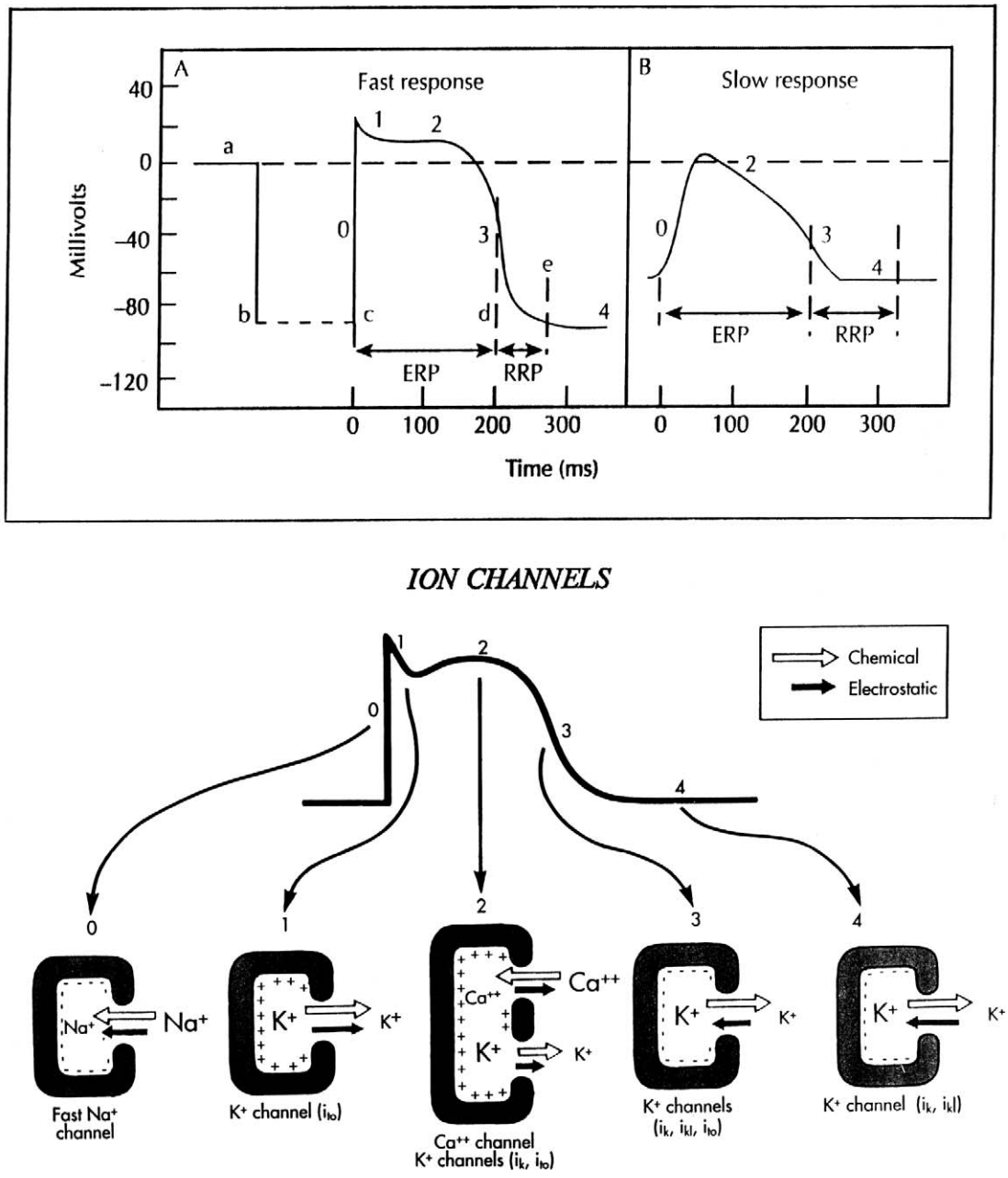

Figure 1. Cardiac action potentials.

permit a multicellular structure to function electrically like a synchronized unit. For repeated stimuli to be conducted, the cells must have sufficient time to recover between stimuli. If the stimulus is premature, the neighboring cells may not have time to recover completely and the impulse will not be conducted. The time a cell requires to recover before it can be depolarized is known as the refractory period. Many drugs or medications (eg, antiarrhythmic medications) may affect the refractory period of cells, thus affecting conduction through the heart.

Sinus Node

The sinus node is a group of cells in the superolateral portion of the right atrium with automaticity responsible for generating the impulse of the heart (heart beat). This area is actually a collection of cells with slow response (calcium channel) action potentials but with different rates of automaticity. The cells of the sinus node are influenced by vagal nerve inputs (decreases automaticity) and circulating catecholamines (increases automaticity).

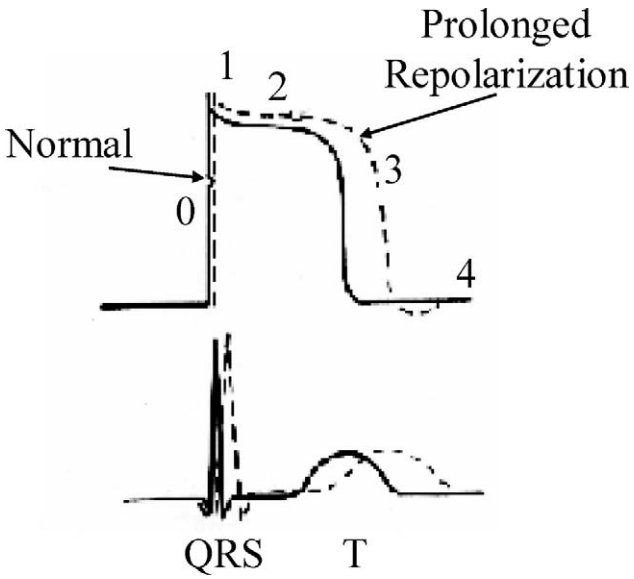

Figure 2. Prolonged repolarization manifests as prolonged QT interval on ECG.

Table 1—*Causes of Repolarization Abnormalities*

ST-Segment or T-wave abnormalities
Drugs or medications
Myocardial ischemia
LV hypertrophy with strain
Cardiomyopathy
Metabolic abnormalities
Neurologic disorders
Hyperventilation
Mitral valve prolapse
Stress
Postural changes
Pericarditis
GI disorders
Endocrine disorders
Prolonged QT interval
Congenital (autosomal dominant or recessive)
Drugs or medications
Cardiomyopathy
Neurologic disorders
MI
Metabolic abnormalities

AV Node

The AV node is a group of cells in the crux of the heart that maintain electrical continuity between the atria and the ventricles. Similar to sinus node cells, the AV node is a cluster of cells with slow response action potentials but with different conduction and refractory properties. Automaticity from this portion of the conduction system is usually slower than automaticity from sinus node area. AV node cells are also influenced by vagal inputs (slow conduction and automaticity) and circulating catecholamines (increases conduction and automaticity).

His-Purkinje System

The His-Purkinje system is the portion of the conduction system below the AV node responsible for ventricular conduction. This system consists of cells with fast response (sodium channel) action potentials. Automaticity from this system is slower and less reliable than automaticity from the AV node. Conduction through the His-Purkinje system is minimally influenced by vagal inputs. Abnormal conduction can be seen with congenital heart disease or severe metabolic abnormalities. Right or left bundle branch block is commonly seen following cardiac surgery or myocardial infarction. Another common phenomenon is known as rate-related bundle-branch block. This occurs if a rapid atrial tachycardia is conducted through the AV node normally but finds either the right (or less commonly the left) bundle refractory causing bundle branch block.

Ventricular Repolarization

Ventricular repolarization is primarily caused by the outward flow of potassium channels during phases 1, 2, and 3 of the action potential. Repolarization abnormalities are manifest as abnormalities in the ST-segment, T wave, or QT interval on the 12-lead ECG (Fig 2). Some common causes of repolarization abnormalities are shown in Table 1.

Benign Arrhythmias

Several benign arrhythmias may be seen in the ICU setting. These include premature atrial beats, premature ventricular beats, or accelerated junctional or ventricular rhythms. Although these arrhythmias are usually well tolerated, they may cause hemodynamic instability in critically ill patients. If metabolic abnormalities or mechanical causes such as intracardiac central lines or thrombi have been addressed, treatment with antiarrhythmic agents may be warranted.

Table 2—*Causes of Sinus Bradycardia*

Increased vagal tone
Anatomic changes to the sinus node
Drugs (eg, β-blockers, digoxin, calcium channel blockers, antiarrhythmic agents, cholinergic agents, lithium)
Anorexia nervosa
Cardiac transplant
Obstructive jaundice
Hypoxia
Hypothermia
Pneumothorax
Cardiac tamponade
Toxins
Metabolic abnormalities (eg, acidosis, hypokalemia, hyperkalemia)
Endocrine abnormalities (eg, hypothyroidism, hypoglycemia)
Cardiomyopathy
Collagen vascular disease
Neurologic disease (increased intracranial pressure)
Infectious disease (eg, sepsis, endocarditis, myocarditis, Chagas disease)
MI or myocardial ischemia

Bradyarrhythmias

Sinus Bradycardia

Sinus bradycardia is defined as a rhythm arising from the sinus node area but at a rate lower than 60/min. Some of the common causes of sinus bradycardia are listed in Table 2. Anatomic change to the sinus node, resulting in sinus node dysfunction, is one of the most common causes of bradycardia in elderly patients. The term "sick sinus syndrome" encompasses a number of sinus node abnormalities, including (1) persistent sinus bradycardia not caused by extrinsic causes; (2) sinus arrest or exit block; (3) a combination of sinus and AV node conduction abnormalities; and (4) sinus bradycardia in combination with paroxysmal episodes of atrial tachycardia (bradycardia-tachycardia syndrome). When sinus bradycardia is seen in conjunction with AV block, increased vagal tone should be suspected (eg, vasovagal response). This is often confirmed if the physiologic circumstances are appropriate. Therapy for sinus bradycardia is directed at the cause and any associated symptoms. Acute management of sinus bradycardia includes the use of medications such as isoproterenol, dopamine, epinephrine, or atropine (when the cause is thought to be the result of increased vagal tone). Temporary cardiac pacing can be employed using transvenous or transcutaneous systems. Management of the bradycardia-tachycardia syndrome is a particular challenge, often requiring the use of a temporary or permanent pacemaker to prevent severe bradycardia to allow administration of antiarrhythmic medications.

AV Block

AV nodal block (heart block) refers to disturbance of normal conduction between the atrium and the ventricles. Heart block is categorized into first-degree block, second-degree block (types 1 and 2), and third-degree or complete AV block (Fig 3).

First-degree AV block occurs when the PR interval is greater than the upper limits of normal for age. This is usually caused by slowed conduction through the AV node but can also be caused by slowed conduction between the sinus node and the AV node as with diseases of the atria. Conditions associated with first-degree AV block include rheumatic fever, Chagas disease, rubella, mumps, hypothermia, cardiomyopathy, metabolic abnormalities, and hypervagotonia. A number of medications may also cause this finding. Acute treatment is usually not indicated for first-degree AV block. However, this may be a warning sign as to the development of higher grade AV block caused by one of the aforementioned abnormalities.

Second-degree AV block is divided into Mobitz type I block (Wenckebach) and Mobitz type II block. Wenckebach block occurs when there is progressive lengthening of the PR interval followed by a nonconducted P wave. This usually indicates slowed conduction in the AV node tissue and can be seen most commonly in instances of hypervagotonia. Mobitz type II block is seen less commonly but thought to indicate more significant conduction system disease. It is manifested as a nonconducted P wave with no progressive lengthening of the PR intervals seen in preceding beats. It usually indicates disease in the conduction system below the AV node (His-Purkinje system) and is associated with various forms of a congenital heart disease, cardiomyopathies, injury following cardiac surgery, or following acute myocardial infarction.

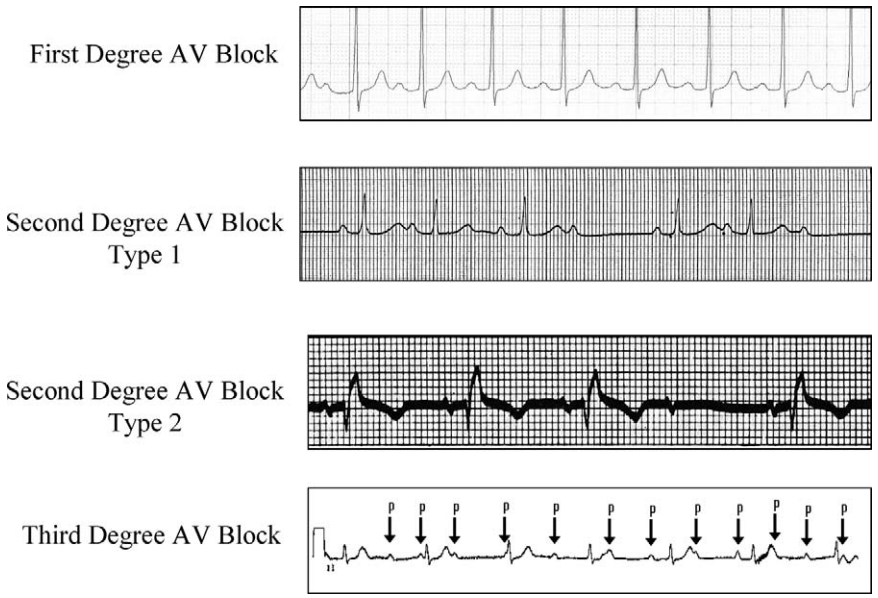

Figure 3. Types of AV block.

Complete heart block or third-degree block is characterized by the absence of communication of electrical activity between the atria and ventricles. Causes of complete AV block include injury from surgery, hypervagotonia, metabolic abnormalities, cardiomyopathy, congenital (usually caused by maternal lupus), infectious disorders (eg, Lyme disease, Chagas disease), drugs or medications, hypoxia, hypothermia, or collagen vascular disorders.

Acute management of AV block is directed at reversible causes. Treatment with medications such as isoproterenol, epinephrine, or atropine can be used. Ventricular pacing either with transvenous or epicardial pacing wires can be performed. Transcutaneous pacing can be used in emergent situations.

Bradycardia and Acute ST-Segment Elevation Myocardial Infarction

Bradycardia following acute myocardial infarction (MI) may occur because of disruption of blood flow to the sinus node, AV node, or His-Purkinje system. It may also be caused by increased vagal tone (seen mostly with inferior MI) or other factors such as increases in local adenosine, hyperkalemia, or systemic metabolic derangements. Sinus bradycardia occurs frequently and accounts for up to 50% of acute myocardial infarction-associated arrhythmias. AV block may occur in 6% to 14% of patients, with the majority being first-degree AV block. Intraventricular conduction delay may occur in 10% to 20% of patients with acute myocardial infarction. Although indicative of extent of ischemia/infarction, AV block is not predictive of long-term mortality in those who survive to hospital discharge.

Treatment of sinus bradycardia is recommended if there is significant hemodynamic compromise, sinus pauses >3 s, or heart rate <40/min associated with hypotension. Atropine may be effective in the first 6 h after inferior MI because of the increase in parasympathetic tone. Glucagon may be effective for bradycardia cause by toxic doses of β-blockers or calcium channel blockers. Isoproterenol and aminophylline should be avoided as they may increase myocardial oxygen demands and worsen the ischemic zone. Recommendations for temporary transcutaneous or transvenous pacing in patients with acute myocardial infarction are shown in Table 3.

Tachyarrhythmias

Mechanism

The mechanisms of arrhythmias are commonly classified as caused by abnormal automaticity, reentry, or triggered automaticity. Automatic tachycardias behave similar to sinus

Table 3—*Recommendations for Temporary Pacing After Acute Myocardial Infarction*

Class I
1. Asystole
2. Symptomatic bradycardia
3. Bilateral bundle-branch block
4. New bifascicular block with first-degree AV block
5. Mobitz type II, second-degree AV block
Class IIa
1. RBBB with LAFB or LPFB
2. RBBB with first-degree AV block
3. New LBBB
4. Overdrive pacing for incessant VT
5. Sinus pauses >3 s
Class IIb
1. Bifascicular block
2. New RBBB
Class III
1. First-degree AV block
2. Mobitz type I, second-degree AV block
3. Accelerated idioventricular rhythm
4. Pre-existing BBB

RBBB = right bundle-branch block; LAFB = left anterior fascicular block; LPFB = left posterior fascicular block; VT = ventricular tachycardia; BBB = bundle-branch-block.

rhythm in that there is a warm-up and cool-down pattern to initiation and termination. They are sensitive to catecholamines and not able to be terminated with cardioversion or overdrive pacing. Automatic tachycardias include ectopic or multifocal atrial tachycardia, junctional tachycardia, and some ventricular tachycardias (VT). Reentry tachycardias may occur in the atrium, ventricle, or within the AV junction. Three conditions are usually present for reentry to occur: unidirectional conduction block, two or more conduction pathways, and slow or delayed conduction. Reentry tachycardias include atrial flutter, AV node reentry tachycardia, AV reentry tachycardia, and some ventricular tachycardias (postinfarct, idiopathic left ventricular [LV]). Reentry tachycardias have an abrupt onset and termination, can be started and stopped with pacing, and are responsive to cardioversion. Triggered reentry tachycardias are caused by spontaneous depolarizing currents occurring during phase 3 of the action potential. These are described as early afterdepolarizations (torsade de pointes) or delayed after depolarizations (digoxin toxicity). Arrhythmias caused by triggered automaticity have features of both automaticity and reentry and may be terminated with cardioversion or pacing.

Sinus Tachycardia

Sinus tachycardia is defined as an accelerated rhythm arising from the sinus node area >100/min. Sinus tachycardia is often caused by increased levels of circulating catecholamines. The ECG features include a narrow complex QRS tachycardia with a one-to-one relationship between the atria and ventricles and P-wave morphology identical to that seen during normal sinus rhythm. The management of sinus tachycardia is directed at the underlying etiology.

Ectopic Atrial Tachycardia

Ectopic atrial tachycardia is defined as an abnormal tachycardia arising from a single focus or cluster of cells in the atrium outside of the sinus node area. Rates may vary but are usually between 150 to 200/min. Ectopic atrial tachycardia may occur as a primary arrhythmia in patients with a structurally normal heart or may be caused by excessive catecholamine or metabolic abnormalities. It may also be seen as a transient phenomenon in postoperative patients following surgery for cardiac disease. The ECG shows a narrow complex QRS tachycardia with an abnormal P-wave morphology and a one-to-one relationship between the atria and ventricles (Fig 4). At times, there may be AV dissociation with persistence of tachycardia. The management includes treatment of any underlying metabolic or electrolyte abnormalities (eg, digoxin toxicity). Antiarrhythmic agents may be used to control the ventricular response rate (AV nodal blocking agents) or convert the rhythm to a sinus rhythm. Ectopic atrial tachycardias are usually not responsive to the direct current (DC) cardioversion or IV adenosine.

Multifocal Atrial Tachycardia

Multifocal atrial tachycardia is defined as multiple ectopic foci arising from the atrium resulting in an atrial tachycardia. Multifocal atrial tachycardia is usually associated with pulmonary disease, heart failure, or administra-

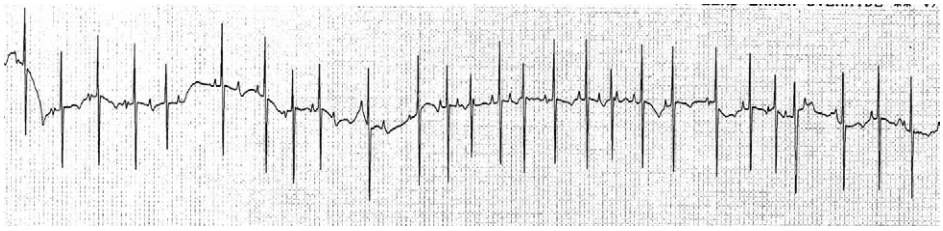

Figure 4. Ectopic atrial tachycardia.

tion of theophylline. The ECG findings are consistent with a narrow complex tachycardia with variable AV conduction and multiple P-wave morphologies. The treatment is similar to that for ectopic atrial tachycardia.

Junctional Ectopic Tachycardia

Junctional ectopic tachycardia (JET) is an automatic tachycardia arising from the AV node or AV junction. It results in a narrow complex tachycardia with variable heart rates. Junctional ectopic tachycardia is most often seen in the immediate postoperative period following cardiac surgery. The etiology of junctional ectopic tachycardia has been proposed to be caused by a combination of stretching or irritation of AV junction tissue during surgery, metabolic abnormalities, and/or use of inotropic medications in the postoperative period. The ECG shows a narrow complex tachycardia with variable rates and either retrograde P waves or ventriculo-atrial (VA) dissociation (Fig 5). The management of postoperative JET has evolved with time and currently involves cooling the patient (or avoiding fever), decreasing use of inotropes (if possible), and correcting metabolic abnormalities. Medications such as IV procainamide or IV amiodarone may be used if the arrhythmia persists.

Atrial Fibrillation

Atrial fibrillation is the most common narrow complex arrhythmia in the ICU. It is a chaotic atrial tachycardia with variable ventricular response. The ECG shows an irregular chaotic baseline with variable and often irregular ventricular response rate (Fig 6). Risk factors include advanced age, structural heart disease, hypertension, left ventricular hypertrophy, and valvular heart disease. Toxic and metabolic abnormalities such as thyrotoxicosis may account for a substantial portion of atrial fibrillation in the ICU. Atrial fibrillation following cardiac surgery is common with an incidence of 25% to 40% (peak postoperative day 2). This usually resolves in more than 90% of patients by 6 to 8 weeks after surgery. Atrial fibrillation may be paroxysmal (spontaneous conversion to sinus rhythm), persistent (requiring intervention to convert to sinus rhythm), or permanent (unresponsive to interventions). Treatment includes control of ventricular rate with AV nodal blocking agents or chemical cardioversion with class I or class III antiarrhythmic agents. DC cardioversion is also effective and the treatment of choice if there is associated hemodynamic instability. Conversion of atrial fibrillation that has persisted for greater than 48 h is associated with an increased risk for stroke. Therefore, anticoagulation and echocar-

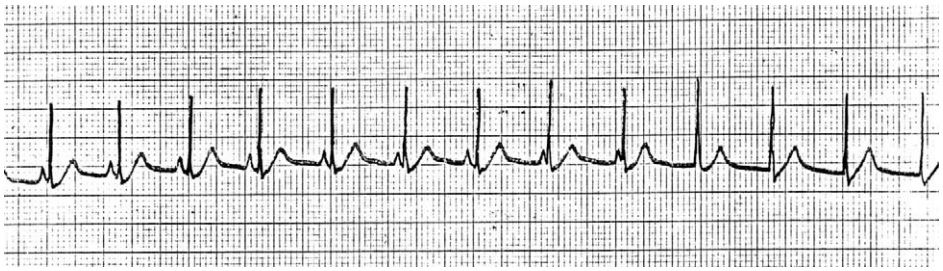

Figure 5. Junctional ectopic tachycardia.

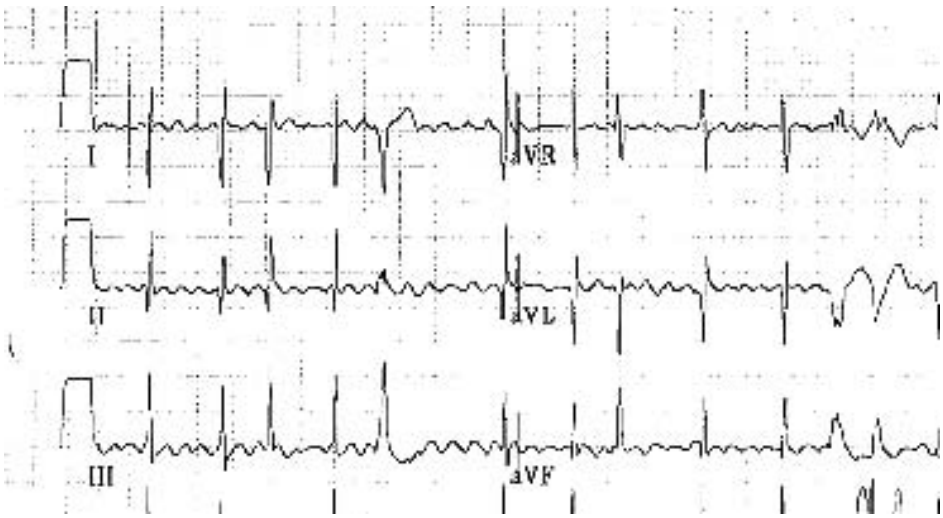

Figure 6. Atrial fibrillation.

diographic evaluation is recommended prior to cardioversion.

Atrial Flutter

Atrial flutter is defined as a single reentry loop of electrical activity contained within the atrium. It may occur in those without structural heart disease or as a result of toxic or metabolic conditions such as thyrotoxicosis, alcoholism, or pericarditis. It is often associated with structural heart diseases such as mitral stenosis, cardiomyopathy, or congenital heart diseases such as atrial septal defects. This is presumably caused by a combination of surgical atrial incisions and scarring as well as pressure and volume overload. The typical ECG findings include either discrete or a sawtooth pattern of P waves with rates of 250 to 350/min (Fig 7). There is variable AV conduction. Acute management includes control of the ventricular response with AV nodal blocking agents such as digoxin, β-blockers, or calcium channel blockers. Chemical cardioversion can be performed with medications such as procainamide, amiodarone, or ibutilide. Atrial overdrive pacing can be used to terminate the tachycardia as well as DC cardioversion. IV adenosine is usually not effective for termination of atrial flutter but may unmask the atrial arrhythmia, leading to the correct diagnosis. Conversion of atrial flutter that has persisted for greater than 48 h is associated with an increased risk for stroke. Therefore, anticoagulation and echocardiographic evaluation is recommended prior to cardioversion.

AV Reentry Tachycardia

AV reentry tachycardia is a result of a reentry circuit using both atrial and ventricular tissue. The reentry circuit involves the AV node as one limb and an accessory AV connection as the other

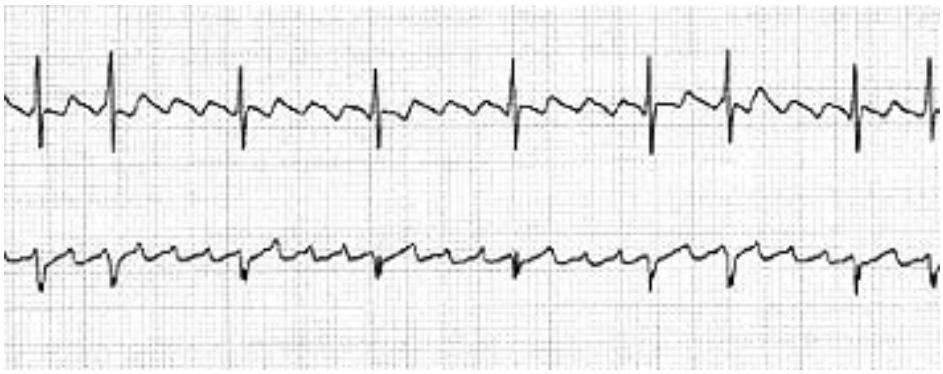

Figure 7. Atrial flutter.

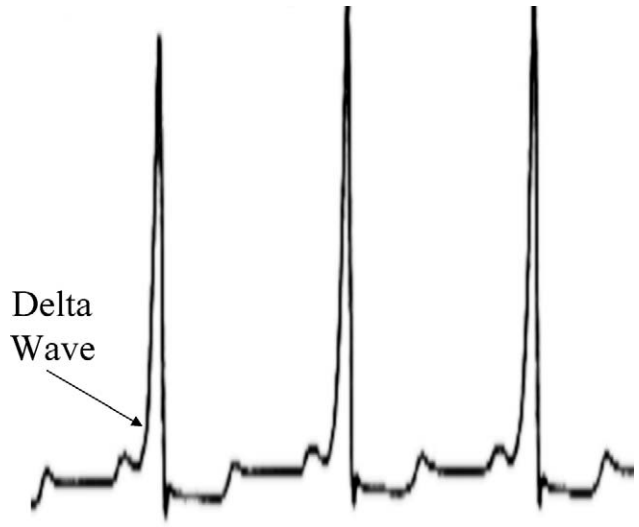

Figure 8. Ventricular pre-excitation.

limb. Accessory AV connections are described as muscle fibers or strands that pierce through the fibrous ring of the AV valves and allow for electrical continuity of the atria and ventricles. The presence of accessory AV connections results in a number of syndromes and tachycardias as described below:

1. Pre-excitation: Ventricular pre-excitation is defined as a short PR interval on ECG with a slurred and widened QRS complex. The initial portion of the slurred QRS complex is known as the delta wave (Fig 8).
2. Orthodromic reciprocating tachycardia (ORT): ORT is the most common form of tachycardia seen in patients with accessory AV connections. The reentry circuit during ORT consists initially of conduction from the atrium to the ventricle over the AV node (antegrade). The retrograde limb from the ventricle back up to the atrium occurs over the accessory AV connection. Tachycardia rates range between 150 to 250/min. The ECG shows a narrow complex QRS tachycardia with no pre-excitation and retrograde P waves (Fig 9).
3. Antidromic reciprocating tachycardia (ART): ART accounts for less than 10% of AV reentry tachycardias. The tachycardia circuit is opposite of that seen with ORT. Conduction from the atrium down to the ventricle occurs over the accessory connection (antegrade) and back up to the atrium via the AV node (retrograde). The ECG shows a wide complex QRS tachycardia with the QRS pattern similar to ventricular pre-excitation seen during sinus rhythm. There are also retrograde P waves usually buried in the QRS complex.

AV reentry tachycardia occurs with an incidence of 1 to 3:1,000 patients. Among those with AV reentry tachycardia, 20% have associated congenital heart disease (eg, Ebstein's anomaly of the tricuspid valve). The combination of ventricular pre-excitation and clinical episodes of tachycardia is known as Wolff-Parkinson-White (WPW) syndrome. The incidence of sudden cardiac death with WPW syndrome is approximately 1.5 per 1,000 patient years and is caused by rapid antegrade conduction over the accessory connection.

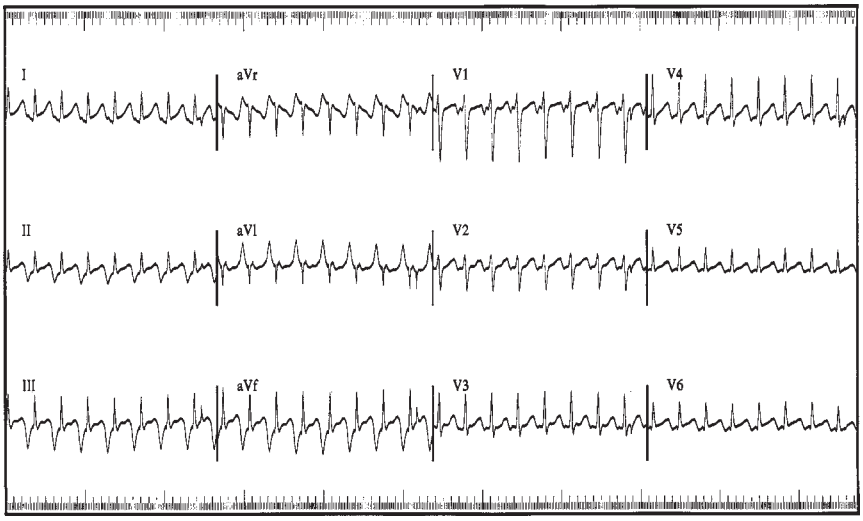

Figure 9. Orthodromic reciprocating tachycardia.

Table 4—*Differential Diagnosis of SVT*

Mode of Initiation	Mechanism
1. Warm up, cool down	Sinus tach, EAT, JET
2. Abrupt onset, termination	AVNRT, AVRT, atrial flutter
Regular SVT	AVNRT, AVRT, atrial flutter
Irregular SVT	Atrial fibrillation, MAT
Response to Vagal/Adenosine	
1. Abrupt termination	AVNRT, AVRT
2. Gradual slowing/no response	Sinus tach, EAT, MAT, atrial fibrillation, atrial flutter

EAT = ectopic atrial tachycardia; JET = junctional ectopic tachycardia; AVNRT = AV node reentry tachycardia; AVRT = AV reentry tachycardia; MAT = multifocal atrial tachycardia.

Acute management of AV reentry tachycardia includes vagal maneuvers, adenosine, β-blockers, digoxin, or calcium channel blockers causing slowed AV node conduction and termination of tachycardia. DC cardioversion or atrial overdrive pacing can also be effective. Class I or class III antiarrhythmic agents may also be used in resistant cases. In patients with atrial fibrillation and ventricular pre-excitation, AV nodal blocking agents should be avoided as this may promote more rapid conduction over the accessory pathway, leading to increased risk of ventricular arrhythmias. In these cases, DC cardioversion or use of class I or class III antiarrhythmic agents should be initiated.

AV Nodal Reentry Tachycardia

AV nodal reentry tachycardia is caused by a reentry circuit involving fast and slow conducting cells within the AV junction. These pathways occur in up to 30% of patients and are thought to develop over time. This accounts for the fact that this arrhythmia is the most common narrow complex tachycardia in adults. The rate of tachycardia is usually slower than ORT and may vary depending on the amount of circulating catecholamines. The ECG shows a narrow complex QRS with retrograde P waves. Treatment is similar for AV reentry tachycardia.

Differential Diagnosis

The mechanism of narrow complex tachycardias can be aided by assessing mode of initiation, regularity during SVT, and response to vagal maneuvers or adenosine (Table 4).

The relationship of the P-wave to the QRS complex may also help with the mechanism of tachycardia. Short R-P tachycardias (R-P < P-R) include AV node reentry tachycardia (<70 ms) or AV reentry tachycardia (>70 ms). Long R-P tachycardias (P-R > R-P) include sinus or ectopic atrial tachycardia, atypical AVNRT, or AVRT with slow conduction (permanent junctional reciprocating tachycardia).

Ventricular Tachycardia

VT is defined as an abnormal accelerated rhythm arising from below the bundle of His. The mechanisms of ventricular tachycardia include reentry, automaticity, or triggered automaticity. Ventricular tachycardia may be monomorphic or polymorphic, sustained (greater than 30 s), or nonsustained (at least three beats). Ventricular tachycardia arising from either the right ventricular outflow tract (RVOT VT) or the left ventricular apex (idiopathic LV VT) can occur in patients with a structurally normal heart and usually carries a benign prognosis. Malignant ventricular arrhythmias may occur in the setting of metabolic abnormalities or following cardiac surgery. Nonsustained VT occurs frequently within the first 48 h after acute MI but has no prognostic significance. However, nonsustained VT occurring more than 1 week after acute MI increases risk for sudden cardiac death, especially in those with reduced LV function.

The ECG during VT shows a wide complex tachycardia with variable rates and either retrograde P waves or VA dissociation (Fig 10). The differential diagnosis of a wide QRS complex arrhythmia includes SVT with aberrancy, antidromic reciprocating tachycardia (ART), or SVT with fixed pre-existing bundle-branch block. ECG criteria have been described to help

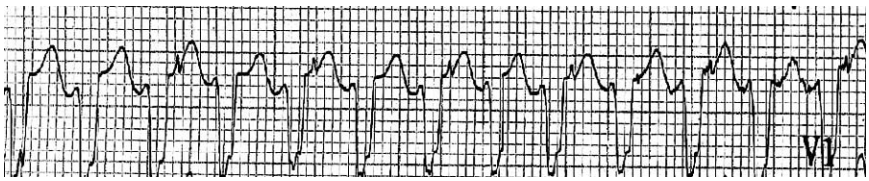

Figure 10. Ventricular tachycardia with VA dissociation.

differentiate VT from SVT with aberrancy (Table 5). An unstable, polymorphic ventricular tachycardia with a distinct sinusoidal pattern on ECG (torsade de pointes) has been described in patients with prolongation of the QT interval.

Management of ventricular tachycardia begins with documentation of the arrhythmia ideally with a 12-lead ECG to confirm the diagnosis and assessment of hemodynamic stability. Acute therapy for symptomatic, hemodynamically unstable ventricular tachycardia is defibrillation. Intravenous amiodarone, lidocaine, or procainamide may be used in resistant VT. VT with stable hemodynamics can be treated with medications or DC cardioversion. Verapamil or β-blockers have been described for treatment of RVOT or idiopathic LV tachycardias. Acute therapy for torsade de pointes includes IV magnesium, isoproterenol, overdrive pacing, or defibrillation. Prophylactic treatment of premature ventricular contractions, couplets, or nonsustained VT post-MI is not recommended unless they are associated with hemodynamic compromise.

Miscellaneous Causes of Cardiac Electrical Disturbances

- Electrolyte abnormalities:
  1. Hyperkalemia: Tall, narrow (peaked) T waves, diffuse widening of the QRS, ST-segment elevation or depression, sine-wave QRS pattern, AV block, sinus arrest, ventricular fibrillation.
  2. Hypokalemia: ST-segment depression, reduced T-wave amplitude, U waves, prolonged QTU interval.
  3. Hypercalcemia: Short QT interval.
  4. Hypocalcemia: Prolonged QT interval, flattened T waves.
  5. Hypermagnesemia: Possible prolonged PR interval, AV block.
  6. Hypomagnesemia: Similar to hypokalemia.
- CNS disease: Inverted T waves, prolonged QT interval, U waves, ST-segment depression or elevation.
- Hypothermia: Bradycardia, prolonged PR or QT interval, Osborn wave, atrial fibrillation.
- Pneumothorax: Shift of QRS axis, decreased QRS voltage, T-wave inversions.
- Digoxin toxicity: ST-segment depression (hockey stick appearance), short QT interval, mild PR prolongation, premature ventricular contraction, accelerated junctional rhythm, SVT with AV block, bradycardia, AV block, VT, VF.
- Hyperthyroidism: Prolonged PR interval, U waves, SVT, atrial fibrillation.
- Hypothyroidism: T-wave flattening, prolonged QT, bradycardia, low-voltage QRS.

Table 5—*Criterion for Differentiating VT From SVT With Aberrancy*

Favors VT	Favors SVT With Aberrancy
Fusion beats	Terminates with vagal maneuver
AV dissociation	Onset with P wave
Compensatory pause	Long-short (Ashman's phenomenon)
Left axis deviation	Critical rate for aberrancy
Concordance of QRS in precordial leads	Alternating bundle branch block
QRS morphology	QRS morphology
1. Absence of RS in leads V_1–V_6	1. rSR′ in V_1 (RBBB)
2. R-S interval > 100 msec	2. Triphasic QRS in V_6 (LBBB)
3. Monophasic R, Rr′ in V_1 (RBBB)	
4. Notched S in V_1 (LBBB)	

Table 6—*Commonly Used Cardiac Medications*

Medication	Dosage	Comments
Antiarrhythmics		
Procainamide	10–20 mg/kg, 1–4 mg/min	
Amiodarone	150–300 mg IV, 1 mg/min × 6 h, then 0.5 mg/min	
Lidocaine	0.5-1.5 mg/kg IV/IO, 30–50 mcg/kg/min	May repeat dose every 5–10 min
Ibutilide	1 mg IV over 10 min	May repeat dose
Atenolol	5 mg IV/IO over 5 min	May repeat dose
Metoprolol	5 mg IV/IO over 5 min	Max 15 mg
Esmolol	0.5 mg/kg, 50-200 mcg/kg/min	
Propranolol	0.1 mg/kg IV	May repeat dose
Verapamil	2.5–5 mg IV over 3 min, repeat with 5–10 mg IV	
Diltiazem	15–20 mg (0.25 mg/kg) over 2 min, 5–15 mg/h	
Digoxin	0.5–1 mg IV	Divided 50% initially, then 25% × 2 every 8 h
Inotropes		
Dopamine	2–10 mcg/kg/min	
Epinephrine	1 mg IV/IO, 2–10 mcg/min	
Isoproterenol	2–20 mcg/min IV	
Others		
Adenosine	6–12 mg IV push	May repeat dose
Atropine	0.5–1 mg IV/IO	<0.5 mg dose may cause bradycardia
Vasopressin	40 units IV/IO	
Magnesium	1–2 g IV/IO	
Glucagon	3 mg IV, 3 mg/h	

- Adrenal insufficiency: Bradycardia, low-voltage QRS, prolonged QT, AV block, inverted T waves.

Nothing to Disclose

The author has disclosed that no relationships exist with any companies/organizations whose products or services may be discussed in this chapter.

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Chapter 12. Infections in AIDS Patients and Other Immunocompromised Hosts

George H. Karam, MD, FCCP

Objectives:

- Propose an approach to the immunocompromised patient based on identification of defects in three major host defense systems.
- Review the likely pathogens, their clinical presentations, and therapeutic options in patients with neutropenia.
- Summarize the various limbs in humoral immunity, with particular attention to the clinical situations of asplenia and splenic dysfunction.
- Outline the categories and clinical presentations of pathogens likely to be encountered with deficits of cell-mediated immunity.
- Focus on the broadening number of clinical issues in patients whose cell-mediated immunity defect is on the basis of HIV infection.

Key words: asplenia; cell-mediated immunity; HIV; humoral immunity; neutropenia

Synopsis:

The identification of a defect in neutrophil function, humoral immunity, or cell-mediated immunity allows the clinician to better focus on the most likely pathogens involved in an infectious process. An approach to the immunocompromised patient based on pathogenesis of disease should result in more directed, cost-effective therapy and in improved patient outcome.

In the clinical approach to patients with fever presumed to be infectious in etiology, a basic consideration is whether the patient is a normal host or one who is immunocompromised. A traditional method has been to consider host defense in immunocompromised patients as being in one of two categories: (1) mechanical factors, including barrier systems such as skin and mucous membranes (which are protective against infection) or foreign bodies such as intravascular and urinary catheters (which predispose to infection); and (2) cellular host defense, which includes the three major categories of primary neutrophil defense, humoral immunity, and cell-mediated immunity. Use of an approach that identifies the defective limb of host defense allows for directed therapeutic decisions that are based on likely pathogens for the involved site.

Attention has been focused on the concept of type 1 and type 2 immunity as they interrelate with humoral and cell-mediated immunity.[1] Subpopulations of $CD4^+$ lymphocytes are important in both humoral immunity and cell-mediated immunity, with T helper type 1 (Th1) and T helper type 2 (Th2) cells being the most relevant. All T helper lymphocytes start out as naive Th0 cells, which, after being activated, are capable of "polarizing" or differentiating into either Th1 or Th2 effector cells. Although multiple factors are involved, the key to polarization of Th0 cells into the Th1 phenotype is interleukin (IL)-12, whereas IL-4 is needed for Th2 polarization. These events may not occur until an activated T cell arrives at the site of danger and samples the local cytokine milieu to determine if an inflammatory or antibody response is appropriate. In questionable circumstances, the Th2 outcome is favored over the Th1 differentiation because IL-4 dominates IL-12. Th1 cells, which are involved with type 1 immunity, secrete interferon-gamma (IFN-7), IL-2, and lymphotoxin-a as the cytokines chiefly responsible for their proinflammatory effect. The Th1 cell is associated with strong cell-mediated immunity and weak humoral immunity. Th2 cells are involved with type 2 immunity, are influenced by IL-4, IL-10, and IL-13, stimulate high titers of antibody production, and are associated with suppression of cell-mediated immunity and with strong humoral immunity. When integrated into the traditional approach of cell-mediated immunity and humoral immunity, type 1 and type 2 immunity have important therapeutic implications in the care provided for immunocompromised patients.

Primary Neutrophil Function

The polymorphonuclear leukocyte is the major phagocyte for both primary neutrophil

defense and humoral immunity. Once a pathogen is ingested by these cells and is intracellular, killing is generally an easy process. Pathogens that classically infect patients with primary neutrophil problems are those that may be ingested without opsonization. The system of neutrophil defense has been described as being responsible for defending against organisms that are easy to eat and easy to kill.[2]

An important pathophysiologic consideration is that polymorphonuclear leukocytes may have either an extravascular or intravascular location. After leaving the bloodstream, these phagocytes go to two major sites: the subepithelial area of skin and the submucosal area of the GI tract. Recognition of this fact allows for an understanding of the organisms that classically infect neutropenic patients.

As represented in Table 1, neutrophil dysfunction may occur on either a qualitative or quantitative basis. Qualitative defects characteristically occur in children and are associated with polymorphonuclear leukocytes that are normal in number but abnormal in function. Classic qualitative defects of polymorphonuclear leukocytes are related to dysfunction in one of the following processes: (1) diapedesis (the ability to leave the intravascular space via endothelial channels); (2) chemotaxis (movement to the site of infection); (3) ingestion (the process of attaching to the pathogen and then getting that pathogen within the cell, where killing takes place); and (4) intracellular killing (which may occur via either oxygen-dependent or oxygen-independent mechanisms).

Quantitative defects, which are the more characteristic neutrophil problems in adults, clinically present as the entity interchangeably referred to as either granulocytopenia or neutropenia. Characteristic conditions that may lead to neutropenia are listed in Table 1. Although eosinophils are classified as granulocytes, for most clinical purposes the granulocyte count is calculated by adding the percentage of polymorphonuclear leukocytes and band forms, and then multiplying the total WBC count by that percentage. In the guidelines of the Infectious Diseases Society of America (IDSA) for management of febrile, neutropenic patients, a calculated granulocyte count of <500 cells/mm^3 indicates absolute neutropenia; a granulocyte count $<1{,}000$ cells/mm^3 with a predicted decline to <500 cells/mm^3 should be considered neutropenia.[3] In the setting of neutropenia and fever, the clinician must assume that the patient has impaired natural defense against the pathogens defended against by this limb of host defense.

The clinical course of patients with neutropenia is variable and may be explained in part by the integrity of the gut mucosa. In conditions such as aplastic anemia or HIV-associated neutropenia, the gut mucosa is usually intact, and those patients have a lower incidence of bacteremia. In contrast, patients who receive chemotherapeutic agents that cause mucositis have loss of both the mechanical barrier of gut mucosa and submucosal polymorphonuclear leukocytes. These patients are more likely to experience gram-negative bacteremia and fungemia.

Infections caused by bacteria are classically encountered when the neutropenia is either rapid in development or profound (especially with counts <100 cells/mm^3). The pathogens most likely to infect neutropenic patients are listed in Table 2. The bacteria characteristically involved are skin and gut flora, as might be predicted from the loss of subepithelial and submucosal polymorphonuclear leukocytes. Although any of the enterobacteriaceae (eg, *Escherichia coli* or *Klebsiella*) may cause infection in this setting, the most life-threatening pathogen is *Pseudomonas aeruginosa*. Because of this (and despite the relative decline in the incidence of infection caused by this pathogen in neutropenic patients), a basic principle in empiric therapy for febrile neutropenic patients is coverage of *P aeruginosa*. The classic skin lesion that suggests such an infection is ecthyma gangrenosum. These lesions have a central area of hemorrhage surrounded by a halo of uninvolved skin with a narrow pink or purple rim. Histologically, the infection involves dermal veins, and clinically it may progress to bullae formation. Although other gram-negative pathogens have been reported to cause such a process, the clinician should assume that ecthyma gangrenosum is caused by *P aeruginosa* until this pathogen has been excluded.

In recent years, infections caused by gram-positive organisms have significantly increased in neutropenic patients. These pathogens, which

Table 1—*Conditions Causing Neutrophil Dysfunction*

Qualitative Defects
Impaired diapedesis
Impaired chemotaxis
Impaired ingestion
Impaired intracellular killing
Quantitative Defects (Neutropenia)
Acute leukemia
Invasion of bone marrow by neoplasms
Treatment with agents toxic to marrow
Drug idiosyncrasy
Splenic sequestration syndromes
HIV-associated neutropenia
Idiopathic chronic neutropenia

Table 2—*Important Pathogens Causing Infection in Neutropenic Patients*

Gram-Positive Organisms
Staphylococcus aureus
Coagulase-negative staphylococci
Viridans streptococci
Enterococci
Corynebacterium jeikeium
Enterobacteriaceae
Pseudomonas aeruginosa
Anaerobes, including *Bacteroides fragilis*
Fungi
Yeasts, most notably *Candida* spp
Filamentous fungi, most notably *Aspergillus* spp

are listed in Table 2, have increased in part because of the expanded use of invasive devices such as intravascular catheters, which breach the mechanical barrier of the skin. The important clinical finding of cavitary pulmonary infiltrates may be a clue to infection by either *Staphylococcus aureus* or *Coryne-bacterium jeikeium*. Notable among the gram-positive pathogens is infection caused by viridans streptococci (eg, *Streptococcus mitis*), which may result in the viridans streptococcal shock syndrome. In a prospective study of 485 episodes of bacteremia in neutropenic patients with cancer,[4] viridans streptococci caused a total of 88 episodes (18%). Ten of these 88 cases (11%) were associated with serious complications, including ARDS plus septic shock (5 cases), ARDS (3 cases), and septic shock (2 cases). Of the patients with serious complications of their streptococcal bacteremia, 3 (30%) had a cutaneous rash, which in other reports has been associated on occasion with desquamation. Severe oral mucositis, high-dose chemotherapy with cyclophosphamide, and allogeneic bone marrow transplantation were the only variables found to be significantly associated with the development of complications. In patients with complications, 36% of these pathogens showed diminished susceptibility to penicillin, and approximately one half were resistant to ceftazidime. In one review,[5] two additional risk factors for viridans streptococcal bacteremia in neutropenic patients were cytosine arabinoside and antimicrobial prophylaxis with either trimethoprim/sulfamethoxazole or a fluoroquinolone.

The experience with antibiotic prophylaxis during the neutropenic period after autologous peripheral blood stem cell transplantation provides an important insight into a potential problem regarding viridans streptococci.[6] Despite the use of levofloxacin prophylaxis, viridans group streptococcal bacteremia developed in 6 of 37 patients (16.2%) who underwent transplantation over a 2-month period in 2001. All 6 patients presented with fever and mucositis after a mean of 4.5 days of neutropenia, and septic shock developed in 3 days. All six viridans group streptococcal isolates from these patients exhibited distinct patterns on pulsed-field gel electrophoresis. A conclusion of this paper was that the use of levofloxacin may select viridans group streptococci with diminished susceptibility to levofloxacin and other quinolones with enhanced activity against gram-positive organisms and, therefore, may not be optimal for preventing viridans group streptococcal bacteremia in neutropenic patients.

A life-threatening complication that may occur in patients who have received chemotherapy is neutropenic enterocolitis. Previously referred to as typhlitis because of the cecum as the predominant site in many cases, neutropenic enterocolitis may involve the terminal ileum, the cecum, and the colon (with the ascending portion the most frequently involved). Pathogenetically, the process may occur on several bases, including destruction of GI mucosa by chemotherapy, intramural hemorrhage caused by severe thrombocytopenia, and alterations in GI tract flora. Patients characteristically present with the triad of fever, abdominal pain, and diarrhea, but these findings may be seen with other conditions, including *Clostridium difficile* toxin-induced coli-

tis and ischemic colitis. Ultrasound findings include echogenic thickening of the mucosa and bowel wall. Although isodense cecal wall thickening is the most notable CT finding, the distal ileum and remaining colon are also frequently involved. Although optimal therapy has not been definitively established, conservative medical management appears to be effective for most patients.[7]

Although the level of temperature elevation that mandates antimicrobial therapy in neutropenic patients may be influenced by the degree of neutropenia, fever in neutropenic patients has been defined as a single oral temperature of >38.5° C (101° F) or as a temperature of ≥38.0° C (100.4° F) over at least 1 h. In such patients, empiric antibiotics should be started after appropriate cultures are obtained. Because the patients do not have adequate neutrophils to provide natural host defense, all antimicrobial agents administered should be bactericidal. The classic regimen has been an antipseudomonal β-lactam antibiotic (eg, piperacillin or ceftazidime) in combination with an aminoglycoside. Although some centers acknowledge a decreasing prevalence of infection caused by *P aeruginosa,* the recommendation for coverage against this pathogen in febrile neutropenic patients is prompted by the higher rates of mortality that may occur when this pathogen infects neutropenic patients. According to a review of 410 episodes of Pseudomonas bacteremia in patients with cancer from 1972 to 1981, outcome was related to the interval between the onset of the bacteremia and the institution of appropriate therapy.[8] Of the neutropenic patients in this study who had *P aeruginosa* bacteremia and in whom therapy was delayed, 26% died within 24 h and 70% died within 48 h. In an update of these data from 1991 to 1995 in the same institution, the incidence of *P aeruginosa* bacteremia decreased between the two study periods from 4.7 to 2.8 cases per 1,000 admissions.[9] *P aeruginosa* bacteremia remained the most common in acute leukemia, where the frequency did not change. Overall cure rate was 80% in the latter study period vs 62% in the earlier study. The outcome among 230 patients who received appropriate therapy was related to the duration of bacteremia, with cure rates similar among patients who had bacteremia from 1 to 3 days (85%) but greater among patients with >3 days of bacteremia (for which the cure rate was only 50%). A conclusion of the latter paper was that antibiotic regimens for empiric therapy in neutropenic patients and especially patients with acute leukemia should still provide coverage against *P aeruginosa*.[9]

Influenced by multiple factors, including the potential for acute mortality in neutropenic patients who are bacteremic with *P aeruginosa,* in its recommendations for management of febrile neutropenic patients, the IDSA has offered suggestions for empiric antimicrobial therapy.[3] In these recommendations, it was noted that the initial evaluation should determine (1) whether the patient is at low risk for complications (with the specifics defined in these guidelines), and (2) whether vancomycin therapy is needed. For low-risk adults only, an oral regimen using ciprofloxacin plus amoxicillin-clavulanate was suggested. Options in patients for monotherapy with vancomycin not being needed included one of the following agents: cefepime or ceftazidime; or imipenem or meropenem. Options for combination therapy were an aminoglycoside plus an antipseudomonal penicillin, cephalosporin (cefepime or ceftazidime), or carbapenem. In those patients in whom vancomycin is indicated (discussed in the following paragraph), three options were presented: cefepime or ceftazidime plus vancomycin, with or without an aminoglycoside; carbapenem plus vancomycin, with or without an aminoglycoside; or an antipseudomonal penicillin plus an aminoglycoside and vancomycin. Prior to the publication of the 2002 IDSA guidelines, a prospective, multicenter, double-blind, randomized clinical trial showed piperacillin-tazobactam given as monotherapy to be as effective as the combination of piperacillin-tazobactam plus amikacin for the treatment for adults who were febrile and neutropenic.[10] Even though an antipseudomonal penicillin was offered as an option in the 2002 IDSA guidelines for combination therapy without vancomycin and for therapy in which vancomycin was indicated, it was not presented as an option for monotherapy when vancomycin was not indicated.

An ongoing controversy remains regarding whether an agent such as vancomycin, which would cover such pathogens as methicillin-

resistant *S aureus*, penicillin-resistant and cephalosporin-resistant *Streptococcus pneumoniae*, and *C jeikeium*, should be included in the initial regimen. Because of the risk of selecting vancomycin-resistant enterococci or vancomycin-resistant staphylococci with injudicious use of vancomycin, the IDSA guidelines for management of febrile neutropenic patients discouraged vancomycin use in routine empiric therapy for a febrile neutropenic patient and recommended that this agent be used in the following settings: (1) clinically suspected serious catheter-related infections (eg, bacteremia, cellulitis); (2) known colonization with methicillin-resistant *S aureus* or penicillin-resistant and cephalosporin-resistant *S pneumoniae*; (3) positive results of blood cultures for gram-positive bacteria before final identification and susceptibility testing; and (4) hypotension or other evidence of cardiovascular impairment.[3]

The guidelines of the American Society of Clinical Oncology (ASCO) for colony-stimulating factors were published in the *Journal of Clinical Oncology*.[11] Clinical situations for which recommendations were made in adults include the following: (1) when the expected incidence of neutropenia is $\geq$40% (although there are some special circumstances detailed in the ASCO guidelines that might be a valid exception); (2) as adjuncts to progenitor-cell transplantation; (3) after completion of induction chemotherapy in patients $\geq$55 years of age who have acute myeloid leukemia; and (4) after completion of the first few days of chemotherapy for the initial induction or first postremission course in patients with acute lymphoblastic leukemia. In the 1996 ASCO guidelines, colony-stimulating factors were recommended after documented febrile neutropenia in a prior chemotherapy cycle to avoid infectious complications and maintain dose intensity in subsequent treatment cycles when chemotherapy dose reduction is not appropriate.[12] This was modified in the 2000 guidelines because there were no published regimens that have demonstrated disease-free or overall survival benefits when the dose of chemotherapy was maintained and secondary prophylaxis was instituted. Based on these data, it was recommended that, in the setting of many tumors but exclusive of curable tumors (eg, germ cell tumors), dose reduction after an episode of severe neutropenia should be considered as a primary therapeutic option. Colony-stimulating factors should be avoided in patients receiving concomitant chemotherapy and radiation therapy, particularly involving the mediastinum. Because no large-scale prospective, comparative trials evaluating the relative efficacy of granulocyte colony-stimulating factor vs granulocyte-macrophage colony-stimulating factor were available, guidelines about the equivalency of these preparations were not proposed. Certain patients with fever and neutropenia are at higher risk for infection-associated complications and have prognostic factors that are predictive of poor clinical outcome. The use of a colony-stimulating factor in such high-risk patients may be considered, but the benefits in these circumstances have not been proven. Potential clinical factors mentioned in the 2000 guidelines include profound neutropenia (absolute neutrophil count $<$100/μL), uncontrolled primary disease, pneumonia, hypotension, multiorgan dysfunction (sepsis syndrome), and invasive fungal infection. Age $>$65 years and posttreatment lymphopenia were mentioned as potentially being other high-risk factors, but it was acknowledged that these have not been consistently confirmed by multicenter trials.

Prolonged neutropenia is a major predisposition to fungal infection. Although the list of fungal organisms identified in neutropenic patients has increased significantly in recent years, the most important pathogens to consider are *Candida* spp and *Aspergillus* spp. On the basis of neutropenia, indwelling catheters, broad-spectrum antibiotics, and mucositis, neutropenic patients are at risk for candidemia. The clinical presentation may range from unexplained fever to a septic appearance. Autopsy series have suggested that as many as 50% of patients with evidence of metastatic candidal infections in visceral organs may have had negative antemortem blood cultures for *Candida*.[13] The characteristic clinical infection in this setting is chronic disseminated candidiasis, which has also been referred to as hepatosplenic candidiasis. This illness may present as unexplained fever, right upper quadrant tenderness, and elevated alkaline phosphatase. During the period of neutro-

penia, imaging studies may be negative, but as the granulocyte count improves, patients may demonstrate bull's-eye liver lesions on ultrasound and hypodense liver defects on abdominal CT scan.[14] In the 2004 guidelines of the IDSA for treatment of candidemia, the options for neutropenic patients included amphotericin B, liposomal amphotericin B, and caspofungin.[15] Noteworthy is that fluconazole, which was recommended in the treatment of candidemia in nonneutropenic patients, was not included as a treatment option in neutropenic patients. This recommendation is probably an acknowledgement of the evolving trend toward *nonalbicans* species of *Candida* and of the potential role of azole therapy in selecting for such pathogens.

Aspergillus is a nosocomial pathogen that may be associated with vascular invasion and extensive tissue necrosis. The lungs are a prime site of infection, with a spectrum of disease that includes pulmonary infiltrates or cavitary lung lesions; infection of the paranasal sinuses and CNS may also occur.[16] Because of the nosocomial nature of this organism, it may be introduced into the skin with catheter insertion. With the lack of both intravascular and subepithelial polymorphonuclear leukocytes, and because of the vascular invasion, the skin lesions may be concentrically enlarging and necrotic. Blood cultures are not likely to reveal this pathogen. In a randomized trial comparing voriconazole with standard amphotericin B for primary treatment of invasive aspergillosis, voriconazole was demonstrated to be more effective than amphotericin B.[17]An evolving body of clinical data regarding this topic has led to the comment that voriconazole will likely become the drug of choice for treatment of invasive aspergillosis.[18]

There is not a consensus recommendation about when empiric antifungal therapy should be started for neutropenic patients who have persistent fever. The IDSA's clinical guidelines for treatment of infections caused by *Candida* suggest starting antifungal treatment when there is persistent unexplained fever despite 4 to 7 days of appropriate antibacterial therapy,[15] but the IDSA guidelines for therapy in febrile neutropenic patients suggest beginning empirical antifungal treatment when there is persistent fever for >3 days after antibacterial therapy is instituted in patients expected to have neutropenia for longer than 5 to 7 more days.[3] Because amphotericin B has activity against most *Candida* spp as well as *Aspergillus*, it has been the agent most often used. Liposomal amphotericin B has been shown to be as effective as conventional amphotericin B for empiric antifungal therapy in patients with fever and neutropenia, and it is associated with fewer breakthrough fungal infections, less infusion-related toxicity, and less nephrotoxicity.[19] A randomized, international, multicenter trial found that voriconazole (a new second-generation triazole with both *Aspergillus* and *Candida* activity) was comparable with liposomal amphotericin B for empiric antifungal therapy.[20] A statistically significant and noteworthy observation in this report was that patients receiving voriconazole had more episodes of transient visual changes (22%) than did those receiving liposomal amphotericin B (1%). In a blinded, randomized, international multicenter noninferiority study of caspofungin (50 mg daily; 70 mg on day 1) vs liposomal amphotericin B (3 mg/kg daily) for therapy for persistently febrile neutropenic patients, both agents were comparable in overall success; however, caspofungin was associated with more successful outcome in patients with baseline fungal infections ($P = 0.043$) and had fewer drug-related adverse events ($P < 0.001$).[21]

Humoral Immunity

To be ingested by polymorphonuclear leukocytes, there is a requirement that certain organisms undergo opsonization, a process in which those organisms are encased by a factor that then allows the phagocyte to attach. Once intracellular, these organisms are readily killed by the phagocyte. The humoral immune system provides for such opsonization through its major components of antibody and complement and may be summarized as providing protection against pathogens that are hard to eat but easy to kill.[2]

The antibody component of humoral immunity is dependent on the transformation of B lymphocytes into plasma cells, which produce as major opsonins IgG and IgM. A structural part of these antibodies is a component referred to as the

Fc segment. Polymorphonuclear leukocytes have a receptor for this Fc segment. These Fc segments attach to the Fc receptor on the phagocyte, allowing the polymorphonuclear leukocyte to ingest the organism in a process that has been referred to as the "zipper" phenomenon of phagocytosis.

In addition to antibody, complement may serve as an opsonizer. Of the various complement components, the one most important for opsonization is C3b, which may be generated through two different pathways. In the classic complement pathway, the formation of antigen-antibody complexes turns on the complement cascade. Once C3 is activated, it is cleaved by C3 esterase to yield C3b. A limitation of the classic complement pathway is the requirement for antibody production, which may take hours to develop. In situations such as the acute development of pneumococcal infection, there is an immediate need for host defense that cannot wait for antibody production. It is in this setting that the alternative complement pathway (also known as the properdin system) becomes important. Instead of requiring an antigen-antibody complex to turn on the cascade, the alternative pathway is dependent on cell wall components such as teichoic acid and peptidoglycans found in gram-positive organisms and lipopolysaccharides found in gram-negative organisms. These lead to proteolytic cleavage of C3 to generate C3b, and this mechanism can lead to immediate opsonization. In addition to its opsonizing ability and its initiation of the membrane attack complex of complement, C3b can be joined by factors B and D to form a C3 convertase, which is highly labile. When bound by properdin, the C3 convertase is stabilized and can then cleave more C3 to generate more C3b, with a resultant amplification of the alternative complement pathway. Some clinical evidence exists that patients who have undergone splenectomy have a decrease in alternative pathway-mediated activation of C3.[22]

There are four clinically relevant situations within the category of defective humoral immunity: (1) disorders of immunoglobulin production; (2) asplenia or hyposplenic states; (3) hypocom-plementemia; and (4) impaired neutralization of toxins.

The major clinical situations that result in disorders of immunoglobulin production are summarized in Table 3. Included in these processes is the lack of B-cell regulation, with its resultant production of abnormal immunoglobulins occurring on the basis of T-cell deficiency states in conditions such as HIV infection.

The characteristic pathogens infecting patients with impairment of immunoglobulin production are included in Table 4. Among the bacteria, the common feature is encapsulation, with the capsule essentially making them slippery and therefore dependent on opsonization for phagocyte attachment. Of the pathogens defended against by humoral immunity, the one that most frequently causes an acute life-threatening infection is *S pneumoniae*. In recent years, it has been noted that the severity of infection with *S pneumoniae* may be accentuated in patients with alcoholism or in those who are HIV infected. In both patient groups, this pathogen may initially present as the etiologic agent of community-acquired pneumonia, which may be multilobar, with a high incidence of bacteremia and an increased risk of ARDS. An important consideration regarding infection with this pathogen is the increasing prevalence of penicillin resistance. Despite appropriate antibiotics and supportive care, the mortality in this setting remains high.

Also included among the pathogens that infect patients with defects in immunoglobulin production are certain viruses, including enteroviruses, influenza viruses, and arboviruses. Enteroviruses, particularly echovirus 24, have been associated with a clinical complex consisting of dermatomyositis-like skin lesions, edema, and neurologic problems. This has been referred to as chronic enteroviral meningoencephalitis.

Common variable immunodeficiency (CVI) is associated with functional abnormalities of both B and T cells but is usually classified as a primary antibody deficiency syndrome. Characterized by hypogammaglobulinemia and recurrent bacterial infections, CVI usually does not become clinically apparent until the second or third decade of life. Affected patients have an increased risk of autoimmune, granulomatous, and lymphoproliferative diseases. Even though recurrent bacterial infections of the respiratory tract are the most

Table 3—*Major Clinical Situations Resulting in Disorder of Immunoglobulin Production*

Congenital agammaglobulinemias
Common variable immunodeficiency (acquired hypogammaglobulinemia)
Heavy chain disease
Waldenström macroglobulinemia
Multiple myeloma
B-cell lymphomas
Chronic lymphocytic leukemia
T-cell deficiency states
Hyposplenic states

Table 4—*Pathogens in Patients With Defective Humoral Immunity*

Disorders of Immunoglobulin Production
Streptococcus pneumoniae
Haemophilus influenzae
Encapsulated strains of gram-negative bacilli
Enteroviruses, particularly echovirus 24
Influenza viruses
Arboviruses
Pneumocystis jiroveci (formerly *P carinii*)
Giardia lamblia
Asplenic State or Splenic Dysfunction
Streptococcus pneumoniae
Capnocytophaga canimorsus
Babesia microti
Plasmodium spp
Haemophilus influenzae
Neisseria spp

common, diarrhea caused by *Giardia lamblia* is frequently encountered. This reflects the importance of local immunoglobulin production in the GI tract as a component of defense against *G lamblia*. Because some of the common pathogens infecting the respiratory or GI tracts are dependent on antibody production for host defense, concomitant infection of these two body sites should raise the suspicion of immunoglobulin deficiency states such as CVI. IV immunoglobulin may be efficacious in patients with this clinical entity, but anaphylaxis with such therapy has been reported.

Anatomicasplenia, as well as the hyposplenic states that occur in persons with sickle cell disease (caused by autoinfarction of the spleen) and in patients with Hodgkin disease (especially after therapy), are also important predispositions to infection. The propensity for infection in these patients occurs on the basis of impairment of several immunologic functions: (1) relative to other lymphoid organs, the spleen has a greater percentage of B lymphocytes and is therefore involved in the production of antibody to polysaccharide antigens; (2) the spleen participates as a phagocyticorgan, removing opsonin-coated organisms or damaged cells from the circulation; and (3) alternative complement-mediated activation of C3 may be decreased in patients after splenectomy. An important clinical clue to heighten awareness of both functional and anatomic asplenia is the presence of Howell-Jolly bodies on the peripheral blood smear.

The important pathogens involved in infections in patients without a spleen or with splenic dysfunction are summarized in Table 4.[23] Responsible for about 80% of overwhelming infections in asplenic patients, *S pneumoniae* should be given a particularly high index of suspicion because the clinical entity of postsplenectomy pneumococcal sepsis may initially present as only a flulike illness with fever and myalgias.[24] Within the course of a few hours, untreated patients may develop a fulminant course that includes disseminated intravascular coagulation, purpurafulminans, symmetrical peripheral gangrene, shock, and ultimately death. Although *S pneumoniae* and *Haemophilus influenzae* are pathogens encountered in patients with either disorders of immunoglobulin production or splenic dysfunction, the pathogens infecting the asplenic or hyposplenic patient are otherwise different. Also included are two pathogens, *Babesia microti* and *Plasmodium* spp, that infect erythrocytes to cause hemolytic states and that require removal of parasitized RBCs by the spleen as a protective defense. *Capnocytophaga canimorsus* produces an acute illness with eschar formation following dog bites to asplenic individuals.[25]

Patients with deficiencies in the late complement components (C5 through C8) may present with recurrent *Neisseria* spp infections. The total hemolytic complement (CH_{50}) is the best screening test for this population. If the assay is normal, one can essentially exclude complement deficiency. In addition, an X-linked properdin deficiency associated with absence of the alternative complement pathway may pro-

duce a similar picture of severe meningococcal disease.

Completing the spectrum of clinical problems that may occur on the basis of defective humoral immunity is less than optimal neutralization of toxins produced in diphtheria, tetanus, and botulism.

IV gammaglobulin is a polyvalent antibody product containing the IgG antibodies that regularly occur in the donor population as well as traces of IgA and IgM and immunoglobulin fragments. Its half-life of 3 weeks allows for once-monthly dosing for prophylaxis in patients with primary humoral immunodeficiency. For bone marrow transplant patients $\geq$20 years of age, it has been shown to decrease the risk of septicemia and certain other infections, interstitial pneumonia of infectious or idiopathic etiology, and acute graft-vs-host disease in the first 100 days posttransplant.[26] In this patient population, dosing is more frequent than in prophylaxis for primary humoral immunodeficiency. Contraindications to its use include selective IgA deficiency and severe systemic reactions to human immune globulin.

Prevention of disease with vaccine is important in patients with defects in humoral immunity, although responses to vaccine may be attenuated. The 23-valent pneumococcal vaccine is recommended for adults with functional or anatomic asplenia, chronic cardiovascular disease, chronic pulmonary disease, diabetes mellitus, alcoholism, chronic liver disease, cerebrospinal fluid (CSF) leaks, and immunocompromised states, including malignancy and HIV infection. In the review by the Centers for Disease Control and Prevention,[27] revaccination once was recommended for two groups: (1) persons aged $\geq$2 years who are at highest risk for serious pneumococcal infection and those who are likely to have a rapid decline in pneumococcal antibody levels (eg, functional or anatomic asplenia, HIV infection, leukemia, lymphoma, Hodgkin disease, multiple myeloma, generalized malignancy, chronic renal failure, nephrotic syndrome, other conditions associated with immunosuppression [including transplantation], and those receiving immunosuppressive chemotherapy [including steroids]), provided that 5 years has elapsed since receipt of the first dose of pneumococcal vaccine; and (2) persons aged $\geq$65 years if they received the vaccine 5 years previously and were $<$65 years old at the time of the primary vaccination. In an overall analysis not limited to immunocompromised patients, the effectiveness of pneumococcal conjugate vaccine has been demonstrated to prevent disease in young children for whom the vaccine is indicated and may be reducing the rate of disease in adults.[28] This report noted that the vaccine provides an effective tool for reducing disease caused by drug-resistant strains. Routine vaccination with the quadrivalent *Neisseria meningitidis* vaccine is recommended for certain high-risk groups, including persons who have terminal complement component deficiencies and those who have anatomic or functional asplenia.[29] Although the need for revaccination of adults has not been determined, antibody levels to *N meningitidis* rapidly decline over 2 to 3 years, and revaccination may be considered 3 to 5 years after receipt of the initial dose. Prophylaxis options against meningococcal infection based on the patient population being treated include rifampin (600 mg orally q12h for 2 days), ciprofloxacin (500 mg orally as single dose in nonpregnant adults), or ceftriaxone (250 mg IM as a single dose). *H influenzae* B vaccines are immunogenic in splenectomized adults and may be considered for this group.[30] When elective splenectomy is planned, pneumococcal, meningococcal, and *H influenzae* B vaccination should precede surgery by at least 2 weeks, if possible.

Cell-Mediated Immunity

The cell-mediated immune system is dependent on the interrelationship of T lymphocytes with macrophages. In contrast to primary neutrophil defense and humoral immunity, in which the polymorphonuclear leukocyte is the major phagocyte, the predominant phagocytic cell in cell-mediated immunity is the macrophage. On initial exposure to an antigen, T lymphocytes become sensitized. When restimulated, these sensitized T lymphocytes produce a group of lymphokines, including macrophage activation factor. It is this substance that stimulates macrophages to better ingest and kill pathogens. In contrast to polymorphonuclear leukocytes, mac-

Table 5—*Important Clinical Situations Associated With Defects in Cell-Mediated Immunity*

Aging
During and following certain viral illnesses
Thymic dysplasia
Congenital situations associated with defects in cell-mediated immunity
Third trimester of pregnancy
Lymphatic malignancies of T-cell origin
Immunosuppressive therapy, especially corticosteroids and cyclosporine
AIDS and HIV-related disorders

rophages can readily ingest microorganisms but have a difficult time with intracellular killing. This system may be summarized as providing protection against pathogens that are easy to eat but hard to kill.[2]

Some of the disorders and clinical situations associated with defects in cell-mediated immunity are listed in Table 5. With aging alone, patients have a decrease in cell-mediated immunity. Pregnant women in their third trimester have a transient loss of cell-mediated immunity, which spontaneously reconstitutes itself within about 3 months of delivery.[31] Immunosuppressive drugs (including corticosteroids and cyclosporine) and HIV infection are associated with defects in this limb of host defense. Both steroids and HIV infection decrease total T lymphocyte numbers, resulting in production of abnormal amounts of lymphokines like macrophage activation factor. In contrast, cyclosporine does not decrease lymphocyte numbers but decreases the functional capacity of lymphocytes to produce lymphokines. Irrespective of the mechanism, a decrease in the production of macrophage activation factor decreases the stimulus for macrophages to optimally serve as the primary phagocytic cell in this host defense system.

The pathogens infecting patients with defects in cell-mediated immunity are summarized in Table 6 and can be divided into five categories: (1) bacteria (having as a common characteristic an intracellular location); (2) fungi (which often become clinically manifested in the setting of previous epidemiologic exposure); (3) viruses (most characteristically, DNA viruses); (4) parasites and protozoa; and (5) a miscellaneous group (some include spirochetes in this category).

Intracellular Bacteria

Mycobacterium tuberculosis

Although TB can be a problem in any patient with defective cell-mediated immunity, it has attracted attention because of the copathogenesis that may occur in individuals who are dually infected with the intracellular pathogens *M tuberculosis* and HIV-1. It has been suggested by some that mycobacteria and their products may enhance viral replication by inducing nuclear factor κ-B, the cellular factor that binds to promoter regions of HIV.[32] The presentation of TB in HIV-infected persons is variable and is influenced by the level of immunosuppression. With $CD4^+$ counts >300 cells/μL, the pattern of typical reactivation TB with cavitary disease or upper lobe infiltrates is more common. When $CD4^+$ cells fall to <200/μL, the pattern of disease is more typically middle to lower lobe disease with or without intrathoracic lymphadenopathy.[33] In patients with $CD4^+$ counts at this level, extrapulmonary TB has been reported in at least 50%. Persons with serologic evidence of HIV infection and pulmonary TB fulfill the case definition for AIDS. These individuals with drug-susceptible strains tend to respond well to standard antituberculous therapy given as a short-course regimen for 6 months.[34] After initiation of antituberculosis therapy, some patients experience a paradoxical reaction, which is the temporary exacerbation of TB symptoms in the form of hectic fevers, lymphadenopathy, worsening of chest radiographic findings, and worsening of extrapulmonary lesions. These reactions are not associated with changes in *M tuberculosis* bacteriology, and patients generally feel well with no signs of toxicity. Such reactions have been attributed to recovery of delayed hypersensitivity response and an increase in exposure and reaction to mycobacterial antigens after bactericidal antituberculosis therapy is initiated. These reactions have been especially notable in individuals concurrently treated with antituberculosis and antiretroviral therapy. A noteworthy issue in HIV-infected patients is the interaction between antituberculosis drugs and antiretroviral therapy, including that with protease inhibitors. The rifamycins (eg, rifampin and

Table 6—*Pathogens in Disorders of Cell-Mediated Immunity*

Bacteria	Fungi	Viruses	Parasites/Protozoa	Others
Mycobacteria	*Cryptococcus*	Herpes simplex	*Pneumocystis*	*Treponema pallidum*
Listeria	*Histoplasma*	Varicella-zoster	*Toxoplasma*	Chlamydiae
Nocardia	*Coccidioides*	Cytomegalovirus	*Strongyloides*	Rickettsiae
Rhodococcus	*Blastomyces*	Epstein-Barr virus	*Giardia*	
Salmonella	*Candida*	Polyoma viruses	*Cryptosporidium*	
Legionella	*Aspergillus*	Adenoviruses	*Isospora*	
Brucella		Measles virus	*Trypanosoma*	
Bartonella (formerly *Rochalimaea*)			*Microsporidia*	
			Leishmania	
			Amebae	

rifabutin) accelerate the metabolism of protease inhibitors through induction of hepatic P_{450} cytochrome oxidases. Rifabutin has comparable antituberculous activity but with less hepatic P_{450} cytochrome enzyme-inducing effect than rifampin. The joint document of the American Thoracic Society, Centers for Disease Control and Preventation, and IDSA on the treatment of tuberculosis includes recommendations for use of rifamycins in the treatment of TB.[34]

Two clinically relevant trends related to TB deserve comment. One is an apparent increase in TB reactivation associated with tumor necrosis factor-α inhibitors (eg, infliximab) used to treat rheumatoid arthritis and Crohn disease, with extrapulmonary TB being especially noted.[35] The other relates to the reports of liver failure and death after 2 months of therapy with rifampin and pyrazinamide.[36]

Some attention has focused on measures that foster type 1 immunity as a means of treating patients with TB, including those who may not have responded to initial therapy. Because IL-2 has a central role in regulating T-cell responses to *M tuberculosis,* a randomized, placebo-controlled, double-blinded trial in 110 HIV-negative, smear-positive, drug-susceptible pulmonary TB patients was conducted using adjunctive immunotherapy with recombinant IL-2.[37] In this trial, IL-2 did not enhance bacillary clearance or improvement in symptoms in HIV-seronegative adults with drug-susceptible TB.

A significant change has occurred regarding TB infection. For many decades, the terms "preventive therapy" and "chemoprophylaxis" were used to describe the status of persons with a positive tuberculin test but no symptoms or signs of active TB. The word *preventive* was inaccurate in that it referred to use of an agent such as isoniazid to prevent development of active TB in persons known or likely to be infected with *M tuberculosis;* it was not intended to imply prevention of true primary infection. To more accurately describe such therapy, in an official statement in 2000 the American Thoracic Society introduced the terminology "latent tuberculosis infection" (LTBI) as a substitute for "preventive therapy" and "chemoprophylaxis."[38] It acknowledged the role of LTBI as an important element in control of TB. It has been noted that HIV-infected persons with a positive tuberculin skin test have about a 7% chance per year of developing TB disease, which exceeds the standard estimated lifetime risk of approximately 10% for the reactivation of LTBI in nonimmunocompromised persons with positive purified protein derivative tests.[39] In a prospective cohort study of persons with HIV infection in the United States, the annual risk of active TB among HIV-infected persons with a positive tuberculin test was 4.5 cases per 100 person-years of observation.[40] Based on such facts, it is recommended that HIV-infected persons with a tuberculin skin test with $\geq$5-mm induration be given treatment for latent tuberculosis. In the 2000 guidelines for treatment of LTBI, tuberculin positivity was also set at $\geq$5-mm induration for patients with organ transplants and other immunosuppressed patients receiving the equivalent of $\geq$15 mg/day of prednisone for 1 month or more. The risk of TB increases with a higher dose and longer duration of corticosteroids.

Mycobacterium avium Complex

Among individuals with defective cell-mediated immunity, *Mycobacterium avium* complex (MAC) classically infects HIV-infected persons when their $CD4^+$ cells are $<50/\mu L$. In patients with AIDS, there are several lines of evidence suggesting that most patients with disseminated MAC have recently acquired the organisms, in contrast to the reactivation that is common with TB.[41] Adherence of the organisms to the gut wall is the initial event in invasion, followed by entry into the lamina propria and then phagocytosis by macrophages. Local replication of organisms leads to the endoscopically visible 2-mm to 4-mm punctate lesions that are the hallmark of MAC disease in the gut. The clinical presentation is that of a wasting syndrome marked by fever, night sweats, weight loss, diarrhea, anorexia, and malaise. Despite positive sputum cultures, serious pulmonary infection is not common in HIV-infected patients. The organism is most characteristically isolated from blood, stool, respiratory secretions, bone marrow, GI tract mucosa, and lymph nodes (although granuloma formation is minimal or absent). A unique pathophysiologic abnormality seen in about 5% of AIDS patients with MAC disease is marked elevations (20 to 40 times normal) in serum alkaline phosphatase with little elevation of transaminases, bilirubin, or other parameters of hepatic function. This is believed to occur on the basis of interference with enzyme metabolism rather than because of hepatic tissue destruction.

In those patients with symptomatic disease, a multidrug regimen is recommended that should include either clarithromycin or azithromycin in combination with ethambutol.[42] With advanced immunosuppression ($CD4^+ <50/\mu L$), with high mycobacterial loads, or in the absence of effective antiretroviral therapy, the treatment guidelines recommend that adding a third drug be considered. Additional drugs that may be added to this regimen include rifabutin (as an A-1 recommended agent) or ciprofloxacin, levofloxacin, or amikacin (as C-III recommendations). The response to therapy is variable among patients, and the acquisition of drug resistance is common, especially with monotherapy. Although rifabutin was the initial agent approved for prophylaxis against MAC infection, more recommendations for the prevention of opportunistic infections in HIV-infected persons have listed azithromycin or clarithromycin as the agent of choice when the $CD4^+$ count is $<50/\mu L$.[43]

Listeria monocytogenes

This intracellular gram-positive rod characteristically infects persons with malignancy, diabetes mellitus, or renal transplantation followed by immunosuppressive therapy.[44] Neonates and pregnant women are also at risk, and the infection occurs with increased frequency with cirrhosis. About one-third of patients in some series have no known risk factor, and *Listeria* has been considered a cause of febrile GI illness in immunocompetent persons.[45] *Listeria* may be acquired via consumption of certain contaminated raw vegetables (with coleslaw as a source in some outbreaks), certain contaminated canned products (with sterile canned corn kernels as the source in one outbreak), raw food from animal sources (eg, beef, pork, or poultry), unpasteurized milk, or foods made from raw milk (notably, certain soft cheeses).

The most common clinical presentations are of CNS infection, sepsis, or a flulike illness. When it causes acute meningitis, *Listeria* may be associated with a variable glucose level or with a CSF lymphocytosis or monocytosis. Gram stain of the CSF is positive in only about one quarter of patients. The infection has a predilection for the base of the brain with resultant focal neurologic signs, particularly cranial nerve involvement, in up to 40% of patients. Hydrocephalus may be a complication of this localization. Bacteremia is another common presentation, with cerebritis or brain abscess being less frequent.

Therapy is with high-dose IV ampicillin or penicillin.[46] Some favor the addition of a parenteral aminoglycoside with these agents even for treatment of meningitis, recognizing that the aminoglycosides administered parenterally in adults will not cross the blood-brain barrier but may help eradicate infectious sites outside the CNS.[47] For penicillin-allergic patients, trimethoprim-sulfamethoxazole is possibly effective. Extremely noteworthy is that cephalosporin therapy has no role in treating infection caused

by *Listeria*. Because of the intracellular location of the organisms, 3 weeks of therapy is recommended for serious infections.

Nocardia asteroides

These filamentous aerobic gram-positive rods are weakly acid-fast and characteristically produce disease in patients who have lymphoreticular neoplasms or have received long-term corticosteroid therapy. Because the organism most commonly infects humans through the respiratory tract, the classic pattern of infection is pulmonary disease, which may take the form of nodular infiltrates, cavitary lesions, or diffuse infiltrates with or without consolidation. Pustular skin lesions and neurologic disease in the form of encephalitis or brain abscess complete the triad of the most common presentations by this pathogen. The liver and kidneys are less likely to be involved. In the report from the Johns Hopkins Hospital of 59 patients diagnosed with nocardiosis over an 11-year time span, *Nocardia* was isolated most commonly from the respiratory tract (76%), followed by soft tissue (13%), blood (7%), and CNS (5%).[48] In this series, the infection was common in AIDS patients as well as in transplant recipients. In both groups of patients, disease developed in some despite prophylactic therapy against other pathogens with trimethoprim/sulfamethoxazole.

Standard therapy is with sulfonamides.[49] Trimethoprim-sulfamethoxazole is often used because of its convenient IV dosing; however, it has not been definitively proven that the combination is synergistic at the drug ratios that usually are achieved in serum or CSF.

Rhodococcus equi

Formerly called *Corynebacterium equi*, this partially acid-fast, aerobic, intracellular gram-positive rod-coccus was first described in 1967 as the cause of disease in humans.[50] Even though the organism has been rarely reported to cause infection in immunocompetent patients, immunocompromised patients, especially those with HIV infection, are the ones most likely to develop clinical disease because of this pathogen. The most characteristic pattern of infection is described as a progressive pneumonia that may cavitate. Bacteremia is common in immunocompromised patients. Like *Nocardia*, it has also been associated with neurologic and skin lesions.

The intracellular location has made the organism difficult to treat, and principles of therapy include a prolonged duration of antibiotics, often in association with drainage. In vitro, *R equi* is usually susceptible to erythromycin, rifampin, fluoroquinolones, aminoglycosides, glycopeptides (eg, vancomycin), and imipenem; it has been suggested that immunocompromised patients and patients with serious infections receive IV therapy with two-drug or three-drug regimens that include vancomycin, imipenem, aminoglycosides, ciprofloxacin, rifampin, and/or erythromycin.[51] The choice of agents used and the duration of therapy are dependent on both the patient's host defense status and the site of infection. Oral antibiotics may be an option in certain immunocompetent patients with localized infection.

Salmonella spp

Patient populations with defective cell-mediated immunity that develop bacteremia with this intracellular gram-negative rod include those with hematologic malignancies, systemic lupus erythematosus, and HIV infection. In those persons with HIV infection, a febrile typhoidal illness without diarrhea accounts for about 45% of the disease caused by this pathogen. More common is an illness associated with fever, severe diarrhea, and crampy abdominal pain. Compared with *Shigella* and *Campylobacter,* there is a lower incidence of bloody diarrhea and fecal leukocytes with *Salmonella* infection. Recurrent nontyphoidal bacteremia is considered an indication for secondary antibacterial prophylaxis in HIV-infected persons.[43]

Legionella spp

Legionella is a pathogen recognized to have the potential for causing acute mortality in patients with pulmonary infections, including even those who are not immunocompromised.[52] This pathogen causes more severe disease in transplant recipients, patients who receive corticosteroids, and HIV-infected persons. Immuno-

compromised patients with legionellosis may present with variable patterns of multisystem disease. Fever with a scanty productive cough is often described. In individuals receiving corticosteroids, cavitary lung lesions with abscess formation may occur. Dissemination seems to occur via bacteremic spread of the organism. In a review of legionnaires' disease, the most common extrapulmonary site was reported to be the heart (including myocarditis and pericarditis), and one would need to assume that such organ system involvement might be possible in immunocompromised patients.[53] Other patterns of extrapulmonary involvement by *Legionella* may take the form of sinusitis, cellulitis, pyelonephritis, and pancreatitis. Patients with hairy-cell leukemia, a disorder of monocyte deficiency and dysfunction, have an increased incidence of *Legionella* pneumonia. *Legionella* infection should be suspected in those individuals who do not respond to therapy with a (β-lactam antibiotic. Useful in the acute diagnosis is the *Legionella* urinary antigen assay, which has been stated to be 70% sensitive and 100% specific in diagnosing infection caused by *Legionella pneumophila serogroup I*.

Erythromycin has traditionally been considered the agent of choice for treatment of this infection,[54] but reviews have suggested that the fluoroquinolones may be more efficacious.[53] Because of increased efficacy and the fact that macrolides such as erythromycin may have pharmacologic interactions with immunosuppressive agents used in transplant patients, some investigators feel that a fluoroquinolone should be added to the standard regimen for treating legionnaires' disease in transplant recipients with nosocomial pneumonia if the causative agent has not been identified. Some have suggested that rifampin be used as adjunctive therapy for severe *Legionella* infections, but this must be taken in context with the facts that (1) no prospective studies have evaluated such therapy, and (2) rifampin has the potential to induce the cytochrome P_{450} system and, therefore, cause a significant interaction with immunosuppressive therapy.

Brucella spp

Even though intracellular brucellae require cell-mediated immunity for eradication, the spectrum of brucellosis in immunocompromised hosts has not been frequently described. Because of the ability for splenic localization with the formation of suppurative lesions that might require splenectomy, this organism may cause further impairment of an otherwise compromised immune system.

Bartonella (Formerly Rochalimaea) spp

The small gram-negative organisms in this genus may be demonstrated with Warthin-Starry staining or by electron microscopy. The patterns of infection in HIV-infected persons include the following: (1) bacteremia (in the absence of focal vascular proliferative response in tissue); (2) bacillary angiomatosis; and (3) peliosis hepatitis.[55] Bacillary angiomatosis presents in the later phases of HIV infection, usually with $CD4^+$ counts <100 cells/μL. The condition is associated with a unique vascular lesion that may involve virtually every organ system, either alone or in association with other sites of involvement.[56] Of these, skin lesions are the most commonly recognized, with characteristic lesions being red and papular and therefore resembling Kaposi sarcoma. Lesions characteristically are associated with a long duration of symptoms or physical findings prior to diagnosis. Species causing such a process include *Bartonella henselae* and *Bartonella quintana*. Peliosis hepatitis refers to the blood-filled peliotic changes in the parenchyma of the liver or spleen that occur because of infection with these two species. Because these organisms are at present difficult to culture from blood or tissue, histopathology may be the study that directs further diagnostic evaluation. Erythromycin or doxycycline is considered the preferred agent.[42]

Fungi

Cryptococcus neoformans

Cryptococcal meningitis is an important infection in HIV-infected persons, particularly when $CD4^+$ counts are <100 cells/μL, but may also occur in other populations, including elderly persons. The organism enters the body through the lungs, and the associated finding of pulmo-

nary infiltrates in an HIV-infected person with meningitis should raise the suspicion of this diagnosis. The organism has a propensity to enter the bloodstream and may be detected in routine blood cultures. The resulting fungemia is often associated with multisegment pulmonary infiltrates and with skin lesions. Infection in the HIV population may present as a noninflammatory infection of the CNS, and the clinical features are therefore different from what one might expect in classic forms of meningitis caused by other pathogens. The history is frequently of a subacute or chronic illness associated mainly with headache. Physical examination may not reveal classic findings such as nuchal rigidity. Because of the lack of inflammation in the CNS, the CSF formula may include <20 WBC/mm^3, normal glucose, and normal protein. These findings make CSF studies such as India ink stain, cryptococcal antigen, and fungal culture mainstays in the diagnosis.

The National Institute of Allergy and Infectious Diseases Mycoses Study Group and AIDS Clinical Trials Group reported their findings in 381 patients with cryptococcal meningitis treated in a double-blind multicenter trial.[57] Conclusions from this trial of AIDS-associated cryptococcal meningitis were that induction treatment for 2 weeks with the combination of amphotericin B (0.7 mg/kg/day) plus flucytosine (100 mg/kg/day in patients who were tolerant of this agent), followed by therapy with fluconazole (400 mg/day orally for 8 weeks) is safe and effective and should be considered the treatment of choice. The authors noted that high intracranial pressures have been associated with catastrophic neurologic deterioration and death in the absence of hydrocephalus. Of the patients in this study, 13 of 14 early deaths and 40% of deaths during weeks 3 through 10 were associated with elevated intracranial pressure. Based on the association between elevated intracranial pressure and mortality in patients with cryptococcal meningitis, it was suggested that measurement of intracranial pressure be included in the management of such patients. Included in the recommendations were daily lumbar punctures, use of acetazolamide, and ventriculoperitoneal shunts for asymptomatic patients with intracranial CSF pressure >320 mm H_2O and for symptomatic patients with pressures >180 mm H_2O. It has been recommended that in the absence of focal lesions, opening pressures ≥ 250 mm H_2O should be treated with large-volume CSF drainage (defined in this report as allowing CSF to drain until a satisfactory closing pressure had been achieved, commonly <200 mm H_2O).[58] IDSA guidelines for the management of cryptococcal meningitis in HIV-infected persons with opening CSF pressure of >250 mm H_2O recommended lumbar drainage sufficient to achieve a closing pressure ≥ 200 mm H_2O or 50% of initial opening pressure.[59]

Maintenance therapy is required after completion of primary therapy, and studies have identified fluconazole as the agent of choice.[60,61] In an international observational study reported by the International Working Group on Cryptococcosis, discontinuation of maintenance therapy for cryptococcal meningitis was stated to be safe if the $CD4^+$ cell count increases to >100 cells/μL while the patient is receiving highly active antiretroviral therapy (HAART).[62] These findings were consistent with previous recommendations by the US Public Health Service and the IDSA that discontinuation of secondary prophylaxis may be an option when $CD4^+$ cells are >100 to 200 cells/μL for >6 months.[43] Recurrent cryptococcal infection should be suspected in patients whose serum cryptococcal antigen test results revert back to positive after discontinuation of maintenance therapy.[62]

Histoplasma capsulatum

The clinical entity of progressive disseminated histoplasmosis has become increasingly recognized because of HIV infection. The illness may occur on the basis of either reactivation or primary disease, making the epidemiologic history of travel to or residence in endemic areas crucial. Although patients may present with such nonspecific findings as fever, fatigue, weakness, and weight loss, a characteristic presentation in about half of patients is diffuse interstitial or miliary pulmonary infiltrates that are associated with hypoxemia and mimic *Pneumocystis jiroveci* (previously *Pneumocystis carinii*) pneumonia. These patients may concomitantly demonstrate reticuloendothelial involvement in the forms of

hepatosplenomegaly, lymphadenopathy, and bone marrow involvement. A subgroup may present with a septic syndrome that can include disseminated intravascular coagulation. Small intracellular periodic acid-Schiff positive, yeast-like organisms are the characteristic morphologic form of the organism. Although the organism may be isolated from sputum, tissue, or blood, the *H capsulatum* polysaccharide antigen from blood, urine, or CSF may serve as a more rapid diagnostic study. In the IDSA guidelines for treating disseminated histoplasmosis, immunocompromised patients were divided into those with AIDS and those without AIDS.[63] In those without AIDS who were sufficiently ill to require hospitalization, amphotericin B (0.7 to 1.0 mg/kg/day) was recommended. It was noted that most patients respond quickly to amphotericin B and can then be treated with itraconazole (200 mg qd or bid) for 6 to 18 months. For patients with AIDS, it was recommended that therapy be divided into an initial 12-week intensive phase to induce a remission in the clinical illness and then followed by a chronic maintenance phase to prevent relapse. Amphotericin B was recommended for patients sufficiently ill to require hospitalization, with replacement by itraconazole, 200 mg twice daily (when the patient no longer requires hospitalization for IV therapy), to complete a 12-week total course of induction therapy. Itraconazole (200 mg tid for 3 days and then bid for 12 weeks) was recommended for patients who have mild or moderately severe symptoms and do not require hospitalization. Maintenance therapy with itraconazole for life was included in the recommendations.

Coccidioides immitis

In HIV-infected persons as well as in transplant recipients, this fungal pathogen occurs most commonly in those individuals from endemic areas. The illness may resemble *Pneumocystis* pneumonia with diffuse reticulonodular infiltrates. The classic clinical pattern of disease, manifested as dissemination to sites such as meninges, skin, and joints, is not altered by HIV infection. In the IDSA guidelines for the treatment of coccidioidomycosis, it was noted that the presence of bilateral reticulonodular or miliary infiltrates produced by *C immitis* usually implies an underlying immunodeficiency state.[64] In such circumstances, therapy usually starts with amphotericin B. Several weeks of therapy is often required for improvement, at which point an oral azole may replace amphotericin. The IDSA guidelines for treatment of coccidioidomycosis offer recommendations for the management of meningitis, including a role for oral fluconazole in certain patients.

Candida spp

Host defense against *Candida* is provided by both neutrophils and cell-mediated immunity. In addition, the immunocompetent host may develop bloodborne infection with this pathogen, and notable risk factors for this include surgery (particularly of the GI tract), broad-spectrum antibiotics, hyperalimentation, and intravascular catheters.[15] With HIV infection, *Candida* may present in a hierarchical pattern. With $CD4^+$ counts in the 400 to 600 cells/μL range, women may develop recurrent vulvovaginal candidiasis. At $CD4^+$ levels of ~250 cells/μL, oral candidiasis is the expected clinical entity. The clinical presentation of odynophagia in a patient with oral candidiasis and a $CD4^+$ count of <100 cells/μL strongly raises the diagnosis of *Candida* esophagitis. These candidal infections generally respond well to therapy, and because of this, primary prophylaxis is not generally recommended. One trend has been toward *nonalbicans* strains of *Candida*[65] and toward strains of *Candida albicans* that are fluconazole resistant.[66] Patterns of azole use have probably contributed to such problems. Recurrent use of fluconazole in HIV-infected patients has been associated with an increasing number of reports of *Candida* spp resistant to this agent. In a bone marrow transplant unit in which patients were given fluconazole (400 mg/day, oral or IV) for the first 75 days after transplantation, 5% of patients became colonized with fluconazole-resistant strains of *C albicans*, and 53% of patients had at least one mouthwashing sample that yielded *nonalbicans* species of *Candida* during the course of their bone marrow transplantation.[67]

Aspergillus spp

As is the case with *Candida, Aspergillus* may cause infection in patients with defects in either neutrophil function or cell-mediated immunity. In addition to being a nosocomial pathogen, infection with this agent may represent reactivation disease. This may be especially notable in patients who have received a bone marrow transplant or solid organ transplant. In AIDS patients with the concomitant problems of neutropenia, corticosteroid therapy, or ethanol use, invasive pulmonary or disseminated aspergillosis may occur. This tends to present in the later stages of HIV infection, especially when $CD4^+$ cells are $<50/\mu L$. Voriconazole is the preferred therapy for invasive aspergillosis in HIV-infected patients.[42]

Aspergillus infection and its treatment provide some important insights into the evolving clinical importance of type 1 immunity. Patients with chronic granulomatous disease have an increased incidence of infection with *Aspergillus*. Treatment of these patients with recombinant IFN-γ stimulates killing of this pathogen and reduces the frequency and severity of clinically apparent fungal infection.[1] This observation is important in that it conveys a treatment option for IFN-γ based on an understanding of the role of type 1 immunity in defending against certain fungal pathogens. The traditional treatment for *Aspergillus* has been amphotericin B given at maximum tolerated doses (eg, 1–1.5 mg/kg/d) and continued despite modest increases in serum creatinine.[68] Lipid formulations of amphotericin have noteworthy roles in two circumstances: (1) for the patient who has impaired renal function or develops nephrotoxicity while receiving amphotericin B deoxycholate[68] and (2) for patients who have undergone bone marrow transplantation.[69] The echinocandin caspofungin has been approved for patients in whom amphotericin fails. Itraconazole has been suggested as an alternative form of therapy in certain settings of *Aspergillus* infection. In a randomized trial comparing voriconazole with standard amphotericin B for primary treatment of invasive aspergillosis, voriconazole was demonstrated to be more effective than amphotericin B.[17] An evolving body of clinical data regarding this topic has led to the comment that voriconazole, which is available in both IV and oral formulations, will likely become the drug of choice for treatment of invasive aspergillosis.[18,42]

Viruses

Herpes Simplex Virus

The patterns of herpes simplex virus (HSV) infection vary according to the underlying immunosuppression status. Patients with hematologic or lymphoreticular neoplasms may develop disseminated mucocutaneous HSV lesions. In transplant patients, esophagitis, tracheobronchitis, pneumonitis, or hepatitis are characteristic presentations, with hepatitis caused by HSV presenting most classically as the triad of high fever, leukopenia, and markedly elevated aminotransferase levels.[70] HIV-infected persons can have a vast array of clinical conditions caused by HSV, including esophagitis, colitis, perianal ulcers (often associated with urinary retention), pneumonitis, and a spectrum of neurologic diseases. Acyclovir remains the drug of choice for these infections. However, acyclovir-resistant strains have emerged, for which foscarnet may be the alternative therapy.

Varicella-Zoster Virus

As is the case with HSV infection, varicella-zoster virus (VZV) may present differently according to the underlying type of immunosuppression. With both chickenpox and shingles in patients with solid and hematologic malignancies, cutaneous dissemination may occur and may be associated with such visceral involvement as pneumonitis, hepatitis, and meningoencephalitis. Herpes zoster may be multidermatomal in HIV-infected persons, and this may be the initial clue to the diagnosis of HIV infection. Treatment options for both varicella and zoster have been summarized.[71] Acyclovir, famciclovir, and valacyclovir are discussed according to the disease, the pattern of immunosuppression, and the requirement for IV vs oral therapy. With the depression of cell-mediated immunity that occurs during the third trimester of pregnancy,[31] there is increased risk of dissemination of VZV to the

lungs during pregnancy. A case-control analysis of 18 pregnant women with VZV pneumonia compared with 72 matched control subjects identified cigarette smoking and >100 skin lesions as markers for the development of varicella pneumonia in pregnancy.[72] In immunocompromised patients and pregnant women who are exposed to chickenpox and in whom there is no clinical or serologic evidence of immunity to VZV, administration of varicella-zoster immune globulin may prevent or significantly modify VZV infection.[71]

Cytomegalovirus

For perspective, it is important to recognize the three major consequences of cytomegalovirus (CMV) infection in solid organ transplantation recipients: (1) CMV disease, including a wide range of clinical illnesses; (2) superinfection with opportunistic pathogens; and (3) injury to the transplanted organ, possibly enhancing chronic rejection.[73] The virus may be present in the forms of latency (infection without signs of active viral replication), active infection (viral replication in blood or organs), and primary infection (active infection in a previously nonimmune seronegative person). One study addressed the impact of primary infection in bone marrow recipients who were CMV seronegative and who received stem cells from CMV-seropositive recipients.[74] These patients died of invasive bacterial and fungal infections at a rate greater than that of patients who did not have primary infection, and it was hypothesized that primary CMV infection has immunomodulatory effects that predispose to such secondary infections.

The spectrum of clinically active CMV infection in immunocompromised patients is broad and may vary according to the immunosuppressive condition. In HIV-infected patients, the classic presentation has been chorioretinitis but may also include GI ulcerations, pneumonitis, hepatitis, encephalopathy, adrenalitis, and a painful myeloradiculopathy. Some immunosuppressed patients present with only a mononucleosis-like syndrome consisting of fever and lymphadenopathy.

New approaches in both hematopoietic stem cell or solid organ transplant recipients emphasize the use of prophylactic or preemptive therapy based on CMV monitoring.[75] Although serologic tests have previously been suggested to have a potential role in directing CMV therapy in bone marrow transplant patients and heart transplant patients, serologies are not the most reliable studies in predicting the presence of CMV infection or clinical disease. The appearance of CMV protein pp65 in peripheral blood leukocytes has proved to be superior to tests based on virus isolation[73] and has correlated with subsequent development of CMV disease. In addition to CMV antigenemia, DNA/RNAemia (especially quantitative polymerase chain reaction) is clinically useful, and detection tests for both are methods of choice for diagnosis and monitoring of active CMV infection after organ transplantation.

For the purpose of developing consistent reporting of CMV in clinical trials, definitions of CMV infection and disease were developed and published.[76] In addition, an approach to the management of CMV infection after solid organ transplantation has been published, and several clinically relevant messages provided it.[73] In managing CMV infection, the clinician needs to be aware of four types of treatment options: (1) therapeutic use (treatment based on the presence of established infection); (2) prophylactic use (use of antimicrobial therapy from the earliest possible moment); (3) preemptive use (antimicrobial therapy before clinical signs of infection); and (4) deferred therapy (initiation of therapy after onset of disease). In the therapeutic setting of CMV disease after solid organ transplantation, IV ganciclovir is the drug of choice, with anti-CMV hyperimmunoglobulin preparations being useful adjuncts in seronegative recipients of seropositive organs and with foscarnet (because of its inherent toxicity) being considered as rescue therapy. Although ganciclovir has for years been the mainstay of therapy for CMV retinitis in AIDS patients, valganciclovir (an oral prodrug of ganciclovir) has been approved as an effective treatment option. In addition, studies are ongoing using valganciclovir as both preemptive and definitive treatment of CMV infections in transplant patients. An immune reconstitution syndrome including visual blurring months after successful therapy for CMV

retinitis has been described in AIDS patients who have started HAART.[77]

The role for prophylaxis against CMV was summarized based on the type of organ transplanted.[76] With detection of CMV antigenemia at a predefined level, IV ganciclovir may have a role in preventing CMV disease in certain patient populations. Secondary prophylaxis has been recommended but may be discontinued if the $CD4^+$ cell count reaches >100 to 150 cells/μL and remains at this level for ≥6 months with no evidence of active CMV disease.[43]

Epstein-Barr Virus

The pathobiology of Epstein-Barr virus (EBV) is important in understanding the evolution of EBV-associated disease in immunocompromised patients. Although early studies indicated that EBV replicated in epithelial cells in the oropharynx, more studies suggest that B cells in the oropharynx may be the primary site of infection.[78] This has led to the thought that resting memory B cells are the site of persistence of EBV within the body, with the number of latently infected cells remaining stable for years.[79] What has not been definitively elucidated at the present time is the role of oral epithelial cells in the transmission and latency of EBV. Even though the finding of antibodies against EBV viral proteins and antigens is consistent with the fact that there is some degree of humoral immunity to the virus, it is the cellular immune response that is the more important for controlling EBV infection. Important among the proteins produced by EBV is latent membrane protein 1, which acts as an oncogene and whose expression in an animal model has resulted in B-cell lymphomas. In patients who have AIDS or have received organ or bone marrow transplants, an inability to control proliferation of latently EBV-infected cells may lead to EBV lymphoproliferative disease, which in tissue may take the form of plasmacytic hyperplasia, B-cell hyperplasia, B-cell lymphoma, or immunoblastic lymphoma.[78] It has been suggested that therapy for EBV lymphoproliferative disease should include reduction in the dose of immunosuppressive medication when possible. More specific, definitive recommendations for therapy are not available, but potential options have been reviewed.[78]

Completing the spectrum of EBV disease in immunocompromised patients is oral hairy leukoplakia, a common, nonmalignant hyperplastic lesion of epithelial cells seen most characteristically in HIV-infected patients. In its classic presentation, hairy leukoplakia presents as raised white lesions of the oral mucosa, especially on the lateral aspect of the tongue. Contributing to the ongoing attempts to elucidate the pathobiology of EBV, a study of serial tongue biopsy specimens from HIV-infected patients demonstrated EBV replication in normal tongue epithelial cells (in contrast to the lack of active viral replication in certain EBV-associated malignancies) and suggested that the tongue may be a source of EBV secretion into saliva.[80] In this clinical trial, valacyclovir treatment completely abrogated EBV replication, resulting in resolution of hairy leukoplakia when it was present, but EBV replication returned in normal tongue epithelial cells after valacyclovir treatment. These findings are consistent with clinical experience that the lesions of hairy leukoplakia respond to antiviral therapy but recur once therapy is stopped. Topics not evaluated in this study but important in the understanding of EBV are whether other oral epithelial cells support viral replication and whether oral epithelial cells participate with B cells in viral latency.

Polyoma Viruses (Including JC Virus and BK Virus)

Clinically important members of this class of double-stranded DNA viruses include BK virus and JC virus. Primary infection with BK virus is generally asymptomatic and occurs in childhood. Following primary infection, the virus can remain latent in many sites, with the most notable being the kidney. With cellular immunodeficiency, the virus can reactivate and cause clinical disease. Although the kidney, lung, eye, liver, and brain are sites of both primary and reactivated BK virus-associated disease, the most characteristic disease entities are hemorrhagic and nonhemorrhagic cystitis, ureteric stenosis, and nephritis, and these occur most often in

recipients of solid organ or bone marrow transplants.[81]

JC virus is the etiologic agent in progressive multifocal leukoencephalopathy (PML). In this primary demyelinating process involving the white matter of the cerebral hemispheres, patients present subacutely with confusion, disorientation, and visual disturbances, which may progress to cortical blindness or ataxia. CSF is characteristically acellular. A feature on neuroradiology imaging studies is lack of mass effect. No definitive therapy is presently available for this infection, and clinical efforts have focused on the role of immune reconstitution in modifying the clinical course of the illness. In a multicenter analysis of 57 consecutive HIV-positive patients with PML, neurologic improvement or stability at 2 months after therapy was demonstrated in 26% of patients who received HAART in contrast to improvement in only 4% of patients who did not receive HAART ($P = 0.03$).[82] In this study, decreases in JC virus DNA to undetectable levels predicted a longer survival. In the context that untreated PML may be fatal within 3 to 6 months, such potential for preventing neurologic progression and improving survival by controlling JC virus replication becomes clinically relevant.

Adenoviruses

In immunocompromised patients, these DNA viruses may produce generalized illness that classically involves the nervous system, respiratory system, GI tract, and liver. This class of viruses has emerged as a major problem in some bone marrow transplant units. The infections may have a fulminant course, which may result in death. No drug has been shown to be definitively beneficial in these patients, although IV ribavirin may be effective in some.

Measles Virus

Because individuals are protected against measles by cell-mediated immunity and since measles may cause severe illness in HIV-infected persons, protection via vaccine is an important consideration. A basic tenet in infectious diseases has been that live-virus vaccines should not be administered to immunocompromised patients. An exception has been use of measles vaccine, a live-virus vaccine, in asymptomatic HIV-infected individuals and potentially in those with symptomatic HIV infection. Fatal giant-cell pneumonitis has been described in a young male measles vaccine recipient with AIDS.[83] Even with the overwhelming success of measles immunization programs, this case has prompted reappraisal of recommendations and some have suggested that it may be prudent to withhold measles-containing vaccines from HIV-infected persons with evidence of severe immunosuppression.

Emerging Viral Pathogens in Persons With Defects in Cell-Mediated Immunity

There have been increasing reports of infections caused by respiratory syncytial virus or parainfluenza virus, particularly in persons who have received bone marrow or solid organ transplantation. The spectrum of disease caused by these pathogens is evolving, with the lung being an important target organ. These viruses should be considered to be among the pathogens that may cause pneumonia in patients with defects in cell-mediated immunity.

Parasites and Protozoa

P jiroveci (Previously P carinii)

In recognition of its genetic and functional distinctness, the organism that causes human *Pneumocystis* pneumonia has been renamed *P jiroveci*, but despite this change, the use of the acronym PCP is not precluded because it can be read *Pneumocystis* pneumonia.[84] The clinical setting in which *P jiroveci* pneumonia (PCP) develops continues to evolve. In the pre-AIDS era, this pathogen was described as a cause of rapidly progressive infection in patients with malignant diseases, especially during the time of steroid withdrawal. Following the onset of the AIDS epidemic in the early 1980s, PCP was most often diagnosed in HIV-infected persons. Following the widespread use of HAART in the mid-1990s, HIV-associated PCP has decreased, and it has been reported that PCP may in certain settings be diagnosed more often in non-HIV

immunocompromised patients than in those with HIV infection.[85] Host defense against *Pneumocystis* includes humoral immunity; however, because of the overwhelming predominance of infection by this pathogen in HIV-infected persons, it has been included in this section of pathogens that infect patients with defective cell-mediated immunity.

Although diffuse interstitial infiltrates are the most characteristic pulmonary finding with PCP, patients may present with focal infiltrates, cavitary lesions, or nodular lung lesions. Findings that support, but do not prove, the diagnosis of PCP in an HIV-infected patient with pulmonary infiltrates include a $CD4^+$ cell count <250 cells/μL, a WBC count $<8{,}000$ cells/mm^3, and an elevated serum lactate dehydrogenase. PCP may occur as part of the presentation of the acute retroviral syndrome. In the review of PCP from the Clinical Center at the National Institutes of Health,[85] diagnostic studies for PCP were reviewed. It was noted that traditional stains on sputum or from BAL specimens for the cyst form of *P jiroveci* have been the mainstay of diagnosis in most settings. Direct immunofluorescent staining using monoclonal antibody 2G2 (which detects both cysts and trophozoites) has been used for many years in the algorithm of the National Institutes of Health Clinical Center for diagnosing PCP. This stain is performed first on induced sputum, and if that smear is negative, then a BAL specimen is obtained for the same study. Ongoing investigation has been focused on the development of a quantitative polymerase chain reaction assay that can be performed on oral washes or gargles and that might allow a clinician not only to diagnose PCP at an earlier stage than has traditionally been possible, but also to distinguish between colonization and disease with *P jiroveci*.

Trimethoprim-sulfamethoxazole is the current first-line therapeutic agent. As alternative therapy, pentamidine has been recommended for severe PCP.[42] Clindamycin/primaquine has been compared with trimethoprim-sulfamethoxazole in a clinical trial and found to be a reasonable alternative therapy for mild to moderate PCP.[42] Also listed as alternative therapy for mild to moderate disease are dapsone plus trimethoprim, atovaquone, or trimetrexate with leucovorin. Adjunctive corticosteroid therapy is recommended for patients with PCP whose room air Pa_{O_2} is <70 mg Hg or whose arterial-alveolar oxygen gradient is >35 mm Hg.[86] It is important that steroids are started at the time antipneumocystis therapy is initiated in an attempt to prevent the lung injury that may occur when this pathogen is killed. The dramatic decrease in the number of cases of PCP relative to the number of patients with HIV infection has been attributable to prophylaxis, which is recommended for those patients with a $CD4^+$ cell count <200 cells/μL, $CD4^+$ cells $<14\%$ of total lymphocyte count, constitutional symptoms such as thrush or unexplained fever $>100°$ F for ≥ 2 weeks (regardless of the $CD4^+$ count), or a previous history of PCP. Based on several clinical investigations, it seems that discontinuing prophylaxis in patients with adequate immune recovery is a useful strategy that should be widely considered.[43,87–89]

Toxoplasma gondii

Patient populations at higher risk for toxoplasmosis include those with hematologic malignancies (particularly patients with lymphoma), bone marrow transplant, solid organ transplant (including heart, lung, liver, or kidney), or AIDS.[90] In the vast majority of immunocompromised patients, toxoplasmosis results from reactivation of latent infection, but in heart transplant patients and in a small number of other immunocompromised patients, the highest risk of developing disease is in the setting of primary infection (ie, a seronegative recipient who acquires the parasite from a seropositive donor via a graft).[91]

Although pulmonary disease caused by this pathogen is associated with nonspecific radiographic findings of which bilateral pulmonary interstitial infiltrates are most common, neurologic disease is the classic pattern. In HIV-infected persons, it classically presents as fever, headache, altered mental status, and focal neurologic deficits, especially in individuals whose $CD4^+$ count falls below 100 cells/μL. Because the disease is caused by reactivation of latent infection in about 95% of cases, IgG antibody to *Toxoplasma* is generally present. Imaging studies of the brain show multiple (usually ≥ 3) nodular

contrast-enhancing lesions, found most commonly in the basal ganglia and at the gray-white matter junction. Mass effect is characteristic with these lesions.[92]

In the classic setting, empiric therapy with sulfadiazine and pyrimethamine is recommended; the total duration of acute therapy should be at least 6 weeks.[42] Clindamycin-containing regimens may have a role in sulfa-allergic patients. Brain biopsy should be considered in immunocompromised patients with presumed CNS toxoplasmosis if there is a single lesion on MRI, a negative IgG antibody test result, or inadequate clinical response to an optimal treatment regimen or to what the physician considers to be an effective prophylactic regimen against *T gondii.*[90] Trimethoprim-sulfamethoxazole given for PCP prophylaxis serves as primary prophylaxis for toxoplasmosis but should not be used for therapy. After acute therapy for toxoplasmic encephalitis, maintenance therapy is recommended but may be discontinued when the $CD4^+$ cell count is $>200/\mu L$ for ≥ 6 months.[43]

Strongyloides stercoralis

Infection with this parasite has often been described in patients with COPD who have been receiving chronic steroid therapy and who present with gram-negative bacteremia. Among patients with defects in cell-mediated immunity, bacteremia secondary to the hyperinfection is uncommon in two groups: (1) transplant recipients who receive cyclosporine (because of the anthelminthic properties of this rejection agent); and (2) HIV-infected patients, unless the $CD4^+$ cell count is ≤ 200 cells/mm^3 and the patient is concomitantly receiving corticosteroids.[91] The bacteremia occurs because of this organism's hyperinfection cycle, during which filariform larvae penetrate the intestinal mucosa, pass to the lungs by way of the bloodstream, break into alveolar spaces, and ascend to the glottis where they are swallowed into the intestinal tract to continue their process of autoinfection. Infection with this pathogen should be suspected in a patient with a defect in cell-mediated immunity who presents with clinical features that include generalized abdominal pain, diffuse pulmonary infiltrates, ileus, shock, and meningitis. Eosinophilia is often absent in steroid-treated patients.

In recent years, recommendations for therapy have changed based on the recognition that thiabendazole may not be consistently efficacious and that albendazole may be superior. Ivermectin may also be more effective than thiabendazole.

Cryptosporidium parvum

Although self-limited diarrhea associated with waterborne outbreaks has been noted in normal hosts, the clinical presentation of watery diarrhea, cramping, epigastric pain, anorexia, flatulence, and malaise in an HIV-infected patient suggests the diagnosis of cryptosporidiosis. Four clinical syndromes have been identified[93]: chronic diarrhea (in 36% of patients); choleralike disease (33%); transient diarrhea (15%); and relapsing illness (15%). Biliary tract symptoms similar to cholecystitis have been noted in 10% of cases. Diagnosis is confirmed by finding characteristic acid-fast oocysts on examination of feces.

No predictably effective antimicrobial therapy is available, and management consists largely of symptomatic treatment of diarrhea. Effective antiretroviral therapy (to increase $CD4^+$ count to >100 cells/μL) has been noted to result in complete, sustained clinical, microbiologic, and histologic resolution of HIV-associated cryptosporidiosis.[42]

Isospora belli

Like cryptosporidiosis, this pathogen is acid-fast and can cause a very similar diarrheal illness. In contrast to cryptosporidiosis, the pathogen is larger, oval, and cystic, and very importantly, responds to therapy with trimethoprim-sulfamethoxazole.[42]

Microsporidia

These obligate intracellular protozoa are probably transmitted to humans through the ingestion of food contaminated with its spores, which are resistant to environmental extremes. *Enterocytozoon bienuesi* produces a protracted diarrheal illness accompanied by fever and weight loss similar to that caused by *Cryptospo-*

ridium; it is reported to occur in 20% to 30% of patients with chronic diarrhea not attributable to other causes. *Enterocytozoon cuniculi* has been described as an etiologic agent for hepatitis, peritonitis, and keratoconjunctivitis.

Transmission electron microscopy with observation of the polar filament is considered the gold standard for diagnosis, but the Brown-Brenn stain and the Warthin-Starry silver stain are commonly used for detecting microsporidia in tissue culture. The modified trichrome stain has been used in clinical diagnostic laboratories to detect microsporidia in fluids.[94]

Treatment guidelines have recommended the initiation and optimization of antiretroviral therapy with immune reconstitution to a $CD4^+$count >100 cells/μL.[42] Albendazole may be the most effective drug to treat disseminated (not ocular) and intestinal infection attributed to microsporidia other than *E bienuesi*.[42] For GI infections caused by *E bienuesi,* fumagillin has been suggested as being effective. For ocular infection, fumidil in saline eye drops and albendazole for management of systemic infection have been recommended.

Amoebae

Naegleria and *Acanthamoeba* are free-living amoebae that have the potential to infect humans. Of these, *Acanthamoeba* spp may infect individuals with defects in cell-mediated immunity (including patients who have AIDS or have undergone organ transplantation) and result in granulomatous amebic encephalitis. Clinical manifestations include mental status abnormalities, seizures, fever, headache, focal neurologic deficits, meningismus, visual disturbances, and ataxia. An important clinical clue may be preexisting skin lesions that have been present for months before CNS disease is clinically manifested; lesions may take the form of ulcerative, nodular, or subcutaneous abscesses. Pneumonitis may also be a part of the clinical presentation.

There are few data regarding therapy for granulomatous amebic encephalitis, but it appears that the diamidine derivatives pentamidine, propamidine, and dibromopropamidine have the greatest activity against *Acanthamoeba*.

Leishmania spp

In endemic areas of the world, these pathogens infect patients with defective cell-mediated immunity and cause a febrile illness with visceral involvement, most notably hepatomegaly and splenomegaly. Leishmaniasis has been increasingly described in HIV-infected persons from endemic regions and may take a chronic relapsing course. Pentavalent antimonials (with sodium stibogluconate as the representative agent) may be useful for this infection. Notable is that the drug may cause dose-related QT prolongation on ECG, with arrhythmias (atrial and ventricular) and sudden death occasionally. It is contraindicated in patients with myocarditis, hepatitis, or nephritis. Antimony resistance has been noted in some HIV-infected patients; in such situations, liposomal amphotericin B has been shown to be potentially effective because it targets infected macrophages and reaches high levels in plasma and tissues.

Of the relevant disease models influencing the understanding of the clinical significance of type 1 and type 2 immunity, leishmaniasis is important. Biopsy specimens from patients with localized infection with *Leishmania braziliensis* were consistent with a protective type 1 immune response that included prominent messenger RNA coding for IL-2 and IFN-γ.[95] As the lesions in patients became more destructive, there was a switch to a marked increase in the level of IL-4 messenger RNA, which is consistent with a failed type 2 immune response. Such data have been interpreted as an eloquent demonstration of the facts that type 1 immunity is the key to protection against *Leishmania* infections in humans and that a high infectious burden suppresses the human immune system from mounting type 1 responses. This has implications for therapy, which has included the use of IFN-γ as an adjunctive agent for visceral leishmaniasis.

Trypanosoma cruzi

With immunosuppression including HIV infection, reactivation of this pathogen can occur. In both posttransplantation infection and HIV-associated infection, patients may present with headache, cognitive changes, seizures, and hemi-

paresis.[42] In addition to the characteristic lesions seen with Chagas disease, immunosuppressed patients have an increased incidence of neurologic disease, with neuroimaging studies showing large solitary or multiple ring-enhancing lesions with surrounding edema.[42]

Miscellaneous Pathogens

Chlamydiae

This group of intracellular pathogens has been listed in some reviews of pathogens defended against by cell-mediated immunity. Although patients with a defect in this host defense system may be at increased risk for chlamydial infections, such problems have not been classically described.

Rickettsiae

As with chlamydiae, rickettsiae are intracellular pathogens defended against by cell-mediated immunity. Reviews have not described immunocompromised patients as being at increased risk for infection by pathogens in this group.

Treponema pallidum

Defense against this pathogen may include a role for macrophages and other antigen-presenting cells, such as dendritic cells, that process and present treponemal antigens to helper T cells. HIV-infected patients can have abnormal serologic test results, including unusually high, unusually low, or fluctuating titers. However, aberrant serologic responses are uncommon, and most specialists believe that both treponemal and nontreponemal serologic tests for syphilis can be interpreted in the usual manner for patients who are infected with both HIV and *T pallidum*.[95] With HIV infection, treponemal infection is more likely to have an atypical clinical presentation, be aggressive, or invade sites such as the CNS. A reactive CSF-VDRL and a CSF WBC count $\geq$10 cells/mm^3 support the diagnosis of neurosyphilis.[42] Although the VDRL test on CSF is the standard serologic test for neurosyphilis, it may be nonreactive when neurosyphilis is present. The CSF fluorescent treponemal antibody absorption test is less specific for neurosyphilis than the VDRL-CSF, but the high sensitivity of the study has led some experts to believe that a negative CSF fluorescent treponemal antibody absorption test excludes neurosyphilis.[96] Such considerations are important, since HIV-1 infection might be associated with mild mononuclear CSF pleocytosis (5–15 cells/mm^3), particularly among persons with peripheral blood CD4$^+$ counts $>$500 cells/mm^3.[42] In addition to meningitis, a characteristic clinical presentation of syphilis in the CNS is stroke in a young person.

The recommended regimen for the treatment of patients with neurosyphilis is aqueous penicillin G (18 to 24 million U/d, administered as 3 to 4 million U IV q4h or as continuous infusion) for 10 to 14 days.[42,95] If compliance with therapy can be ensured, an alternative regimen is procaine penicillin (2.4 million U IM once daily) plus probenecid (500 mg orally qid), both for 10 to 14 days. Because the duration of treatment recommended for neurosyphilis is shorter than for latent syphilis, some experts recommend administering benzathine penicillin (2.4 million IM once weekly) for up to 3 weeks on completion of the neurosyphilis regimen to provide a comparable total duration of therapy. It is recommended that all HIV-infected persons be tested for syphilis and that all persons with syphilis be tested for HIV. Spinal fluid examination has been recommended for all HIV-infected persons with latent syphilis or with neurologic abnormalities. Some experts have recommended spinal fluid examination for any HIV-1-infected person with syphilis, regardless of stage.[42]

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Chapter 13. Liberation From Mechanical Ventilation

John F. McConville, MD

Objectives:

- Recognize criteria used to assess readiness for spontaneous breathing trials (SBT).
- List criteria for successful SBT.
- Identify nonventilator strategies for reducing duration of mechanical ventilation.
- Identify risk factors for extubation failure despite passing a SBT.
- Understand how/when to use NIPPV in the postliberation period.

Key words: liberation; mechanical ventilation; spontaneous breathing trial

Synopsis:

Liberation from mechanical ventilation, rather than weaning, is a better description of the transition from assisted ventilation requiring an endotracheal tube to spontaneous breathing. Earlier liberation from mechanical ventilation (MV) reduces ICU-related complications and, thus, clinicians are often motivated to minimize the duration of MV. Trials of spontaneous breathing with minimal ventilator assistance remain the best method of determining which patients might be ready for liberation. Clinicians should assess a patient's readiness for spontaneous breathing every day and, when appropriate, conduct a spontaneous breathing trial (SBT). This approach results in a decreased duration of MV. Studies have demonstrated that SBTs performed on pressure support or T-piece are equally effective at identifying patients able to breathe spontaneously, and a 30-min SBT has been shown to be as effective longer trials. Importantly, there is increasing evidence that sedation strategies, timing of SBTs, and possibly early mobilization of mechanically ventilated patients may be essential components of an overall strategy to minimize the duration of MV. Because patients requiring reintubation after extubation failure have an increased risk of death, several recent studies have started to tease out the difference between liberation readiness and SBT success. For those patients who are at risk of developing respiratory distress in the postextubation period, early use of noninvasive positive pressure ventilation appears effective at reducing the need for reintubation.

Overview

Mechanical ventilation (MV) is commonly used as a treatment of respiratory failure in the ICU. There has been a tremendous amount of research to determine how to best transition patients from MV to spontaneous breathing once the underlying etiology of respiratory failure has started to improve. Unfortunately, the term "weaning" is often used to describe this transition. "Weaning" suggests that this process is gradual and is NOT an accurate description of this process for the vast majority of patients with respiratory failure. "Liberation" is a better description of the transition from MV to spontaneous breathing and also implies that this transition requires both spontaneous respiration as well as the removal of the endotracheal tube.

Figure 1 describes a typical algorithm used by many clinicians to liberate patients from MV. Patients are assessed daily for their "readiness" to perform a spontaneous breathing trial (SBT). Typical criteria used to determine readiness include: hemodynamically stable patient off vasoactive drugs and Pa_{O_2}/F_{IO_2} ratio (P:F ratio) of >200 with positive end-expiratory pressure ≤ 5 cm H_2O. Protocol-driven assessments of readiness are often carried out by nurses or respiratory therapists in many ICUs. If a patient is deemed ready for a SBT and is awake free from sedative infusions, then the ventilator is switched to a "minimal support" mode, such as: pressure support (PS) ≤ 7 cm H_2O, CPAP ≤ 5 cm H_2O, or a T-piece. If the patient is able to breathe spontaneously on any of these settings for 30 min without becoming hypertensive, tachypneic, tachycardic, hypoxic, or anxious/agitated, then the patient is said to have "passed" the SBT. At this point the patient's ability to protect his/her airway if the endotracheal tube is removed, the amount of airway secretions, and his/her cough are assessed. If the mental status, cough, and amount of secretions are deemed adequate, then the endotracheal tube should be removed. Alternatively, a patient who is deemed not ready for or who fails a SBT should be transitioned back to full mechanical ventilator support, and the mechanism of respiratory failure should be elucidated and treated.

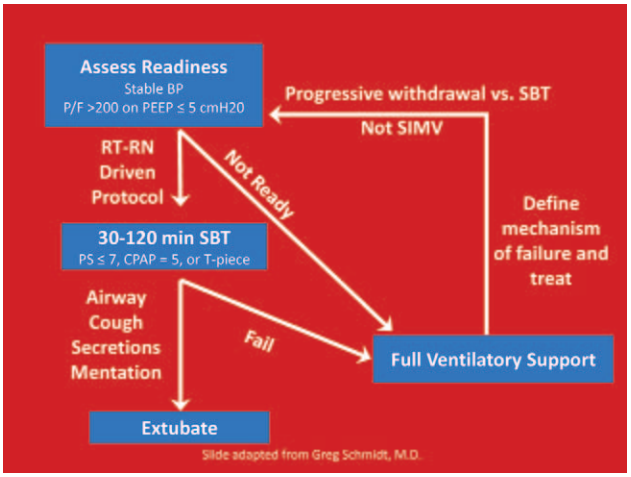

Figure 1. Common algorithm for transition from MV to spontaneous breathing (see text for details).

There have been several cross-sectional studies that have examined how intensivists utilize MV. One such prospective study of 361 ICUs in 20 countries described 5,183 patients with ≥12 h of MV.[1] Almost 70% of the patients receiving MV had acute respiratory failure in the setting of the postoperative period, pneumonia, congestive heart failure, sepsis, trauma, or ARDS. Coma, acute or chronic respiratory failure from chronic lung disease, and neuromuscular weakness comprised the other 30% of MV patients. Several other studies suggest that 40% of the total MV time is spent treating the underlying cause of respiratory failure and 60% is spent liberating patients from the respirator.[2,3] Thus, efforts to decrease MV time can be directed at: earlier recognition and treatment of respiratory failure, earlier appreciation of readiness for and initiation of SBT, and/or decreased time spent liberating patients from MV.

There is some literature that supports the commonly held belief that earlier liberation from MV reduces ICU-related complications.[4] The 2000 study by Coplin et al compared brain-injured patients liberated within 48 h of meeting defined readiness criteria with similar patients who had more than a 48-h delay in liberation after meeting readiness criteria. The delayed group had a higher mortality, increased risk of pneumonia, and a longer hospital length of stay than the group that was liberated in a more timely fashion. Thus, clinicians should be motivated to minimize the duration of MV.

Predictors of SBT Success and Weaning Studies

Many studies have tried to identify simple measurements that can help clinicians predict which patients are most likely to pass a spontaneous breathing trial. Yang and Tobin demonstrated that a respiratory rate/tidal volume ratio (f/V_T) of <105 after a 1-min breathing trial on a T-piece was quite accurate in predicting which patients would pass a subsequent SBT (positive predictive value of 0.78 and negative predictive value of 0.95).[5] Meade and colleagues[6] subsequently performed a meta-analysis and review of 51 weaning predictors. They found that five measurements were able to predict success on a subsequent SBT: negative inspiratory force, minute volume, tidal volume, respiratory rate, and f/V_T ratio. However, these predictors were not very powerful, and most experts agree that the best method of determining if a patient is ready to breathe spontaneously is to place them on a SBT once they meet readiness criteria.

Currently, SBTs remain the best method of determining which patients might be ready for liberation, but many earlier studies investigated the best mode of MV to use for patients who failed their initial SBT. In the 1990s, Esteban and colleagues[7] and Brochard and colleagues[8] conducted two landmark studies that compared a gradual reduction of either synchronized intermittent mandatory ventilation or PS with SBTs using a T-piece in medical-surgical patients who failed their initial SBT. These studies showed that the constrained synchronized intermittent mandatory ventilation weaning protocol increased the duration of MV when compared with both T-piece SBT and the protocol utilizing a gradual reduction in PS. Most importantly, 76% of patients passed their initial SBT.

How to Conduct an SBT

One of the take-home messages from the Esteban and Brochard studies was that the majority of patients are able to successfully complete an SBT on their first attempt. A 1996 study by Ely and colleagues[9] supported the notion that early SBTs result in a reduction in

MV time and also stressed the importance of assessing patients "readiness" for a SBT on a daily basis. In this study, patients were deemed ready for SBT if they met the following criteria: P:F ratio >200, positive end-expiratory pressure ≤5 cm H_2O, adequate cough, no vasopressor or sedatives in use, and a f/V_T ratio ≤105 during 1-min CPAP trial on 5 cm H_2O. The control group received a daily screen for readiness, whereas the intervention group had a daily screen followed by an SBT if appropriate. In the intervention group, treating physicians were notified if their patient passed a 2-h SBT. The trial was terminated if any of the following occurred during the SBT: RR >35 for more than 5 min, oxygen saturation <90%, heart rate >140/min, sustained change in heart rate by 20%, systolic BP >180 mm Hg or <90 mm Hg, and increased anxiety or diaphoresis. The intervention group had a decrease in duration of MV, reintubation rate, and ICU cost when compared with the control group, despite having higher severity of illness and lung injury scores. The important message of this study, and others that have reproduced the conclusions, is that protocolized assessment of a patient's readiness followed by a SBT, when appropriate, results in decreased duration of MV when compared with physician judgment. Subsequent studies have demonstrated that SBTs performed on PS or T-piece are equally effective at identifying patients able to breathe spontaneously and have similar reintubation rates.[10,11] In addition, a 30-min SBT has been shown to be as effective as a 120-min SBT.[12]

SBT Failure and New Classification Schemes

The pathologic mechanisms that result in failure of an SBT are numerous. Often respiratory mechanics worsen during an SBT, resulting in increased work of breathing that is not able to be maintained by critically ill patients.[13] Deterioration of respiratory mechanics can be the result of increased respiratory resistance (asthma), decreased lung compliance (pulmonary fibrosis, pulmonary edema, or ARDS), and air trapping (COPD). In addition, trials of spontaneous breathing challenge the circulation, and SBT failure is often the result of cardiac dysfunction. Figure 2

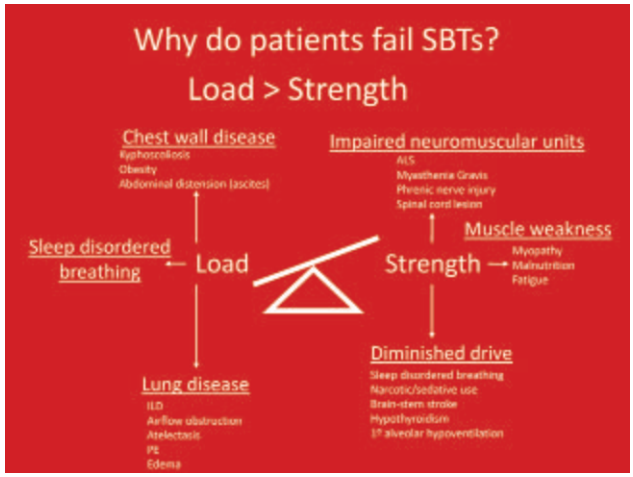

Figure 2. Adapted with permission from Figure 264–1B in McConville and Solway.[14]

reviews many of the pathologic states that result in an imbalance between respiratory muscle strength and respiratory load that can result in respiratory failure and inability to pass an SBT.[14]

New classification schemes utilize the results of SBTs to characterize a patient's ability to move from MV to independent breathing.[15] The simple category includes those patients able to successfully complete their first SBT and subsequently be liberated from MV. Patients in the difficult category require up to three SBTs and less than 7 days between their first failed SBT and successful liberation from MV. The prolonged-category patients fail at least three SBTs or require greater than 7 days of MV following their initial failed SBT. There is emerging evidence that patients in the prolonged group have increased hospital mortality, and possibly overall mortality, as compared to patients in the simple and difficult categories.[16]

Additional Strategies to Reduce the Duration of MV

Several studies have now conclusively shown that sedation strategies can impact the duration of MV. The landmark study of Kress et al demonstrated that MV duration and ICU length of stay are reduced in patients who had a daily interruption of sedation as compared with patients treated with continuous IV sedation.[17] Patients in the interruption group had their sedation resumed once they were deemed to be awake (able to follow three of four commands) or they became agitated. A subsequent study showed that patients who had

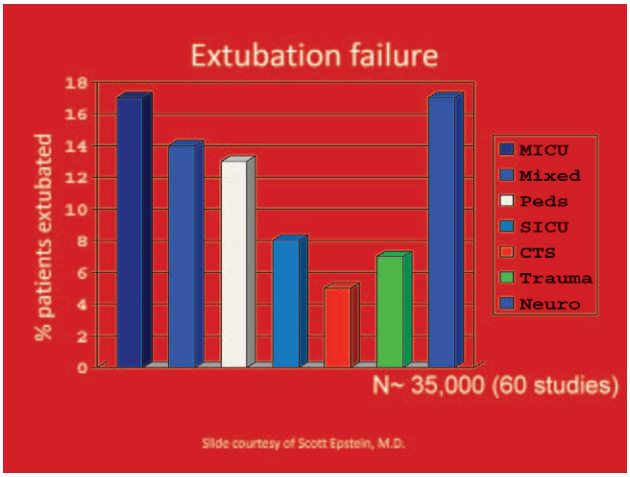

Figure 3. Estimated rates of extubation failure. Read columns left to right, starting with MICU and ending with Neuro.

sedation stopped and were awake during an SBT had increased MV-free days, decreased duration of MV, and shortened hospital length of stay when compared with patients who performed an SBT while still receiving sedatives.[18] Finally, another study[19] suggests that earlier initiation of physical therapy for mechanically ventilated patients results in an increase in MV-free days. Thus, there is increasing evidence that sedation strategies, timing of SBTs, and possibly early mobilization of mechanically ventilated patients may be essential components of an overall strategy to minimize the duration of MV.

Predicting Liberation Failures After SBT Success

Figure 3 shows the extubation failure rates for different ICUs. This figure and several other studies demonstrate that ~13% of patients will require reintubation after an attempt to liberate them from MV. Importantly, patients requiring reintubation have an increased risk of death, longer hospital stay, and decreased likelihood of returning home following an ICU admission when compared with patients who are successfully liberated from MV.[20] Thus, identifying patient risk factors for extubation failure despite passing a SBT is an important task of ICU physicians. Several recent studies have started to tease out the difference between liberation readiness and SBT success. One such study by Salam and colleagues[21] measured peak cough flow, amount of secretions, and mental status in 88 patients who had passed an SBT prior to liberation. However, all patients with poor cough, increased secretions, and poor mental status required reintubation despite passing an SBT, whereas only 3% failed liberation if they had adequate cough, minimal secretions, and were awake. Another study using logistic regression described higher f/V_T ratio at the end of an SBT, positive fluid balance prior to liberation, and a diagnosis of pneumonia as additional risk factors for liberation failure after passing an SBT.[22] These studies suggest that after patients pass an SBT intensivists need to assess additional factors prior to proceeding with removal of an endotracheal tube.

Noninvasive Positive Pressure Ventilation (NIPPV) for Postliberation Respiratory Distress

Several studies have looked at the use of NIPPV in patients developing respiratory distress within 48 h of extubation. Two studies randomized patients with postliberation respiratory distress to standard care (oxygen mostly) or NIPPV.[23,24] There was no difference in the number of patients requiring reintubation, and in the Esteban study the use of NIPPV to treat postliberation respiratory distress actually increased mortality. However, two additional studies[25,26] prospectively identified risk factors that placed patients at increased risk of extubation failure and randomized these patients to usual care or preemptive NIPPV in the immediate postextubation period. Some of the risk factors included: fail >1 SBT, congestive heart failure, P_{ACO_2} >45 postliberation, weak cough, comorbidity, stridor, age >65, and acute physiology and chronic health evaluation score >12 on extubation day. Both of these studies showed that the group receiving NIPPV had a reduced need for reintubation as compared with the standard care groups. Thus, early use of NIPPV in the postliberation period for patients deemed to be at increased risk of extubation failure appears effective at reducing the need for reintubation. However, using NIPPV after patients develop respiratory distress in the post-

extubation period may not be beneficial, and in fact may be harmful for some patients.

Nothing to Disclose

The author has disclosed that no relationships exist with any companies/organizations whose products or services may be discussed in this chapter.

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Chapter 14. Trauma and Burns

Bennett P. deBoisblanc, MD, FCCP

Objectives:

- List common organ injuries associated with different types of blunt force and penetrating trauma such as traumatic brain and spinal cord injuries, hemopneumothorax, aortic injury, esophageal injury, bronchial rupture, cardiac contusion, solid organ injury in the abdomen, and pelvic fracture.
- Identify the preferred diagnostic and management approaches to each of the above injuries and their complications.
- Identify the common complications and the appropriate management of burn and electrical injuries.

Key words: aortic injury; bronchial rupture; burn injury; cardiac contusion; electrical injury; esophageal injury; hemopneumothorax; pelvic fracture; smoke inhalation; solid organ injury in the abdomen; trauma coagulopathy; traumatic brain and spinal cord injuries

Synopsis:

Trauma is the fifth leading cause of death in the United States. Motor vehicle accidents are the major cause of life-threatening blunt force injuries while gunshot wounds lead the list of causes of serious penetrating traumatic injury. Understanding the mechanism of injury is helpful in identifying occult injuries that may be missed on a primary survey. Traumatic brain injury and uncontrolled hemorrhage caused by trauma coagulopathy are the most common mechanisms of death. Damage control resuscitation and damage control surgery have reduced morbidity and mortality of traumatic injuries. Smoke inhalation injury is the most common mechanism of deaths caused by fire. Both low-voltage and high-voltage electrocution can be fatal, but the mechanisms and management are often different.

Overview

Trauma is the fifth leading cause of death in the United States and blunt injuries from motor vehicular accidents are the most common cause of fatal trauma. Mortality may be predicted by the severity of injury of six body regions (Injury Severity Score [ISS]). Brain injury and uncontrolled hemorrhage account for most deaths. Age, ISS, Glasgow Coma Scale score, duration of shock, presence of hypothermia or acidosis on arrival, and coagulopathy are adverse prognostic signs.

The primary survey begins with an assessment of the airway, breathing, and circulation, and is followed immediately with a careful neurologic exam. The secondary physical exam targets anatomic sites of concern using the known mechanism of injury as a guide. A focused assessment with sonography for trauma (FAST) exam can be performed simultaneously if appropriate. Stabilization is focused on prevention of secondary brain injury and damage-control surgery. In the absence of brain injury, permissive hypotension in the field with fluid resuscitation in the operating room appears to be associated with better outcomes than aggressive crystalloid resuscitation by emergency medical services. There is no clear evidence to support colloid over crystalloid, hypertonic saline over normal saline, or lactated ringers over normal saline. However, it does appear that whole blood has advantages over other resuscitation fluids.

Coagulopathy

Of deaths in the operating room, 80% are the result of uncontrolled hemorrhage while 20% are directly related to coagulopathy. Whole blood transfusions are preferred over crystalloid. The etiology of the coagulopathy may be multifactorial: dilution of clotting factors with intravenous fluids, clotting factor consumption, hypothermia, acidosis, and hypocalcemia.

Damage-control surgery involves minimizing the scope and number of initial operative procedures to stanch hemorrhage and decontaminate injuries. Definitive repair of injuries is delayed until the patient is more stable.

In patients requiring massive transfusion, whole blood or fresh frozen plasma, packed RBCs, and random donor platelets in a 1:1:1 ratio is preferred. In polytrauma, the routine early use of tranexamic acid, a synthetic antifibrinolytic derivative of lysine, within 3 h of injury reduces transfusion requirements and trauma mortality

without increasing the risk of major thrombotic complications. The use of activated factor VII concentrates remains controversial.

Traumatic Brain and Spinal Cord Injuries

Traumatic brain injury may be focal (subdural or epidural hematoma) or diffuse (subarachnoid hemorrhage or diffuse axonal injury). Subdural hematoma results from a tearing of bridging veins and most commonly affects older individuals on anticoagulation. Epidural hematoma is most commonly associated with skull fracture across the middle meningeal artery. Subarachnoid hemorrhage and diffuse axonal injury (DAI) are often seen in association with closed head injuries. The CT scan appearance in DAI may be normal or near normal. The neurologic prognosis with DAI is poor. Following neurosurgical intervention, management is focused on maintaining cerebral perfusion pressure and avoiding hypoxemia, hypercarbia, hyperthermia, and hyperglycemia. Intensive insulin therapy, routine hyperventilation, and therapeutic hypothermia have not been shown to be superior to usual care. A 7-day course of antiepileptics reduces the risk of seizures.

Intracranial hypertension can be a devastating complication of traumatic brain injury. The normal intracranial pressure (ICP) is $<$15 mm Hg. Cerebral perfusion pressure (CPP) is best estimated by the equation CPP = MAP (mean arterial pressure) − ICP. Signs of elevated ICP include alterations in the level of consciousness, posturing, papilledema, symptoms of herniation (see below), and systemic hypertension, bradycardia, and bradypnea (Cushing's Triad). Ideally, CPP should be kept at 60 to 75 mm Hg in patients with elevated ICP.

Herniation syndromes are many and varied depending on what part of the brain is compressed. They may be broadly classified by the opening through which the brain is herniating: (1) Subfalcine. The cerebral cortex gets squeezed through the falx cerebri from one side to the other. Commonly presents with anterior cerebral artery occlusion, that is, contralateral leg weakness. (2) Transtentorial. (*a*) The medial part of the temporal lobe, that is, the uncus, may be forced down through the tentorium. Presents as ipsilateral third nerve palsy and decerebrate posturing. (*b*) The thalamus is pressed down through the tentorium. (3) Foramen magnum herniation. Most often the cerebellar tonsil compresses the medulla, leading to stiff neck and apnea. (4) Transcalvarial. Cerebral cortex squeezes through a traumatic or surgical hole in the calvarium. Presentation varies by the location.

On a board examination question, suspect impending brain herniation in a patient at risk who develops a new neurologic defect and depressed level of consciousness or posturing. Herniation should be aggressively managed with head elevation, temporary hyperventilation, removal of cerebrospinal fluid, mannitol, and/or blood pressure elevation. Patients should be kept sedated, normothermic, euvolemic, and normoosmolar to slightly hyperosmolar.

Although hypertonic saline lowers ICP, its utility in improving outcomes is uncertain. Therapeutic hypothermia has also not been proven to be beneficial in this setting. Glucocorticoids increase mortality in traumatic brain injury. Decompressive craniectomy may be beneficial in highly selected cases (eg, nondominant hemispheric intracranial hemorrhage).

Spinal cord injury is often associated with other significant injuries, but symptoms of these other injuries may be masked by sensory deficits. Initial management is with spinal stabilization. The use of glucocorticoids remains controversial. Treatment of initial spinal shock is with IV fluids and vasoconstrictors. Tachycardia and catecholamine hypersensitivity may develop over time as a result of upregulation of β-adreneric receptors.

Thoracic Trauma

Unstable patients go directly to the operating room. Stable patients can be immediately evaluated with a FAST examination and standard anterior-posterior chest radiographs.

Tube thoracostomy is the initial procedure for pneumothorax or hemothorax. Beware of the deep sulcus sign of pneumothorax in a supine patient. Ultrasound that shows a pleural "slide" sign over several points along the anterior and lateral chest wall has a negative predictive value (rules out pneumothorax) that approaches 100%.

Blunt force trauma to the chest wall may cause a pulmonary contusion that presents as a radiographic area of consolidation, often in an area of rib fracture. Other radiographic presentations include parenchymal lacerations, intrapulmonary hematoma formation, or pneumatocoel. Treatment is usually supportive. The severity of the underlying lung parenchymal injury will be the primary determinant of which patients with a flail chest will require mechanical ventilation. Lung protective mechanical ventilation and fluid restriction are appropriate. Liberal analgesics are often required. Suspect aortic transection, cardiac contusions, and bronchial rupture with high-velocity deceleration injuries.

Penetrating trauma to the chest is divided into injuries that involve the lung only and injuries to the heart, great vessels, or esophagus. Penetrating injuries to the lung are initially managed with tube thoracostomy. Greater than 1,500 mL of blood on tube placement or more than 300 mL/h generally requires operative management. Persistent air leak should suggest injury to a larger bronchus, the trachea, or the esophagus.

Aortic rupture is associated with a mortality of 90% at the scene; however, aortic dissections and pseudoaneurisms are survivable with early diagnosis. Most aortic injuries occur at the level of the ligamentum arteriosum near the left subclavian artery. Suspect an aortic injury with a first rib fracture, a widened mediastinum, a blunted aortic knob, an apical pleural cap or deviation of the trachea, a nasogastric tube, or left mainstem bronchus. CT angiography is the initial diagnostic procedure of choice. All patients should eventually undergo operative management, but mortality rates appear to be lower in patients where the repair is delayed to allow other injuries to stabilize. Preoperative management is the same as for a dissection (blood pressure and heart rate control). Paraplegia may develop as a result of anterior spinal artery occlusion. Manage this complication with a lumbar drain to reduce the intrathecal pressure, which improves the perfusion pressure to the spinal cord.

Most esophageal injuries are caused by penetrating trauma. The cervical esophagus is more susceptible to penetrating injury than the thoracic and abdominal esophagus. Pneumomediatinum and high amylase pleural effusions are the keys to this diagnosis. Evaluate with esophagogastroduodenoscopy or gastrograffin swallow. A primary repair is often possible unless there is mediastinitis, in which case exclusion is the treatment of choice.

Cardiac contusions were historically most commonly associated with steering wheel injuries. Airbags have reduced this complication of motor vehicle accidents, but any significant blunt force to the sternum may be causal. The diagnosis is suspected when there are arrhythmias or ST segment or T wave changes on ECG. Cardiac troponin-I and MB fraction of creatine kinase are often elevated without serious injury to the myocardium. Echocardiography and/or cardiac MRI may be diagnostic. Treatment is usually symptomatic unless there is significant valvulopathy or tamponade. Beware of late complications such as tricuspid chordae rupture. Penetrating cardiac injuries that make it to the operating room are often managed by oversewing the injury. Systemic air embolism or systemic thromboembolism is a potential complication.

Abdominal and Pelvic Trauma

Unstable patients with blunt or penetrating trauma to the abdomen should undergo a FAST examination. If blood is present on FAST, exploration in the operating room is indicated. Stable patients should undergo CT scanning. Not all solid organ injuries need operative intervention. In particular, even significant injuries to the liver, spleen, or kidneys can often be carefully observed nonoperatively in the ICU. Eligible patients must be devoid of significant brain of spinal cord injury that could mask clinical signs of injury progression. Patients must be hemodynamically stable without the need for ongoing transfusions, and they should be free of an indication that would require surgery anyway. The nonoperative approach requires continuous bed rest, frequent vital sign monitoring, repeat abdominal girth measurements, and hemoglobin measurements every 4 h. To safely institute a nonoperative protocol, hospitals should have access to a CT scanner and Interventional Radiology at all times. Presence of a contrast blush or extravasation on dynamic CT scan is an indication for embolization.

Pelvic fractures may be associated with significant retroperitoneal blood loss, fat embolism syndrome, or venous thromboembolism. Treatment is early immobilization; blood product resuscitation; analgesia; and a search for injuries to the vessels, ureters, bladder, rectum, and vagina. Interventional radiology can be useful in the first 48 h to help control bleeding. The risk of venous thromboembolism is very high in this population.

Burns

The initial assessment of a burn begins with a primary survey of the airway, breathing, and circulation of advanced trauma and life support. Altered mental status is common in burn injury: (1) presenting patients may have anoxic brain injury, carboxyhemoglobinemia (COHgB), methemoglobinemia, or cyanide toxicity; (2) significant head trauma may have occurred during attempts to escape; or (3) the patient may have already been impaired by drugs, alcohol, or head injury as an explanation for failing to escape the fire. A search for other associated such as fractures, corneal injuries, and so on is warranted for the similar reasons.

Up to 80% of fire-related deaths in the United States are caused by smoke inhalation rather than burn injury. Smoke contains particulate matter, noxious products of combustion, carbon monoxide (CO), cyanide, low F_{IO_2}, and hot air. Thermal injury to the tracheobronchial tree is rare because most heat is dissipated in the nose and mouth. The rare exception is steam inhalation caused by the higher specific heat of water vapor compared with dry air. Inhaled products of combustion bind to the tracheobronchial mucosa, causing injury. The location of the injury depends on the water solubility of the inhaled product. Highly water-soluble products such as sulfur dioxide cause more upper airway injury whereas poorly water-soluble products, such as phosgene, are more likely to cause acute respiratory distress syndrome. Symptoms of bronchospasm and airway edema can be delayed up to 36 h after exposure.

Clues to the diagnosis of smoke inhalation are the presence of carbonaceous sputum, nasopharyngeal soot, facial burns, dyspnea, wheezing, hoarseness, stridor, or altered mentation. Upper airway obstruction caused by glottic and supraglottic edema is a life-threatening complication of smoke inhalation. Indications for intubation include the inability to protect the upper airway (eg, Glasgow coma score $\leq$7), respiratory distress, hoarseness or stridor, third-degree facial burns, and CO poisoning with neurologic symptoms. Large-volume resuscitation has been identified as a risk factor for upper airway obstruction in patients with smoke inhalation.

CO poisoning is more than simply COHgB. CO poisoning not only impairs oxygen (O_2) delivery but also impairs utilization by binding to cytochrome oxidase. Therefore, the neurologic manifestations can be out of proportion to the degree of COHgB. The half-life of COHgB is 240 min in breathing room air, 40 min on 10% O_2, and 15 min under hyperbaric O_2. Treatment for suspected CO poisoning is always 100% O_2. Consider intubation if COHgB >20% and patient is symptomatic or if COHgB >30. Wean O_2 when COHgB <10 and HCO_3 >20 mEq/L. Cyanide toxicity is treated with hydroxocobalamin (Cyanokit; Meridian Medical Technologies).

There may be large third space and evaporative fluid losses, so burn resuscitation is a critical element of management in the ICU. The goals of fluid resuscitation are to maintain adequate organ function such as urine output 0.5 to 1.5 mL/kg/h. Standard resuscitation formulae such as the Parkland formula and the Brooke formula have been advocated. Recommended fluid resuscitation ranges from 2 to 4 mL of lactated Ringer's per kilogram body weight for each percent of second or second/third degree burn for the first 24 h. Approximately one-half is administered over the initial 8 h, and the remaining one-half is administered over the following 16 h. Use the Lund-Browder rule of nines chart: head, 9%; each arm and each leg, 9%; anterior trunk and posterior trunk, each 18%.

IV access may be through burn but not distal to circumferential burns. Both underresuscitation and overresuscitation can be detrimental to wound healing. In one study, 86% of patients were overresuscitated. Determining the adequacy of resuscitation can be challenging. Care must be taken to avoid hypothermia. Organ dysfunction is common with severe burns.

Burn wound infections are most commonly caused by G+ organisms early on (days 2–7). Beyond day 7, G– and fungi predominate. Pseudomonas, candida, and aspergillus carry the highest mortality. Escharotomies are performed to remove dead tissue that will support bacterial growth. Prophylactic systemic antibiotics are not indicated because they do not penetrate into burned tissue or prevent systemic infections. Topical antibiotics, however, do decrease incidence of invasive infections. The most common topical agents administered are mafenide acetate and silver sulfadiazine. Mafenide is painful and causes normal anion gap metabolic acidosis (it is a carbonic anhydrase inhibitor), but it has excellent penetration and there is no known resistance. Silver sulfadiazine is soothing but penetrates poorly, can cause sulfa allergy and transient neutropenia, can inhibit epithelial healing, and there are resistant pseudomonas strains. Tetanus toxoid should be administered to all patients.

Compartment syndromes are common with circumferential 3° burns. Compartment syndrome most commonly occurs in an extremity. The sequence of signs and symptoms is usually pain, followed by numbness, then weakness, and lastly a decreased pulse signal by Doppler. The diagnosis is confirmed by demonstrating increased muscle compartment pressure. Faciotomies must be emergently performed when compartment pressure is >30 mm Hg or when diastolic blood pressure-compartment pressure is <30 mm Hg. Severe burns to the trunk and abdomen can rarely cause compartment syndrome. Suspect this syndrome if the airway pressure increases alarmingly in the first 8 h.

Electrical Injury

Electrocution may cause injury by the direct effect of the electrical current on body tissues (eg, arrhythmias), by causing thermal heating of tissues as electrical current flows through body parts, or by causing trauma indirectly such as during a fall. Electrical injuries may be classified as low voltage (<1,000 volts) or high voltage (>1,000 volts). At a constant body resistance, a lower voltage source will cause less current to flow through tissues. Low-voltage electrocution can cause cardiac arrhythmias and even sudden cardiac death but often there is little deep tissue or cardiac damage. Once patients have been stabilized and observed, they may often be able to be treated as outpatients. However, higher voltage sources cause higher current to flow through tissues, leading to thermal injury along the current path. With high-voltage electrocution (eg, lightning strike), neurologic and cardiac injuries are common. There may be extensive muscle necrosis with compartment syndrome. Rhabdomyolysis may lead to acute kidney injury. The rule of nines is not useful because the major injuries may be below intact skin. Damage to CNS, peripheral nerves, solid organs, lungs, and viscera may initially be occult. A careful secondary survey should focus on nerves, heart, and organs near exit wounds; however, the path of current may be difficult to predict from the surface wounds. Treatment is supportive with continuous ECG monitoring.

Nothing to Disclose

The author has disclosed that no relationships exist with any companies/organizations whose products or services may be discussed in this chapter.

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Chapter 15. Airway Management, Sedation, and Paralytic Agents

John P. Kress, MD, FCCP

Objectives:

- Discuss principles of airway management in the ICU patient.
- Discuss principles of sedation and analgesia in the ICU patient.
- Discuss the use of paralytic agents in the ICU patient.

Key words: airway; analgesia; endotracheal intubation; neuromuscular blockade; sedation

Synopsis:

Knowledge of airway management, sedation, and analgesia are essential components of care in the mechanically ventilated ICU patient. This knowledge is important to formulate a management plan that ensures skills for securing an airway, maintaining patient comfort during invasive mechanical ventilation, and maximizing short-term and long-term outcomes.

Airway Management

Airway management, with knowledge of sedation and analgesia,[1] in the ICU is an important skill for all who work in this setting. In contrast to the operating room, airway management in the ICU is associated with higher complication rates, since it rarely occurs as an elective procedure. Accordingly, a thorough assessment of airway anatomy often is not possible. Furthermore, cardiopulmonary instability is the rule in ICU patients who require endotracheal intubation. Basic principles to open the obstructed airway include either the head-tilt chin-lift technique or the jaw-thrust technique. Knowledge of likelihood of difficulty with mask ventilation is important. Those risk factors for difficult mask ventilation include obesity, a Mallampati class IV airway, presence of a beard, a history of snoring, and lack of teeth.[2] Predictors of a difficult intubation include a mouth opening less than 3 cm, a cervical range of motion of less than 35 degrees, a thyromental distance of less than 7 cm, large incisor teeth, a short, thick neck, and a narrow palate.[3] The operator should always be prepared for complications during intubation in the ICU. Availability of others who are free to provide assistance, optimal patient positioning and lighting, and equipment for intubation should be checked before proceeding. A reliable source of 100% oxygen, suction equipment that is functional, and a reliable IV line that is running freely are mandatory requirements before proceeding. Full face masks of various sizes, a functional bag-valve device (Ambu-bag), and oral and nasal airways should be available. A laryngoscope with blades of various sizes and types with functional batteries and light should also be available. The "sniffing position," though recommended by traditional teaching, has not been validated in the ICU setting.[4,5] Preoxygenation is less reliable in ICU patients than in patients undergoing elective intubation in the operating room.[6,7]

The patient with a possible cervical spine injury is not an uncommon occurrence in the ICU. Cervical spine precautions such as manual in-line immobilization during airway instrumentation are recommended. Awake fiberoptic intubation is another technique that may be useful for airway management in a patient with a cervical spine injury.

The laryngeal mask airway (LMA) can be used as a rescue device in patients for whom direct laryngoscopy fails. This device can be placed into the mouth and over the laryngeal opening blindly, and then an endotracheal tube can be placed through the positioned LMA with or without the guidance of a fiberoptic bronchoscope.[8,9]

If initial attempts at endotracheal intubation fail, an alternative strategy for providing ventilation to the patient, and ultimately for securing the airway, must be used. The difficult airway is defined as a circumstance in which "a conventionally trained anesthesiologist experiences difficulty with face mask ventilation, difficulty

with intubation, or both."[10] The ICU is a particularly challenging environment in which to address a difficult airway, since such patients are likely to deteriorate more rapidly than in the elective setting of the operating room. The LMA is a particularly important tool to consider in the management of an ICU patient with a difficult airway. Other options include the Combitube (Covidien) and retrograde intubation (passage of a guide wire through the cricothyroid membrane in a cephalad direction until the guide wire tip is retrieved through the mouth; the endotracheal tube is then placed over the guide wire into the trachea). If an airway cannot be established, a surgical airway via cricothyroidotomy or tracheostomy is indicated.

Analgesia

It is important to remember that many mechanically ventilated patients experience pain and that analgesia is an important component of "sedation" in the ICU.[11,12] There are many reasons that ICU patients experience pain. Pain from surgical incisions is usually self-evident. The presence of an endotracheal tube can be quite painful for some (but not all) patients. Tissue injury from malignancy, infection, or ischemia may result in pain. Likewise, indwelling catheters and monitors can be uncomfortable. Prolonged bed rest is frequently associated with severe back pain. Other routine nursing activities such as turning in bed may be extremely painful.[13,14] Accordingly, pain should be addressed in order to ensure patient comfort and potentially reduce accompanying adverse events.[15] Recent evidence suggests that analgesic drugs (ie, opiates) may be all that is needed for many mechanically ventilated ICU patients. Strom and colleagues[16] described a strategy of "morphine only" for the management of intubated, mechanically ventilated ICU patients. They noted that approximately 80% of patients could be successfully managed with this strategy, and that it resulted in fewer ventilator, ICU, and hospital days. It is also important to recognize that, while pain is common in mechanically ventilated patients, it is not universal. A recent paper by Puntillo and colleagues[11] described the experiences of 171 ICU patients at high risk of dying. Only 40% of these patients reported pain when interviewed for a period of up to 2 weeks. Accordingly, the ICU care provider should aggressively search for the presence of pain, treating it when present and avoiding unnecessary pharmacologic treatment when it is not needed.[17] If the care provider is able to communicate with the patient, he/she can effectively address analgesia when it is a relevant concern.[18–23]

It is important to recognize that the pharmacokinetics of sedative and analgesic drugs in ICU patients is quite different than what is described with single administered doses of these drugs in healthy volunteers. The use of continuous infusions or repeated doses of these drugs alters their pharmacology substantially.[24] Patients in shock may have decreased hepatic and/or renal blood flow, which can alter metabolism and clearance of medications. Obese patients have an altered volume of distribution, which affects the volume of distribution. This can affect how the patient responds to sedative and analgesic drugs.[25] Because sedatives and analgesics are often given for prolonged periods of time, it is important to recognize that these drugs can accumulate in the body. Accordingly, the pharmacological principle known as the "context-sensitive half-time"[26,27] must be recognized. For all sedative and analgesic agents used in the ICU, plasma concentration depends on the drug concentration gradients present between various "compartments" (ie, bloodstream, adipose tissue, CNS). The context-sensitive half-time describes the time required for the plasma drug concentration to decline by 50% after an infusion is stopped. For most sedative and analgesic drugs, the context-sensitive half-time increases as the duration of the infusion increases; certain drugs are particularly prone to this problem of accumulation and increasing context-sensitive half-time. Benzodiazepines are most notorious for this problem, though opiates may also accumulate when given for prolonged time periods.[28] Certain drugs are less vulnerable to accumulation (eg, propofol, remifentanil, inhalational anesthetic agents), which may offer an advantage when sedating patients for extended time periods.[29]

The most commonly used analgesics are in the opioid family. The mu-1 opioid receptor inhibits the CNS pain response. Other opiate

receptors mediate the respiratory depression and sedative effects.[30] Opiates raise the CO_2 response threshold—a property that may be desirable in some patients suffering from subjective air hunger. The resulting reduction in respiratory drive seen with opiates may not be detected by pulse oximetry, particularly when patients are receiving supplemental oxygen. Naloxone reliably antagonizes the respiratory depressive effects of opiates. A dose of 0.4 mg is appropriate when dealing with apneic patients. However, one may be able to titrate smaller doses of naloxone (eg, 40 μg) in hypoventilating patients, thereby restoring adequate respiratory drive without completely reversing analgesia. Because naloxone has a shorter half-time than opiate agents, repeated dosing and/or careful titration may be necessary. A common side effect seen with opiates is GI ileus. This may be treated with stool softeners and laxatives as well as physical mobilization. IV neostigmine has been shown to be beneficial in treating colonic pseudoobstruction.[31] Nausea and vomiting, itching, and urinary retention are other side effects seen with opiates. These are generally less concerning to the sedated ICU patient. The "stiff chest" syndrome is a rare complication seen with certain synthetic opiates (eg, fentanyl). Its mechanism is not entirely understood. It is typically seen in the operating room and is extremely rare in the ICU. Succinylcholine is the treatment of choice to relax the respiratory muscles in order to allow ventilation.

Opiates Used in the ICU

Morphine is the prototypical opiate agent used in the ICU. It is relatively water-soluble; therefore, its onset time is somewhat delayed (peak effect seen in 20–30 min). Histamine release, while described, is rarely a clinically relevant concern. In general, all opiates are hepatically metabolized and renally cleared. Morphine is broken down into active metabolites, which can accumulate in renal failure. Hydromorphone is 5 to 10 times more potent than morphine and does not have active metabolites, but the parent drug can accumulate in renal failure, leading to increasing plasma concentrations. Hydromorphone's peak effect and duration are similar to morphine. It does not release histamine. This drug is 5 to 10 times more potent than morphine. Because it is lipophilic, fentanyl has a very rapid onset of action (peak onset is 2–3 min). It has a duration of 30 to 40 min when administered as a single dose. Like all opiates, the duration of effect increases with repeated dosing. Fentanyl's lipophilic pharmacokinetics also leads to deposition into adipose tissue. Patients receiving infusions without interruption may suffer from prolonged effects after discontinuation[32]; however, fentanyl does not have any renally excreted metabolites. Fentanyl does not release histamine. It is a very potent drug—10 μg is approximately equal to 1 mg of morphine. Meperidine has largely fallen out of favor as an opiate in the ICU. Apart from its effectiveness in treating shivering/rigors, it offers no discernible benefits over other opiates. The metabolite normeperidine accumulates in kidney failure and has a proconvulsant effect. It releases histamine and has an anticholinergic effect that leads to tachycardia in some patients (mechanism similar to atropine). Remifentanil is a newer opiate that has a very short onset of action and is metabolized into inactive metabolites by nonspecific enzymes in the blood, so it is not affected by hepatic or renal failure.[33] The starting dose for light analgesia in the ICU is 0.01 to 0.05 μg/kg/min. This can be titrated up to 0.1 to 0.2 μg/kg/min for a deeper level of analgesia, as may be used in the operating room. This is a promising drug that has potential to decrease the prolonged effects of analgesia and potentially reduce the amount of sedative required.[34–37] However, the potential for rapid tolerance to remifentanil—a condition referred to as hyperalgesia—has been described.[38,39] Since remifentanil is eliminated from the body so rapidly, in some circumstances it may lead to a circumstance in which patients are left with no analgesia. If remifentanil is used, care must be taken to anticipate this potential problem. Transient bradycardia is another problem that occasionally occurs with the use of this drug.

Sedation

After the absence of pain is ensured, a patient's sedation needs can be assessed. Pain

control alone may allow patients to be comfortable enough to require no sedation.[16] While nonpharmacologic interventions such as repositioning or verbal reassurance may be considered for some patients, some will require pharmacological intervention to help relieve discomfort, improve synchrony with mechanical ventilation, and decrease the overall work of breathing. Sedation can reduce oxygen consumption, which may be important in some patients with marginal gas exchange.[40]

Sedative Medications

Benzodiazepines act through the gamma aminobutyric acid receptor, producing anxiolytic, sedative, and hypnotic effects at increasing doses.[24] The two drugs used almost exclusively for ICU sedation are midazolam and lorazepam. The lipophilicity of these drugs allows them to quickly cross the blood-brain barrier, resulting in a rapid onset of action. Midazolam has a more rapid onset of action than lorazepam (less than 1 min vs approximately 2 min). Lipophilicity also causes both midazolam and lorazepam to accumulate in adipose tissues, where they are not readily metabolized.[41] Benzodiazepine metabolism occurs via the CYP450 enzyme system in the liver, so that with liver dysfunction the duration of action of benzodiazepines increases. Midazolam is broken down into active metabolites that accumulate with kidney failure; as such, lorazepam is preferable to midazolam in patients with kidney dysfunction.[42] The pharmacologic properties of benzodiazepines make these drugs notorious for long-lasting effects when given repeatedly in the ICU.[43] Lorazepam can be associated with propylene glycol toxicity. This problem is manifest by an anion gap with acute tubular necrosis and an increased osmolar gap. It is typically seen with higher doses by continuous infusion (eg, 15–20 mg/h).

Benzodiazepines cause respiratory depression with a shift of the CO_2 response curve to the right. They have antiseizure properties and are often used to treat alcohol withdrawal.[44] These drugs are very deliriogenic—another reason that they have fallen out of favor as sedatives in the ICU.[45]

Propofol is a commonly used ICU sedative that appears to act at the γ-aminobutyric acid receptor, though at a different part of this receptor than the benzodiazepines.[46,47] It is an extremely lipophilic drug (it is suspended in intralipid solution) and therefore quickly crosses the blood-brain barrier, with an onset time of less than 1 min when given by IV bolus.[48] There is also an extremely rapid redistribution of propofol to peripheral tissues, again on the order of minutes, coupled with a very large volume of distribution. These pharmacokinetic properties make propofol ideal for rapid emergence from sedation after interruption of the continuous infusion. Propofol appears to have antiseizure properties as well as neuroprotective effects in cases of brain ischemia.[48,49] Hypotension may occur as a result of venodilation and direct cardiac suppression, though these effects are typically minimal in volume-resuscitated patients.[50] Propofol is formulated in a lipid emulsion, so triglycerides should be monitored; there is 1.1 kcal/mL of propofol, which must be accounted for when formulating a nutrition plan.[51] The propofol infusion syndrome is a rare adverse reaction characterized by dysrhythmias and cardiac and kidney failure, as well as by rhabdomyolysis and hyperkalemia. This condition was originally described in children[52,53] and led to warnings against propofol in pediatric intensive care.[54] The propofol infusion syndrome typically occurs at high infusion doses.[55]

Fospropofol, a prodrug of propofol, is a potential alternative agent for sedation in the ICU. It is metabolized in vivo to the active drug propofol, but the parent drug is water-soluble with a much smaller volume of distribution than propofol.[56] The potential implications of this characteristic include a lower propensity for accumulating in adipose stores during prolonged infusions, although thus far it has only been studied in phase III clinical trials for colonoscopy, bronchoscopy, or minor surgical procedures.[56–58] Contamination of the drug, which is a problem in the lipid formulation of propofol, is less of a concern with the water-soluble fospropofol. The onset of action is slightly longer than for propofol since it must be first metabolized to the active form, but it is still on the order of minutes. It is safe to use in moderate renal insufficiency but has

not been studied yet in liver failure. Further study is necessary to determine if it is safe and effective to use for prolonged infusions in the ICU.

Dexmedetomidine is an α_2 agonist that acts centrally to inhibit norepinephrine release. It has both sedative and analgesic effects, making it a potentially ideal drug for ICU sedation. It has no respiratory depressant effects.[59] Patients awaken and are able to follow commands when stimulated; there is less delirium than is seen with benzodiazepines.[60–62] Riker et al[61] studied the drug for longer-term infusions and found that dexmedetomidine compared to midazolam in the ICU resulted in less ICU delirium and fewer days on the ventilator. Bradycardia and hypotension are the most concerning side effects; these occur less commonly when loading doses are avoided.[61,63]

Ketamine is rarely used for sedation/analgesia in the ICU. It is a dissociative hypnotic drug with amnestic and potent analgesic properties. It is a sympathomimetic drug, causing increased heart rate and blood pressure, though it may also have negative inotropic effects. Its propensity to cause unpleasant dreams and hallucinations is a main reason for its limited use in the ICU. It does not cause respiratory depression. It is a bronchodilator but also increases respiratory secretions. It may be used for brief procedures, such as endotracheal intubation.

Etomidate is an anesthetic that is sometimes used to facilitate endotracheal intubation. It has amnestic properties but is not an analgesia. It is popular because it has a low incidence of hypotension. The major side effect of concern is adrenal suppression. A paper comparing etomidate to ketamine for facilitating endotracheal intubation found both drugs to be effective; etomidate had a higher incidence of adrenal suppression.[64]

Inhaled volatile anesthetics, such as isoflurane and sevoflurane, have been used in the operating room for many years but so far have not been used in the ICU on a widespread basis. The impediment to using these drugs in the past has been difficulty with conservation of the volatile gases. This has been simplified with use of a special system, which can be attached to mechanical ventilators to recycle the anesthetic drug.[65] However, to date, no prospective randomized trials exist to determine efficacy and safety in long-term ICU use.[66,67]

Sedation Strategy

Validated sedation scales and protocols should be used to guide titration of sedative and analgesic medications. The Ramsay Sedation Scale is one of the most widely used sedation tools for evaluating level of consciousness.[68] The Sedation Agitation Scale is another scale that expanded upon the Ramsay Sedation Scale to further stratify the agitation end of consciousness.[69] The Richmond Agitation Sedation Scale evaluates arousal, cognition, and sustainability of response. It has been validated for interrater reliability in the ICU and for titration of sedation over time.[70,71] This scale is the most extensively validated and is, accordingly, one of the most widely utilized in the management of critically ill patients. Use of these sedation scales in a protocolized manner, particularly with input from the bedside nurse, can help guide therapy to a targeted sedation level.[72,73] There are a variety of sedation strategies that have been studied, including daily interruption of sedation and goal-directed sedation algorithms implemented by the bedside nurse. Daily interruption of continuous sedation infusions was shown to decrease the number of days on a mechanical ventilator and in the ICU. It also allowed for a better assessment of neurologic status, decreasing the need for diagnostic neurologic testing. Nursing-implemented protocols have also demonstrated promising results. Brook and colleagues[72] used a bedside nursing protocol to titrate analgesia and sedation to a specific goal of 3 on the Ramsay Sedation Scale. This resulted in shorter duration of mechanical ventilation, ICU stay, and hospital stay when compared to usual care.[16] Strom and colleagues[16] recently reported the results of a randomized trial comparing a strategy of "no sedation" with daily sedative interruption. Patients in the "no sedation" group received morphine as needed. Patients receiving no sedation had more days without ventilation and reduced ICU and hospital lengths of stay. Self extubations were not different between the groups.

Sedation strategy is important to consider for the potential short-term outcomes benefits of fewer days on a ventilator or in a hospital, but there are also long-term effects related to the sedation strategy utilized in the ICU. Pairing daily interruptions with spontaneous breathing trials leads to more ventilator-free days than spontaneous breathing trials on their own, and it also leads to decreased mortality at 1 year.[74] The alert patient can also more fully participate in rehabilitation; and initiation of physical and occupational therapy during daily awakenings improves recovery of function by the end of hospital stay.[75] Posttraumatic stress disorder following critical illness with respiratory failure is well described and may be associated with increased sedation use.[76,77] Daily sedative interruption has been shown to reduce posttraumatic stress disorder.[76] Sedative and opioid exposure is a risk factor for delirium in the ICU, which may be an indicator of poor prognosis in the critically ill patient.[78,79]

Neuromuscular Blockade

The use of neuromuscular blocking agents has fallen out of favor over the last 2 decades, as evidence of prolonged neuromuscular weakness with ICU paralytic use has accumulated.[80,81] One recent study has reintroduced these drugs as agents to consider in a select subgroup of patients with severe ARDS. Papazian and colleagues[82] noted that neuromuscular blockade with cisatracurium for 48 h improved survival in such patients. Cisatracurium is the preferred neuromuscular blocking agent, since it undergoes spontaneous metabolism by Hofmann degradation. It should be noted that neuromuscular blocking agents do not have amnestic properties, and sedation to a point of amnesia is required if these drugs are utilized in order to avoid an awake paralyzed patient. The use of tools that measure the level of consciousness by algorithmic analysis of a patient's EEG, such as bispectral index, may be useful to ensure amnesia in the pharmacologically paralyzed patient.[83] If neuromuscular blocking agents are used in the ICU, one should consider a daily discontinuation. Hypothetical indications for neuromuscular blockade include: facilitation of endotracheal intubation, use in the unmanageable patient with extreme ventilator dyssynchrony that persists despite optimal sedation, improvement in chest wall compliance in extreme circumstances such as tetanus, and redistribution of blood flow away from active respiratory muscles in patients whose oxygenation is marginal.

Succinylcholine is often used to facilitate endotracheal intubation. Its onset time is very rapid (60–90 s), and its duration is short (5–7 min). After administration, patients demonstrate muscle fasciculations followed by flaccid paralysis. The drug is metabolized by pseudocholinesterase. Side effects include bradycardia, hyperkalemia, and increased intracranial and intraocular pressure secondary to muscle fasciculations. It is relatively contraindicated in patients with stroke, trauma within the past 2 to 3 months, hemiplegia or paraplegia within 6 months, or burns within 1 year because of concerns over severe hyperkalemia. Succinylcholine is known to cause malignant hyperthermia.

Rocuronium is a nondepolarizing neuromuscular blocking agent with an onset time similar to succinylcholine. Its duration of action is similar to cisatracurium (ie, 30–45 min). It is used most often as a substitute for succinylcholine to facilitate rapid intubation when the latter drug is contraindicated (eg, burns, tissue injury, hyperkalemia). It has minimal effects on heart rate and blood pressure. Pancuronium and vecuronium are older aminosteroid neuromuscular blocking agents that are used rarely in the ICU. Pancuronium typically lasts between 100 to 180 min after a single dose. It has a vagolytic effect, typically leading to mild increases in heart rate. Pancuronium is renally excreted. Vecuronium typically lasts between 30 to 60 min after a single dose. The metabolite 3-desacetylvecuronium can accumulate in patients with kidney failure, leading to prolonged paralysis.[81]

Delirium

Delirium is characterized by an acute onset of disturbance in cognitive abilities with a fluctuating course over time. Risk factors are multifactorial (eg, dementia, hypertension, severity of illness, alcoholism, medications [especially sedatives and opioids]).[79,84] There is an association between delirium and decreased functional

status at hospital discharge.[85] The Confusion Assessment Method for the ICU (CAM-ICU) is a well-validated tool for delirium assessment and may be helpful in tailoring therapy.[86,87] The Intensive Care Delirium Screening Checklist is the other commonly used tool for ICU delirium assessment.[88] There is some evidence to support the effect of nonpharmacological interventions on ICU delirium. Many of the predisposing factors that affect ICU patients also affect other hospitalized patients, and interventions targeted towards these risk factors have been effective to decrease the incidence of delirium in these other populations.[89] Simple strategies such as reorientation, enhancement of the sleep environment, and minimization of medications associated with delirium can help decrease the incidence. Early mobilization has been shown to decrease delirium in the ICU.[90] Dexmedetomidine has been studied with specific interest in its decreased propensity to cause delirium and improved mortality when compared to benzodiazepine-based sedation; this effect may be more pronounced in septic patients.[60,91] Antipsychotics may be used to treat delirium in the ICU. Haloperidol is the most commonly used drug, although other atypical antipsychotics are recently becoming more widespread in use, with a suggestion of efficacy in treating delirium.[92,93] More data are needed to test whether these preliminary studies will translate into improved outcomes with regard to ICU delirium. Atypical antipsychotics, such as quetiapine, risperidone, olanzapine, and ziprasidone, block both dopamine and serotonin receptors. They may be as effective as haloperidol with fewer extrapyramidal side effects.[94] A recent trial[95] evaluated the cholinesterase inhibitor rivastigmine for the treatment of ICU delirium. Patients with delirium were randomized to receive either rivastigmine or placebo. In an interim analysis after randomization of 104 patients—54 of whom received rivastigmine—the trial was stopped due to a higher mortality in the rivastigmine group (22% vs 8%; $P = .07$).

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Notes

Chapter 16. Acute Lung Injury/Acute Respiratory Distress Syndrome

Jesse B. Hall, MD, FCCP

Objectives:

- Review the pathophysiology and epidemiology of acute lung injury (ALI)/ARDS.
- Review research guiding thinking about the use of standard ventilator approaches, salvage, and innovative therapies that can be used in addition or in lieu of standard techniques.
- Examine long-term outcomes from this ICU syndrome.

Key words: acute lung injury; acute respiratory distress syndrome; mechanical ventilation; respiratory failure

Synopsis:

Patients with diverse surgical and medical conditions may suffer acute lung injury, characterized by damage to the endothelial-epithelial lung interface with resultant interruption of endothelial barrier function. When this injury is significant, lung flooding occurs despite normal cardiovascular function, so-called low-pressure pulmonary edema or pulmonary capillary leak. Gross gas exchange and pulmonary mechanical abnormalities result with associated hypoxemic respiratory failure. When this syndrome occurs, supportive management is necessary while the patient is protected from further lung injury (eg, intubation to prevent further aspiration) and/or underlying predisposing conditions are treated (eg, management of septic shock). Supportive management requires a ventilator strategy that recruits collapsed and flooded lung while avoiding further lung damage associated with the interaction of the ventilator with the damaged respiratory system. Much research has helped to identify the details of implementing lung-protective ventilation, but interest continues in new modalities of treatment to further improve outcome in these challenging patients. Even when patients are supported through the period of respiratory failure, significant morbidity may persist for extended periods and with incomplete resolution.

Pathophysiology

ARDS and the related acute lung injury (ALI) syndromes are forms of type I or acute hypoxemic respiratory failure. This form of lung dysfunction arises from diseases causing the collapse and/or filling of alveoli, with the result that a substantial fraction of mixed venous blood traverses non-ventilated airspaces, effecting a right-to-left intrapulmonary shunt (Fig 1, *b*). In addition to the adverse consequences on gas exchange, interstitial and alveolar fluid accumulation result in an increase in lung stiffness, imposing a mechanical load with a resulting increase in the work of breathing (Fig 1, *a*). When intrapulmonary shunting of blood is significant, the response of arterial hypoxemia to supplemental oxygen therapy is poor, and this failure of the patient to respond to oxygen is both a clinical sign of this syndrome and a reason that additional measures will need to be undertaken to achieve alveolar recruitment before the patient progresses to abject respiratory failure, tissue hypoxia, and death (Fig 2).

Definition

Patients with ARDS/ALI have a large number of underlying medical and surgical etiologies, and there has been broad recognition of a need for specific definitions of these entities. The widely applied definitions offered by a joint American-European Consensus Conference published in 1994 are given in Table 1.

ALI/ARDS may result from injury to the lung microcirculation sustained from direct lung insults (eg, aspiration, inhalation, or infectious agents) or indirectly by systemic processes (eg, sepsis, pancreatitis, or traumatic shock with large-volume blood product resuscitation). The former is termed pulmonary ARDS and the latter extrapulmonary ARDS. Some studies have suggested different lung mechanical properties for these entities and a different response to ventilator maneuvers directed at alveolar recruitment. In addition to the distinction between pulmonary and extrapulmonary forms of ARDS/ALI, it is also useful to distinguish between the early phases of ALI and the events occurring subsequently (Fig 3).

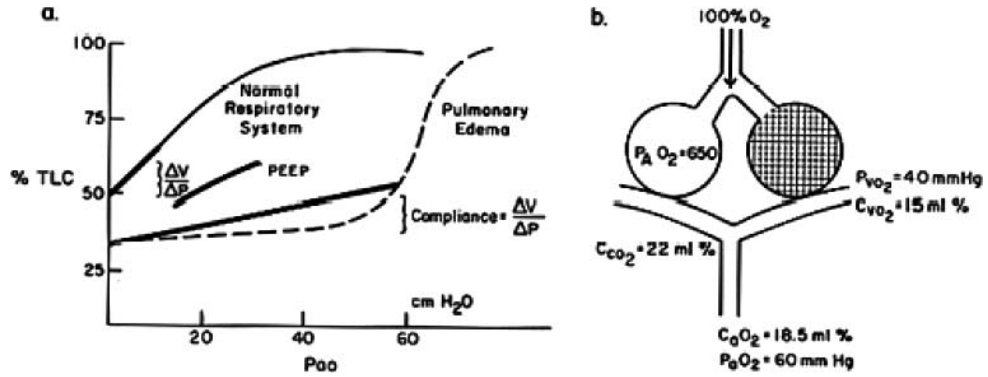

Figure 1. Gas exchange (*a*), and interstitial and alveolar fluid accumulation *(b*) in ARDS. Reprinted with permission from *ACCP Critical Care Medicine Board Review.* 20th ed. Northbrook, IL: American College of Chest Physicians; 2009.

By light microscopy, early ARDS/ALI is characterized by flooding of the lung with proteinaceous fluid and minimal evidence of cellular injury. To the pathologist, this is a lung injury termed diffuse alveolar damage (DAD). By electron microscopy, changes of endothelial cell swelling, widening of intercellular junctions, increased numbers of pinocytotic vesicles, and disruption and denudation of the basement membrane are prominent. This early phase of DAD has been termed exudative; it is a period of time during which pulmonary edema and its effects are most pronounced and intrapulmonary shunt is a primary problem dictating ventilatory strategies. Over the ensuing days, hyaline membrane formation in the alveolar spaces is prominent, and inflammatory cells become more numerous. The latter phase of DAD is dominated by disordered healing. This can occur as early as 7 to 10 days after the initial injury and often exhibits extensive pulmonary fibrosis, which is not dissimilar microscopically to the pathology of patients with longstanding pulmonary fibrosis. This has been termed the proliferative phase of DAD. Pulmonary edema may not be as prominent in this latter phase of lung injury, and the clinician managing the patient is challenged by the large dead-space fraction and high minute ventilation requirements. These patients may also exhibit progressive pulmonary hypertension, even if the pulmonary circulation was normal at baseline; slightly improved intrapulmonary shunt that is less responsive to PEEP; further reduction in lung compliance; and a tendency toward creation of zone I conditions of the lung if hypovolemia develops in the patient.

Epidemiology

With an agreed-on definition of ALI/ARDS available, a number of studies have addressed the incidence of this syndrome. Tracking ICU admissions in Kings County in the state of Washington, Rubenfeld and colleagues determined the crude incidence of ALI to be 78.9 per 100,000 person-years and for ARDS 58.7 per 100,000 person-years, with ALI and ARDS mortalities of 38.5% and 41.1%. To the extent that this large sample was representative of the

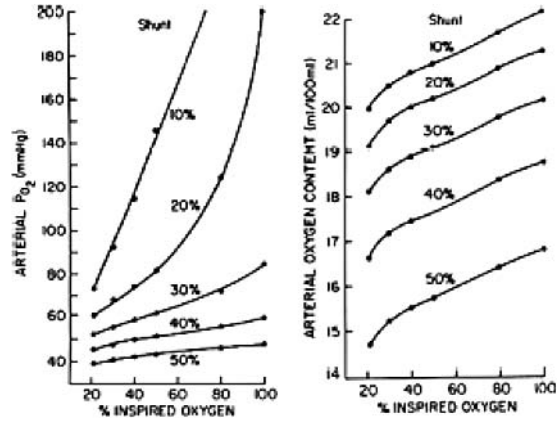

Figure 2. *Left:* the impact of shunt fraction on oxygenation. Note that when shunt is 30% and above, the response to oxygen as judged by arterial Po_2 is minimal. *Right:* Even though the arterial Po_2 changes with oxygen are minimized by large shunt fraction, the increase in arterial oxygen content are large given the steep slope of the hemoglobin-oxygen dissociation curve in this range. Reprinted with permission from *ACCP Critical Care Medicine Board Review.* 20th ed. Northbrook, IL: American College of Chest Physicians; 2009.

Table 1—*The 1994 American-European Consensus Conference Definitions of ALI and ARDS*

Criteria	Timing	Oxygenation	CXR	PCPW
ALI	Acute onset	Pao_2/Fio_2 ratio, <300 mm Hg (regardless of PEEP level)	Bilateral infiltrates	<18 mm Hg or no clinical evidence of right atrial hypertension
ARDS	Acute onset	Pao_2/Fio_2 ratio, <200 mm Hg (regardless of PEEP level)	Bilateral infiltrates	<18 mm Hg or no clinical evidence of right atrial hypertension

broader experience in the United States, these data would yield and estimated number of cases across the country of 190,600 for ALI and 141,500 for ARDS, with 74,500 deaths attributable to ALI and 59,000 deaths to ARDS. The health-care burden of these syndromes is enormous, with an estimated 3,622,000 days in hospital for patients with ALI and 2,154,000 days in ICUs across the United States. Relevant to the "graying" of the population, the incidence of ALI/ARDS increases with increasing age. An encouraging sign is that mortality for ALI/ARDS appears to have fallen over recent decades, although the extent to which this has been driven by earlier identification of less ill patients vs improved treatments is unclear.

Treatment

This discussion will focus on ventilator and circulatory strategies for patients with ARDS/ALI, but it cannot be overemphasized that simultaneously a search for and treatment of the underlying cause of the lung failure must be conducted. Absent an identification and treatment of the underlying processes causing lung injury, supportive therapy alone will likely ultimately result in mounting complications and irreversible organ failures.

Ventilatory Management of ARDS

Lung Mechanics, Ventilator-Induced Lung Injury, and Ventilator-Associated Lung Injury

Over the past decade or more, a body of knowledge has accrued from both bench and clinical investigations that has motivated intensivists to reconsider how they ventilate patients with ARDS. Much of this work was based on early observations that mechanical ventilation using large tidal volumes (V_T) and high inflation pressures could cause lung injury in animals with normal lungs or worsen a baseline lung injury. This phenomenon was termed ventilator-induced lung injury (VILI). VILI is indistinguishable morphologically, physiologically, and radiologically from DAD caused by other etiologies of ALI. VILI is unique because one can identify that mechanical ventilation is the cause of lung injury, hence the term ventilator-induced lung injury. Ventilator-associated lung injury (VALI) is defined as lung injury that resembles ARDS and occurs in patients receiving mechanical ventilation. VALI is invariably associated with a preexisting lung pathology such as ARDS. However, while the experimental data are overwhelming in demonstrating the existence of VILI, one cannot be sure in any particular case whether and to what extent VALI is caused by a particular ventilator strategy; rather, VALI is associated only with mechanical ventilation.

Studies in animal models of VILI have demonstrated that lung injury during mechanical ventilatory support appears to be related to the distending volume to which the lung is subjected rather than to distending pressure as measured at

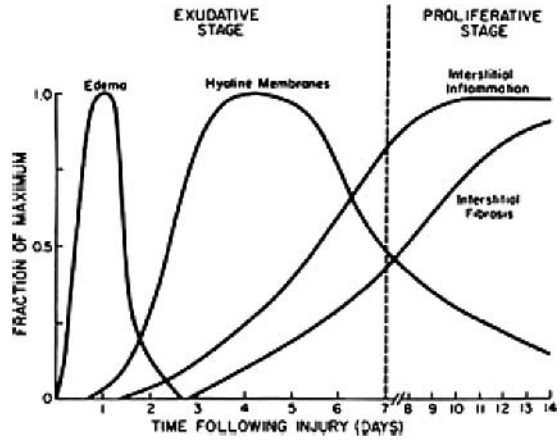

Figure 3. Depiction of the pathologic phases of ALI/ARDS. Reprinted with permission from *ACCP Critical Care Medicine Board Review.* 20th ed. Northbrook, IL: American College of Chest Physicians; 2009.

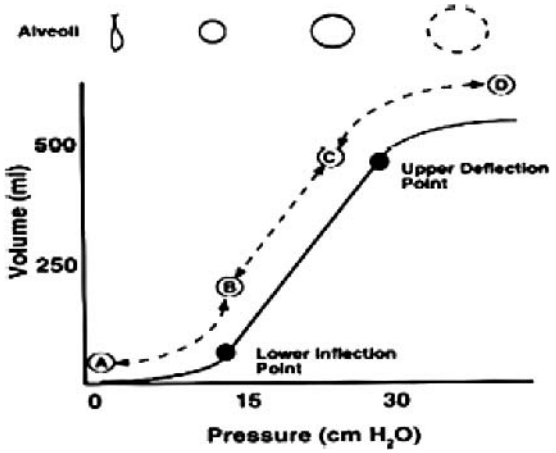

Figure 4. An idealized and simplified depiction of the PV curve of the injured lung during inflation, with the state of alveolar collapse and inflation. Reprinted with permission from *ACCP Critical Care Medicine Board Review.* 20th ed. Northbrook, IL: American College of Chest Physicians; 2009.

the mouth. For instance, in animal experiments in which the chest is banded and mechanical ventilation is conducted with high airway pressures but low V_T resulting from the restricted chest wall, lung injury is not present. Such observations have caused the term volutrauma to be coined for this form of microstructural injury, a refinement of the standard term barotrauma, which is applied to the grosser forms of extraalveolar air collections that are sought on routine radiographs obtained in patients receiving mechanical ventilation.

In addition to the detrimental effects of overdistension, numerous investigations have suggested a protective or ameliorating effect of PEEP on VILI. This protective effect has been postulated to result from the action of PEEP to avoid alveolar collapse and reopening. In the aggregate, these studies offer a view of VILI that is portrayed in Figure 4. During the respiratory cycle, alveolar opening and collapse occur if end-expiratory pressure is zero or only modestly positive, and, depending on end-inspiratory lung volume, alveolar overdistension may occur.

Both in animal models of lung injury and in patients with ARDS, the respiratory system inflation pressure-volume (PV) curve exhibits a sigmoidal shape, with a lower inflection point (LIP) and an upper inflection point. Marked hysteresis is often noted when the inflation and deflation limbs are compared. The presence of the LIP is consistent with the edematous lung behaving as a two-compartment structure, one population of alveoli exhibiting near-normal compliance and another population recruitable only at higher transpulmonary pressure. As transpulmonary pressure is raised to the LIP, effecting alveolar recruitment, lung compliance improves, as reflected by the increase in the slope of the PV curve. Volume tends to increase in a nearly linear fashion as pressure is increased, until the upper inflection point is reached, with a flattening of the curve taken to represent alveolar overdistension with the attendant risks of alveolar injury.

Clinical Studies of Ventilator Strategies for ARDS

These descriptions of VILI in animals and physiologic observations in patients resulted in strategies that have been tested at the bedside and have demonstrated improved patient outcome. In the field of critical care medicine, this is one of the most substantive examples of bench-to-bedside transfer of knowledge that now provides an evidence-based approach to patient care.

The first prospective randomized trial testing a strategy of limiting V_T and utilizing PEEP to avoid alveolar recruitment-derecruitment (so-called open lung ventilation) was conducted by Amato and colleagues, who randomized patients with ARDS to the following two treatments: (1) assist-control ventilation with V_TS of 12 mL/kg, PEEP sufficient to maintain an adequate arterial oxygen saturation on a fraction of inspired oxygen (F_{IO_2}) of <0.6, respiratory rates sufficient to maintain arterial carbon dioxide levels of 25 to 38 mm Hg, and no effort made to control peak inspiratory or plateau airway pressures (Pplat) (ie, the conventional approach), or (2) pressure-controlled inverse ratio ventilation, pressure-support ventilation, or volume-assured pressure-support ventilation with V_TS of <6 mL/kg, recruitment maneuver, peak pressures of <40 cm H_2O, and PEEP titrated to maintain lung inflation above the LIP (ie, the open-lung approach). Patients managed with the open-lung approach demonstrated a more rapid recovery of pulmonary compliance, a decreased requirement for high F_{IO_2}, a lower rate of barotrauma, a higher

Table 2—*ARDSnet Low-Vt Protocol*[a]

Variables	Protocol
Ventilator mode	Volume assist-control
Vt	≤6 mL/kg predicted body weight
Plateau airway pressure	≤30 cm H_2O
Ventilation rate/pH goal	6-35/min, adjusted to achieve arterial pH of >7.30 if possible
Inspiratory flow	Adjust for I:E of 1.1:1.3
Oxygenation	Pao_2 ≥55 and ≤80 mm Hg or Sao_2 ≥88% and ≤95%
Combinations of FIO_2, mm Hg/PEEP, mm Hg	0.3/5, 0.4/5, 0.4/8, 0.5/8, 0.5/10, 0.6/10, 0.7/10, 0.7/12, 0.7/14, 0.8/14, 0.9/14, 0.9/16, 0.9/18, 1.0/18, 1.0/22, and 1.0/24
Weaning	Attempt by PS when FIO_2/PEEP combination is <0.4 mm Hg/8 mm Hg

[a]I:E = inspiratory/expiratory flow ratio. Predicted body weight for men: 50 + (2.3 × [height in inches − 60]) or 50 + (0.91 × [height in centimeters − 152.4]). Predicted body weight for women: 45 + (2.3 × [height in inches − 60]) or 45 + (0.91 × [height in centimeters − 152.4]).

rate of liberation from the ventilator, a decreased rate of death associated with respiratory failure, and a decreased mortality rate at 28 days (although not at hospital discharge).

While these results were striking, a number of concerns regarding this study deserve consideration. The number of patients included in the study was small (only 53). Furthermore, there were multiple treatment differences between the two groups, including PEEP strategy, Vt, Pco_2, minute ventilation, lung recruitment maneuvers, and mode of ventilation. Importantly, the mortality rate was extremely high in the conventional ventilation group (71%), and the early differences in mortality rate seen between the groups did not seem consistent with those of the two ventilator strategies differing by the accrual of progressive lung injury. Finally, patients with severe metabolic acidosis, which is a common feature of patients with overwhelming sepsis and ARDS, were excluded from study. Even if one accepts the results of this study, perhaps the benefit was simply due to Vt reduction, not to the PEEP strategy. Even if this PEEP strategy prevented VILI, the PEEP value selected from the LIP on the inflation of edematous lungs from zero end-expiratory pressure is considerably larger than the PEEP value required to maintain alveolar recruitment during tidal ventilation while receiving PEEP. In addition, several other investigations evaluating the effect of Vt manipulation on outcome did not show a similar salutary effect of low-Vt ventilation.

The controversy over proper Vt for the ventilation of patients with ARDS was resolved largely by the performance of a trial conducted by the National Institutes of Health-funded ARDSnet, a network that enrolled 861 patients randomized to a Vt strategy of either 12 or 6 mL/kg, based on ideal body weight. If Pplat, used as a surrogate of end-inspiratory lung "stretch," exceeded 30 cm H_2O pressure in the low-Vt group, Vt was further reduced as necessary to reduce Pplat to this target value. The experimental protocol is summarized in Table 2.

The trial was stopped sooner than the anticipated end point since the findings were striking. The strategy achieved a significant difference in Vt as intended. The mean Vt on days 1 to 3 were 6.2 and 11.8 mL/kg, respectively, in the low-Vt and high-Vt groups ($P < .001$) and were associated with Pplat values of 25 and 33 cm H_2O, respectively ($P < .001$). PEEP levels were minimally higher in the low-Vt group from days 1 to 3 (averaging <1 cm H_2O, lower on day 7). The low-Vt group had a modest increase in $Paco_2$ relative to the traditional group and a very modest decrease in pH; the potential for greater degrees of respiratory acidosis between the groups was minimized by the higher respiratory rates used in the low-Vt group. The primary end point of the study, 28-day mortality, was significantly improved with low-Vt ventilation, falling from 39.8% in the traditional group to 31.0% with low-Vt ventilation ($P = .007$). In addition, the number of ventilator-free days in the first 28 days was greater in the low-Vt group.

This trial is a benchmark and confirms earlier basic and clinical studies suggesting that low-V_T ventilation can be protective for patients with ARDS and will improve outcome. Perhaps the best evidence-based recommendation for the routine management of patients with ARDS undergoing mechanical ventilation is to implement the ARDSnet protocol. While questions surround other elements of ventilatory strategy (eg, the "best PEEP" level, the trade-off between Fio_2 and PEEP, the use of recruitment maneuvers, and patient positioning), the current evidence strongly supports the use of the ARDSnet strategy, pending additional information to guide these other components of ventilatory support.

Practical Points for Managing the Patient With ALI/ARDS

On presentation, the patient should receive oxygen provided by high-flow or rebreather mask, although these devices rarely achieve a tracheal F_{IO_2} much >0.6 in dyspneic, tachypneic patients. The administration of supplemental oxygen is a diagnostic as well as therapeutic maneuver.

Patients whose oxygenation improves dramatically with supplemental oxygen generally have a small shunt and a larger component of ventilation-perfusion mismatch (or hypoventilation). Even when the Pa_{O_2} improves only slightly, indicating a large shunt, oxygen delivery may rise importantly because of the steep nature of the hemoglobin saturation relationship at low Pa_{O_2} (Fig 2). The role of noninvasive positive-pressure ventilation has not been fully established in the treatment of ARDS. Although we have used noninvasive positive-pressure ventilation successfully in this setting, we believe that it is generally not a good choice, and patients must be carefully selected. Since the course of ARDS is usually longer than the length of time that patients will tolerate noninvasive positive-pressure ventilation and since ARDS is so often associated with hemodynamic instability, coma, and multiorgan system failure (including ileus), we believe that all but exceptional patients should be endotracheally intubated.

Intubation should be performed early and electively when it is clear that mechanical ventilation will be required, rather than waiting for frank respiratory failure. If hypoperfusion is present, as in the patient with hypotension, cardiovascular instability, or the hyperdynamic circulation of sepsis, oxygen delivery may be compromised not only by hypoxemia but by an inadequate cardiac output as well. In this circumstance, sedation and muscle relaxation should be considered as a means to diminish the oxygen requirement of the skeletal muscles. Patients with extreme hypoxemia despite ventilator management may also benefit from sedation or paralysis.

The initial ventilator settings should pursue the protocol given in Table 2. While the use of low V_T is strongly supported by current evidence, the proper PEEP level is less clear. Some intensivists recommend a "least-PEEP" approach, using PEEP only as necessary to achieve adequate oxygenation and avoid toxic levels of F_{IO_2} (although these thresholds are not well established). Others would recommend higher PEEP levels with a goal of achieving maximal lung recruitment and avoiding mechanical events, such as collapse-reinflation, that could lead to VALI. Some even advocate the use of the PV curve of the lung measured during the respiratory cycle as a guide to this PEEP titration. A trial completed by the ARDSnet comparing the PEEP strategy as implemented in the trial of low-V_T vs high V_T against a higher PEEP level did not show a difference in survival; although this study was prospective and randomized, a difference in age and severity of illness existed between the two cohorts, somewhat confounding interpretation. A Canadian and then French trial did not demonstrate a difference in survival based on high-PEEP vs low-PEEP strategy, although the French study did demonstrate an improvement in ventilator-free days with the high-PEEP strategy.

Regardless of specific strategy, reducing PEEP, even for short periods of time, is often associated with alveolar derecruitment and hence, rapid arterial hemoglobin desaturation. Thus, once endotracheal tube suctioning has been accomplished for diagnostic purposes, nursing and respiratory therapy staff should be instructed to keep airway disconnections to a minimum or to use an in-line suctioning system

that maintains sterility and positive pressure, usually via the suctioning catheter residing in a sterile sheath and entering the endotracheal tube via a tightly sealed diaphragm. These suctioning systems are generally effective for lower levels of PEEP (ie, <15 cm H_2O) but often leak if higher levels are attempted.

Innovative Therapies for ARDS

While the general strategy described above will provide adequate ventilatory support for the majority of patients with ALI/ARDS, a fraction of patients will have severe hypoxemia or other adverse consequences of these approaches, and innovative or salvage therapies have been reported in the literature. In general, these approaches are not supported by large prospective trials (or trials have been conducted without seeing a benefit), but they may have some role in individual patient management.

High-Frequency Ventilation: If excessive lung excursion is associated with injury to the lung and high mean airway pressure may avoid alveolar opening and closing, then it seems reasonable that ventilation with very small V_T at high frequencies would be associated with the least possible VILI and would be associated with improved outcome. High-frequency jet ventilation typically employs V_T of 1 to 5 mL (or higher) and respiratory rates of 60 to 300 breaths/min. Gas exchange is complex under these conditions and clearly not explained by bulk convective flow. Large prospective trials are not available to compare high-frequency jet ventilation to lung protective ventilation as defined by the ARDSnet protocol.

Extracorporeal Gas Exchange: The use of extracorporeal gas exchange (ie, extracorporeal membrane oxygenation or ECMO) to adequately oxygenate and ventilate the blood while allowing the lung to rest has been an attractive strategy for the management of patients with ALI for decades. In the recent past, the technologies supporting ECMO in the ICU have become much improved, including double-lumen catheters for conducting veno-venous ECMO and circuits less complex and prone to interruption during extended use outside the operating room. This has permitted wider application of ECMO in the treatment of ALI/ARDS in the ICU. A recent trial conducted in England randomized patients with ALI/ARDS to either remain in their regional hospital or be transferred to a regional center of excellence that offered ECMO as part of treatment. Using a combined end point of survival and avoidance of severe neurologic injury, there was a significant difference between the groups favoring referral to the regional center. This study does not permit a clear conclusion of the use of ECMO per se but does support a comprehensive approach to care of these patients with availability of advanced technologies or centers with extensive experience. Recent publications tracking the use of ECMO during periods of increased respiratory failure incidence such as influenza pandemics have, not surprisingly, shown that significant regional differences in the use of ECMO exist.

Inhaled Nitric Oxide: Nitric oxide (NO) is a potent endogenous vasodilator that, when administered by inhalation, selectively vasodilates the pulmonary circulation. Inhaled NO (iNO) has several potentially salutary effects in ARDS patients. It selectively vasodilates pulmonary vessels, which subserve ventilated alveoli, diverting blood flow to these alveoli (and away from areas of shunt). The rapid inactivation of iNO via hemoglobin binding prevents unwanted systemic hemodynamic side effects but also mandates the continuous delivery of gas to the ventilator circuit. In numerous studies evaluating the short-term response to iNO, there has been a consistent finding of approximately 50% to 70% of patients improving oxygenation. However, two prospective trials have failed to demonstrate improved long-term outcome from iNO administration in ARDS patients receiving mechanical ventilation; thus, this remains a salvage therapy at best.

Neuromuscular Blockade for ARDS: There is a long history of using neuromuscular blockers (NMBs) to facilitate the ventilator management of patients with ARDS who are often dysynchronous with mechanical ventilation. As awareness of profound weakness complicating episodes of critical illness grew and observational studies reported that NMBs were associated with this complication of critical illness, many authorities recommended avoidance of these agents. On the

other hand, some studies suggested that NMBs might improve outcomes in patients with ARDS. In view of this clinical equipoise, a recent multicenter prospective placebo-controlled trial evaluated the use of cis-atracurium in patients with severe ARDS, defined by the gas exchange criterion of a Pa_{O_2}/Fi_{O_2} <150. Patients were enrolled within 48 h of the onset of the syndrome and treated for 48 h. The primary end point of the trial—90-day mortality—when analyzed by intention to treat was not significantly different. However, when adjustment was made for baseline differences between the groups (in Pa_{O_2}/Fi_{O_2}, plateau airway pressure, and severity of illness score), there was a statistical difference favoring the use of cis-atracurium. Patients were followed for the development of neuromuscular weakness, and differences were not noted between the groups, although the study did not report long-term follow-up of the patients studied. While it would be helpful to have additional studies supporting this pharmacologic therapy to facilitate or improve mechanical ventilation in these patients, this investigation does support the use of NMBs for at least a brief period of time early in the course of very severe ARDS.

Circulatory Management of ARDS

For many years, debate has surrounded the proper circulatory management of patients with ARDS. On the one hand, animal studies and some clinical studies have suggested that edemagenesis can be reduced by reducing pulmonary microvascular pressures in patients with ALI in a fashion similar to the management of cardiogenic pulmonary edema. Of course, since these microvascular pressures are normal in these patients despite their lung flooding, the possibility of reducing cardiac preload exists, thus engendering inadequate organ perfusion in a patient population known to be at risk of multiple organ failure and, indeed, in whom outcome appears dictated in large part by the accrual of organ failures.

In addition, the proper monitoring tools for assessing the adequacy of the circulation in these patients and whether monitoring should include invasive hemodynamic measurement was equally controversial. It seemed reasonable to state that mere monitoring with invasive measurements that were not coupled to a strategy to achieve predefined goals would be unlikely to be helpful.

The ARDSnet completed a large multicenter trial addressing these questions. Patients were randomized to receive management with either a central venous catheter or a right heart catheter, and then each group was additionally randomized to receive a liberal or conservative fluid strategy. This 2×2 factorial study showed no discernable benefit for the use of the right heart catheter with a protocolized management algorithm. However, the use of a conservative fluid strategy (ie, central venous pressure, <4 mm Hg; pulmonary capillary wedge pressure [PCWP], <8 mm Hg) as opposed to a liberal fluid strategy (ie, central venous pressure, 10 to 14 mm Hg; or PCWP, 14 to 18 mm Hg) was associated with improvements in oxygenation index and lung injury score as well as with increased ventilator-free days and days not spent in the ICU. There was no difference in shock or the need for renal replacement therapy between the groups. A mortality difference between the conservative and liberal fluid strategy groups was not seen.

Management of Proliferative Phase of ARDS

A subset of patients with ARDS will progress over the first week of mechanical ventilation to disordered healing and severe lung fibrosis. This is usually characterized by increasing airway pressures or a falling V_T while receiving pressure-control ventilation, a further fall in lung compliance, less response to PEEP, a "honeycomb" appearance on the chest radiograph, progressive pulmonary hypertension, and rising minute ventilation requirements (>20 L/min). Barotrauma is a prominent feature, and multiple organ failures often accrue. A number of observations regarding their supportive therapy should be made. Increased vascular permeability at this point in the course of treatment may be minimal, and strategies to reduce preload and edema are fraught with complications. Patients are prone to increases in zone I lung conditions, and attempts to reduce the PCWP may result in increased dead space and hypoperfusion. Thus, seeking the lowest PCWP providing adequate cardiac output is no longer appropriate; instead, the liberalization of fluid

intake to provide a circulating volume in excess of one that is just adequate is a better strategy in this later phase of ARDS.

Interventions to directly influence the course of lung fibrosis are not well established, but high-dose corticosteroid therapy has its advocates. One prospective trial has shown an improved survival with the use of corticosteroids in patients with late ARDS, but a prospective trial conducted by the ARDSnet did not, although an earlier return to spontaneous breathing and extubation was seen.

If corticosteroids are used in this setting, aggressive measures to monitor for ventilator-associated pneumonia are warranted. This complication of mechanical ventilation has a high incidence and high mortality in patients with ARDS. In view of the abnormal chest radiograph findings and gas exchange, the multiple causes of fever and leukocytosis, and the high incidence of colonization of the airway, diagnosis is difficult and may be aided by various techniques to obtain protected specimens.

Long-term Sequelae of ALI/ARDS

There is a variability to the recovery of lung function following ALI. Patients may recover with minimal or no abnormality by routine lung function testing shortly after acute lung insult, or they may remain substantially impaired for a year or longer, if not permanently. In most studies, approximately one-fourth of patients show no impairment at 1 year, one-fourth of patients show moderate impairment, roughly one-half show only mild impairment, and a very small fraction show severe impairment. Exertional dyspnea is the most commonly reported respiratory symptom, although cough and wheezing are common as well. A reduced single-breath carbon monoxide diffusing capacity is the most common pulmonary function abnormality. Spirometry and lung volumes tend to reveal mixed restrictive-obstructive abnormalities.

More importantly than these findings, Herridge and colleagues have reported that lung dysfunction may be of only minor significance in terms of returning to prior functional status and that weight loss, neuromuscular weakness, and neuropsychiatric dysfunction related to critical illness or supportive management may be much more significant than respiratory dysfunction per se. This group has followed and reported a cohort of patients after recover from ALI/ARDS for 5 years and describe incomplete recovery of functional status in many patients even over this length of time. Age and comorbid conditions appeared to be significant determinants of the pace and degree of recovery.

Nothing to Disclose

The author has disclosed that no relationships exist with any companies/organizations whose products or services may be discussed in this chapter.

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Chapter 17. Coma and Delirium

John F. McConville, MD

Objectives:

- Distinguish coma and delirium from other neurologic conditions.
- Identify predictors of outcome for patients in a coma.
- Be able to assess delirium at the bedside.
- Identify treatment strategies for delirium.

Key words: coma; Confusion Assessment Method for ICU (CAM-ICU); delirium

Synopsis:

Cerebral dysfunction is very common in the ICU. CNS dysfunction can result from primary (acute stroke) or secondary (severe sepsis) insults. Coma is a transitional state wherein patients are unable to respond to their environment. Coma occurs in up to 15% of mechanically ventilated patients, 80% of patients with cardiac arrest, and approximately 16% of patients with sepsis. Drug overdose is the most common toxic-metabolic cause and trauma and hypoxic-ischemic encephalopathy are the most frequent primary cerebral events resulting in coma. A quick neurologic exam that assesses level of consciousness and brainstem reflexes, motor exam, and respiratory exam should be completed as soon as possible. A physical exam remains the best determinant that clinicians use to prognosticate for patients with cerebral dysfunction. Five neurologic signs predict death or poor neurologic outcome in survivors of cardiac arrest: absent corneal reflexes or pupillary response at 24 h, absent withdrawal response to pain at 24 h, and no motor response at 24 h or 72 h. In addition to coma, delirium is another common cause of cerebral dysfunction in the ICU. Delirium is defined as a fluctuating acute confused state that includes impaired attention and disorganized thinking. Inattention, which is measured using the Confusion Assessment Method for ICU, is required to diagnose delirium. Several studies have conclusively demonstrated that ICU delirium increases 6-month mortality. Small studies support medication and nonpharmacologic interventions in the treatment of delirium.

Overview

Cerebral dysfunction is very common in the ICU. As with other organ dysfunction syndromes in critically ill patients, CNS dysfunction can result from primary (acute stroke) or secondary (severe sepsis) insults. Cerebral blood flow is maintained over a wide range of cerebral perfusion pressure values. This is beneficial in the ICU, where systemic blood pressure is often reduced. For clinicians, it is often a challenge to distinguish acute brain dysfunction from chronic cognitive impairment as both conditions can result in alterations of consciousness. Wakefulness and awareness are essential components of consciousness, and both can be altered in the ICU setting. Conscious patients are aware of themselves and their environment; in addition, they are responsive to their needs and external stimulation. Importantly, awareness *cannot* occur without wakefulness, but wakefulness *can* occur without awareness (a vegetative state, for example). Wakefulness is mediated by the reticular activating system, which is localized in the pons and midbrain but more diffuse in the cerebral hemispheres. Awareness requires integrity of cerebral cortex and subcortical connections.

Coma

Coma is a transitional state wherein patients are unable to respond to their environment with any verbal, motor, or psychological interaction; in other words, comatose patients are neither awake nor aware. In addition, the sleep–wake cycle is absent in comatose patients. This is contrasted with patients in a vegetative state, who have intact sleep cycles, exhibit some signs of wakefulness (able to spontaneously open eyes, for example) but are not aware and, thus, do not make any purposeful movements. Coma is very common in the ICU, occurring in up to 15% of mechanically ventilated patients,[1,2] 80% of patients with cardiac arrest,[3] and approximately 16% of patients with sepsis.[4]

The Glasgow coma scale (GCS) was initially designed to evaluate patients with head injury but is still used today to assess a patient's level of consciousness. A patient's responses to verbal and tactile stimuli are graded. The three components to the GCS are eye opening, best verbal

response, and best motor response. For example, a patient who is able to open his or her eyes spontaneously (4 points), is oriented to person/place (5 points), and is able to follow simple commands (6 points) would have a GCS score of 15. However, the GCS has limitations, including limited ability to detect subtle changes in arousal, no assessment of brainstem function, and difficulty of obtaining a verbal response in patients who are endotracheally intubated, sedated, or aphasic. Another scoring system, the FOUR score (Full Outline of UnResponsiveness), assesses eye and motor responses as well as brainstem reflexes and respiration pattern to help discern a patient's level of consciousness. Some studies have shown that this scoring system is able to accurately predict neurologic outcomes in many patients.[5]

Drug overdose is the most common toxic-metabolic cause of coma in ICU patients. Other toxic-metabolic causes include sepsis, hypoxia, hypercapnia, hypothermia, electrolyte/glucose disorders, and hepatic/renal dysfunction. Trauma and hypoxic-ischemic encephalopathy are the most frequent primary cerebral events resulting in coma. Regardless of etiology, there are initial diagnostic and therapeutic steps that need to be taken as soon as coma is suspected. Ensuring that the patient has adequate respiration and a secure airway, and stabilizing the circulation, should be the first priorities in management. When appropriate, the neck should be immobilized. Empiric treatment of comatose patients with glucose and thiamine is recommended, and seizure activity, if present, should be treated immediately. Other additional tests that may be appropriate include chemistry panel, arterial blood gas, CBC, toxicology screen, liver/thyroid function tests, imaging of the head (CT scanning or MRI), lumbar puncture, and EEG.[6] A quick neurologic exam that assesses level of consciousness and brainstem reflexes, as well as motor exam and respiratory exam, should be completed as soon as possible. *Plum and Posner's Diagnosis of Stupor and Coma*[7] provides a detailed description of how to perform an exam of a comatose patient and details the significance of common findings. The physical exam remains the best determinant that clinicians use to prognosticate for patients with cerebral dysfunction.

The etiology of coma is also an important piece of data to consider when predicting the neurologic outcome for comatose patients. Typically, patients with trauma fare better than comatose patients with anoxic injury from cardiac arrest.[8] Booth and colleagues[3] described five neurologic signs that predict death or poor neurologic outcome in survivors of cardiac arrest: absent corneal reflexes or pupillary responses at 24 h, absent withdrawal response to pain at 24 h, and no motor response at 24 or 72 h. Other findings that predict poor neurologic outcome include the burst suppression pattern on EEG and bilateral absence of somatosensory-evoked potentials.[9] However, several studies suggest that survivors of cardiac arrest have improved outcomes if they are cooled to 32 to 34°C for 24 h and then passively rewarmed.[10,11] Whether specific exam findings after cooling are able to predict neurologic outcome remains to be determined.

Delirium

Delirium is another form of acute brain dysfunction that often complicates the course of ICU patients. Wide ranges of delirium prevalence (20% to 80%) have been reported in the literature, and these differences are likely related to the cohort examined and the delirium instrument used.[12–14] Nevertheless, delirium is defined as a fluctuating acute confused state that includes impaired attention and disorganized thinking. One common misconception is that delirious patients are typically agitated, hallucinatory, and hyperactive. In fact, recent studies suggest that hyperactive delirium is rare.[15] Risk factors for ICU delirium include host factors (elderly, history of dementia, hearing impaired), acute illness factors (severe sepsis, metabolic derangements, drug overdose), and iatrogenic factors (sedative medications, restraints, sleep deprivation).[16]

Several validated scoring systems are used to diagnose delirium in the ICU.[12,14,17] The Confusion Assessment Method for ICU (CAM-ICU) is one such scoring system that was designed for nonpsychiatrists. If a patient develops an acute change or fluctuation in mental status, then his or her attention should be assessed. Typically, this is

accomplished by showing pictures of five common objects at 3-s intervals. Subsequently, they are shown 10 pictures and asked if they have just seen this image. Inattention is defined by three or more incorrect responses, which then necessitates assessment of disorganized thinking and/or level of consciousness. Making the diagnosis of delirium requires acute onset of changes or fluctuations in mental status, *and* inattention *and* either disorganized thinking *or* altered level of consciousness. Importantly, inattention is required to make the diagnosis of delirium. Several studies have conclusively demonstrated that ICU delirium increases 6-month mortality and increased ICU and hospital costs.[1,18]

Treatment of delirium is an area that has garnered increased attention over the past decade. Obviously, life-threatening causes of delirium, such as shock, hypoxia, and metabolic derangements, need to be excluded first. Although primary prevention strategies have not been extensively studied in the ICU setting, it seems prudent to make commonsense interventions when caring for delirious patients. Such interventions might include recognizing patients at risk for delirium early in the course of critical illness, maintaining normal sleep/wake cycles for ICU patients as much as possible, mobilizing patients early, removing unnecessary hardware, maintaining adequate pain control, and involving the patient's family in the daily routine if feasible. When these interventions are not enough, small studies support the use of typical antipsychotic (haloperidol) and atypical antipsychotic (risperidone, ziprasidone, quetiapine, and olanzapine) medications. Of course, patients treated with these medications need to be monitored closely for side effects. Some evidence suggests that benzodiazepines, although effective in preventing alcohol or sedative withdrawal, may increase the risk of developing delirium in the ICU.[19] In addition, some recent studies suggest that dexmedetomidine, an alpha-2 agonist, may reduce the incidence of delirium if used for sedation instead of benzodiazepines.[20–22] Finally, a recent study that incorporated early mobilization in mechanically ventilated ICU patients demonstrated shorter duration of delirium compared with patients receiving usual care.[23]

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The author has disclosed that no relationships exist with any companies/organizations whose products or services may be discussed in this chapter.

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Chapter 18. The Acute Abdomen, Pancreatitis, and the Abdominal Compartment Syndrome

Bennett P. deBoisblanc, MD, FCCP

Objectives:

- Identify the risk factors for selected abdominal complications of critical illness.
- Recall the diagnostic approach to acute pancreatitis, bowel obstruction, mesenteric ischemia, *Clostridium difficile* colitis, acalculous cholecystitis, and the abdominal compartment syndrome.
- Select the appropriate treatment approach to each of the above illnesses when they are encountered in the ICU.

Key words: abdominal compartment syndrome; acalculous cholecystitis; acute pancreatitis; bowel obstruction; *Clostridium difficile* colitis; mesenteric ischemia

Synopsis:

Because patients who develop acute pancreatitis, acute bowel obstruction, mesenteric ischemia, or *Clostridium difficile* colitis are at increased risk of developing infectious, cardiopulmonary, and renal complications, they are usually cared for by intensivists in the ICU. Furthermore, bowel ischemia, acalculous cholecystitis, pseudomembranous colitis, or abdominal compartment syndrome may complicate non-GI illnesses within the ICU. This chapter focuses on the diagnosis and management of selected abdominal illnesses that critical care physicians commonly encounter and therefore are likely to encounter on the board exam.

Overview

The term "acute abdomen" is used to describe the abrupt onset of severe, sharp, abdominal pain. The differential diagnosis of the acute abdomen is broad and includes appendicitis, peptic ulcer disease, cholecystitis, pancreatitis, intestinal ischemia, volvulus, diverticulitis, perforated viscus, ureteral colic, pyelonephritis, diabetic keto acidosis, ectopic pregnancy, and adrenal crisis. The correct diagnosis can usually be established by history and imaging. Ultrasound is excellent for the right upper quadrant. CT is used for everything else. Oral contrast can help differentiate bowel from abscess while IV contrast is necessary to evaluate the pancreas and ischemic colitis. In this chapter, we will focus on the most likely entities to show up in the ICU.

Acute Pancreatitis

More than 80% of pancreatitis is caused by alcohol or gallstones. Pancreatitis can be a very morbid illness associated with multiorgan dysfunction. Predictors of mortality include the presence of shock, acute lung injury, acute kidney injury, GI bleeding, and abscess formation. The approach is supportive. IV fluid therapy should be guided by predictors of fluid responsiveness. There is no apparent advantage to bowel rest in patients who can tolerate enteral feedings. Therapy with somatostatin is controversial.

Infection tends to develop within areas of pancreatic autolysis most commonly after the first week. The risk of infection is proportional to the CT grade of necrosis, with multiple fluid collections carrying the highest risk. Prophylactic antibiotics are not indicated unless there is >30% necrosis by dynamic CT. Because they penetrate well into abscesses and have good activity against gut flora, carbapenems are the drugs of choice. In high-risk patients, such as those receiving total parenteral nutrition, those with diabetes, and those who have been on prolonged antibiotics, it is important to also consider *Candida* sp. The general approach when a pancreatic abscess is suspected is to perform serial dynamic CT scans and then to use ultrasound or endobronchial ultrasound to aspirate areas of necrosis for culture. Microbiology is G– in ~60%, G+ in ~50%, and fungal in ~25%. Pancreatitis in a patient with gallstones suggests the stone has migrated into the common bile duct. Consider magnetic resonance cholangiopancreatography for definitive diagnosis and endoscopic retrograde cholangiopancreatography for stone removal. Abscesses need to be drained and debrided. In high-risk patients, either percutaneous drainage by Interventional Radiology or endobronchial ultrasound drainage may be used. Splenic vein thrombosis and abdominal

compartment syndrome are sequelae with high board exam potential.

Acalculous Cholecystitis

Acalculous cholecystitis represents only 5% to 10% of all cases of acute cholecystitis, but it is an important entity to recognize because it tends to occur in critically ill patients without prior warning. Postoperative patients, HIV-positive patients, those supported by total parenteral nutrition (TPN), and those with diabetes or acute Epstein Barr virus infections seem to be at higher risk. The pathogenesis of acalculous cholecystitis seems to a triad of biliary stasis plus increased lithogenicity of bile plus gall bladder ischemia. Without intervention, 40% to 60% of patients will develop gangrene and perforation of the gall bladder. It should be suspected in any critically ill patient with right upper quadrant pain or tenderness, with unexplained fever, or with an unexplained elevation of bilirubin or alkaline phosphatase. The gall bladder can be imaged with CT or ultrasound. Distension, thickening of gall bladder wall (>5 mm), pericholecystic fluid, intramural or intraluminal gas, and mucosal sloughing and sludging within the gall bladder lumen are characteristic signs. Cholescintigraphy, also known as a hepatobiliary iminodiacetic acid scan, is best thought of as an ejection fraction for the gall bladder. Its usefulness as a diagnostic test in acalculous cholecystitis is limited, and some studies have shown that it has a negative predictive value of <25% in this disorder. When the diagnosis is highly considered, treatment is with percutaneous cholecystostomy or cholecystectomy.

Mesenteric Ischemia

Mesenteric ischemia is another diagnosis that is overrepresented in the ICU. The symptoms and signs are often vague and nonspecific. The most commonly affected segment of bowel is the splenic or transverse colon (ischemic colitis) because of its relatively poor blood supply. Consider the diagnosis in patients with risk factors for a cardiac source of emboli (eg, atrial fibrillation), in patients with extensive aortic atheromatous plaque (especially after aortoiliac surgery), in patients using vasoconstricting drugs (cocaine, digitalis, midodrine), and in patients with a low flow (shock, congestive heart failure, hypovolemia). Rarely, mesenteric ischemia will be caused by mesenteric vein thrombosis caused by an inherited or acquired thrombophilia, portal hypertension, pancreatitis, or cancer. The abdomen is often distended with gas and the pain is crampy. On digital rectal exam, fecal occult blood is usually positive.

The diagnosis can often be confirmed by CT angiography (sensitivity ~70%), which can show thrombus, mesenteric venous gas, pneumatosis intestinalis, bowel thickening or dilatation, fat stranding, or ascites. Colonoscopy can show characteristic petechial hemorrhages interspersed with areas of pale, edematous mucosa. Treatment is to normalize the circulation. Consider embolectomy or catheter thrombolysis and anticoagulation in cases of atrial fibrillation. Papaverine may be used if there is vasospasm.

Bowel Obstruction and Pseudo-Obstruction

Mechanical obstruction in the small bowel is most commonly caused by adhesions from prior surgery. In the large bowel, it is usually caused by volvulus, intussusception, tumors, or fecal impaction. Presenting symptoms and signs include colicky pain, copious vomiting, abdominal distention, and high-pitched bowel sounds. The high intraluminal pressures lead to compromise of venous blood flow and subsequently bowel ischemia and necrosis. Later on the abdomen becomes silent and tender. Up to 85% of patients will improve with nasogastric suction and IV fluids. Leukocytosis, tachycardia, and hypotension suggest infarction and the need for emergent surgery.

During critical illness, arrested peristalsis may occur in the stomach, small bowel, or large intestines. Colonic pseudo-obstruction (aka Ogilvie's Syndrome) is most commonly seen in the elderly or debilitated, those with heart failure, hypothyroidism, or electrolyte disturbances, following GI surgery, and in patients on opiates or anticholinergics. Treatment is decompression with a rectal tube or colonoscope. Correct electrolyte abnormalities and avoid fluid overload or precipitating drugs. Prokinetic agents,

such as erythromycin, neostigmine, or lactulose, may be tried. Jejunostomy or cecostomy is sometimes necessary in refractory cases.

Clostridium Difficile Colitis

C difficile colitis is likely to show up on the boards because its epidemiology has been changing. Up to 20% of hospitalized patients will be carriers. Risk factors for colitis are prior antibiotics (especially fluoroquinolones), older age, use of proton pump inhibitors, and enteral tube feedings. It may occur in epidemics within the ICU. In the last several years, the emergence of a strain of *C difficile* called BI/NAP1, or ribotype 027, has increased the severity of symptoms. This strain is more virulent, expresses more toxin A and toxin B as well as a binary toxin, and produces more spores. It is more likely to be associated with toxic megacolon and septic shock. Because of the increased permeability of the colon, endotoxin or live bacteria may translocate, leading to either culture negative or polymicrobial sepsis. Consider the diagnosis in any critically ill patient with diarrhea and fever, abdominal pain, leukocytosis, lactic acidosis, and so on. Mortality is ~20%. The ELISA has a sensitivity of ~75% for the toxin. The cytotoxicity assay is more sensitive for the toxin. Polymerase chain reaction of stool for the toxin encoding genes is rapid and sensitive and is rapidly replacing the ELISA and cytotoxicity assays. Treatment is with either metronidazole by mouth or IV or vancomycin by mouth. For severe disease caused by BI/NAP1, vancomycin plus IV metronidazole is preferred. Retention enemas may be given if an ileus is present. Colectomy and ileostomy may be necessary for toxic megacolon. Relapse occurs in 10% to 25% of treated patients.

Abdominal Compartment Syndrome

Abdominal compartment syndrome (ACS) is the combination of intraabdominal hypertension and organ dysfunction. Dysfunctional organs may include kidney, splanchnic, pulmonary, CNS (especially with pre-existing elevation of ICP), hemodynamic, or skin. Oliguric renal failure, hypotension, gut ischemia, and decreased respiratory system compliance are the most common presentations. Untreated the mortality is ~50%. Risk factors for ACS include cirrhosis, pancreatitis, intraabdominal trauma, peritoneal dialysis, liver transplantation, pelvic injury, abdominal aortic aneurism, and large volume resuscitation (>5 L/24 h) resuscitation. The incidence of ACS appears to be lower in the era of damage-control laparotomy.

The key to diagnosis is suspicion in high-risk patients. Intravesicular (bladder) pressure is a surrogate for abdominal compartment pressure. Normal is <10 cm H_2O. When there is accompanying organ dysfunction and bladder pressure rises to 16 to 25 cm H_2O, gut decompression with an nasogastric tube and/or rectal tube, paracentesis (if fluid is present), and muscle relaxants are indicated. When organ dysfunction is observed in the setting of bladder pressure >25 cm H_2O, surgical decompression with delayed fascial closure is the treatment of choice. Immediately following the decompression of ACS, the flood of venous return from poorly perfused pools may cause sudden hyperkalemia or lactic acidosis.

Nothing to Disclose

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Chapter 19. Hypothermia/Hyperthermia and Rhabdomyolysis

Janice L. Zimmerman, MD, FCCP

Objectives:

- Understand the physiologic responses associated with hypothermia.
- Outline supportive measures and rewarming techniques for the management of hypothermia.
- Describe predisposing factors for heat stroke, its clinical manifestations, and cooling methods.
- Discuss the clinical presentations and management of malignant hyperthermia and neuroleptic malignant syndrome.
- Describe the etiologies, clinical manifestations, and treatment of rhabdomyolysis.

Key words: heat stroke; hyperthermia; hypothermia; malignant hyperthermia; neuroleptic malignant syndrome; rhabdomyolysis

Synopsis:

Hypothermia results from an increase in heat loss, decrease in heat production, or impaired thermoregulation. Moderate to severe hypothermia presents with multiorgan involvement with prominent cardiovascular manifestations. Rewarming techniques are chosen based on clinical manifestations and availability of resources. Passive external rewarming is used for all patients to prevent further heat loss. Active external rewarming and active core rewarming techniques are often combined and used for patients with moderate to severe hypothermia.

Heat stroke results from an increase in heat production or decrease in heat loss. Heat stroke is classified as classic (nonexertional) or exertional heat stroke. In addition to supportive care, cooling is accomplished with conductive or evaporative methods. Overaggressive hydration should be avoided in the elderly patients to avoid cardiac decompensation with cooling.

Malignant hyperthermia results from a genetic muscle defect triggered by exposure to anesthetic agents. The syndrome is characterized by hyperthermia, muscle contracture, and cardiovascular instability. Prompt recognition allows discontinuation of the precipitating agent and institution of dantrolene. Neuroleptic malignant syndrome is an idiosyncratic reaction, usually to neuroleptic drugs, that is characterized by hyperthermia, muscle rigidity, alterations in mental status, autonomic dysfunction, and rhabdomyolysis. Treatment is removal of the agent, use of dantrolene for muscle rigidity, dopamine agonists, and supportive care.

Rhabdomyolysis results from muscle injury caused by a wide variety of etiologies. The maintenance of intravascular volume and renal perfusion is the most important aspect of preventing renal failure. Electrolyte abnormalities, particularly hyperkalemia, should be anticipated and treated expeditiously.

Body Temperature Regulation and Measurement

The anterior hypothalamus is responsible for temperature perception and the initiation of physiologic responses to alter body temperature. Information is received from temperature-sensitive receptors in the skin, viscera, and great vessels as well as receptors located in the hypothalamus. When a temperature increase is sensed, hypothalamic mechanisms are initiated to lower body temperature. This modulation includes increased sweating (a cholinergically mediated response), cutaneous vasodilation, and decreased muscle tone. Conversely, a decrease in temperature results in decreased sweating, cutaneous vasoconstriction, increased muscle tone, and shivering to raise body temperature. These homeostatic mechanisms deteriorate with age.

At rest, the trunk viscera supply 56% of body heat; during exercise, muscle activity may account for 90% of generated heat. Heat production may increase twofold to fivefold with shivering and more than sixfold with exercise. Most heat loss (50%–70%) normally occurs through radiation. The conduction of heat through direct contact with cooler objects or loss of heat because of convection accounts for a smaller percentage of heat loss. The evaporation of sweat from the skin is the major mechanism of heat loss in a warm environment.

Standard thermometers do not measure temperatures at high and low extremes. Temperature measured by an intravascular device is considered the gold standard, but this approach is not practical. Bladder catheters with thermistors provide readings similar to intravascular devices. A rectal or esophageal thermistor probe

is another alternative. The reliability of tympanic temperature devices has not been established in critically ill patients.[1]

Hypothermia

Definition and Etiologies

Hypothermia is defined as the unintentional lowering of core body temperature to <35° C (<95° F). Predisposing factors that can lead to increased heat loss, decreased heat production, or impaired thermoregulation are listed in Table 1.[2–4] Hypothermia may be characterized as primary (accidental), caused by exposure to cold temperatures, or secondary, resulting from a disease process such as hypothyroidism or sepsis. Risk factors for hypothermia-related death include age ≥65 years, mental impairment, substance abuse, homelessness, dehydration, and serious medical conditions.[5] Immersion hypothermia is often distinguished from nonimmersion hypothermia because it occurs more rapidly and is more often accompanied by asphyxia. Hypothermia is frequently noted in trauma patients and is associated with increased mortality rates.[3,6]

To facilitate management and anticipate physiologic changes, hypothermia is commonly classified by severity. Mild hypothermia refers to core temperatures of 32 to 35° C (90–95° F); moderate hypothermia, 28 to 32° C (82–90° F); and severe hypothermia, <28° C (<82° F). The classification for trauma victims is more conservative because of the poor prognosis associated with hypothermia. In these patients, moderate hypothermia is 32 to 34° C (90 to 93.2° F), with temperatures of <32° C (90° F) considered to be severe.[3,7]

Pathophysiology

General Metabolic Changes: Hypothermia produces multisystemic involvement that varies with core temperature (Table 2). The initial response to cold is cutaneous vasoconstriction to decrease heat loss, which results in the shunting of blood from colder extremities to the body core. Vasodilation secondary to ethanol can prevent this normal compensatory response. Vasoconstriction fails at temperatures <24° C (<75° F), and the rate of heat loss increases because of relative vasodilation. Heat production is increased by the onset of shivering at core temperatures of 30 to 35° C (86–95° F). Shivering continues until glycogen stores are depleted,

Table 1—*Factors Predisposing to Hypothermia*

Increased heat loss
Environmental exposure
Skin disorders
Burns
Dermatitis
Psoriasis
Vasodilation
Alcohol
Drugs (phenothiazines)
Iatrogenic
Heat stroke treatment
Environmental cold (operating suite)
Decreased heat production
Endocrine disorders
Hypopituitarism
Hypothyroidism
Hypoadrenalism
Inadequate fuel
Hypoglycemia
Anorexia nervosa
Malnutrition
Extreme exertion
Neuromuscular inefficiency
Extremes of age
Inactivity
Impaired shivering
Impaired thermoregulation
Peripheral dysfunction
β-blockers
Neuropathies
Spinal cord injury
Central dysfunction
CNS hemorrhage/trauma
Cerebrovascular accident
Dementia
Drugs
Sedatives
Alcohol
Cyclic antidepressants
Narcotics
Neuroleptics
Neoplasm
Older age
Parkinson's disease
Anorexia nervosa
Miscellaneous states
Carcinomatosis
Pancreatitis
Sepsis
Shock
Uremia

Adapted with permission from *ACCP Critical Care Medicine Board Review.* 20th ed. Northbrook, IL: American College of Chest Physicians; 2009.

Table 2—*Manifestations of Hypothermia*

Core Temperature, °C	Musculoskeletal	Neurologic	Other
Mild hypothermia			
38			
36	Shivering begins	Slurred speech	
34	Maximal shivering	Increased confusion	
33	Decreased shivering	Stupor	Decreasing BP; respiratory alkalosis, cold diuresis
Moderate hypothermia			
32	Shivering nearly absent; onset of muscle rigidity	Pupils dilated	Arrhythmias; J waves on ECG
30		DTRs absent	Severe hypoventilation
28	Extreme muscle rigidity	No voluntary movement	Shock; inaudible heart sounds
Severe hypothermia			
26			
24	Patient appears dead		Severe risk of VF; minimal cardiac activity
22			
20		Isoelectric EEG	Asystole
18		Isoelectric EEG	Asystole

DTR = deep tendon reflex; VF = ventricular fibrillation. Reprinted with permission from *ACCP Critical Care Medicine Board Review.* 20th ed. Northbrook, IL: American College of Chest Physicians; 2009.

which usually occurs when the body temperature reaches 30° C (86° F).

Cardiovascular System: An initial tachycardia that is usually not present in the hospital setting is followed by progressive bradycardia. The pulse rate decreases by 50% when the core temperature reaches 28° C (82° F). Bradycardia is secondary to alterations in conductivity and automaticity that are generally refractory to standard treatment (eg, atropine). Cardiac function and blood pressure also decline proportionately as the core temperature decreases. Systemic vascular resistance increases because of vasoconstriction.

Hypothermia produces a variety of myocardial conduction abnormalities. Atrial fibrillation is common and usually converts to sinus rhythm spontaneously during rewarming. At temperatures of <29° C (<84° F), ventricular fibrillation (VF) can occur spontaneously or be induced by movement or invasive procedures (eg, central line or nasogastric tube). Asystole occurs at temperatures <20° C (<68° F). VF and other arrhythmias are extremely refractory to defibrillation and drug treatment until the core temperature increases to approximately 30° C (approximately 86° F).

Although many ECG abnormalities have been described, the most characteristic of hypothermia is the J wave (also called the Osborne wave) at the junction of the QRS complex and ST segment (Fig 1). The J wave can occur in patients with core temperatures of <32° C (<90° F), and it is almost always present at temperatures of <25° C (<77° F). It has been observed that the size of the J wave may be inversely correlated with temperature.[8] The presence of this wave is not pathognomonic for hypothermia, nor does it have prognostic value. It is important to distinguish J waves from ST-segment elevation that may indicate myocardial infarction. Prolongation of the PR, QRS complex, and QT intervals may be noted.

Other Organ Systems: As temperature decreases, tidal volume and respiratory rate will decrease. The cough reflex may be blunted, and

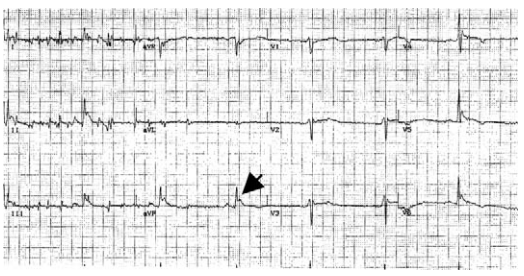

Figure 1. ECG of hypothermic patient showing J wave (arrow). Reprinted with permission from *ACCP Critical Care Medicine Board Review.* 20th ed. Northbrook, IL: American College of Chest Physicians; 2009.

cold-induced bronchorrhea may contribute to atelectasis. Hypoxemia may develop early depending on the circumstances (eg, water immersion or aspiration). Although renal blood flow and the glomerular filtration rate decrease during hypothermia, there is an initial cold-induced diuresis caused by the relative central hypervolemia resulting from peripheral vasoconstriction. Additional contributory factors include the inhibition of antidiuretic hormone release and renal tubular concentrating defects. Ethanol exacerbates the diuresis. With warming, volume depletion may become evident.

With mild hypothermia, patients may exhibit confusion, lethargy, or combativeness. Below a core temperature of 32° C (90° F), the patient is usually unconscious with diminished brainstem function. Pupils dilate below a core temperature of 30° C (86° F). Intestinal motility decreases at temperatures of <34° C (<93° F), resulting in the common finding of ileus. Hepatic dysfunction affects the generation of glucose as well as drug metabolism.

Laboratory Findings: The physiologic changes of hypothermia are reflected in clinical laboratory tests. An increased hematocrit value is usually found, with normal or low platelet and WBC counts. The increase in hematocrit value is caused by hemoconcentration and splenic contraction. However, the restoration of intravascular volume and warming often results in a mild anemia. Platelet and WBC counts may drop as temperatures decrease because of sequestration. Platelet dysfunction occurs with hypothermia and contributes to a bleeding diathesis. Although disseminated intravascular coagulation (DIC) may develop, initial coagulation study results (ie, prothrombin time and partial thromboplastin time) are often normal as these laboratory measurements are performed on warmed blood. Electrolyte levels are variable, and no consistent changes are predictable. Increased values of BUN and creatinine result from hypovolemia. Hyperglycemia is common as a result of catecholamine-induced glycogenolysis, decreased insulin release, and inhibition of insulin transport. Hypoglycemia may be evident in malnourished and alcoholic patients. Hyperamylasemia is common and may be related to a preexisting pancreatitis or pancreatitis induced by hypothermia. The acid-base status is difficult to predict in hypothermia, but factors such as hypoventilation, lactate generation from shivering, decreased acid excretion, and decreased tissue perfusion contribute to a respiratory and metabolic acidemia.[9] There is general agreement that arterial blood gas values do not need to be corrected for temperature. However, the Pa_{O_2} should be corrected for calculations of oxygen delivery and alveolar-arterial P_{O_2} gradient.

Diagnosis

The clinical manifestations of hypothermia vary with the etiology, acuteness of onset, severity, and duration. It is imperative to recognize the early signs of mild hypothermia, especially in the elderly. These patients may present with confusion, lethargy, impaired judgment, and the unusual manifestation of "paradoxical undressing." More severe hypothermia results in the following manifestations that are easily recognizable: muscle rigidity, decreased respiratory rate, bradycardia, hypotension, and even the appearance of death. The clinical suspicion of hypothermia should be confirmed with a core temperature thermistor measurement. Thermistors in bladder catheters may be the most practical way to measure temperature and monitor rewarming. A rectal probe is an alternative even though it may lag behind core changes. The probe should be inserted to an adequate depth (approximately 15 cm), avoiding cold fecal material. An esophageal probe is another alternative, but readings may be falsely elevated in the intubated patient who receives heated oxygen.

Management

Hospital Management: The severity of hypothermia, clinical findings, and comorbid conditions of the patient determine the aggressiveness of the resuscitation techniques. The following measures should be instituted as indicated:

1. *Airway management*. Intubation is often necessary for airway protection and/or the delivery of supplemental oxygen for more severely affected patients. The orotracheal route is preferred because of the risk of

traumatic bleeding with the nasal route. However, muscle rigidity may preclude orotracheal intubation. Blind nasotracheal intubation in a hypothermic patient with spontaneous respiration may be facilitated by topical vasoconstrictors and a smaller size endotracheal tube. Endotracheal tube cuff pressures should be monitored after rewarming because of volume and pressure changes.

2. *Supplemental oxygen*. An oxygen concentration of 100% should be administered by mask or via endotracheal tube until Pa_{O_2} can be assessed. Pulse oximetry cannot usually be relied on to guide therapy in conditions of hypothermia and hypoperfusion.
3. *Arrhythmia management and cardiopulmonary resuscitation*. Cardiopulmonary resuscitation should be initiated if the patient is pulseless (assess for 30–45 s) or has a nonperfusing rhythm such as asystole or VF. Chest wall compression is often difficult, and compressors may need to rotate more frequently than every 2 min. In patients with bradycardia, avoid pharmacologic manipulation and pacing. In patients with VF, initial defibrillation should be attempted once even if the temperature is <30 to 32° C (<86–90° F). If unsuccessful, rewarming should be instituted. Defibrillation can be attempted after every 1 to 2° C (2–3.6° F) increase in temperature or when the core temperature reaches 30 to 32° C (86–90° F). Avoid the IV administration of drugs until the temperature increases to approximately 30° C (approximately 86° F) and then use the lowest effective dose. Dosing intervals should be increased in hypothermic patients. The efficacy of amiodarone has not been established in patients with hypothermia, but it is a reasonable initial antiarrhythmic drug. Magnesium sulfate has also been used successfully. Lidocaine has limited efficacy, and procainamide may increase the incidence of VF. In patients with asystole, follow advanced life support guidelines and administer pharmacologic agents when the temperature approaches 30° C (86° F).
4. *Rewarming* (see "Rewarming Methods").
5. *IV fluids*. All patients require fluids for hypovolemia. Warm normal saline solution containing glucose is a reasonable choice. Increased fluid requirements are often necessary during rewarming to prevent or treat hypotension that may occur with vasodilation. Lactated Ringer solution should be avoided because of the potential impaired hepatic metabolism of lactate.
6. *Vasopressor drugs*. Hemodynamic instability should first be managed with volume replacement. Vasopressor drugs have a minimal effect on constricted vessels and increase the risk of arrhythmias.
7. *Nasogastric or orogastric tube*. Insert to relieve gastric distention.
8. *Urinary catheter*. Insert to monitor urine output and/or monitor bladder temperature.
9. *Venous access*. Peripheral venous catheters are preferred. The use of central venous lines (eg, subclavian or internal jugular) is not routinely recommended because they may precipitate arrhythmias.
10. *Laboratory studies*. Studies should include CBC count, prothrombin time, partial thromboplastin time, electrolyte levels, creatine kinase (CK) level, and arterial blood gas levels. Thyroid function evaluation, toxicology screening, and blood cultures are obtained as warranted.
11. *Search for associated conditions* requiring urgent intervention, such as hypoglycemia, sepsis, adrenal insufficiency, and hypothyroidism.

Rewarming Methods: Although warming is the primary treatment for hypothermia, controversy exists as to the optimal method, duration, and rate of rewarming. Rapid rewarming has not been demonstrated to improve survival, and experience with therapeutic hypothermia suggests slow rewarming may be associated with fewer complications. There are no controlled studies comparing rewarming methods, and rigid treatment protocols are not recommended. Options include the following types of rewarming techniques: passive external rewarming (PER); active external rewarming (AER); and active core rewarming (ACR).[2–4,10]

PER is the least invasive and slowest method. This method involves placing the patient in a warm environment, providing an insulating

cover, and allowing the body to regain heat. This technique should be applied as a sole method only in patients with mild hypothermia and as an adjunct in patients with moderate and severe hypothermia. The patient must be able to generate heat for PER to be effective. Rewarming rates with PER in patients with mild hypothermia range from 0.5 to 2.0° C/h (1–3.6° F/h).

AER involves the external application of heat to the body using methods such as warming blankets, heating pads, radiant heat lamps, or immersion in warm water. Currently, forced-air warming devices or resistive polymer blankets are the most effective and practical means of applying AER in the hospital, particularly in the perioperative period.[11–13] A potential disadvantage of AER is the theoretical concern of temperature "after-drop." Peripheral vasodilation can occur with external heat application and colder peripheral blood is then transported to the relatively warmer core, thereby reducing the core temperature. After-drop has been hypothesized to increase the incidence of VF. In response to this concern, it has been suggested that heat be applied only to the thorax, leaving the extremities vasoconstricted. The advantages of AER are its ease of use, ready availability, low cost, and noninvasiveness. Earlier studies showing high mortality when AER was utilized are not supported by more recent experience. AER is often combined with ACR techniques in patients with moderate or severe hypothermia.

ACR includes more invasive rewarming methods and involves the application of heat to the body core. ACR is indicated in patients with a core temperature of <28° C (<82° F) or with a nonperfusing cardiac rhythm. Techniques for ACR include heated humidified oxygen, heated IV fluids, thoracic lavage, peritoneal lavage, gastric/rectal/bladder lavage, hemodialysis, continuous venovenous rewarming, extracorporeal membrane oxygenation (ECMO), and cardiopulmonary bypass.

One of the simplest ACR methods to institute is warm, humidified, inhaled oxygen (42–45° C or 107.6-113° F), which prevents further respiratory heat loss and may result in a modest heat gain. A rewarming rate of 1 to 2.5° C/h (2–4.5° F/h) can be expected. This technique should be used routinely for intubated patients with moderate to severe hypothermia. Heated IV fluids (40–42° C or 104–107.6° F) are also easy to administer, but considerable heat is lost through IV tubing. If transfusion is indicated, blood should be warmed. Although gastric, bladder, and rectal lavage with warm fluids are simple procedures, efficacy is limited because of the small surface area for heat conductance. Gastric lavage may predispose the patient to aspiration, and it cannot be performed during chest compressions. Lavage of small cavities should be used only as an adjunct until more effective rewarming methods can be initiated.

For patients with severe hypothermia, the following more invasive methods of ACR are preferred: peritoneal lavage, thoracic lavage, hemodialysis, continuous venovenous hemofiltration,[14] ECMO,[15] and cardiopulmonary bypass.[16] These procedures require specialized expertise and intensive care and are not available in all hospitals. They are efficient at rewarming and, in the case of cardiopulmonary bypass, may provide for hemodynamic stabilization of the patient. Peritoneal lavage can be instituted through a peritoneal dialysis catheter, using dialysate heated to 40 to 45° C (104–113° F). Closed thoracic lavage involves the placement of anterior and posterior chest tubes, the infusion of heated saline solution (40–42° C or 104–107.6° F) through the anterior tube, and gravity drainage from the posterior tube.[17] Hemodialysis, utilizing a two-way-flow catheter, can rewarm patients but can potentially worsen the patient's hemodynamics. Continuous venovenous hemofiltration utilizes a modified fluid warmer with water or dialysate infused through the inner chamber.[18] ECMO may yield better survival rates than cardiopulmonary bypass because of the ability to support cardiopulmonary function after rewarming.[15] Cardiopulmonary bypass (femoral-femoral or atrial-aortic) is the most invasive and labor-intensive technique for rewarming. This technique can provide complete hemodynamic support and rapid rewarming rates (1–2° C every 3–5 min). Endovascular devices have been reported to be effective in rewarming patients with a pulse but experience is very limited.[19,20]

The choice of rewarming methods may combine techniques, such as AER with ACR, using heated oxygen and heated IV fluids. The

Table 3—*Predisposing Factors for Heat Stroke*

Increased heat production
Exercise
Fever
Thyrotoxicosis
Hypothalamic dysfunction (stroke, head injury)
Drugs (sympathomimetic agents)
Environmental heat stress (high heat)
Decreased heat loss
Environmental heat stress (high heat and humidity)
Cardiac disease
Peripheral vascular disease
Dehydration
Obesity
Skin disease (burns, scleroderma, psoriasis)
Anticholinergic drugs (antidepressants, antihistamines, antipsychotics)
Ethanol
β-blockers

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availability of resources may be a decisive factor in choosing the method of rewarming. In all cases, the complications of rewarming, such as DIC, pulmonary edema, compartment syndromes, rhabdomyolysis, and acute tubular necrosis, must be anticipated.

Outcome From Hypothermia

There are no strong predictors of death or permanent neurologic dysfunction in patients with severe hypothermia. Therefore, there are no definitive indicators to suggest which patients can or cannot be resuscitated successfully. Core temperature before rewarming and time to rewarming do not predict outcome. Severe hyperkalemia (>10 mEq/L) may be a marker of death.[21] In general, resuscitative efforts should continue until the core temperature is 32° C (90° F). However, the decision to terminate resuscitation must be individualized based on the circumstances. Patients found indoors are more severely affected and have higher mortality.

Hyperthermia

Heat Stroke

Definition: Heat stroke is a life-threatening emergency that occurs when homeostatic thermoregulatory mechanisms fail. This failure usually results in the elevation of body temperature to >40° C (>104° F), producing multisystem tissue damage and organ dysfunction. Two syndromes of heat stroke occur: classic heat stroke (nonexertional) and exertional heat stroke. Classic heat stroke typically affects infants and elderly individuals with underlying chronic illness. The occurrence of classic heat stroke is usually predictable when heat waves occur. The syndrome develops over several days and results in significant dehydration and anhidrosis. Exertional heat stroke typically occurs in young individuals such as athletes and military recruits exercising in hot weather. These individuals usually have no chronic illness, and this syndrome occurs sporadically and often unpredictably. Dehydration is less severe, and approximately 50% of individuals will have profuse sweating.

Predisposing Factors: Heat stroke results from increased heat production and/or decreased heat loss (Table 3). Environmental factors of high heat and humidity contribute to heat production as well as to the limitation of heat loss. Sympathomimetic drugs, such as cocaine and amphetamines, increase muscle activity and may also disrupt hypothalamic regulatory mechanisms. Drugs with anticholinergic effects inhibit sweating and disrupt hypothalamic function. Ethanol may contribute to heat stroke by vasodilation resulting in heat gain, impaired perception of the environment, and diuresis. β-adrenergic blockers may impair cardiovascular compensation and decrease cutaneous blood flow.

Diagnosis: The diagnosis of heat stroke requires a history of exposure to a heat load (either internal or external), severe CNS dysfunction, and elevated temperature (usually >40° C or >104° F). The absolute temperature may not be critical because cooling measures are often instituted before the patient is admitted to a health-care facility. Sweating may or may not be present.

Clinical Manifestations: Symptoms of heat stroke vary with the rapidity of onset, severity of exposure (temperature intensity and duration), and comorbid conditions. Profound CNS dysfunction is a defining characteristic of heat stroke that separates it from heat exhaustion. Dysfunction may range from bizarre behavior, delirium, and confusion to decerebrate rigidity,

cerebellar dysfunction, seizures, and coma. These changes are potentially reversible although permanent deficits can occur. Lumbar puncture results may show increased protein, xanthochromia, and lymphocytic pleocytosis.

Tachycardia, an almost universal cardiovascular finding in patients with heat stroke, occurs in response to peripheral vasodilation and the need for increased cardiac output. The peripheral vascular resistance is usually low unless severe hypovolemia or cardiac dysfunction is present. Compensatory vasoconstriction occurs in the splanchnic and renal vascular beds. If the patient is unable to increase cardiac output, hypotension develops. A variety of ECG changes have been described in patients with heat stroke, including conduction defects, increased QT interval, and nonspecific ST-T changes.

Tachypnea may result in a respiratory alkalosis. However, metabolic acidosis is the most common acid-base disturbance and the prevalence increases with the severity of hyperthermia.[22] Lactic acid may be generated by anaerobic muscle metabolism (exertional heat stroke) or hypoperfusion (classic heat stroke). Hypoglycemia may be present in patients with exertional heat stroke as a result of increased glucose utilization and impaired hepatic gluconeogenesis. Rhabdomyolysis and renal failure occur more commonly with exertional heat stroke and may be caused by myoglobinuria, thermal parenchymal damage, or decreased renal blood flow because of hypotension. Hematologic effects include hypocoagulability, which may progress to DIC. Hepatic injury results in cholestasis and the elevation of transaminase levels.

An inflammatory response may cause or contribute to the clinical manifestations of heat stroke. Increased concentrations of endotoxin, tumor necrosis factor, soluble tumor necrosis factor receptor, and interleukin-1 have been demonstrated in heat stroke victims.[23] Interleukin-6 and nitric oxide metabolite concentrations correlate with the severity of illness. Endothelial cell activation/injury is suggested by findings of increased concentrations of circulating intercellular adhesion molecule-1, endothelin, and von Willebrand-factor antigen.

Electrolyte concentrations are variable in patients with heat stroke. Hyperkalemia can result from rhabdomyolysis, but hypokalemia occurs more commonly. Hypocalcemia can occur, particularly with rhabdomyolysis, but usually does not require therapy.

Differential Diagnosis: A history of heat exposure and physical findings usually indicate the diagnosis of heat stroke. In the absence of an adequate history, other considerations to consider include CNS infection, hypothalamic lesions, thyroid storm, and other hyperthermic syndromes such as neuroleptic malignant syndrome (NMS).

Treatment: Along with resuscitative measures, immediate cooling should be instituted for any patient with a temperature of >41° C (>105.8° F). The following two methods of cooling have been used: conductive cooling and evaporative cooling.[23–25] Because definitive human studies are lacking, the optimal cooling method remains controversial.

Direct cooling by enhancing conduction of heat from the body can be accomplished by immersing the patient in cold water. Skin massage to prevent cutaneous vasoconstriction in the limbs has been recommended. Shivering can also result in an undesirable increase in heat production. Immersion may make it difficult to treat seizures and perform other resuscitative measures. Variants of this method include ice-water soaks; the application of ice or cold packs to the axillae, groin, and neck; and ice applied to the entire body. Cooling based on conduction is safe and effective in young patients with exertional heat stroke but is not well tolerated in elderly patients with classic heat stroke.[24]

Evaporative cooling is a cooling method that is practical in hospital settings. The patient is placed nude on a stretcher and sprayed with warm (not cold) water. Air flow is created with the use of fans to enhance evaporative cooling.[26] This method allows personnel to institute other resuscitative measures while cooling occurs. Although the cooling rate may be slower than conductive cooling, evaporative cooling is well tolerated and results in good outcomes.[24] Other cooling methods, such as peritoneal lavage, gastric lavage, or cardiopulmonary bypass, have not been effectively tested in humans.[24] There are a few reports of surface and endovascular cooling devices used for therapeutic hypothermia after

cardiac arrest being used in heat stroke victims, but their use is not currently recommended because of cost and invasiveness.[27,28] The use of antipyretic agents is not indicated, and dantrolene is ineffective.

In addition to cooling, many patients (especially those with nonexertional heat stroke) will require intubation for airway protection. Supplemental oxygen therapy should be instituted when indicated. The type and quantity of IV fluids should be individualized based on the assessment of electrolyte levels and volume status. Overaggressive hydration may result in cardiac decompensation during cooling, especially in the elderly. Hypotension usually responds to cooling as peripheral vasodilation diminishes. Vasopressor agents are not recommended for initial management of hypotension because vasoconstriction can decrease heat exchange. Patients who remain hypotensive after cooling may require additional hemodynamic monitoring. A thermistor probe should be used for monitoring core temperature during cooling efforts. Cooling should be stopped at 38.0 to 38.8° C (100.4-102° F) to prevent hypothermic overshoot.

Outcome: With appropriate management, the survival rate of patients with heat stroke can approach 90%. Morbidity is related to the duration and intensity of hyperthermia and to underlying conditions. Advanced age, cardiac disease, hypotension, coagulopathy, hyperkalemia, acute renal failure, and prolonged coma are associated with a poor prognosis.[29,30] Elevated lactate levels are associated with poor prognosis in patients with classic heat stroke but not in those with exertional heat stroke. In retrospective studies, rapid cooling (in <1 h) was associated with a decreased mortality.

Malignant Hyperthermia

Definition: Malignant hyperthermia (MH) is a drug-induced or stress-induced hypermetabolic syndrome that is characterized by hyperthermia, muscle contracture, and cardiovascular instability.[31,32] The syndrome results from a genetic defect of calcium transport in skeletal muscle. The primary defects are postulated to be the impaired reuptake of calcium into the sarcoplasmic reticulum, the increased release of calcium from the sarcoplasmic reticulum, and a defect in the calcium-mediated coupling contraction mechanism. Sustained muscle contraction results in increased oxygen consumption and heat production. It is genetically transmitted as an autosomal-dominant trait and occurs in 1 in 50 to 1 in 150,000 adults who receive anesthesia.

Triggers: Halothane and succinylcholine have been involved in the majority of reported cases of MH. Additional potentiating drugs include other inhalational anesthetic agents and drugs such as ethanol, caffeine, sympathomimetics, parasympathomimetics, cardiac glycosides, and quinidine analogs. Less commonly, MH can be precipitated by infection, physical or emotional stress, anoxia, or high ambient temperature.

Clinical Manifestations: Manifestations of MH usually occur within 30 min of anesthesia in 90% of cases. However, onset of the syndrome may occur postoperatively. Muscle rigidity begins in the muscles of the extremities or the chest.[33] In patients receiving succinylcholine, the stiffness most commonly begins in the jaw. The development of masseter spasm after the administration of a paralyzing agent may be an early sign of possible MH. Tachycardia is another early, although nonspecific, sign. The monitoring of arterial P_{CO_2} or end-tidal CO_2 levels may detect an early increase in CO_2. Hypertension and mottling of the skin also occur. The increase in temperature usually occurs later, but it is followed rapidly by acidosis, ventricular arrhythmias, and hypotension. Laboratory abnormalities include increased sodium, calcium, magnesium, potassium, phosphate, CK, and lactate dehydrogenase levels. Lactate levels are increased, and arterial blood gas levels indicate hypoxemia and an increase in Pa_{CO_2}.

Treatment: Once the diagnosis of MH is entertained, the inciting drug should be discontinued immediately. Alternative anesthetic agents should be instituted and if possible, surgery should be discontinued. The most effective and safest therapy is dantrolene, which prevents the release of calcium into the cell by the sarcoplasmic reticulum.[34] Uncoupling of the excitation contraction mechanism in skeletal muscle decreases thermogenesis. Dantrolene should be administered by rapid IV push, beginning at a dose of 2.5 mg/kg and repeated every 5 min until the

Table 4—*Diagnostic Criteria for NMS*[a]

Major criteria
Fever
Muscle rigidity
Increase in creatinine kinase concentration
Minor criteria
Tachycardia
Abnormal BP
Tachypnea
Altered consciousness
Diaphoresis
Leukocytosis

[a]Diagnosis of NMS is suggested by the presence of all three major criteria or by the presence of two major and four minor criteria. Reprinted with permission from *ACCP Critical Care Medicine Board Review.* 20th ed. Northbrook, IL: American College of Chest Physicians; 2009.

symptoms subside or the maximum dose of 10 mg/kg has been reached. Decreasing muscle rigidity should be evident within minutes. Subsequent doses of 1 mg/kg every 4 to 6 h should be continued for 36 to 48 h. If dantrolene is ineffective or slowly effective, evaporative cooling methods can also be utilized. Calcium channel blockers are of no benefit in patients with MH and should not be used to treat arrhythmias.

The Malignant Hyperthermia Association of the United States provides a hotline for assistance in managing MH (1-800-MH-HYPER, 1-800-644-9737, or 1-315-464-7079 if outside of the US). The organization also maintains a website with useful information online (www.mhaus.org).

NMS

Definition: NMS is an idiosyncratic reaction, usually to neuroleptic drugs, that is characterized by hyperthermia, muscle rigidity, alterations in mental status, autonomic dysfunction, and rhabdomyolysis.[35] It may occur in up to 1% of all patients receiving therapy with neuroleptic agents; it affects the young more than the old, and affected individuals are more likely to be male than female.[36] The pathogenesis is unknown, but it may be related to CNS dopamine antagonism and altered hypothalamic temperature set point.

Triggers: Although the majority of cases have been associated with haloperidol, the following agents have been associated with NMS: butyrophenones (eg, haloperidol); phenothiazines (eg, chlorpromazine and fluphenazine); thioxanthenes (eg, thiothixene); dopamine-depleting agents (eg, tetrabenazine); dibenzoxazepines (eg, loxapine); and withdrawal of levodopa/carbidopa or amantadine. The newer atypical antipsychotic drugs such as clozapine, risperidone, olanzapine, ziprasidone, aripiprazole, and quetiapine have also been reported to induce NMS. Rechallenge with an inciting drug may not result in recurrence of NMS. Various diagnostic criteria have been proposed (Table 4), but NMS remains a clinical diagnosis based on exposure to neuroleptic agents or other dopamine antagonists in association with characteristic clinical manifestations.

Clinical Manifestations: NMS usually occurs 1 to 3 days after initiating therapy with a potential inciting agent or changing the dose, and the syndrome may last for a period of 1 to 3 weeks. Hyperthermia is universally present, and the average maximal temperature is 39.9° C (103.8° F). NMS has rarely been reported to occur without temperature elevation. Autonomic dysfunction includes tachycardia, diaphoresis, BP instability, and arrhythmias. Autonomic dysfunction may precede changes in muscle tone. A general increase in muscle tone or tremors occurs in >90% of patients. Early manifestations of changes in muscle tone include dysphagia, dysarthria, or dystonia. Altered mental status occurs in 75% of patients and can range from agitation to coma. Rhabdomyolysis occurs frequently with elevations of CK levels and may lead to significant electrolyte abnormalities. WBC counts are often increased (10,000–40,000 cells/μL) and may demonstrate a left shift. DIC has also been reported. Volume depletion or renal injury from rhabdomyolysis can result in elevated BUN and creatinine levels.

Treatment: Dantrolene is the most effective agent for reducing muscle rigidity and decreasing temperature. It is administered in the same doses as those described for MH. In addition, dopamine agonists have been reported to have beneficial effects in patients with NMS.[37] These drugs include bromocriptine (2.5-10 mg three times daily), amantadine (100–200 mg twice daily), and levodopa/carbidopa. Bromocriptine may cause vomiting and increase the risk of aspiration. Benzodiazepines may decrease symptoms in

Table 5—*Causes of Rhabdomyolysis*

Trauma	Infections	Toxins/Drugs	Metabolic Disorders
Burns	Coxsackie virus	Alcohol	Diabetic ketoacidosis
Crush syndrome	Gas gangrene	Amphetamines	Enzyme deficiencies
Electrical injury	Epstein-Barr virus	Carbon monoxide	Hypernatremia
Exertion (including work of breathing)	Hepatitis	Cocaine	Hypersosmolar states
Heat stroke	Herpes simplex	Daptomycin	Hypocalcemia
Hypothermia	HIV	Fibrates	Hypokalemia
Malignant hyperthemia	Influenza A and B	Heroin	Hypomagnesemia
Muscle compression	Legionella	Methamphetamines	Hypophosphatemia
Neuroleptic malignant syndrome	Salmonella	Phencyclidine	Hypothyroidism and hyperthyroidism
Seizures	Shigella	Propofol	Inflammatory muscle disease
Vascular occlusion	Tetanus	Snake/spider venom	Vasculitis
		Statins	
		Steroids	

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milder cases. Supportive therapies must also be instituted as indicated. Complications may include respiratory failure, cardiovascular collapse, renal failure, arrhythmias, or thromboembolism. The Neuroleptic Malignant Syndrome Information Service (www.nmsis.org) maintains a hotline for medical professionals (1-888-667-8367) if assistance is needed.

Rhabdomyolysis

Definition

Rhabdomyolysis is a clinical and laboratory syndrome resulting from skeletal muscle injury with the release of cell contents into the plasma. Rhabdomyolysis occurs when demands for oxygen and metabolic substrate exceed availability. This syndrome may result from primary muscle injury or secondary injury caused by infection, vascular occlusion, electrolyte disorders, or toxins. Table 5 provides an overview of the multiple causes of rhabdomyolysis.[38] Statin use is currently one of the most frequent causes of mild rhabdomyolysis, but severe cases also occur.[39] Rhabdomyolysis can develop postoperatively following bariatric surgery because of elevated deep tissue pressures.[40]

Manifestations

Typical clinical manifestations of rhabdomyolysis consist of myalgias, muscle swelling and tenderness, discoloration of the urine, and features of the underlying disease. However, overt symptoms or physical findings may not be present. The results of laboratory tests reflect muscle cell lysis with elevation of the levels of muscle enzymes (ie, CK, myoglobin, aldolase, lactate dehydrogenase, and aspartate aminotransferase), hyperkalemia, hyperphosphatemia, and hypocalcemia. Measurement of muscle enzymes other than CK is not warranted. Coagulation abnormalities consistent with DIC may occur. Renal failure may result secondary to the release of myoglobin and other toxic muscle components. A urine dipstick that is positive for blood and an absence of RBCs on microscopic examination suggest the presence of myoglobinuria.

Treatment

The treatment of rhabdomyolysis is aimed at treating the underlying disease and preventing complications. The maintenance of intravascular volume and renal perfusion is the most important aspect of preventing renal failure.[41,42] Volume resuscitation should target a urine output of 2 to 3 mL/kg/h. Although increased urine output is beneficial, other interventions to prevent renal failure are more controversial. Alkalinization of the urine may be helpful, but clinical relevance has not been established. The greatest benefit of administering sodium bicarbonate may be the restoration of intravascular volume rather

than a change in pH. If treatment with bicarbonate is considered, it should be individualized, based on the patient's ability to tolerate the sodium and fluid load. Alternating use of normal saline and sodium bicarbonate may prevent the development of hyperchloremic metabolic acidosis. Therapy with loop diuretics and osmotic diuretics has been advocated as being protective of the kidneys, but convincing clinical data are lacking. Loop diuretics theoretically can worsen renal tubular acidosis, which is thought to potentiate myoglobin-induced nephropathy. Diuresis should not be attempted prior to adequate volume replacement.

Electrolyte abnormalities should be anticipated and treated expeditiously. The most life-threatening abnormality is hyperkalemia, and potassium concentrations should be monitored frequently as well as the ECG for evidence of QRS changes. Hypocalcemia does not require treatment unless the patient is symptomatic (seizures or tetany), and the empiric administration of calcium may exacerbate muscle injury. Renal replacement therapy may be required for refractory hyperkalemia, acidosis, progressive renal failure and volume overload.

The patient must be closely observed for the development of a compartment syndrome. The monitoring of intracompartmental pressures may be required. Fasciotomy is often recommended for intracompartmental pressures of >30 to 35 mm Hg.

Relationships Disclosed

The author has disclosed the following relationships: Product/procedure/technique that is considered research and is NOT yet approved for any purpose: glucagon, insulin for beta-blocker and calcium channel blocker overdose; lipid emulsion for overdose. The ACCP Education Committee has reviewed these relationships and resolved any potential conflict of interest.

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Notes

Chapter 20. Ventilatory Crises

Gregory A. Schmidt, MD, FCCP

Objectives:

- Review bases for the distressed ventilated patient.
- Examine the role of patient-ventilator dyssynchrony.
- Propose analyzing respiratory mechanics to guide diagnosis.
- Discuss approaches to critical hypoxemia.
- Introduce ventilator changes in autoPEEP.

Key words: autoPEEP; auto-positive end-expiratory pressure; barotrauma; endotracheal tube; hypercapnia; hypoxemia; ICU ultrasound; mechanical ventilation; patient-ventilator synchrony; pneumothorax; ventilator alarm

Synopsis:

The ICU course of mechanical ventilation is characterized by an apparently comfortable patient, silent ventilator alarms, and acceptable gas exchange. This peaceful picture may be punctuated, however, by abrupt crises of distress and alarming or severe hypoxemia or hypercapnia. By their very nature, such crises demand a rapidly paced response. At the same time, the stakes are high: the treatment (eg, needle thoracostomy or a sedative bolus) may be lifesaving (if accurate) or life ending (if wrong). This chapter describes the most common crises during mechanical ventilation; provides a framework for rapid, bedside evaluation; and emphasizes the use of ventilator flow, pressure waveforms, and bedside ultrasonography to guide therapy. This chapter is divided into the following categories: (1) the distressed patient, (2) high-pressure and low-pressure alarms, (3) critically impaired gas exchange, and (4) high levels of auto-positive end-expiratory pressure (autoPEEP), a particular scenario that may provoke distress, alarming, or gas exchange failure.

The Distressed Patient

One of the first principles of dealing with the acutely distressed, ventilated patient is that either the ventilator or the patient may be the source of the distress. It is often helpful to bag-ventilate the patient briefly to separate the person from the machine, potentially clarifying which is provoking the crisis. Possible machine-induced bases for the crisis include mechanical failure of the ventilator; disconnections of tubing (from source to ventilator or from ventilator to patient); endotracheal (or tracheostomy) tube malfunction, occlusion, or dislodgement; and ventilator settings that fail to match patient demands (patient-ventilator dyssynchrony). Patient-related sources of distress include barotrauma, pain, myocardial ischemia, hypoxemia or hypercapnia, delirium, and anxiety.

The differential diagnosis is aided by a focused, 60-s examination, during which the patient should be hand-bagged, with attention on the endotracheal tube (position, patency, cuff integrity), evidence of pneumothorax (tracheal deviation, absence of breath sounds, ultrasound exam for lung sliding), oximetry, and vital signs. Generally, the respiratory therapist should attempt to ventilate the patient sufficiently to suppress vigorous respiratory effort because doing so facilitates measurement of respiratory mechanical properties. At the same time, the ventilator circuit integrity should be checked, looking for leaks or disconnections. If bagging calms the patient, the cause of distress is likely to be related to ventilator settings or function, rather than something intrinsic to the patient (such as pneumothorax or a distended urinary bladder). If the patient calms, a return to machine ventilation may allow a careful measurement of respiratory mechanical properties, as detailed below, to provide further diagnostic information. If oximetry reveals new hypoxemia, both lung and circulatory function need further assessment as discussed below.

Often, this brief, initial survey identifies the source of distress or narrows the list of possibilities sufficiently to suggest one of a few, discrete, confirmatory tests. Other patients should have immediate blood gas analysis, full bedside pleural ultrasound, chest radiography, or, in appropriate circumstances, electrocardiography or other examinations.

Typically, the question of sedative administration arises with the onset of the crisis. An agitated patient presents an immediate threat to self and staff, and a sedative (occasionally to include a paralytic drug) may be just the right treatment, especially when pain or delirium is the fundamental problem. However, if agitation is

merely signaling some underlying problem, a sedative may (at best) mask that problem or (at worst) unravel the patient's last efforts to compensate. Thus, sedative treatment must always be paired with an understanding of the cause of the crisis or with a continuing plan to solve it.

Barotrauma as the Basis for Crisis

Pneumothorax complicates roughly 3% of the courses of mechanical ventilation, and most of those occur near the onset of ventilation,[1] especially during the first 24 h. Nevertheless, the risk persists, even in patients ventilated for weeks. Risk factors for pneumothorax include lung necrosis, decreased lung compliance, trauma, elevated plateau airway pressures, and use of tidal volumes that are not lung-protective. There is no clear relationship to levels of PEEP or peak airway pressure. In a trial of *cis*-atracurium for severe ARDS, subjects in the paralytic arm had an unexpected reduction in the incidence of pneumothorax (4.0% vs 11.7%).[2]

Because this complication is both lethal and treatable, a pneumothorax should be considered in the evaluation of any distressed patient. Signs may include hemodynamic deterioration, tracheal shift, reduced chest wall movement and increased size on the affected side, a change in breath sounds, increased airway pressures (or, during pressure-preset modes of ventilation, reduced tidal volume), and falling oxygen saturations. The sensitivity and specificity of all of these signs are unknown, so they cannot be relied on except in dire circumstances. Rather, confirmatory tests (ultrasonography or radiography) should be carried out to confirm or refute the clinical impression. Ultrasound, in particular, has proved quite accurate in detecting and excluding pneumothorax[3] and is more rapidly available than chest radiography. The absence of lung sliding suggests pneumothorax, especially if it had been present previously. Identification of a "lung point" is virtually diagnostic of pneumothorax.

Suboptimal Ventilator Settings and Patient-Ventilator Dyssynchrony

Ventilator settings may be guided by protocol (eg, to protect the lungs from overdistension) or may be tailored to achieve particular gas-exchange goals. The settings arrived at may or may not meet the patient's demand for flow rate, flow pattern, tidal volume, or minute ventilation. Alternatively, the settings may be adjusted primarily to attain comfort, at the cost of deleterious alveolar overdistension or autoPEEP. Most often, both comfort and safe ventilatory settings can coexist, but that often requires sedation. Patients are at risk for distress, occasionally of crisis proportions, when sedation is interrupted or reduced, or when resolving illness allows a greater level of alertness. Evidence that ventilator settings are not meeting patient demand can be inferred readily by examining the flow and pressure waveforms. Specific examples follow.

Lung-Protective Ventilation in Acute Lung Injury (ALI)/ARDS

Most patients with ALI/ARDS should be ventilated with tidal volumes of 6 mL/kg of predicted body weight. At that tidal volume, a high respiratory rate is necessary to meet the demand for minute ventilation. In the Acute Respiratory Distress Syndrome trial, the mean respiratory rate in the low-tidal-volume group was 30 breaths/min,[4] and some patients will need rates well in excess of 30 breaths/min. A common error in treating a patient with ALI is to set a low rate, such as 18 breaths/min, which may suffice in the initial hours when the patient is deeply sedated, but that will be insufficient when the patient awakens. Then sedative discontinuation may unmask the discrepancy between what is set and what is needed, provoking distress and agitation. This crisis can often be averted by attention to the airway pressure waveform by recognizing triggered breaths (especially double-triggering), concavity of the inspiratory pressure rise, or breath-to-breath variability in pressure, as illustrated in Figure 1.

AutoPEEP and the Effort to Trigger

The presence of autoPEEP presents an inspiratory threshold load, making it difficult for the patient to trigger the ventilator. When the end-expiratory pressure greatly exceeds PEEP (as in

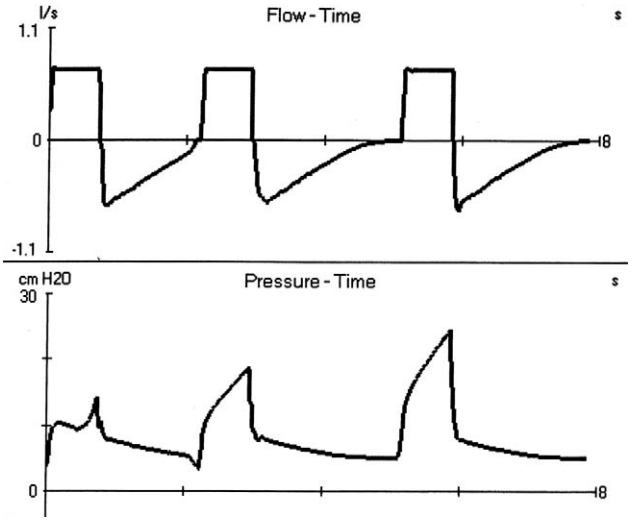

Figure 1. Evidence of patient triggering can be seen in the airway pressure waveform.

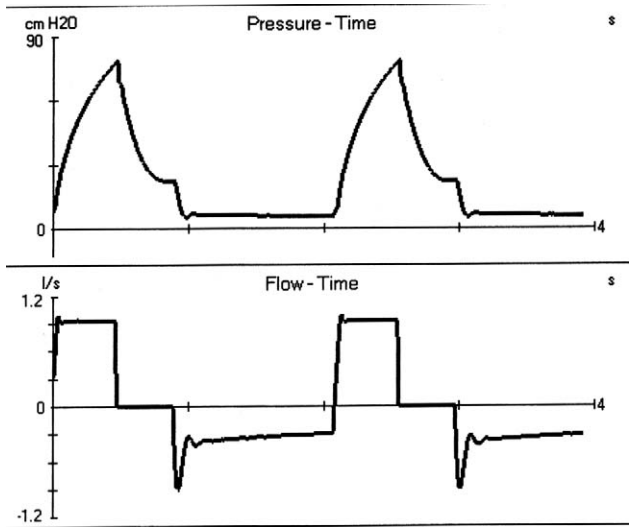

Figure 2. The end-expiratory flow is roughly 0.3 L/s (should be zero).

severe airflow obstruction), the patient must exert sufficient effort to lower alveolar pressure from the autoPEEP level to the PEEP level (and further yet, to trigger the ventilator). The work of triggering may be so high that the patient becomes distressed. This is apt to occur when ventilator rates are reduced, transitioning the patient from full ventilation (no need to trigger) to only partial support (must trigger) or, similarly, when sedatives are withdrawn. Recognizing this scenario entails knowing when it is likely to occur—in the patient with status asthmaticus or severe COPD exacerbation. Ventilator waveforms provide clues: end-expiratory flow, delayed triggering, and failed trigger efforts (Fig 2); all of which may signal the presence of autoPEEP. In passive patients, the end-expiratory port occlusion technique allows quantitation of its magnitude. One solution to the triggering difficulty of autoPEEP is to raise the PEEP level, which has the effect of reducing the inspiratory threshold load. It is worth emphasizing that changing the level of the pressure trigger, or shifting from pressure-triggering to flow-triggering, has no meaningful effect on the work of breathing.

Patient-Ventilator Dyssynchrony

Both examples given above involve patient-ventilator dyssynchrony, but a mismatch between the patient's desires and what the intensivist has ordered can arise in any ventilated patient. Such a mismatch is often subclinical, rising to the level of crisis only when sedatives are withheld or the patient's ventilatory demand rises, such as during bathing or use of the bedpan. In both this setting and in the setting described above for ALI, resedating the patient can "solve" the crisis, but a superior approach may be to adjust the ventilator instead. Patients at risk for clinically important dyssynchrony can often be identified by regular examination of ventilator waveforms, with attention to the signs exhibited in Figure 1. Neurally adjusted ventilatory assist has been shown to reduce asynchrony,[5] but its clinical value is yet unknown.

High Ventilator Pressure Alarm

During volume-preset modes of ventilation, the high-pressure alarm is one of the most useful clues to a new problem. At any point during inspiration, the pressure at the airway opening is the sum of pressures to (1) overcome the end-expiratory alveolar pressure (PEEP or autoPEEP), (2) drive flow across the inspiratory resistance, (3) distend the lungs and chest wall, and (4) counter any effect of expiratory muscles. Surely, the most common cause of a high-pressure alarm is coughing or expiratory muscle activity during inspiration, a form of patient-ventilator dyssynchrony typically called "bucking." Other reasons for the airway pressure to rise include biting, kinking, or occlusion of the endotracheal tube;

Table 1—*Differential Diagnosis of Elevated Airway Opening Pressure*

Classification	Cause
Expiratory effort	Coughing, bucking
	Respiratory distress
Elevated resistive pressure	Endotracheal tube secretions, concretions
	Biting the endotracheal tube
	Bronchospasm
	Fixed airway obstruction
	Malignant or inflammatory airway masses
	Excessive inspiratory flow rate
Elevated plateau pressure because of lungs	Pulmonary edema
	Pulmonary fibrosis
	Atelectasis
	ALI/ARDS
	Severe pneumonia
	Lung cancer
Elevated plateau pressure because of chest wall	Abdominal compartment syndrome
	Massive obesity
	Pneumothorax
	Large pleural effusions
Elevated autoPEEP	Status asthmaticus
	Severe COPD
	Other obstruction or very high minute ventilation

bronchospasm; pulmonary edema; atelectasis; pneumothorax; and abdominal distension (Table 1). The basis for an elevated airway opening pressure may not be clear initially. A systematic approach to gaining useful physiologic information follows: (1) get the patient relatively passive; (2) measure the peak airway pressures; (3) stop flow briefly at end-inspiration, measuring the plateau airway pressure; and (4) seek and quantitate autoPEEP.

Get the Patient Passive

Effort can greatly affect the airway pressure waveform (Fig 1), confounding the interpretation of respiratory mechanics, making it necessary for the patient be relatively passive. Many patients will already be passive because of illness, sedatives, paralytics, or a high level of ventilator support. For those who are not, simple ventilator maneuvers (raising modestly the rate or tidal volume) may suffice. In others, additional sedatives may be necessary to accommodate the patient to the ventilator settings, and the intensivist must balance the gain from additional information against the adverse effects of sedation.

Measure the Peak and Plateau Airway Pressures

The peak airway pressure is found at end-inspiration and, in the passive patient, represents the sum of flow-related pressure, the pressure to distend lungs and chest wall, and pressure to overcome PEEP (or autoPEEP). A 0.4-s end-inspiratory pause stops flow, removing the flow-related component, so the airway pressure falls by an amount related to the flow resistance and the inspiratory flow rate. When the endotracheal tube is 7.5 or larger and the flow is set at 60 L/min, the resistive pressure ($Presist = Ppk - Pplat$) is roughly 5 to 10 cm H_2O. The plateau pressure represents the sum of only the pressure to distend the lungs and chest wall and the pressure to overcome PEEP.

Measure PEEP or AutoPEEP

When there is no autoPEEP, the end-expiratory pressure equals PEEP. Thus, the pressure to distend the lungs and chest wall is the plateau airway pressure minus PEEP. The tidal volume divided by the pressure to distend the lungs and chest wall is the static compliance of the respiratory system and has values normally between 70 and 100 mL/cm H_2O. The presence of autoPEEP is usually signaled by the presence of end-expiratory flow. Its magnitude can be found by stopping flow at end-expiration and reading the pressure at the airway opening. Calculations of compliance must consider autoPEEP.

By examining the airway pressure waveform and using a brief end-inspiratory pause, it becomes possible to narrow the differential diagnosis for high peak airway pressure into resistive causes, compliance-related causes, or (rarely) high autoPEEP. Moreover, by remeasuring those mechanical parameters following interventions, it becomes possible to determine the effect of the intervention.

Low Ventilator Pressure Alarm

Low-pressure alarms are uncommon and generally are due to leaks in the system (most often a disconnection between the wye connector and the endotracheal tube). Rarely, a patient will make so much effort that he or she may suck the airway pressure below an alarming threshold. Leaks are readily evident after a brief bedside examination with attention to the endotracheal or tracheostomy tube, ventilator tubing, and (if present) chest tube.

Worsened Oxygenation

There are many potential explanations for acutely deteriorating oxygenation. These can be divided into three main groups: (1) a ventilator or interface problem, (2) a worsened gas exchange in the lung, and (3) a circulatory disruption.

Many patients with severe lung derangement depend critically on the fraction of inspired oxygen, PEEP level, or some other inhaled gas (eg, nitric oxide or prostacyclin). Empty tanks, disconnected lines, dislodged endotracheal tubes, changes in PEEP, and various forms of ventilator malfunctions may provoke acute hypoxemia.

Several forms of new or worsened lung gas exchange may present abruptly, including pulmonary edema; atelectasis; acid aspiration; pneumothorax; pulmonary embolism; or rapid advancement of ARDS, alveolar hemorrhage, or pneumonia. At times, lung gas exchange deteriorates because of distress or increased work of breathing, without requiring any fundamental change in lung function—this is most likely to follow reductions in level of sedation or some new stimulus provoking agitation. It is often useful to get the patient passive, then remeasure the respiratory mechanical properties to gain insight into the crisis. Bedside ultrasound can also be revealing[6] and is more quickly available than portable chest radiography (although that, too, can be useful). With this approach, many patients can be treated comfortably without performing helical CT angiography to exclude pulmonary embolism.

Finally, in patients with diseased lungs, the arterial oxyhemoglobin saturation depends, in part, on the venous oxyhemoglobin saturation. This, in turn, is a function of oxygen delivery and systemic consumption. Thus, a crippled circulation can reveal itself as worsened oxygenation. Measuring the central venous saturation (or otherwise assessing the circulation) may be useful.

When hypoxemia is severe and the fraction of inspired oxygen is greater than 0.6, concerns arise regarding oxygen toxicity. The threshold for oxygen toxicity in humans is unknown. Further, diseased lungs and those already exposed to moderate increased oxygen may be relatively resistant to high fractions. Nevertheless, common practice stresses an attempt to get the fraction to 0.6 or lower within 24 h. Several maneuvers can help accomplish this. First, efforts should be made to accommodate the ventilator to the patient's demand or to sedate the patient to accept the ventilator settings. A trial of PEEP or recruitment maneuvers may show the capacity to open additional alveoli. Other ventilator tactics, such as high-frequency, inverse ratio ventilation, or airway pressure release ventilation, have been tried as salvage measures. Prone positioning is often helpful in improving oxygenation, although, as with high-frequency ventilation, no effect on mortality or other relevant clinical outcomes have been demonstrated. Using the dependence of arterial saturation on venous saturation to advantage, and applying measures to raise cardiac output or arterial oxygen content or to reduce oxygen consumption may be useful. Inhaled gases that redistribute blood flow, such as inhaled nitric oxide or prostacyclin, can raise arterial saturation and favor a reduction in oxygen fraction (but these, too, have no demonstrable effect on clinical outcomes). Venovenous extracorporeal membrane oxygenation raises venous oxyhemoglobin saturation and may improve outcomes in severe ARDS.[7] Finally, it is surprising how often simply turning the fraction of inspired oxygen down leads to little deterioration in saturation (recall that large shunts are relatively refractory to oxygen, both increased and decreased). This, combined with lowering the target for arterial saturation (eg, there is little reason to think that maintaining an arterial oxygen saturation at 0.92 is superior to 0.88), often allows a prompt reduction in the fraction of inspired oxygen.

Worsening Hypercapnia

A rising P_{CO_2} can be explained by referring to the determinants of the arterial P_{CO_2}, including the carbon dioxide production rate, the dead space fraction, and the minute ventilation. An increase in the P_{CO_2} implies that more carbon dioxide is being produced (eg, fever, seizure, overfeeding), the dead space fraction is up (eg, higher PEEP, hypovolemia, pulmonary embolism), or minute ventilation has fallen (lower tidal volume or rate). Examining trends in ventilator parameters, hemodynamic values, and other vital sign and laboratory data may be useful. Sometimes simply increasing the minute ventilation is sufficient to normalize the P_{CO_2} while the underlying problem is addressed. However, many mechanically ventilated patients with hypercapnia have such profound lung derangement that raising the minute ventilation may be ineffective (for example, when the consequence is to raise autoPEEP, boosting the dead space fraction, and preventing any fall in P_{CO_2}) or harmful (as when the acutely injured lung is overstretched or the dynamically inflated lung is further hyperinflated).

At the same time, it is worth emphasizing that hypercapnia is generally well tolerated in the adequately sedated patient.[8] Multiple studies examining permissive hypercapnia have shown that the physiologic effects are modest and generally transient. In particular, blood pressure and cardiac output are not depressed by hypercapnia. The tolerability of elevated P_{CO_2} is less certain when there is active myocardial ischemia, severe pulmonary hypertension, raised intracranial pressure, or pregnancy.

Evaluation of the patient with worsening hypercapnia should focus on the endotracheal tube, ventilator settings, central drive to breathe, evidence of new or worsened systemic inflammation, radiographic changes, magnitude of autoPEEP, intravascular volume state, and end-tidal carbon dioxide trend.

High Levels of AutoPEEP

Persistent end-expiratory flow signals the presence of autoPEEP. In passive patients, the magnitude of autoPEEP can be quantitated with an end-expiratory port occlusion. The maneuver closes the inspiratory and expiratory limbs of the ventilator at the time that the subsequent breath is due, allowing equilibration of pressure between lung and ventilator, a pressure that can be displayed graphically.

High levels of autoPEEP are potentially harmful because they risk hypoperfusion[9] and pneumothorax. Further, a major component of the work of breathing in the severely obstructed patient is the inspiratory threshold load presented by autoPEEP. This load can be counterbalanced by externally applied PEEP, explaining the dramatic benefit of continuous positive airway pressure in patients with severe airflow obstruction. It is also appropriate to use PEEP in the intubated and ventilated patient with status asthmaticus (or COPD) for the same reason. As long as the PEEP is set at less than about 85% of the autoPEEP, there is little to fear from further hyperinflation. Because most ventilated patients tend to trigger the ventilator, PEEP should nearly always be used. This is especially true when sedation (or paralysis) is reduced.

When autoPEEP is high, the two most important approaches to reducing it are to ease the airflow obstruction and to limit the minute ventilation. For an average-sized adult, an initial expired volume (V_E) of roughly 8 L/min (achieved by a tidal volume [V_T] between 5 and 7 mL/kg and a respiratory rate of 14 breaths/min), combined with an inspiratory flow rate of 60 L/min, is a good starting point. After making these settings (and assuming the patient is adequately sedated), the degree of lung hyperinflation should be measured. Reasonable targets are autoPEEP < 15 cm H_2O and plateau airway pressure < 30 cm H_2O. Occasionally, patients can be severely hyperinflated with low measured autoPEEP because of completely trapped, noncommunicating areas of obstructed gas.[10] Once the minute ventilation is set at a reasonable level, such as 8 L/min, further reductions in rate have only a very small effect on autoPEEP.[11]

Heliox may also be administered during mechanical ventilation and is effective in reducing autoPEEP, but many practical problems arise. The flow meters on the ventilator that measure V_T are dependent on gas density and

will underestimate V_T during heliox administration unless recalibrated. Thus, the benefit of diminished airway resistance may be confounded by adjustments of V_E upward if that phenomenon is not appreciated. Before a heliox ventilator is used, it should be validated in a lung model by the respiratory therapists and physicians who will use it clinically. A useful device is a simple spirometer on the expiratory port of the ventilator to confirm V_T during adjustments of heliox.

As long as inspiratory flow is not unusually low (or decelerating), there is little to be gained by increasing it further. To illustrate this point, consider the consequences of the following ventilator settings: V_T, 500 mL; respiratory rate, 15 breaths/min; and peak inspiratory flow rate, 60 L/min. These settings result in an inspiratory time of 0.5 s and an expiratory time of 3.5 s. Raising the inspiratory flow rate dramatically (and unrealistically) to 120 L/min shortens the inspiratory time to 0.25 s but increases expiratory time only from 3.5 to 3.75 s, a trivial gain. On the other hand, simply lowering the respiratory rate from 15 to 14 (without changing the flow rate or V_T) increases expiratory time to 3.8 s. When the goal is to reduce hyperinflation, it is generally more effective to reduce V_E than it is to change any other ventilator setting.

Hypotension Following Intubation

Postintubation hypotension in patients with severe airflow obstruction is extremely common. Causative factors are pulmonary hyperinflation, hypovolemia, and sedation. The degree of pulmonary hyperinflation is directly proportional to minute ventilation (V_E). Dangerous levels of pulmonary hyperinflation can develop if patients are bagged excessively in a misguided attempt to stabilize or resuscitate. With severe airflow obstruction, delivery of even a normal V_E may impair the circulation. Clinically, inspired breaths become difficult to deliver (because there is essentially no room for additional air), breath sounds are diminished, and neck veins are distended. Systemic blood pressure and pulse pressure fall, and the pulse rate increases. In the same patients, hypovolemia related to previous dehydration, sedation, and muscle relaxation all act to decrease mean systemic vascular pressure, further decreasing venous return to the heart. This pathophysiology can be demonstrated by ceasing ventilation temporarily: mean intrathoracic pressure falls, and, within 30 to 60 s, blood pressure rises and heart rate falls. The treatment is augmentation of intravascular volume, combined with strategies to minimize lung hyperinflation (see above). Note that the clinical features of pulmonary hyperinflation mimic those of tension pneumothorax, and, indeed, if cessation of ventilation does not remedy the hypotension, pneumothorax should be excluded (such as with rapid bedside ultrasound).

Nothing to Disclose

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Chapter 21. Poisonings and Overdoses

Janice L. Zimmerman, MD, FCCP

Objectives:

- Describe physical examination and laboratory findings in patients with intoxications.
- Outline measures for the resuscitation and stabilization of the overdose patient.
- Discuss the use of interventions to decrease absorption of toxins and enhance elimination.
- Review indicated interventions and antidotes for poisons and substances of abuse likely to be encountered in ICU patients.

Key words: antidotes; overdose; poisoning; substance abuse; toxicology

Synopsis:

Intentional and accidental poisonings and substance abuse can result in the need for critical care. In many cases, only supportive care is necessary until the effects of the toxin diminish. However, some poisonings require specific antidotes or interventions and intensive supportive care to decrease morbidity and mortality. Vital signs and the neurological examination findings are particularly helpful in the initial evaluation of an overdose patient and determining a possible diagnosis. The initial management priorities are airway, breathing, and circulation. Although multiple interventions are available to decrease GI toxin absorption, activated charcoal offers the greatest potential benefit if administered within 1 to 2 h following ingestion. Acetaminophen should be considered as a potential ingestant in all overdoses so that *N*-acetylcysteine can be administered in a timely manner if toxic levels are present. Other specific antidotes and interventions should be used as indicated for specific toxins. Poisonings may also occur from herbal medications or dietary supplements through product misuse, contamination of the product, or interaction with other medications.

Intentional and accidental poisonings and substance abuse can result in the need for critical care. In many cases, only supportive care is necessary until the effects of the toxin diminish. However, some poisonings require specific antidotes or interventions and intensive supportive care to decrease morbidity and mortality. General management principles of poisonings and substance abuse that are pertinent to intensive care management are presented, as well as interventions for specific overdoses that the clinician is likely to encounter. Little evidence-based information is available, and current recommendations are based on animal data, volunteer studies, case reports, pharmacologic data, and/or consensus opinion.

Diagnosis

Patients with possible overdose may be asymptomatic or present with life-threatening toxicities. The absence of symptoms on the initial examination does not preclude potential deterioration and the development of more severe symptoms. Life-threatening toxicities that often require intensive management include coma, seizures, respiratory depression, hypoxemia, arrhythmias, hypotension, hypertension, and metabolic acidosis.

The diagnosis of the exact substance involved in an overdose or poisoning does not take precedence over the resuscitation and stabilization of the patient (see "Management"). However, the initial evaluation of the patient may identify characteristic signs and symptoms that will enable the physician to make a specific diagnosis quickly and/or assist in directing optimal therapy.

History

Accurate information regarding the substance or substances ingested, the quantity taken, and the time of ingestion should be collected, if possible. Establishing the time of ingestion is important to assess the significance of presenting symptoms. It is also helpful to identify the form of the drug involved (ie, regular or sustained-release) and the chronicity of use. Drugs that may be accessible to the patient should be determined.

Physical Examination

Vital signs and the neurological examination findings are particularly helpful in the initial evaluation of an overdose patient. Tables 1 and 2 list drugs and toxins that are associated with

Table 1—*Clues to Diagnosis in Poisoning: Vital Signs*

Vital Sign	Increased	Decreased
BP	Amphetamines/cocaine	Antihypertensives
	Anticholinergics	Cyanide
	Caffeine	Cyclic antidepressants
	Ephedrine	Ethanol
	Sympathomimetics	Narcotics
		Organophosphates/carbamates
		Sedative/hypnotics
Heart rate	Amphetamines/cocaine	Barbiturates
	Anticholinergics	β-Blockers
	Carbon monoxide	Calcium channel blockers
	Cyanide	Cholinergics
	Cyclic antidepressants	Digitalis glycosides
	Ethanol	GHB
	Sympathomimetics	Sedative/hypnotics
	Theophylline	Organophosphates/carbamates
Respiratory rate	Amphetamines	Alcohols
	Anticholinergics	Barbiturates
	Carbon monoxide	GHB
	Hydrocarbons	Narcotics
	Organophosphates/carbamates	Sedative/hypnotics
	Salicylates	
	Theophylline	
Temperature	Amphetamines/cocaine	Barbiturates
	Anticholinergics	Carbon monoxide
	β-Blockers	Ethanol
	Cyclic antidepressants	Hypoglycemic agents
	Salicylates	Narcotics
	Sympathomimetics	Sedative/hypnotics
	Theophylline	

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Table 2—*Clues to Diagnosis in Poisoning: Neurologic Findings*

Neurologic Findings	Substances Ingested
Pupils pinpoint (miotic)	Barbiturates (late)
	Cholinergics
	Narcotics (except meperidine)
	Organophosphates
	Phenothiazine
	Phencyclidine
Pupils dilated (mydriatic)	Alcohol
	Anticholinergics
	Antihistamines
	Barbiturates
	Ethanol
	Phenytoin
	Sympathomimetics
Nystagmus	Alcohols
	Carbamazepine
	Carbon monoxide
	Phencyclidine
	Phenytoin
	Sedative/hypnotics
Seizures	Amphetamines
	Anticholinergics
	Carbon monoxide
	Cocaine
	Cyanide
	Cyclic antidepressants
	GHB
	Isoniazid
	Lithium
	Organophosphates
	Phencyclidine
	Phenothiazines
	Salicylates
	Strychnine
	Theophylline

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changes in vital signs and neurological alterations. BP may not be helpful in determining the toxin because of other systemic influences. Tachypnea is also fairly nonspecific and may be a compensatory response to metabolic acidosis or hypoxemia. Although the initial neurological examination may demonstrate abnormalities, it is also important to follow changes in neurologic function over time. The evaluation should include an assessment of level of consciousness, pupillary reactivity, ocular movements, and motor responses. Hypoactive bowel sounds may be associated with narcotic or anticholinergic agents, and hyperactive bowel sounds may result from poisoning with organophosphates.

Toxidromes

While the exact drug may not be known, findings on physical examination may enable the physician to categorize the poisoning into a classic "toxidrome," or clinical syndrome of poisoning. This classification may allow the physician to direct the diagnostic evaluation and define appropriate therapy (Table 3).

Laboratory Examination

Laboratory data can supplement the history and physical examination findings. An arterial blood gas measurement will detect hypoxemia,

Table 3—*Toxidromes*

Poisoning Syndrome	Symptoms
Cholinergic (SLUDGE syndrome)	Salivation, bronchorrhea, lacrimation, urination, defecation, GI upset, and emesis; also, bradycardia, fasciculations, confusion, and miosis
Anticholinergic	Dry skin, hyperthermia, mydriasis, tachycardia, delirium, thirst, and urinary retention
Sympathomimetic	Hypertension, tachycardia, seizures, CNS excitation, mydriasis, and diaphoresis
Narcotic	Miosis, respiratory depression, depressed level of consciousness, hypotension, and hyporeflexia
Sedative/hypnotic	Depressed level of consciousness, respiratory depression, hypotension, and hyporeflexia

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hypercarbia, and significant acid-base disorders. In combination with electrolytes, a significant anion-gap metabolic acidosis may be detected. The detection of an osmolal gap (ie, >10 measured osmolality) through comparison of the measured osmolality with calculated osmolality [(2 × sodium + glucose/18) + (BUN/2.8)] may indicate the presence of methanol, ethanol, ethylene glycol, acetone, isopropyl alcohol, or propylene glycol. An ECG should be obtained in unstable patients and when cardiotoxic drug ingestion is suspected.

Qualitative toxicology screens are performed on urine samples. These tests report only the presence or absence of a substance or class of drugs and are limited in scope. Qualitative toxicology screens are helpful in evaluating coma of unknown cause, distinguishing between toxicosis and psychosis, and (rarely) choosing a specific antidote. Qualitative test results seldom change the initial management of poisoned patients. Quantitative analyses provide serum levels of a substance and may identify toxic levels and/or the need for an antidote. Quantitative levels that may be useful to obtain include those for acetaminophen, carbamazepine, carboxyhemoglobin, ethanol, methanol, ethylene glycol, theophylline, phenytoin, lithium, salicylates, barbiturates, digoxin, valproic acid, and cyclic antidepressants. Cyclic antidepressant levels confirm antidepressant ingestion, but the levels correlate poorly with toxicity.

Management

Resuscitation and Stabilization

The initial management priorities are airway, breathing, and circulation. Intubation may be necessary to support oxygenation and ventilation or to protect the airway. Hypotension from toxins is more commonly due to venous pooling than to myocardial depression and should be initially treated with isotonic fluids, rather than vasopressor agents. Oxygen should be administered to the poisoning victim if an assessment of oxygenation by arterial blood gas measurement or pulse oximetry is not immediately available.

In the patient with a depressed level of consciousness, the following additional interventions should be considered:

- 50% glucose (25 to 50 g IV);
- Thiamine (100 mg IV); and
- Naloxone (0.4 to 2 mg IV), especially with classic findings of miosis and respiratory depression.

Flumazenil administration is not routinely recommended in this situation because of the risk of seizures.

Nonspecific Therapy

After stabilization, nonspecific interventions may be considered to decrease absorption of the toxin from the GI tract or to enhance elimination. GI decontamination can be attempted with gastric-emptying procedures (ie, induced emesis and gastric lavage), adsorption of drugs (ie, activated charcoal), and increasing transit through the GI tract (ie, administration of cathartic agents or whole bowel irrigation).

Induced Emesis: Induced emesis with ipecac is not recommended in adults or children.[1] Ipecac is effective in inducing vomiting but is not necessarily effective in removing toxins. Contraindications to the use of ipecac include hydro-

carbon or corrosive ingestion, absent gag reflex, depressed mental status, a risk for CNS depression or seizures, and pregnancy. Potential complications include aspiration pneumonitis, Mallory-Weiss tear, and protracted emesis that delays the use of activated charcoal.

Gastric Lavage: There are no definite indications for use of gastric lavage due to the lack of confirmed benefit.[2] Current recommendations suggest that gastric lavage should be considered only in cases of life-threatening ingestion when lavage can be instituted within 1 h of ingestion. The airway must be protected in patients with a depressed level of consciousness. Lavage is contraindicated in acid or alkali ingestions because of possible esophageal perforation and in the presence of a severe bleeding diathesis. Complications of lavage include aspiration pneumonitis, esophageal perforation, and cardiovascular instability.

Activated Charcoal: Activated charcoal is the most common intervention used for decreasing absorption of orally ingested poisons. The greatest benefit occurs if charcoal is administered within the first hour after ingestion. The current recommendations for decreasing GI absorption of toxins suggest the use of activated charcoal despite the lack of proven benefit.[3] The appropriate dose of charcoal (1 g/kg) may be administered by an orogastric or nasogastric tube if patient cooperation is limited. Substances not adsorbed by activated charcoal include iron, lithium, cyanide, strong acids or bases, alcohols, and hydrocarbons. The only contraindication to the use of charcoal is known or suspected GI perforation.

Cathartics: Cathartic agents have been routinely administered with charcoal in the past, based on the assumption that they decrease GI transit time, help to limit drug absorption, and serve as an adjunct to charcoal therapy. However, there is no evidence of efficacy.[4] Sorbitol is the most commonly used cathartic. Care must be taken with very young and elderly patients because electrolyte abnormalities can ensue due to diarrhea.

Whole-Bowel Irrigation: Whole-bowel irrigation involves large volumes of polyethylene glycol electrolyte solution administered over time (1 to 2 L/h in adults) to mechanically cleanse the bowel. This method has been suggested for the treatment of ingested substances that are not adsorbed by activated charcoal (eg, iron and lithium), ingestions of sustained-release or enteric-coated products, and ingestions of illicit drug packets.[5] This method is labor intensive and may not be practical for many patients. Evidence of benefit has not been demonstrated. Contraindications to this intervention include ileus, GI obstruction or perforation, hemodynamic instability, and intractable vomiting; CNS or respiratory depression and the inability to cooperate are relative contraindications.

Enhanced Elimination: Measures to increase the elimination of toxic substances attempt to utilize the normal detoxification mechanisms of the liver and kidney. Multiple doses of charcoal for the elimination of drugs with an enterohepatic circulation may have potential utility for selected toxins.[6] This technique may be helpful in poisonings with barbiturates, carbamazepine, quinine, dapsone, and theophylline. Although multiple doses of charcoal have been used in the treatment of poisonings with cyclic antidepressants, digoxin, and phenytoin, proof of effectiveness is lacking. The dosing regimen has not been standardized, but currently not $<$12.5 g/h or an equivalent amount at other intervals is recommended. Smaller doses administered more frequently may decrease the occurrence of vomiting. Repeat doses of charcoal should not contain a cathartic. Adequate gastric emptying must be assured before the administration of a subsequent dose.

Forced diuresis to accelerate the renal excretion of drugs has little clinical effect and may predispose the patient to volume overload. Alkaline diuresis is effective in promoting the elimination of barbiturates, primidone, and salicylates.[7] Sodium bicarbonate (75 to 150 mEq) can be added to 1 L of dextrose 5% in a water solution; the rate of administration should be determined by the patient's ability to handle the fluid load and the maintenance of urine pH at $>$7. Hypokalemia is likely and requires correction to achieve urinary alkalinization. Acidification of urine is not recommended. Dialysis is an invasive method of eliminating toxins and may be considered for life-threatening ingestions

Table 4—*Antidotes and Interventions for Specific Toxins*

Toxin	Antidote or Intervention
Acetaminophen	NAC
Amphetamines	Benzodiazepines
Arsenic/mercury/gold/lead	Dimercaprol
Benzodiazepines	Flumazenil
β-Blocker	Glucagon, calcium, insulin, glucose, and pacing
Calcium channel blocker	Calcium, glucagon, insulin, glucose, and pacing
Carbon monoxide	100% oxygen and hyperbaric oxygen
Coumarin derivatives	Vitamin K1
Cyanide	Nitrites, thiosulfate, and hydroxocobalamin
Cyclic antidepressants	Sodium bicarbonate, hypertonic saline, alpha-agonists
Digoxin	Digoxin-specific Fab fragments
Ethylene glycol	Ethanol, fomepizole
Heparin	Protamine
Oral hypoglycemic agents/insulin	Glucose 50%, somatostatin
Iron	Deferoxamine
Isoniazid	Pyridoxine
Lithium	Hemodialysis
Methanol	Ethanol, fomepizole
Narcotics	Naloxone
Nitrites	Methylene blue
Organophosphates/carbamates	Atropine and pralidoxime
Salicylates	Urinary alkalinization, hemodialysis
Theophylline	Multiple-dose charcoal, hemoperfusion

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involving water-soluble substances of low molecular weight. Substances in drug overdoses for which dialysis may be beneficial include alcohols, amphetamines, phenobarbital, lithium, salicylates, theophylline, and thiocyanate. Hemoperfusion is useful in eliminating the same compounds that are dialyzable and involves the passing of blood through a filtering device that contains charcoal or a synthetic resin as an absorbent. Charcoal hemoperfusion may be helpful in the elimination of carbamazepine, phenobarbital, phenytoin, theophylline, and valproate. Hemodialysis and hemoperfusion are efficient methods of removing poisons but are costly, require trained personnel, and may be associated with complications. The use of continuous arteriovenous or venovenous hemoperfusion in the treatment of poisonings has been reported on a limited basis.

Specific Therapy

Although the management of many toxic exposures involves only the nonspecific therapy outlined above, some toxins have specific interventions or antidotes. Table 4 lists toxins and their respective antidotes. Specific poisonings are discussed in detail below.

Specific Drug Poisonings

Acetaminophen

Intentional and unintentional poisoning with acetaminophen can result in acute liver failure. Patients with unintentional overdoses of acetaminophen often ingest multiple medications containing acetaminophen (especially narcotic/acetaminophen combination drugs) and present later. Appropriate management of acetaminophen ingestions is important to prevent significant toxicity and mortality. Acetaminophen exposure should be considered in all overdose patients, and a level should be obtained $\geq$4 h after ingestion. A dose of $\geq$140 mg of acetaminophen per kilogram in a single ingestion is considered potentially toxic, but factors such as age, nutritional status, tobacco use, chronic liver disease, and acute and chronic alcohol use can alter the propensity for toxicity. For single acute ingestions, the Rumack-Matthew nomogram determines the need for IV or oral *N*-acetylcysteine

(NAC) therapy if the acetaminophen level plots above the "possible hepatic toxicity" line.[8] The oral regimen for NAC therapy includes a loading dose of 140 mg/kg followed by 17 oral maintenance doses of 70 mg/kg administered 4 h apart (68-h regimen). A nasogastric tube may be placed for its administration, and antiemetic therapy is often needed to prevent or control vomiting. If the patient vomits the loading dose or any maintenance dose within 1 h of administration, the dose should be repeated. IV NAC is administered as a loading dose of 150 mg/kg over 1 h, followed by 50 mg/kg infused over 4 h, and then 100 mg/kg infused over 16 h. Anaphylactoid reactions may occur in 14% to 18% of patients with IV NAC administration. NAC serves as a substitute for glutathione, which normally metabolizes toxic metabolites of acetaminophen. Activated charcoal adsorbs acetaminophen and many coingestants. Charcoal interferes only slightly with the effectiveness of oral NAC, and the dose of NAC does not require adjustment. NAC is most effective when administered in the first 8 h following ingestion but is recommended up to 24 h after a significant toxic ingestion. It is also reasonable to administer NAC >24 h after ingestion if toxic levels of acetaminophen are present. The late administration of NAC may also be beneficial in patients with fulminant hepatic failure due to acetaminophen toxicity.

There are no firm guidelines for the administration of NAC in chronic ingestions or multiple ingestions over time. A marker of toxicity that may be useful is the evaluation of aspartate aminotransferase and alanine aminotransferase. If enzyme levels are elevated at the time of presentation (ie, >50 IU/L) or the acetaminophen level is >10 μg/mL (66 μmol/L), a course of NAC should be strongly considered.[9] Treatment is continued until the transaminases are stable or decreasing and the acetaminophen level is <10 μg/mL. The local poison control center should be contacted for other NAC regimens. Recommendations for the management of extended-release forms of acetaminophen include the determination of acetaminophen levels 4 and 8 h after ingestion and the initiation of NAC therapy if either level is potentially toxic.

Alcohols

Ethylene glycol and methanol ingestions can result in significant morbidity and mortality. Clinical manifestations, metabolic derangements, and management are similar for the ingestion of both alcohols.

Cardiopulmonary and neurologic symptoms may include pulmonary edema, hypotension, ataxia, seizures, and coma. Abdominal pain, nausea, and vomiting are frequent. Visual disturbances (eg, blurred vision, photophobia, blindness, and optic disk hyperemia) suggest methanol toxicity, and the finding of urinary calcium oxalate crystals may indicate ethylene glycol ingestion. Significant symptoms may be delayed for up to 24 h after methanol ingestion. Both ingestions are classically characterized by an anion-gap metabolic acidosis and an osmolal gap. An anion-gap metabolic acidosis may not be present initially if sufficient time has not elapsed for metabolism of the alcohol to acids or if high levels of ethanol prevent the metabolism of other alcohols. An osmolal gap may not be present in late presentations if the alcohol has been completely metabolized to acid. Many institutions are unable to provide blood levels of methanol or ethylene glycol in a timely manner, and treatment is initiated based on the clinical history and acid-base status.

Treatment of ethylene glycol and methanol ingestion includes the following[10]:

1. Supportive care
   - Maintenance of a secure airway;
   - Consideration of gastric lavage within 1 h of ingestion;
   - Activated charcoal administration, if other substances have potentially been ingested (activated charcoal does not adsorb alcohols);
   - 50% glucose if indicated;
   - Thiamine, folate, and multivitamin supplement;
   - IV fluids to maintain urine output.
2. Inhibition of alcohol metabolism
   - Ethanol orally or intravenously to maintain blood levels at 100 to 150 mg/dL (ethanol is preferentially metabolized by alcohol dehydrogenase). A loading dose is followed by a

maintenance infusion with dosage adjustments during hemodialysis; or

- Fomepizole, a competitive inhibitor of alcohol dehydrogenase that does not cause CNS depression. Fomepizole is administered as a 15-mg/kg loading dose, followed by 10 mg/kg q12h for four doses and then 15 mg/kg q12h until the serum alcohol level has decreased and the patient is asymptomatic with a normal acid-base status. Fomepizole may be preferred over ethanol due to ease of use and decrease in medication errors.[11]

3. Removal of alcohol and metabolites
   - Folinic acid (leucovorin) or folic acid 50 mg can be administered q4-6h for 24 h in cases of methanol ingestion to provide the cofactor for formic acid elimination;
   - Hemodialysis for visual impairment, renal failure, pulmonary edema, significant or refractory acidosis, a methanol or ethylene glycol level of >25 mg/dL.

Isopropyl alcohol is more potent than ethanol and results in similar manifestations at lower doses. The intoxication of hospitalized patients by the ingestion of hand sanitizers that contain isopropyl alcohol in concentrations of >60% has been reported. Isopropyl alcohol ingestions are characterized by an osmolal gap and ketonemia/ketonuria but no metabolic acidosis. Treatment is supportive and may require intubation and mechanical ventilation for the treatment of respiratory depression. Hemodialysis is reserved for evidence of hypoperfusion and failure to respond to supportive therapy.

Propylene glycol is another alcohol that can cause toxicity in patients receiving high doses of IV medications that contain propylene glycol as a diluent. Medications that include this diluent are lorazepam, diazepam, etomidate, phenobarbital, pentobarbital, phenytoin, esmolol, and nitroglycerin. Propylene glycol toxicity is most commonly observed in the ICU with administration of IV lorazepam.[12,13] Laboratory findings in propylene glycol accumulation are anion-gap metabolic acidosis and increased osmolal gap. An elevated osmolal gap correlates with propylene glycol accumulation. Toxicities include renal dysfunction, hemolysis, cardiac arrhythmias, seizures, and CNS depression or agitation. Doses of lorazepam that exceed 0.1 mg/kg/h, and renal or hepatic insufficiency may contribute to the development of toxicity. Although toxicity is more common after longer durations of lorazepam infusion (>3 days), toxicity has occurred with short-term, high-dose use. Management includes discontinuation of lorazepam infusion and use of another agent that does not contain propylene glycol. Hemodialysis removes propylene glycol but is usually considered only when severe renal dysfunction develops.

Amphetamines/Methamphetamines

Amphetamines, methamphetamines, and related agents cause the release of catecholamines, which results in a sympathomimetic toxidrome that is characterized by tachycardia, hyperthermia, agitation, hypertension, and mydriasis. Hallucinations (visual and tactile) and acute psychosis are frequently observed. Acute adverse consequences include myocardial ischemia and arrhythmias, seizures, intracranial hemorrhage, stroke, rhabdomyolysis, renal failure, necrotizing vasculitis, and death.[14,15] The long-term use of these drugs can result in dilated cardiomyopathy.

Methamphetamine hydrochloride in a crystalline form called "ice," "crank," or "crystal" is popular in this class of drugs. It can be orally ingested, smoked, insufflated nasally, or injected intravenously. An amphetamine-like drug, 3-4-methylenedioxymethamphetamine is a designer drug that is associated with "rave" parties. It is commonly known as "ecstasy," "XTC," "E," and "MDMA," and acts as a stimulant and hallucinogen. It increases the release of serotonin and inhibits serotonin reuptake in the brain.[16] Bruxism and jaw clenching are clues to the use of ecstasy. Complications are usually a result of drug effects and nonstop physical activity. Hyponatremia and liver injury progressing to fulminant failure have also been reported.

The management of amphetamine intoxication is primarily supportive. Gastric lavage has little role, since absorption after ingestion is usually complete at the time of presentation. The patient should be carefully assessed for complications, including measuring core temperature, obtaining an ECG, and evaluating laboratory data for evidence of renal dysfunction and

rhabdomyolysis. IV hydration for possible rhabdomyolysis is warranted in individuals with known exertional activities pending the measurement of creatine phosphokinase levels. Benzodiazepines, often in high doses, are useful for the control of agitation.

Benzodiazepines

Benzodiazepine overdoses rarely result in death unless other sedating drugs (eg, alcohol or narcotics) are also ingested. Overdose results in a typical sedative-hypnotic toxidrome that is characterized by a depressed level of consciousness, respiratory depression, hyporeflexia, and potentially hypotension and bradycardia. Alprazolam is one of the most common benzodiazepines found in overdose cases and may result in greater toxicity.[17] Flunitrazepam is a potent illegal benzodiazepine that has been associated with rape. It may not be detected by most urine drug screens.

Benzodiazepine ingestions should be managed according to the clinical presentation of the patient. Activated charcoal is the primary method of GI decontamination for recent ingestion. Supportive care with intubation and mechanical ventilation may be needed for patients with significant toxicity. Hypotension should be initially treated with volume infusion. A benzodiazepine-receptor antagonist, flumazenil, is available as a diagnostic tool and for adjunctive treatment.[18] Flumazenil should not be considered a substitute for intubation in patients with significant respiratory depression. Its use is contraindicated in patients with suspected cyclic antidepressant overdoses and in patients who are physically dependent on benzodiazepines because of the risk of seizures. The initial dose of flumazenil is 0.2 mg over an interval of 30 s, followed by doses of 0.3 and 0.5 mg every minute up to a maximum cumulative dose of 3 mg. A flumazenil dose >1 mg is usually not required. Resedation is likely due to the short half-life of flumazenil (0.7 to 1.3 h) compared with benzodiazepines.

β-Blockers

β-Adrenergic blockers produce toxicity primarily through hypotension and bradycardia, although a depressed level of consciousness may occur with lipid-soluble agents (eg, propranolol, timolol, metoprolol, and acebutolol). Hypotension usually results from negative inotropic effects rather than bradycardia. Glucagon is considered to be the initial antidote of choice for toxicity because it produces chronotropic and inotropic effects and does not act via β-receptors.[19,20] An initial dose of 2 to 5 mg of glucagon is given intravenously, and an infusion of 2 to 10 mg/h can be initiated, adjusted for desired clinical effects, and then tapered over 12 h as indicated. The goal of treatment is an improvement in BP and perfusion rather than an increase in heart rate. Calcium chloride 10% (1 to 3 g) may be effective in reversing hypotension. Transcutaneous pacing and transvenous pacing may be considered in patients who are refractory to treatment with glucagon, although an increase in heart rate may not improve BP. Additional drugs that have had variable efficacy in β-blocker overdoses include atropine, epinephrine, isoproterenol, and dopamine. In some cases, therapy with insulin euglycemia (see below for dosing) has been reported to be beneficial.[21] Treatment with phosphodiesterase inhibitors such as milrinone, intra-aortic balloon pump, or cardiopulmonary bypass may be considered for refractory cases.

Calcium Channel Blockers

A diagnosis of calcium channel blocker overdose should be considered in the hypotensive, bradycardic patient, particularly if there is access to antihypertensive agents. In the presence of hemodynamic instability, 10 mL of 10% calcium chloride should be administered intravenously. Calcium is effective in reversing negative inotropic effects and conduction abnormalities in approximately 50% of overdoses. Higher doses of calcium and continuous infusions may be required for beneficial effects, and ionized calcium levels should be monitored in these patients. As in β-blocker overdoses, glucagon therapy may have beneficial effects.[20] Transcutaneous and transvenous pacing are additional options in refractory cases. Successful treatment has also been reported with amrinone and

insulin euglycemia (insulin, 0.1 to 10 U/kg/h; and glucose, 10 to 75 g/h).[21]

Carbon Monoxide

Carbon monoxide is a colorless, odorless gas that has 240 times greater affinity for hemoglobin than oxygen. Carboxyhemoglobin reduces the oxygen-carrying capacity and shifts the oxyhemoglobin dissociation curve to the left. Carbon monoxide also exerts direct cellular toxic effects. The clinical manifestations of carbon monoxide poisoning are nonspecific. The most common findings are headache, dizziness, and nausea; more severe exposure can result in chest pain, disorientation, seizures, coma, dyspnea, weakness, arrhythmias, and hypotension.[22] Although the diagnosis of carbon monoxide poisoning is confirmed by an increased venous or arterial carboxyhemoglobin level, decisions for aggressive therapy with 100% oxygen should be based primarily on a clinical history that is suggestive of exposure. High-flow oxygen therapy or intubation with the administration of 100% oxygen should be initiated as soon as possible while confirmatory tests are performed. An ECG, chest radiograph, and arterial blood gas measurement should be obtained to assess the severity of toxicity. The finding of metabolic acidosis implies significant exposure with inadequate oxygen availability at the tissue level. The use of hyperbaric oxygen to treat carbon monoxide poisoning is debated but may be considered for patients with a depressed level of consciousness, loss of consciousness, neurologic findings other than headache, cardiac ischemia or arrhythmia, carboxyhemoglobin level of >25% to 40%, or persistent symptoms after normobaric oxygen treatment for 4 to 6 h.[22,23] Hyperbaric oxygen may decrease the incidence of postexposure cognitive deficits.

Cocaine

Significant morbidity and mortality are associated with cocaine use by all routes, including nasal insufflation, IV administration, smoking, and oral ingestion. Toxicities include intracranial hemorrhage (subarachnoid and intraparenchymal), stroke, seizures, noncardiogenic pulmonary edema, arrhythmias, hypertension, myocardial ischemia, barotrauma, bronchospasm, bowel ischemia, hyperthermia, and rhabdomyolysis.[24,25] Cocaine supplies have recently been contaminated with levamisole, an antihelminthic agent used in veterinary medicine, which has been linked to the development of agranulocytosis.[26] Agranulocytosis resolves when drug use is discontinued. Retiform purpura and skin necrosis secondary to thrombotic vasculopathy have also been linked to cocaine contaminated with levamisole.[27] These potential morbidities should be considered in any critically ill cocaine abuser, and treatment should be initiated as indicated. Chest pain thought to be ischemic usually responds to nitroglycerin and/or benzodiazepines. Aspirin should be administered. Phentolamine and calcium channel blockers are considered to be second-line agents for the treatment of chest pain but are rarely needed.[28] It may be appropriate to avoid the administration of β-blockers in patients manifesting acute sympathomimetic findings, but the benefits of these agents should be considered in patients with ongoing myocardial ischemia.[29] Thrombolysis for myocardial infarction should be considered only when other interventions have failed and immediate angiography and angioplasty are not available. In patients with severe hypertension, labetalol may be considered because it has both α-adrenergic and β-adrenergic blocking properties. In most cases, IV fluid hydration should be instituted until rhabdomyolysis can be excluded. The risk of rhabdomyolysis is enhanced by high environmental temperatures and increased physical activity. The agitation and combativeness frequently associated with cocaine use can usually be controlled with benzodiazepines. Neuroleptics such as haloperidol should be administered cautiously for psychotic symptoms refractory to benzodiazepines because they may lower the seizure threshold.

Cyanide

Cyanide exposure is rare but may occur in occupational settings involving metal extraction, electroplating, chemical synthesis, and firefighting. Cyanide inhibits cytochrome oxidase, which halts oxidative phosphorylation. Metabolic acidosis and impaired oxygen consumption result.

Symptoms include nausea and vomiting, agitation, and tachycardia. Serious poisonings can result in seizures, coma, apnea, hypotension, and arrhythmias. Additional complications include rhabdomyolysis, hepatic necrosis, and ARDS. Diagnosis may be difficult in the absence of an exposure history. A cyanide antidote kit is used for management, including the following:

- Amyl nitrite pearls are an immediate source of nitrite to induce methemoglobinemia. Methemoglobin has a higher affinity for cyanide than cytochrome oxidase;
- IV sodium nitrite to induce methemoglobinemia; and
- IV sodium thiosulfate enhances conversion of cyanide to thiocyanate, which is excreted by the kidneys.

Hydroxocobalamin has also been used for cyanide poisoning and relies on the formation of nontoxic cyanocobalamin (vitamin B12).[30] Mixed evidence exists for the use of therapy with hyperbaric oxygen in patients with cyanide poisoning.

Cyclic Antidepressants

Deaths due to overdose with cyclic antidepressants have declined because of the increasing use of safer antidepressants. Toxicities include arrhythmias, seizures, depressed level of consciousness, and hypotension. Life-threatening events usually occur within the first 6 h of hospitalization; most often, they occur within 2 h of presentation. Serum levels may confirm ingestion but do not correlate with toxicity. Altered mental status is the best predictor of a significant ingestion and the risk of complications. Cyclic antidepressants slow sodium influx into myocardial cells, resulting in intraventricular conduction delays, wide complex arrhythmias, and negative inotropy. The ECG findings may be normal in patients with significant ingestions or may demonstrate a QRS complex of >0.10 s or amplitude of the terminal R wave in lead aVR of ≥ 3 mm.[31] Management includes the following measures:

- Maintain a secure airway;
- Stabilize vital signs with isotonic fluids initially for hypotension and tachycardia;
- ECG monitoring;
- Consideration of gastric lavage if ingestion occurred within 1 h of presentation;
- Activated charcoal administration;
- Alkalinization of blood and sodium loading with sodium bicarbonate to a pH of 7.45 to 7.55 for prolonged QRS complex or wide complex arrhythmias.[32] If effective, maintain an infusion for 4 to 6 h and then taper;
- $MgSO_4$ for treatment of torsades de pointes;
- Benzodiazepines for treatment of seizures; and
- Norepinephrine or phenylephrine for the treatment of refractory hypotension rather than dopamine.

Sodium bicarbonate uncouples the cyclic antidepressant from the myocardial sodium channels, and alkalinization therapy with bicarbonate may be superior to hyperventilation. The administration of hypertonic saline solution has been reported to be effective in the treatment of patients with cardiotoxicity refractory to sodium bicarbonate. Bicarbonate may also be beneficial for hypotension associated with myocardial depression that is unresponsive to other interventions. Physostigmine is not indicated in patients with cyclic antidepressant overdoses.

γ-Hydroxybutyrate

γ-Hydroxybutyrate (GHB) is a naturally occurring metabolite of γ-aminobutyric acid, which was banned in 1991 due to reported toxicities. The clinical effects of GHB ingestion may include hypothermia, loss of consciousness, coma, respiratory depression (including arrest), seizurelike activity, bradycardia, hypotension, and death.[33] The concomitant use of alcohol results in synergistic CNS and respiratory effects. More recently, γ-butyrolactone, 1,4-butanediol, and γ-hydroxyvalerate, which are precursors of GHB, have been abused with resultant manifestations similar to those of GHB. Treatment with activated charcoal offers little benefit because of the rapid absorption of these substances. Although patients usually recover spontaneously in 2 to 96 h, supportive therapy with airway protection and mechanical ventilation may be necessary. The use of physostigmine to reverse CNS effects is not recommended. A GHB withdrawal syndrome of

agitation and delirium has been reported in high-dose, frequent abusers.[34]

Isoniazid

Isoniazid toxicity produces seizures (often intractable), an anion-gap metabolic acidosis, coma, and hepatic toxicity. The treatment of choice is intensive supportive care and the use of pyridoxine (vitamin B6, 5 g IV or a dose equivalent to the amount of isoniazid ingested). Treatment with hemoperfusion or hemodialysis may be considered, particularly in patients with renal insufficiency.

Lithium

Neurologic abnormalities are the major manifestation of acute, acute on chronic, and chronic lithium toxicity. CNS manifestations include lethargy, dysarthria, delirium, seizures, and coma. Arrhythmias and symptoms of GI distress and polyuria and polydipsia due to urine concentrating defects may be present. A decreased anion gap is suggestive of a severely elevated lithium level. Patients with a history of chronic ingestion of lithium are more prone to toxic effects. The serum lithium level should be assessed at presentation and 2 h later to assess for increasing concentration. Serum lithium levels greater than 2.5 mmol/L in chronic ingestions and greater than 4 mmol/L in acute ingestions are potentially life-threatening, but lithium levels may not correlate with symptoms. Lithium is not adsorbed by charcoal. Volume resuscitation with isotonic fluids should be aimed at restoring adequate urine output, but forced diuresis is not effective in enhancing lithium excretion. Therapy with diuretics can worsen toxicity and should be avoided. Hemodialysis is indicated in life-threatening cases of toxicity, which may include renal dysfunction, severe neurologic dysfunction, volume overload or levels of $\geq$4 mmol/L in patients with short-term ingestion or $\geq$2.5 mmol/L in patients with chronic ingestion. The lithium level, duration of exposure, and severity of clinical symptoms should be balanced against the risks of hemodialysis.[35] Redistribution between intracellular and extracellular compartments may result in a rebound increase in lithium level 6 to 8 h after dialysis. Improvement in neurologic status lags behind the decrease in serum lithium level. Continuous venovenous hemodiafiltration has also been used to remove lithium and may be associated with less rebound.[36] Treatment with sodium polystyrene sulfonate has been suggested to decrease lithium absorption, but evidence of clinical benefit is lacking, and complications of hypokalemia, hypernatremia, and fluid overload may result.

Narcotics

The classic toxidrome in patients with narcotic overdoses includes depressed level of consciousness, respiratory depression, and miosis. However, manifestations may vary depending on the specific narcotic used and the presence of other drugs or alcohol. Miosis is not seen in patients with propoxyphene and tramadol toxicity. Additional clinical findings may include hypotension, pulmonary edema, bronchospasm (with heroin overdoses), ileus, nausea, vomiting, and pruritus. Methadone abuse has been associated with sudden death. Seizures may be a manifestation of toxicity with propoxyphene. The diagnosis of a narcotic overdose is made by characteristic clinical findings, exposure history, qualitative urine toxicology assay, and response to naloxone. Qualitative urine assays may not detect all narcotic agents (eg, fentanyl).

Naloxone should be used to reverse the morbidity of respiratory depression and depressed level of consciousness that is associated with narcotic overdose. An initial dose of 0.4 to 2 mg should be administered intravenously, with the lower dose for patients known to be addicted and likely to develop acute withdrawal symptoms. Doses of $>$2 mg may be required to reverse the effects of propoxyphene, codeine, pentazocine, methadone, oxycodone, hydrocodone, and fentanyl. Naloxone can be administered at doses up to 10 mg, and occasionally up to 20 mg. Naloxone can also be administered by the IM, sublingual, and endotracheal routes if IV access is not established. Continuous infusion may be necessary because all narcotics have a longer half-life than naloxone. The initial hourly infusion dose should be one half to two thirds of the amount (in milligrams) that was needed to

initially reverse the respiratory depression. Isotonic fluids should be administered for hypotension. Noncardiogenic pulmonary edema may also occur with narcotic overdoses, and it is usually self-limited (24 to 36 h) and managed with supportive care that may require intubation and mechanical ventilation.

Organophosphates/Carbamates/Nerve Gas

Organophosphate and carbamate poisoning producing a cholinergic syndrome is more common in developing countries than in the United States. Some nerve gases (eg, sarin, VX) produce similar toxicity.[37,38] Cholinergic poisoning exerts potential deleterious effects on the following three systems: (1) the muscarinic (parasympathetic) system, inducing bronchorrhea, bradycardia, and salivation, lacrimation, urination, defecation, GI upset, and emesis (ie, the SLUDGE syndrome) (Table 3); (2) the nicotinic autonomic system, resulting in muscle weakness; and (3) the CNS, including confusion, slurred speech, and central respiratory depression. Pulmonary toxicity from bronchorrhea, bronchospasm, and respiratory depression is the primary concern. Both IV atropine and pralidoxime (30 mg/kg bolus followed by an infusion of >8 mg/kg/h, which is recommended by the World Health Organization) are indicated.[38,39] If there are no CNS symptoms, therapy with glycopyrrolate may be substituted for atropine. Atropine does not reverse nicotinic manifestations; therefore, patients with significant respiratory muscle weakness require the use of pralidoxime. Large amounts of atropine may be required, and the initial dose is usually 2 to 4 mg, repeated every 2 to 5 min as needed. A continuous infusion of atropine can be used. The end point of atropinization is the clearing of secretions from the tracheobronchial tree. An intermediate syndrome of respiratory paralysis, bulbar weakness, proximal limb weakness, and decreased reflexes may develop 24 to 96 h after resolution of the cholinergic crisis.

Propofol

Toxicity from propofol administration, propofol infusion syndrome, can be fatal in ICU patients.[40] The clinical features include acute refractory bradycardia progressing to asystole, lactic acidosis, rhabdomyolysis, renal failure, and hyperlipidemia.[41] Although toxicity is usually associated with propofol doses greater than 4 mg/kg/h for longer than 48 h duration, metabolic acidosis can occur within 1 to 4 h after initiation of propofol. Predisposing factors for toxicity include young age, CNS or respiratory conditions, glucocorticoid use, catecholamine use, sepsis, and impaired oxygen delivery. The pathophysiology is hypothesized to be related to mitochondrial utilization of free fatty acids and/or genetic predisposition.

Propofol infusion syndrome can be prevented by early adequate carbohydrate intake (6 to 8 mg/kg/min) to decrease the mobilization of fat stores and to decrease the circulating fatty acid load. Propofol infusions should be limited to doses less than 4 mg/kg/h and no longer than 48 h of infusion to avoid toxicity. Prompt recognition of early signs of toxicity (particularly elevated serum lactate) is essential for successful management. Another clue to possible toxicity is an increase in pressor or inotrope doses when there are no other reasons for the patient's condition to be changing. Management includes discontinuation of propofol and the use of alternative sedative agents. The most effective treatment for severe toxicity is cardiorespiratory support and hemodialysis or hemofiltration to decrease blood levels of metabolic acids and lipids.

Salicylates

Salicylates are found in many over-the-counter preparations. Patients with a history of chronic ingestion of salicylates, rather than acute ingestion, are more likely to develop significant toxicity. Symptoms of salicylate poisoning include tinnitus, nausea and vomiting, and depressed level of consciousness. In addition, fever, an anion-gap metabolic acidosis, coagulopathy, prolonged prothrombin time, transient hepatotoxicity, and noncardiogenic pulmonary edema may be present.[42] The clinical presentation of salicylate toxicity may be mistaken for sepsis. A salicylate level should be measured initially and may need to be repeated to assess for continued

absorption (especially with enteric-coated products). The Done nomogram that is used to estimate the severity of an acute salicylate overdose does not reliably correlate with observed toxicity. Acidemia predisposes the patient to more severe toxicity because more drug crosses the blood-brain barrier. Gastric lavage may be considered for significant ingestions, and activated charcoal should be administered. Alkalinization of the urine (ie, pH $\geq$7.5) is indicated to enhance salicylate excretion if serum levels are $>$35 mg/dL. Supplemental potassium is often needed. Hemodialysis may be indicated with levels of $>$100 mg/dL in acute ingestions, refractory seizures, persistent alteration in mental status, persistent electrolyte abnormalities, volume overload with alkalinization therapy, or refractory acidosis.

Selective Serotonin Reuptake Inhibitors

Poisoning with selective serotonin reuptake inhibitors (SSRIs) is usually less severe than poisoning with cyclic antidepressants. Acute overdoses may result in nausea, vomiting, dizziness, and, less commonly, CNS depression and arrhythmias. There have been reports of cardiac toxicity due to SSRIs responding to the administration of sodium bicarbonate. Therapeutic doses, overdoses of SSRIs alone, or overdoses of SSRIs in combination with other agents can cause serotonin syndrome, which may be life-threatening.[43] This syndrome may be precipitated by the ingestion of SSRIs, monoamine oxidase inhibitors, serotonin precursors (eg, L-tryptophan), lithium, and non-SSRIs (eg, imipramine, meperidine, or trazodone). Clinical manifestations include altered mental status (ie, agitation and coma), autonomic dysfunction (ie, BP fluctuation, hyperthermia, tachycardia, diaphoresis, and diarrhea), and neuromuscular abnormalities (ie, tremor, rigidity, myoclonus, and seizures). The management of an overdose may include administration of activated charcoal. Intensive supportive care may be necessary, including cooling, sedatives, anticonvulsants, and mechanical ventilation. Cyproheptadine (a serotonin antagonist) in varying dose regimens (12 to 32 mg over 24 h) has been most commonly recommended as a treatment option. There is currently no role for the use of bromocriptine or dantrolene. Most cases of serotonin syndrome resolve in 24 to 72 h.

Valproic Acid

Acute and chronic valproic acid (VPA) intoxication can occur. CNS depression is the most common manifestation in an acute overdose and has been reported after IV administration for seizures. Higher drug levels are associated with an increased incidence of coma and respiratory depression requiring intubation.[44] Cerebral edema has been reported 48 to 72 h after ingestion and may be related to hyperammonemia, which can occur in the absence of hepatotoxicity. Massive VPA ingestions can result in refractory hypotension. Pancreatitis has been associated with both chronic ingestion and acute overdose. Metabolic abnormalities include hypernatremia, anion-gap metabolic acidosis, hypocalcemia, and acute renal failure. Serial VPA levels should be obtained due to delayed peak serum levels in patients with overdoses. Ammonia levels should also be measured in patients with an altered level of consciousness. Activated charcoal should be administered if the patient presents early after ingestion. Treatment with whole-bowel irrigation has been proposed, but further studies are needed to determine whether there is any indication for use in patients who have ingested VPA. Although a potential enterohepatic recirculation of the drug suggests that multiple doses of activated charcoal may be beneficial, routine use is not currently recommended. Hemoperfusion, combined hemodialysis-hemoperfusion, or high-flux hemodialysis may be considered in patients with persistent hemodynamic instability or metabolic acidosis.[45] No antidote exists for VPA toxicity. L-carnitine has been proposed for supplementation in patients with VPA toxicity and hyperammonemia but has not been shown to improve outcomes.

Herbal Medicine/Dietary Supplements

Herbal medicines are the most common form of alternative therapy in the United States and can be marketed without testing for safety or

efficacy. Poisoning may result from product misuse, contamination of the product, or interaction with other medications.[46] Cardiac toxicity may result from the use of aconitine and cardiac glycosides. Aconitine or related compounds are common ingredients in Asian herbal medications. Symptoms include paresthesias, hypersalivation, dizziness, nausea, vomiting, diarrhea, and muscle weakness. Sinus bradycardia and ventricular arrhythmias can occur. No antidote is available, but atropine may be considered for the treatment of bradycardia or hypersalivation. Cardiac glycosides or digoxin-like factors can be found in many herbal preparations, particularly teas and laxatives. Manifestations of toxicity are similar to those of digoxin toxicity, with visual disturbances, nausea, vomiting, and arrhythmias. Digoxin levels should be measured but may not correlate with clinical findings because numerous cardiac glycosides will not cross-react in the digoxin immunoassay. With significant toxicity, digoxin-specific antibodies should be administered.

CNS stimulation is characteristic of preparations containing ephedrine and pseudoephedrine, which are often found in products marketed as "herbal ecstasy." A typical sympathomimetic syndrome can result with tachycardia, hypertension, mydriasis, and agitation. Seizures, stroke, myocardial infarction, arrhythmias, liver failure, and death have also been reported. Ephedra-free products have also been associated with cardiovascular toxicity. Supportive care is indicated as in the case of the management of other sympathomimetic syndromes.

Ginkgo biloba has been reported to result in episodes of spontaneous bleeding, including subdural hematomas, which may be due to antiplatelet-activating factor effects. Treatment for bleeding includes supportive care and the administration of blood products as needed. Garlic may also result in bleeding as a result of the inhibition of platelet aggregation, and ginseng has been associated with hypoglycemia. Kava-containing dietary supplements are possibly associated with hepatic failure requiring transplantation. Contaminants found in some products, such as mercury, arsenic, lead, or antihistamines, may cause toxicities.

Relationships Disclosed

The author has disclosed the following relationships: Product/procedure/technique that is considered research and is NOT yet approved for any purpose: glucagon, insulin for beta-blocker and calcium channel blocker overdose; lipid emulsion for overdose. The ACCP Education Committee has reviewed these relationships and resolved any potential conflict of interest.

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Chapter 22. Anemia and RBC Transfusion in the ICU

Karl W. Thomas, MD, FCCP

Objectives:

- Discuss the pathophysiology and causes of anemia in ICU patients.
- Describe the indications and appropriate clinical use of RBC transfusion.
- Describe the positive and negative associations of RBC transfusion with ICU outcomes.
- Discuss the specific risks associated with RBC transfusion, including disease transmission.
- Discuss the components of blood transfusion management and surveillance programs.

Key words: anemia; acute lung injury; blood; erythropoietin; transfusion

Synopsis:

Anemia and RBC transfusion are common in critically ill, surgical, and trauma patients. In the ICU, anemia may occur within the context of exaggerated blood loss through hemorrhage or phlebotomy, intravascular hemolysis, and disordered RBC production. Although anemia has been associated with worse ICU outcomes including length of stay, ventilator days, and mortality, correction of anemia through RBC transfusion has also been associated with these worse outcomes. The most appropriate clinical response to anemia requires systematic evaluation for underlying cause, determination of physiologic status, and careful consideration of transfusion risks. This chapter focuses on the clinical evaluation and management of anemia and RBC transfusion and reviews the pathophysiology, epidemiology, and expected risks and benefits of RBC transfusion in ICU populations.

Epidemiology of Anemia and RBC Transfusion in ICU Patients

Observational studies have demonstrated that one-third of patients admitted to the ICU will have a baseline hemoglobin less than 10 g/dL. Furthermore, two-thirds will have a baseline less than 12 g/dL.[1] By day 3 after admission to an ICU, more than 90% of patients will develop below-normal hemoglobin levels. The average hemoglobin concentration in ICU patients will then show a measurable decline every day until discharge from the ICU. Patients who develop anemia or who have anemia prior to ICU admission are likely to have persistent anemia throughout their entire ICU stay despite treatment with transfusion.[2,3] The occurrence and degree of ICU anemia has a direct relationship with patient outcomes. Anemia and transfusion in critically ill patients consistently correlate with increased ICU mortality, increased ICU length of stay, prolonged mechanical ventilation, severe organ dysfunction, and higher costs.[1,3]

In large, multicenter, observational trials[1,3] conducted in the 1990s and 2000s, one-third to one-half of all patients admitted to an ICU received one or more RBC transfusions. However, at least three factors have contributed to more recent reductions in the rate of RBC transfusion in critically ill patients. First, the 1999 publication of a randomized trial[4] comparing restrictive with liberal transfusion demonstrated no mortality benefit for transfusion at a hemoglobin level of 10 g/dL compared with 7 g/dL. Second, several organizations including critical care professional societies have developed clinical practice guidelines recommending a restrictive approach to transfusion therapy.[5] Third, the proliferation of computerized decision-support and electronic order entry has reduced the rate of unnecessary or inappropriate transfusion.[6] Other factors expected to contribute to lower transfusion rates include increasing recognition of transfusion-related adverse events as well as increased hospital-based monitoring and accountability for transfusion practice mandated by accreditation bodies (see below). Evidence to support the expectation of lower RBC transfusion rate in ICU patients comes from observational studies. A 10-year, single institution observational study in 3,500 patients demonstrated a decrease in transfusion rate from 31% in 1997 to 1998 to 18.5% in 2006 to 2007.[7]

Hemodynamic Pathophysiology and Clinical Manifestations of Anemia

The pathophysiology and cardiovascular effects of anemia are related to reduced oxygen

carrying capacity of the blood. The cardiovascular responses to clinically significant anemia are to maintain the delivery of oxygen (Do_2) to the tissues and organs. Systemic Do_2 is determined by the volume of blood delivered and the content of oxygen in that blood. This relationship can be written with cardiac output (CO) and arterial blood oxygen content (Cao_2) as follows:

$$Do_2 = Cao_2 \times CO$$

The content of oxygen in blood is determined by the following formula:

$$Cao_2 = (1.39 \times [Hgb] \times Sao_2) + (0.003 \times Pao_2)$$

where [Hgb] = hemoglobin concentration, Sao_2 = hemoglobin oxygen saturation, and Pao_2 = partial pressure of oxygen. The systemic oxygen consumption (Vo_2) is the difference between the amount of oxygen delivered in arterial blood minus the amount that is returned to the heart in venous blood. Vo_2 can therefore be represented by the following simplified formulas:

$$Vo_2 = CO \times (Cao_2 - Cvo_2)$$

$$Vo_2 = HR \times SV \times 1.39 \times [Hgb] \times (Sao_2 - Svo_2)$$

where HR = heart rate, SV = stroke volume, and Svo_2 = mixed venous hemoglobin oxygen saturation. This equation predicts that acute compensatory mechanisms for anemia are increased HR and increased extraction of oxygen from arterial blood (leading to lower mixed venous oxygen saturation). Chronic compensation occurs by fluid retention to increase preload and SV as well as stimulation of erythropoietin production to increase Hgb. Hemorrhagic shock can be viewed as a hemodynamic state with inadequate delivery of oxygen to the tissues arising from decreased hemoglobin concentration as well as loss of venous return leading to decreased SV.

Under normal circumstances, the Do_2 in arterial blood is significantly greater than tissue metabolic requirements. Anaerobic metabolism and decreased Vo_2 can occur as the result of low hemoglobin concentration, low hemoglobin oxygen saturation, or inadequate CO. The critical threshold for oxygen delivery is defined as the point below which oxygen delivery is inadequate to sustain normal oxidative metabolism. Critical anemia has been defined as the hemoglobin concentration below which there is a failure of compensatory cardiac and vascular responses to provide adequate tissue oxygenation. Critical anemia therefore depends on both the hemoglobin concentration and the physiologic limitations of the patient's cardiovascular system. In patients with cardiac, vascular, or pulmonary disease, it is likely that critical anemia occurs at higher hemoglobin than in normal subjects. Normal individuals may tolerate decreases in hemoglobin to approximately 5 g/dL.[8] Systemic diseases, such as sepsis, that affect vasoregulation and alter cellular oxidative metabolism, may also disrupt the normal relationship between oxygen delivery and oxygen utilization. Coexisting cardiac dysfunction directly impairs the physiologic compensation for anemia.

Clinical assessment of anemia pathophysiology is based on recognition of the cardiovascular response, markers of systemic oxygen utilization, and assessment of end-organ function. The goal of this clinical evaluation is to determine if the anemia is physiologically compensated or uncompensated and then to consider appropriate therapeutic responses, that is, transfusion vs no transfusion (Fig 1). RBC transfusions should be administered to preserve or augment oxygen delivery. Serum lactate, mixed venous oxygen saturation, and oxygen extraction ratio ($Cao_2 - Cvo_2$)/(Cao_2) are indicators of the adequacy of systemic oxygenation. Organ-specific clinical indicators of anemia include confusion, headaches, fatigue, tachycardia, angina, congestive heart failure, dyspnea, and claudication. Any anemic patient with the presence of these findings that are attributable directly to their anemia should be considered for transfusion. Patients with acute coronary syndromes and massive, ongoing hemorrhage should be considered separately and are managed with a less restrictive transfusion strategy. Patients without indicators of impaired oxygen delivery do not require immediate blood transfusion. Blood should not be used for intravascular volume expansion.

Causes of Anemia in ICU Patients

There are three primary etiologies for anemia: RBC underproduction, extravascular RBC loss, and intravascular RBC destruction. ICU patients

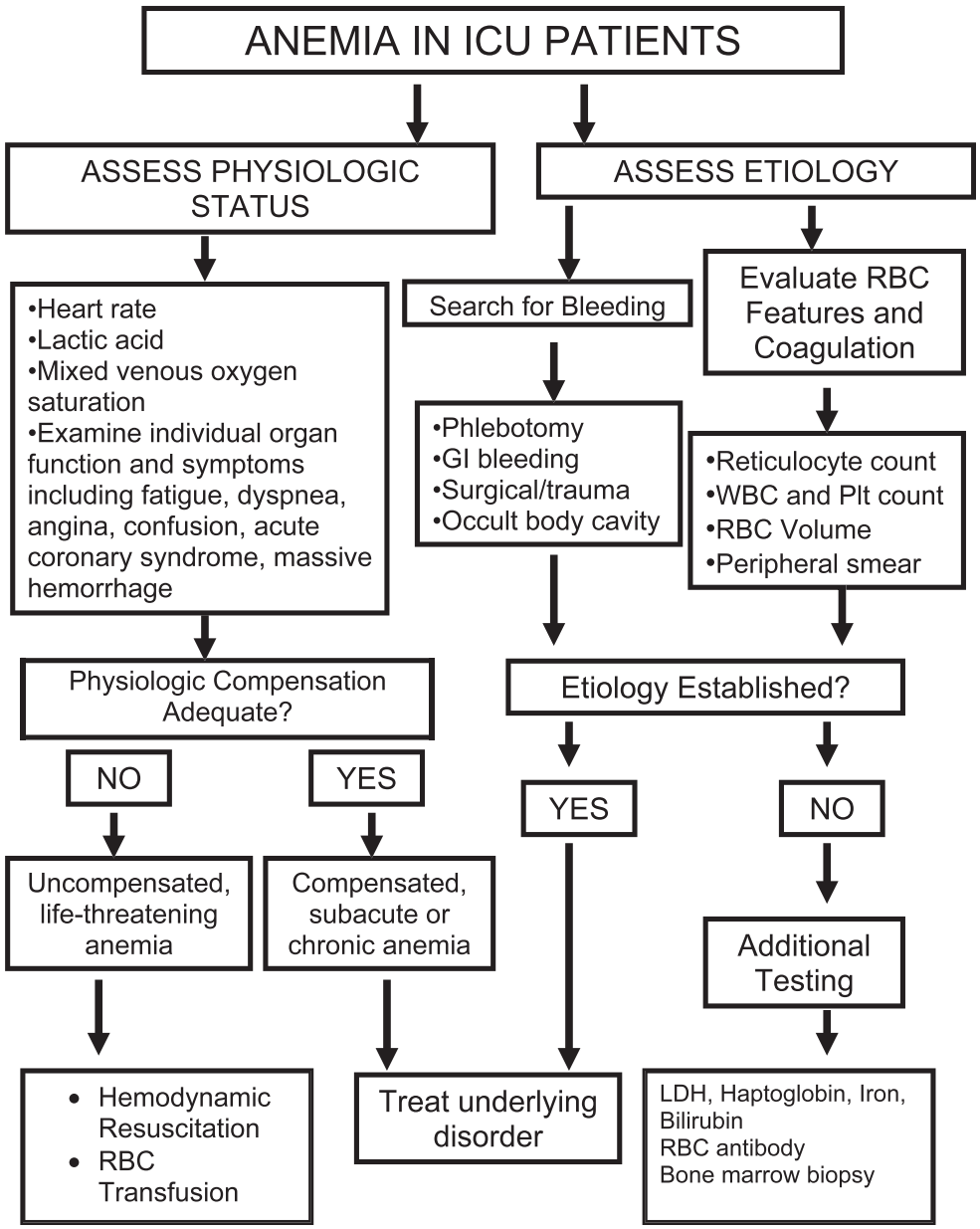

Figure 1. Clinical approach to anemia in the ICU.

are likely to have more than one primary factor contributing to the development of anemia. Table 1 lists the most common causes of anemia in ICU patients.

As the result of diagnostic testing, all ICU patients are subject to high rates of phlebotomy. This results in up to 40 to 70 mL per day average blood losses.[1,9] This high rate of RBC loss may be a significant contributor to ICU anemia. Conditions that predispose to ICU admission and anemia are often the same as conditions that predispose to coagulopathy and extravascular blood loss. This compounds the problem and makes ICU anemia a multifactorial condition.

In acutely ill ICU patients, contributing factors for decreased RBC production include suppressed erythropoietin production, blunted erythropoietin response in the bone marrow, nutritional deficiencies, and abnormal iron metabolism. This state is virtually indistinguishable from the pathophysiologic processes in patients with anemia of chronic disease. The characteristic laboratory features of anemia of chronic disease include low reticulocyte count, reduced serum iron, and reduced total iron binding capacity. It is not unusual for patients with preexisting anemia of chronic disease to develop acute illness, have additional blood loss, and require ICU care.

Table 1—*Causes of Anemia in ICU Patients*

Extravascular RBC loss
Phlebotomy
Trauma or surgery
GI blood loss
Retroperitoneal, thigh, or intrabdominal hemorrhage
Decreased RBC production
Anemia of chronic disease
Iron deficiency
Chronic renal disease
Nutritional deficiencies (B12, folate)
Toxins (alcohol, drugs, chemotherapy, lead)
Endocrinopathy (hypothyroidism, hypopituitarism)
Myelodysplastic syndromes
Intravascular RBC destruction
Immune-mediated hemolysis
Inherited RBC disorders (hemoglobinopathies)
Enzyme disorders (G6PD deficiency)
Microangiopathic hemolytic anemia (DIC)
Infection (malaria)

The etiology of anemia is determined by a systematic search for sources of blood loss and laboratory testing. The laboratory analysis of patients with anemia should include assessment of general hematopoiesis (reticulocyte count, WBC, platelet count) and assessment of RBC features including corpuscular volume and morphology. RBC volume and the peripheral blood smear may contain critical clues to the presence of intravascular hemolysis or hemoglobinopathies and should be routinely obtained in patients with undiagnosed anemia (Table 2). The reticulocyte count is a critical marker of bone marrow function and response.

The majority of ICU patients will have normocytic anemia. The presence of macrocytic or microcytic anemia serves as an important indicator of a primary hematologic disease. Intravascular hemolysis is suggested by the presence of spherocytes, schistocytes, or bite cells. Spherocytes reflect destruction of the RBC membrane by immunoglobulin or complement-mediated disease (eg, autoimmune hemolytic anemia). Schistocytes reflect destruction of RBC in microangiopathic hemolysis (eg, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura), or macroangiopathic hemolysis (eg, turbulent blood flow with shear stress across an endovascular device). Finally, bite cells occur as the result of focal destruction of RBC membranes from oxidant stress or macrophage binding as seen in methhemoglobinemia and G6PD deficiency.

Additional laboratory testing can be performed including measurement of serum ferritin, iron, haptoglobin, lactate dehydrogenase, bilirubin, RBC antibody tests (Coombs test), and bone marrow biopsy. However, these tests are nonspecific and cannot distinguish the major causes of anemia by themselves. Of particular importance is the distinction between anemia related to chronic iron deficiency and anemia secondary to chronic inflammation. Because serum iron, ferritin, transferrin, and iron binding capacity cannot reliably distinguish iron deficiency from anemia of inflammation, several additional tests have been developed to identify iron deficiency. Serum transferrin receptor expression on bone marrow progenitor cells and circulating hematopoietic cells is increased in conditions of iron deficiency. An increased ratio of serum transferrin receptor to the log ferritin concentration has been proposed as a sensitive marker of iron deficiency, although standard assay conditions and laboratory cutoffs have not been well established.[10] In conditions of iron deficiency, zinc may be incorporated into hemoglobin and therefore erythrocyte zinc protoporphyrin can be increased in iron deficiency anemia. Finally, hepcidin is a small peptide that inhibits iron absorption from the GI tract and limits release of intracellular iron stores. Hepcidin is produced in many tissues and cells in response to inflammation and iron overload. Hepcidin is also suppressed in the setting of iron deficiency. Decreased serum hepcidin may therefore be used as a marker of iron deficiency (Table 3).[11]

Clinical Approach and General Guidelines for RBC Transfusion

The decision to give an RBC transfusion should not be made on the basis of hemoglobin concentration or hematocrit value alone. Patients being considered for RBC transfusion require an assessment of the cause of anemia and the physiologic effect of the anemia (Fig 1). The underlying etiology of anemia should be established and treated simultaneously while considering blood transfusion. For virtually all ICU

Table 2—*Morphologic Categorization of Anemia in the ICU*

Anemia Type	RBC Morphology and Clinical Findings
Macrocytic anemias (MCV >100 fL)	
Nutritional deficiency, alcoholism (folate deficiency)	Oval macrocytes, hypersegmented neutrophils
Pernicious anemia	Cobalamin deficiency
Liver disease	Target cells, spur and burr cells
Asplenia/hyposplenism	Acanthocytes, Howell-Jolly bodies, nucleated RBCs
Microcytic anemias (MCV <80 fL)	
Iron deficiency or reduced iron availability	Poikilocytosis, hypochromia, pencil forms
Chronic blood loss	Poikilocytosis, hypochromia
Thalassemia	Basophilic stippling, target cells, polychromasia
Chronic exposure to drugs, toxins	Basophilic stippling
Sideroblastic anemias (hereditary/idiopathic)	Dimorphic cells, reduced reticulocyte count
Normocytic and variable MCV anemias	
Anemia of chronic disease	May have microcytic features; low serum iron and total iron-binding capacity
Acute extravascular blood loss	Clinical and pathophysiologic findings of hemorrhage
Hemolytic anemias	Elevated bilirubin, lactate dehydrogenase, haptoglobin, reticulocyte count
Micro- or macroangiopathic (eg DIC)	RBC fragmentation/schistocytes
Sickle cell anemia	Sickle cells, chronic disorder
Autoimmune hemolytic anemias	Spherocytes, direct antiglobulin test positive
Metabolic defects (eg, G6PD deficiency)	Bite cells
Myelodysplastic syndromes	Round macrocytes, bilobed neutrophils

MCV = mean corpuscular volume.

patients, phlebotomy is a significant contributing factor and every attempt should be made to limit unnecessary blood draws.

The decision to administer a blood transfusion should be approached within the context of three factors:

1. The patient's presenting condition and known comorbidities
2. The adequacy of hemodynamic compensation
3. Whether the underlying condition leading to anemia can be treated and when that treatment can be initiated

Clinical guidelines for RBC transfusion have been developed by professional societies and most recently updated and published in 2009.[5] These guidelines make recommendations for transfusion based on hemoglobin concentration as well as the underlying disease status for critically ill patients. The main guideline recommendations are summarized in Table 4.

RBC Transfusion Best Clinical Evidence

The most robust clinical evidence linking hemoglobin concentration, transfusion trigger, and ICU outcomes comes from the Transfusion Requirements in Critical Care (TRICC) study,[4] which was a prospective randomized trial of restrictive transfusion practice vs liberal transfusion practice. A mixed population of 838 medical and surgical patients with hemoglobin less than 9 g/dL were randomized in this study. Patients assigned to the restrictive group were not transfused until hemoglobin was less than 7 g/dL, and their hemoglobin was maintained from 7.0 to 9.0 g/dL. The liberal transfusion group received transfusion for hemoglobin below 10.0 g/dL and were maintained between 10.0 and 12.0 g/dL. In the overall analysis, there was no difference in 30-day mortality between the two groups. Subgroup analysis demonstrated that patients less than 55 years of age and those with lower APACHE scores had significantly lower mortality with restrictive transfusion. Patients with angina, acute cardiovascular disease, septic shock, and trauma had no mortality difference.[4] These results suggest that the transfusion decisions should account for the underlying comorbid conditions, the severity of illness, and presence of cardiac disease. In general, there does not appear to be a benefit of maintaining hemoglobin levels above 7 to 9 g/dL in the absence of significant heart disease. The restrictive

Table 3—*Serum Markers of Anemia*

	Anemia of Inflammation	Iron Deficiency Anemia	Combination Inflammation and Iron Deficiency
Iron	Decreased	Decreased	Decreased
Transferrin	Decreased	Increased	Normal or decreased
Ferritin	Increased	Decreased	Variable or increased
Serum transferrin receptor	Decreased	Increased	Increased
Erythrocyte zinc protoporphyrin	Normal to mildly increased	Increased	Increased
Hepcidin	Increased	Decreased	Decreased or normal

transfusion strategy appears to be safe and was not associated with higher rates of adverse outcomes. While the hemoglobin level remains an important consideration, the status of the patient should be critical factor in decisions to transfuse.

RBC Transfusion in Patients With Cardiac Disease

For the subset of critically ill patients with acute coronary syndromes and hemodynamically significant cardiac disease, clinical trial evidence is less definitive. A subgroup analysis of cardiovascular disease patients in the TRICC study demonstrated no statistically significant difference in mortality with restrictive compared with liberal transfusion strategy.[12] A retrospective analysis of patients who entered the GUSTO IIb, PURSUIT, and PARAGON B cardiac treatment trials has provided some evidence to suggest no benefit and even harm of transfusion in this patient population. This analysis of 24,000 patients demonstrated that blood transfusion for patients with acute coronary syndromes was associated with higher 30-day mortality for the

Table 4—*Clinical Practice Guidelines for RBC Transfusion*

Clinical Indication	Recommendation
1. Hemorrhagic shock	Early empiric RBC transfusion indicated as component of initial resuscitation.
2. Acute hemorrhage with hemodynamic instability or inadequate oxygen delivery	RBC transfusion may be indicated in patients unresponsive to initial resuscitation to crystalloid infusion; blood lactate may be used to monitor physiologic status and response.
3. Critically ill patients with hemodynamically stable anemia except patients with acute coronary syndromes or unstable angina	A restrictive strategy of RBC transfusion to be administered when hemoglobin value <7 g/dL.
4. Transfusion trigger based on hemoglobin concentration alone	Hemoglobin concentration should not be used alone to determine need for RBC transfusion. Additional considerations should include intravascular volume status, shock, duration and extent of anemia, cardiovascular status, and pulmonary status.
5. Number of RBC transfusions to administer	In the absence of acute hemorrhage or evidence of inadequate tissue oxygenation, RBC transfusion should be administered in single units. Need for multiple transfusions should be assessed with monitoring of clinical response and measurement of posttransfusion hemoglobin concentration.
6. Patients requiring mechanical ventilation	Consider transfusion if hemoglobin value <7 g/dL.
7. Trauma patients who remain critically ill beyond initial resuscitation	Consider transfusion if hemoglobin value <7 g/dL.
8. Stable cardiac disease	Consider transfusion if hemoglobin value <7 g/dL.
9. Acute coronary syndrome patients	RBC transfusion may be beneficial in patients who are anemic with hemoglobin value <8 g/dL on admission.
10. Patients with low tissue oxygen consumption	Transfusion should not be considered as an absolute method to improve tissue oxygen consumption.

Adapted from Napolitano et al.[5]

entire patient group. However, patients who received transfusion were older, had more comorbid illness, and had higher unadjusted 30-day mortality rates. This effect of higher mortality appeared most significant in patients who received transfusion but had baseline hematocrits greater than 25%.[13] In distinction to these results, another retrospective cohort analysis[14] in 78,974 Medicare patients hospitalized with acute myocardial infarction demonstrated a reduced odds of mortality only for patients who received transfusion for baseline hematocrit 33% or lower but an increased mortality for patients transfused with hematocrit greater than 36%. Similarly, a prospective database study[15] in 2,358 patients with acute myocardial infarction demonstrated increased mortality in patents with nadir Hgb >8 g/dL but a decreased mortality in patients with nadir Hgb <8 g/dL.

Although there are many additional observational studies of transfusion in patients with cardiac disease, there are no large, randomized trials for transfusion in patients with acute coronary syndromes or severe cardiac disease. Consensus guidelines have been developed around limited observational trial results. There appears to be no consistent benefit of transfusion for cardiovascular disease patients with Hgb greater than 8 to 10 g/dL. Guidelines state that for patients with stable cardiac disease, consider transfusion when Hgb is less than 7 g/dL; for patients with acute coronary syndromes, transfusion may be beneficial if Hgb is 8 g/dL or less but not at higher levels.[5]

RBC Transfusion and Cardiac Surgery

A prospective, randomized controlled trial[16] comparing a liberal transfusion strategy (maintain hematocrit 30% or greater) with a restrictive strategy (maintain hematocrit 24% or greater) was conducted in 502 consecutive patients who had undergone cardiac surgery to identify the risks and benefits of RBC transfusion. The restrictive group did not have an increase in 30-day all-cause mortality or severe comorbidity. However, the number of RBC units transfused was an independent risk factor for clinical complications or death. On this basis, transfusion should be considered for postoperative cardiac surgery patients when Hgb <8 g/dL or Hct <24%.

RBC Transfusion in Patients With Pulmonary Disease and Mechanical Ventilation

While there would appear to be theoretical benefit to increasing oxygen-carrying capacity in patients with compromised pulmonary function, there is no clinical evidence to support administration of transfusion at higher hemoglobin levels or a more liberal use of transfusion in mechanically ventilated patients. In the subgroup of 713 patients in the TRICC study[17] who received mechanical ventilation, the restrictive strategy group (transfuse for Hgb <7 g/dL), compared with those in the liberal strategy group (transfuse for Hgb <10 g/dL), did not have increased duration of mechanical ventilation, ventilator-free days, or different extubation success rates. In a retrospective analysis, patients receiving prolonged mechanical ventilation for 96 h or longer (n = 4,344), exposure with RBC transfusion was associated with a 21% increase in the risk or hospital death, cost, and length of stay after adjustment for confounders.[18]

There is evidence to suggest that RBC transfusion may contribute to the development of acute respiratory distress syndrome and may increase mortality in patients with established acute lung injury. In a case control study[19] of 4,730 patients admitted to an ICU without ARDS at baseline, the odds of developing ARDS was significantly increased in those receiving transfusion compared with those with no transfusion after adjustment for age, severity of illness, admitting diagnosis, and process of care. Similarly, in an observational trial[20] of 248 consecutive patients with established lung injury, RBC transfusion was associated with increased risk for in-hospital mortality.

Clinical guidelines for transfusion in patients receiving mechanical ventilation endorse a restrictive strategy. In the absence of ongoing hemorrhage or acute coronary syndrome comorbidities, patients receiving mechanical ventilation should be considered for transfusion if hemoglobin value is <7 g/dL. There is no demonstrated

benefit for transfusion at higher hemoglobin levels.[5]

RBC Products

RBC transfusions may be given in the form of packed RBC, whole blood, leuko-reduced blood, autologous stored blood, and autologous reinfused blood. Additional variations include RBC preparations selected on the basis of removal of other plasma components, such as immunoglobulins, or viral infections such as cytomegalovirus (CMV)-seronegative blood (Table 5).

RBC Storage Defects and Storage Lesion

All blood donations undergo component separation to remove plasma and platelets, treatment with preservatives and anticoagulants, and refrigerated storage. After collection, whole blood is subject to centrifugation to remove WBCs, platelets, and most plasma components. Each unit of RBC is then resuspended in a storage solution that contains citrate, phosphate, dextrose, adenine, and other nutrients. This standard storage solution has been designed to give the unit a shelf life up to 42 days. While rare blood types may be frozen in solutions containing glycerol and dimethyl sulfoxide, most blood is stored at 4° C and warmed immediately prior to transfusion.

Storage of packed RBCs results in mild hemolysis, release of potassium into the storage solution, decreased pH of the solution, accumulation of ammonia, and gradual depletion of adenosine triphosphate and 2,3-DPG in the RBCs. During storage, RBC proteins are susceptible to oxidation and the RBC membrane develops lipid peroxidation and loss of deformability. It is likely that these changes as well as other biochemical and biomechanical changes worsen with duration of storage and diminish the expected clinical benefits of transfusion. Together, these changes have been termed "RBC storage lesion." The end result of RBC storage is a decrease in the transfused blood's contribution to oxygen transport and stimulation of vascular endothelial inflammatory cascades.[21]

Randomized clinical trials[22] have been initiated to evaluate the clinical effectiveness and mortality risk of fresh compared with stored blood, but the results are not yet available. An observational study[23] of patients undergoing cardiac surgery has demonstrated increased in-hospital mortality, duration of mechanical ventilation, and sepsis for blood stored more than 14 days compared with blood stored 14 days or less.

The Cross-Match Test and Bedside Administration of Blood

Cross matching and pretransfusion laboratory testing is conducted to determine three critical pieces of data: (1) the ABO/RhD blood type of the patient; (2) the presence of patient antibodies to common red cell antigens; and (3) specific cross-match compatibility of the individual blood unit with the patient. Each of these three tests must be completed prior to transfusion and are the primary method of preventing transfusion of incompatible blood and major transfusion reactions. RhD typing is necessary to prevent exposure and sensitization of the RhD antigen in girls and women of childbearing age. Many steps of pretransfusion testing are performed manually and thus subject to human error. Development of computer-based blood dispensing systems based on bar-code verification of the patient, and the individual blood unit bag may be used in place of the manual cross match.[24] Exceptions to pretransfusion testing exist only for patients with life-threatening hemorrhage when the delay of cross-match testing will increase the likelihood of death of the patient. In this situation the hierarchy of blood products is O-negative blood followed by type-specific blood that is not cross matched followed by cross-matched blood.

Each unit of packed RBCs is delivered in approximately 300 mL of electrolyte/nutrient/anticoagulant solution. In nonemergent conditions, RBCs may be infused over 1 to 4 h. Rapid infusion over minutes may be given in trauma and acute resuscitation. Monitoring during blood transfusion should include continuous bedside presence of nursing staff for the first 15 min to observe for severe transfusion reactions. RBC units are typically warmed to room temperature immediately before transfusion. However, if the blood is rapidly removed from refrigeration and brought to the bedside, it may arrive below room

Table 5—*RBC Transfusion Product*

RBC Transfusion Product	Specific Features	Clinical Indication(s) and Use
Whole blood	Plasma and platelet components not removed.	Rarely used and infrequently available; may be indicated for patients who have massive transfusion requirements to simultaneously replace multiple blood components
Packed RBCs	Plasma and platelet components removed.	Most common in general use
Specialized RBCs	Rare donor phenotypes	Often stored frozen and shipped to hospital on demand; indicated for patients with unusual antibodies and rare blood types and patients with IgA deficiency
Washed RBCs	RBCs are centrifuged and resuspended in saline to remove additional plasma and WBCs.	Used to prevent febrile transfusion reactions and in patients with history of allergic transfusion reactions
Leukoreduced or leukofiltered blood	Blood passed through filter to remove donor leukocytes, reduces WBC contamination 99.9%.	Used to prevent febrile transfusion reactions; preferred in chronically transfused patients, potential transplant recipients, some oncology patients, and CMV-seronegative patients; may reduce risk of viral disease transmission
Irradiated blood	Blood subjected to gamma or x-irradiation to eliminate donor lymphocyte proliferation.	Used to prevent graft vs host disease in high-risk patients
CMV-safe blood	Packed RBCs only from donors who are CMV-negative	CMV-negative infants, CMV-negative bone marrow and solid organ transplant recipients, patients with immunodeficiency syndromes
Autologous stored blood	Patient donates blood for storage prior to anticipated need.	Often used by patients in anticipation of operative blood loss; prepared and stored as either whole blood or packed RBCs
Autologous salvage/ rein fusion	Blood collection pumps, centrifuges, and washes used to retrieve blood from site of massive hemorrhage and rein fuse into same patient.	Intraoperative blood salvage; may be acceptable to Jehovah's Witnesses; reduces need for allogenic blood products.

IgA = immunoglobulin A.

temperature. Blood warming devices should be considered for patients receiving more than 2 to 3 units per hour and attention must be given to multiple transfusion patients to prevent and treat hypothermia.

Clinical Outcomes in Patients Receiving RBC Transfusion

From a practical, bedside viewpoint, the benefits of RBC transfusion are not debated in patients with impaired oxygen delivery, tissue hypoxemia, or major hemorrhage. However, careful review shows that RBC transfusion is associated with important pathophysiologic reactions as well as negative overall ICU outcomes (Table 6). Results of an observational trial[3] in a large U.S. population of 4,892 patients demonstrated that 4% of all RBC transfusions were associated with complications. The most common complications in this group were fever, fluid overload, and hypotension. Beyond immediate reactions, the potential negative impact of RBC transfusions is clinically significant. Patients who receive RBC transfusions generally have worse outcomes compared with patients who did not receive transfusion. Multiple clinical observational trials show higher mortality in patients who have received blood transfusion in the ICU. While univariate and multivariate association analyses cannot establish a causal relationship between transfusion and mortality, at least one propensity scoring model has shown increased mortality in transfused patients. Additional findings in patients who require blood transfusion include higher acute physiology and chronic health evaluation (APACHE) scores, higher sequential organ failure assessment (SOFA)

Table 6—*Adverse Effects and Noninfectious Complications Associated With RBC Transfusion*

Immune and inflammatory reactions
Acute hemolytic reaction
Delayed hemolytic reaction
Allergic and anaphylactic reactions
Febrile transfusion reaction
Posttransfusion purpura
Transfusion-related acute lung injury (TRALI)
Alloimmunization to RBCs
Transfusion-related immunomodulation
Graft vs host disease
Nonimmune adverse consequences (more commonly associated with massive transfusion)
Transfusion-associated circulatory overload
Hypothermia
Intravascular volume overload
Coagulopathy
Citrate toxicity (metabolic alkalosis)
Hypocalcemia (ionized calcium)
Patient outcomes associated with RBC Transfusion (not directly causal)
Increased mortality
Longer ICU length of stay
Higher APACHE and SOFA scores
Increased rate of nosocomial infection

APACHE = acute physiology and chronic health evaluation; SOFA = sequential organ failure assessment.

scores, increased length of ICU stay, and increased costs.[1,3]

Transfusion and Hospital-Acquired Infection Risk

Specific complications that appear to be related to immunosuppressive or immunomodulatory effects of RBC transfusion may contribute to worse clinical outcomes associated with transfusion. A prospective observational study[25] in 2,085 patients has demonstrated that RBC transfusion correlates with an increase in the risk of nosocomial infection rate (14% in transfused patients vs 5.8% in nontransfused patients). In this study, nosocomial infection was carefully defined as not having been present on admission and included the most common ICU infections including sepsis, bloodstream infections/bacteremia, pneumonia, urinary tract infection, peritonitis, and CNS infections. A second observational study[26] in 4,892 ICU patients demonstrated that development of ICU-acquired bloodstream infection was independently associated with RBC transfusion and cephalosporin treatment and higher SOFA score.

Noninfectious Complications in ICU Patients Receiving RBC Transfusion

Acute Hemolytic Transfusion Reactions

Acute hemolytic transfusion reactions are estimated to occur in 1 in 12,000 to 1 in 100,000 of all RBC transfusions. Fatality associated with acute hemolytic transfusion reactions occur in approximately 1 in 600,000 RBC transfusions. In many cases, the causes of these reactions are preventable clerical errors in blood specimen processing, cross-matching, and blood product administration.[27,28] Hemolytic transfusion reactions occur as the result of ABO blood group, RhD, or, less commonly, other RBC surface antigen incompatibility. Hemolysis of donor RBCs occurs as the result of recipient antibody binding. The severity of the reaction is proportional to the volume of blood infused. Rapid clinical deterioration and organ failure results from massive cytokine release, vascular endothelial cell dysfunction, complement activation, and shock. The most severe consequences of hemolytic transfusion reactions include renal failure, ARDS, and disseminated intravascular coagulation. Clinical manifestations of acute hemolytic transfusion reaction include fever, pain at the infusion site, back pain, chest discomfort, anxiety, nausea, dyspnea, tachycardia, tachypnea, and hypotension. Hemolytic reactions may be identified in comatose or unresponsive patients by the development of hypotension, hemoglobinuria, and coagulopathy manifested by bleeding from venipuncture sites, mucosal surfaces, and surgical wounds.

Treatment of acute hemolytic transfusion reactions should include (1) immediate discontinuation of the transfusion; (2) cardiopulmonary monitoring; (3) laboratory monitoring, including hemoglobin, direct antiglobulin (Coombs) testing, and haptoglobin; and (4) IV fluids to maintain urine output 100 to 150 mL/h. The role of diuretics and mannitol has not been definitively established. However, furosemide may be used if intravascular volume overload develops. There is no role for steroids or antihistamines.

Delayed Hemolytic Reactions

Delayed hemolytic reactions occur as the result of development of alloantibodies to non-ABO red cell antigens. The alloimmunization results from prior transfusion or pregnancy of the recipient. Hemolysis may begin and continue over 3 to 14 days and is related to development of an amnestic immune response. Presenting symptoms include fever, chills jaundice, hemolytic anemia with positive Coombs test, elevated lactate dehydrogenase levels, and decreased haptoglobin. Shock, disseminated intravascular coagulation, and renal insufficiency are unlikely to occur. A significant number of patients will be asymptomatic or have very subtle manifestations. There are no specific treatments for delayed hemolytic reactions; however, the occurrence should be documented for the patient. This history is important for appropriate screening and cross matching for future transfusion requirements.

Allergic and Anaphylactic Reactions

Allergic and anaphylactic reactions occur as the result of recipient antibody reaction against a noncellular protein, such as immunoglobulins, found in low concentration in the transfused blood. The most severe anaphylactic reactions usually result from recipient reaction against immunoglobulin A (IgA) found in the transfused blood when the recipient is IgA-deficient. Anaphylactic reactions manifest with symptoms and signs ranging in severity from flushing, dyspnea, hypotension, bronchospasm, abdominal pain, diarrhea, and shock. Mild allergic reactions are characterized by urticaria and pruritus. Patients with anaphylaxis may require treatment with epinephrine, IV fluids, and respiratory support. Antihistamines may be used in urticarial reactions. Patients who are IgA deficient and have anaphylaxis require special attention and should receive blood products including RBCs, plasma, and immunoglobulin from IgA-deficient donors. These blood products are rare and may be difficult to obtain. Patients with urticaria reactions should be considered for washed cell transfusions if the future need arises.

Febrile Nonhemolytic Reactions

Febrile nonhemolytic reactions result from donor reaction to recipient leukocytes or the presence of elevated cytokines that have accumulated in the transfused blood. These are the most common form of acute transfusion reaction and may occur in 0.5% to 5% of all transfusions. These reactions usually do not have significant consequences and require management with antipyretics. The greatest difficulty in the management of febrile nonhemolytic reactions is testing to exclude hemolytic reaction since fever is also a manifestation of that more severe complication. Patients who develop febrile reactions should receive WBC-filtered blood if future transfusion is necessary.

Posttransfusion Purpura

Posttransfusion purpura results from induction of platelet antibodies following transfusion. Although men can develop this complication, it has been described more often in multiparous women, suggesting the possibility of sensitization to platelet antigens during pregnancy. The recipient may also have become sensitized to platelet antigens through prior transfusion. The reaction occurs 3 to 12 days after transfusion and is characterized by thrombocytopenia and bleeding that may be severe. The differential diagnosis for posttransfusion purpura includes disseminated intravascular coagulation and heparin-induced thrombocytopenia. The diagnosis is established by the presence of platelet alloantibodies (to human platelet antigen-1a) in patients who have received recent transfusion.[29] Treatment includes IV immunoglobulin. Alternative proposed treatments include corticosteroids and plasmapheresis.

Transfusion-Related Acute Lung Injury

Transfusion-related acute lung injury (TRALI) is characterized by the development of hypoxemia and acute lung injury shortly after transfusion of RBCs or any other plasma-containing blood product. The symptoms and clinical features of TRALI are the abrupt and rapid development of dyspnea, respiratory distress,

hypoxemia, and fever. Both hypertension and hypotension have been described. Chest radiograph demonstrates bilateral infiltrates that have been described as whiteout. A more precise definition of TRALI is the occurrence of acute respiratory distress, Pao_2/Fio_2 <300 mm Hg and bilateral pulmonary infiltrates within 6 h of transfusion in patients without prior lung injury and without evidence of intravascular volume overload or cardiogenic pulmonary edema (pulmonary artery occlusion pressure <18 mm Hg). The temporal relationship between transfusion and development of respiratory distress must be present to establish the diagnosis.

As the result of difficulties in case difficulties and case ascertainment, the rate of TRALI is generally reported to be between 1 in 1,000 to 1 in 5,000 transfusions; the main risk factors include transfusion of plasma, female donors, the presence of underlying sepsis, alcohol abuse, tobacco use, liver surgery fluid overload, and mechanical ventilation.[30] In the United States, TRALI is the leading cause of transfusion-related mortality and has been associated with up to one-half of all transfusion-related deaths.[30,31] Treatment is supportive, but the majority of patients develop respiratory failure and require mechanical ventilation. TRALI often resolves with days and is associated with a lower mortality rate (estimated 5% to 10%) than other causes of acute lung injury or ARDS.[32] TRALI likely occurs as the result of donor-derived anti-human leukocyte antigen (HLA) antibodies or anti-human neutrophil antigen as well as other substances in the donor blood that react with recipient neutrophils and vascular endothelium.[31] Reducing the use of female donor plasma and requiring male-only plasma donors as well as screening blood supplies for the presence of anti-HLA antibodies may be effective methods to reduce the risk of TRALI.[30]

Transfusion-Related Graft vs Host Disease

Transfusion-related graft vs host disease (GVHD) results from the engraftment of immunocompetent donor lymphocytes in severely immunocompromised recipients. The donor lymphocytes proliferate and react against recipient HLA antigens. This reaction typically becomes evident 10 to 30 days following transfusion and is characterized by skin rash, liver disease, and GI disease as well as bone marrow suppression. Specific findings include erythematous scaly rash, jaundice, elevated liver function tests, diarrhea, and cytopenias. Neonates, organ transplant patients, bone marrow transplant patients, and patients with leukemia and lymphoma are at the highest risk for development of this complication. Transfusion-related GVHD is associated with high mortality rates, and treatment options are limited. Prevention of transfusion-related GVHD should include irradiation of any blood product, including RBCs and platelets, prior to transfusion. It is not necessary to irradiate fresh frozen plasma or cryoprecipitate.

Infectious Complications of RBC and Blood Product Transfusion

All blood products are associated with risks of transmission of viral, bacterial, and parasitic infections. The risks are directly proportional to the origin, behaviors, and social factors of the donor. Prevention of disease transmission revolves around careful screening of donors to identify risks for infectious disease and eliminate high-risk donors from the donor pool. In general, directed donations to patients from friends and family members should not be considered to have lower risk of disease transmission than random donor products. Postdonation testing includes a standardized series of tests to detect proteins, antibodies, and nucleic acids associated with infectious risk. The most significant limitations of disease testing are the time window for disease transmission between initial infection of the donor and development of detectable nucleic acid or antibodies in the donated product. A general principle is that pooled products (platelets and plasma components) from multiple donors are likely to have higher risk of disease transmission than single-donor products. The most important infectious etiologies and risks of transmission are listed in Table 7.[33,34]

Erythropoietin in ICU Patients

Recombinant erythropoietin stimulates RBC production and increases hematocrit in many

Table 7—*Risks of Infectious Disease Transmission With Blood Product Transfusion*

Infectious Agent	Estimated Risk Rate
Human immunodeficiency virus 1 and 2	1/1,500,000 to 1/4,300,000
Hepatitis C virus	1/1,935,000 using nucleic acid testing
Hepatitis B virus	1/250,000 using antigen/antibody testing
Hepatitis A virus	1/1,000,000
Syphilis	No cases reported since 1968
CMV	Recommended that CMV-negative patients at risk for CMV disease receive CMV-safe products or high-efficiency leukofiltration
Malaria	1/4,000,000 (dependent on country of origin)

CMV = cytomegalovirus. Data from Pomper et al[33] and Dwyre et al.[34]

subsets of patients with chronic diseases including chronic renal failure and cancer. The effect of erythropoietin does not occur for several days following administration. This delayed effect is the primary factor that limits its role in the ICU for treatment of acute anemia and diminished oxygen delivery to the organs and tissues. Early clinical trials have demonstrated that administration of erythropoietin can significantly reduce the need for RBC transfusion, decrease the number of transfused units per patient, and increase the mean hemoglobin concentration. However, these trials[35,36] did not demonstrate an improvement in other clinical outcomes including mortality. The most recent prospective, placebo-controlled randomized clinical trial[37] of 40,000 U per week of erythropoietin failed to demonstrate a decrease in the use of RBC transfusion and did not show a benefit in overall mortality except in the subgroup of patients with trauma. This trial demonstrated an increase in the risk of thrombotic events in patients receiving erythropoietin.

Blood Management Programs

Multiple factors require clinicians to reexamine and monitor blood utilization for their patients. The expense and demand for blood products as well as the clear risks of transfusion have focused significant attention on the rate of appropriate blood product utilization. Both internal, institution-specific monitoring and external monitoring and reporting by accreditation bodies require physicians to adopt a proactive, patient-centered approach to blood product prescription. The Joint Commission has developed quality metrics on blood product transfusion, including documentation of informed consent, specific transfusion indication, and preoperative screening.[38] Given these factors, appropriate use of RBC and other blood products should occur within the context of a comprehensive blood management program. These programs should be developed from evidence-based guidelines that are adapted to local conditions and accepted by institutional experts. Comprehensive blood management programs have been built around systematic surveillance and feedback, computerized order entry with electronic decision support, and automated warnings against transfusion in patients without appropriate clinical indications (Table 8). Effective management programs will be interdisciplinary and involve blood bank technicians, pathology-laboratory medicine physicians, prescribing physicians, and other involved providers and nursing staff. Highly functioning blood management programs have demonstrated decreased blood product usage, decreased expense, and improved patient outcomes.[39]

Blood Substitutes

Considerable research has been conducted for the development of blood substitutes and oxygen-carrying solutions. There are two general categories of these replacements: cell-free hemoglobin solutions and perfluorocarbon-based solutions. The hemoglobin solutions are derived from human or bovine sources and are partially polymerized to decrease the rate of clearance from the blood after infusion. The safety and efficacy of cell-free hemoglobin treatments have not been clearly established in the general ICU population.

Table 8—*Components of Blood Product Transfusion Management Programs*

Reviews of evidence-based guidelines and development of locally adapted standards of practice
Established institutional goals and quality metrics for blood product utilization and transfusion rates
Algorithms for evaluation of anemia and blood product transfusion
Hospital-wide surveillance recording of transfusion prescriptions
Feedback reports of transfusion practice to individual providers as well as oversight committees
Feedback and reports shared with all personnel—prescribers, nursing, and technical staff
Computer order entry for blood products
Automated warnings or alerts when prescription ordered for blood products and recent laboratory test demonstrate adequate hemoglobin or coagulation function
Computerized decision support at time of prescription
Focus clinical reviews, education, or redesign task forces on provider groups who demonstrate highly variable use patterns of blood products
Minimize unnecessary phlebotomy and laboratory testing
Specific anemia evaluation and treatment protocols for preoperative patients

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Notes

Chapter 23. Shock

John P. Kress, MD, FCCP

Objectives:

- To describe the clinical evaluation of patients with shock.
- To describe the pathophysiology of different types of shock.
- To describe resuscitation of shock.
- To describe new therapies for septic shock.
- To describe vasoactive drugs used for treatment of shock.

Key words: left ventricular failure; right ventricular failure; septic shock; vasopressors

Synopsis:

Shock is a common condition necessitating admission of the patient to the ICU or occurring in the course of critical care. This chapter discusses the pathophysiology of various shock states, followed by recommendations for the diagnosis and treatment of each category of shock. A brief review of commonly used vasoactive agents is also presented.

Shock Defined

Shock is defined by the presence of multisystem end-organ hypoperfusion. Clinical indicators include reduced mean BP, tachycardia, tachypnea, cool skin and extremities, acute altered mental status, and oliguria. Hypotension is usually, although not always, present. The end result of multiorgan hypoperfusion is tissue hypoxia, which is often clinically seen as lactic acidosis.

Clinical Evaluation of Patients in Shock

Most, but not all, patients who present with shock are hypotensive. Because the mean BP is the product of the cardiac output (CO) and the systemic vascular resistance (SVR), reductions in BP can be categorized by decreased CO and/or decreased SVR. Accordingly, the initial evaluation of a hypotensive patient should evaluate the adequacy of the CO. Clinical evidence of diminished CO includes a narrow pulse pressure (ie, systolic minus diastolic blood pressure—this is a surrogate marker for stroke volume) and cool extremities with delayed capillary refill. Signs of increased CO include a widened pulse pressure (particularly with a reduced diastolic pressure), warm extremities with bounding pulses, and rapid capillary refill. If a hypotensive patient has clinical signs of increased CO, one can infer that the reduced BP is a result of decreased SVR.

In hypotensive patients with clinical evidence of reduced CO, an assessment of intravascular and cardiac volume status is appropriate (discussed in more detail in the Hemodynamic Monitoring chapter). A hypotensive patient with decreased intravascular and cardiac volume status may have a history suggesting hemorrhage or other volume losses (eg, vomiting, diarrhea, and polyuria). The pulse pressure may vary widely with respiration and the jugular venous pulse may be reduced and/or vary with respiration in such a patient. A hypotensive patient with an increased intravascular and cardiac volume status may have S^3 and/or S^4 gallops, increased jugular venous pressure, extremity edema, and crackles on lung auscultation. The chest radiograph may show cardiomegaly, congestion of the vascular pedicle,[1] Kerley B lines, and pulmonary edema. Chest pain and ECG changes consistent with ischemia may also be noted.

In hypotensive patients with clinical evidence of increased CO, a search for the causes of decreased SVR is appropriate. The most common cause of high CO hypotension is sepsis. Accordingly, one should search for signs of the systemic inflammatory response syndrome (SIRS), which include abnormalities in temperature ($\geq$38°C or $\leq$36°C), heart rate ($\geq$90/min), respiratory rate ($\geq$20/min), and WBC count ($\geq$12,000 or $\leq$4,000 cells/μL or $\geq$10 bands).[2] A person with SIRS and a presumed or confirmed infectious process fulfills the criteria for sepsis. A person with sepsis and one or more organ failures fulfills the criteria for severe sepsis. Other causes of high CO hypotension include the following: liver failure,

severe pancreatitis, burns and other trauma that elicit SIRS, anaphylaxis, thyrotoxicosis, and peripheral arteriovenous shunts.

The common categories of shock include cardiogenic, hypovolemic, distributive with decreased SVR, and obstructive shock, wherein there is a mechanical impedence to venous return and/or ventricular outflow. These categories may overlap and occur simultaneously (eg, hypovolemic and septic shock, or septic and cardiogenic shock).

The initial assessment of a patient in shock, as outlined previously, should take only a few minutes. It is important that aggressive, early resuscitation is instituted based on the initial assessment, particularly as there are data suggesting that the early resuscitation of shock (both septic and cardiogenic) may improve survival.[3,4] If the initial bedside assessment yields equivocal or confounding data, more objective assessments such as echocardiography and/or central venous or pulmonary artery catheterization may be useful, although each of these tools have limitations (see Hemodynamic Monitoring chapter for more details). The goal of early resuscitation is to reestablish adequate perfusion to prevent or minimize end-organ injury.

During the initial resuscitation of patients in shock, the principles of advanced cardiac life support should be followed. Because patients in shock may be obtunded and unable to protect the airway, an early assessment of the patient's airway is mandatory during resuscitation from shock. Early intubation and mechanical ventilation are often required. The reasons for the institution of endotracheal intubation and mechanical ventilation during shock include acute hypoxemic respiratory failure and ventilatory failure. Acute hypoxemic respiratory failure may occur in cardiogenic shock (pulmonary edema) as well as septic shock (eg, pneumonia or ARDS). Ventilatory failure often occurs as a result of an increased load on the respiratory system. This load may present in the form of metabolic acidosis (often lactic acidosis) or decreased compliance of the lungs as a result of pulmonary edema. Inadequate perfusion to respiratory muscles in the setting of shock may be another reason for early intubation and mechanical ventilation. Normally, the respiratory muscles receive a very small percentage of the CO.[5] However, in patients who are in shock with respiratory distress for the reasons listed previously, the percentage of CO dedicated to respiratory muscles may increase $\geq$10-fold.[6,7] Mechanical ventilation may relieve the patient of the work of breathing and permit the redistribution of a limited CO to other vital organs. Such patients often demonstrate signs of respiratory muscle fatigue, including the following: inability to speak full sentences, accessory respiratory muscle use, paradoxical abdominal muscle activity, extreme tachypnea (>40 breaths/min), and decreasing respiratory rate despite an increasing drive to breathe.

Endotracheal intubation and mechanical ventilatory support with sedation will decrease oxygen demand of the respiratory muscles allowing improved oxygen delivery to other hypoperfused tissue beds.[8] Patients in shock should be intubated before other procedures are performed (eg, central venous catheterization), as attention to the airway and breathing may wane during such procedures.

Resuscitation

Resuscitation should focus on improving end-organ perfusion, not simply increasing the BP. Accordingly, a patient with a reduced CO by clinical assessment with a decreased intravascular and cardiac volume status should receive aggressive IV fluid resuscitation. The question of which type of IV fluid to use is controversial,[9] although data[10] from the 2004 Saline versus Albumin Fluid Evaluation study suggest that colloid (albumin) is not better than crystalloid, and may even be associated with increased morbidity and mortality. There are some studies that question the conventional wisdom of aggressive fluid resuscitation of patients with hypovolemic shock. One study[11] reported improved outcomes in trauma patients whose volume resuscitation was delayed until definite surgical repair (average time to operation, approximately 2 h). A recent study of fluid resuscitation in African children with severe infection likewise reported improved outcomes in those who did not receive IV fluid bolus therapy[12]; nonetheless, at present, most would agree that aggressive volume resuscitation in

patients with reduced intravascular and cardiac volume status is merited until further data become available to refute this view. The early administration of vasoactive drugs in fluid responsive (ie, hypovolemic) patients to increase BP is not recommended, although assessing intravascular volume status in patients with shock is often a complex endeavor (see chapter on Hemodynamic Monitoring). This practice may impair the assessment of the patient's circulatory status and potentially delay definitive treatment. The transfusion of packed RBCs to anemic patients to improve oxygen delivery is physiologically rational; however, some data[13] have suggested that, as long as hemoglobin levels remain >7 g/dL, this practice may not improve outcomes and perhaps may even worsen outcomes in select subgroups of patients. Certainly, a conservative transfusion strategy does not apply to hemorrhaging hypovolemic patients who are in shock. Blood products should be administered through a blood warmer to minimize hypothermia and subsequent disturbances in coagulation. It is important to remember that oxygen delivery is the product of CO, the oxygen-carrying capacity of the blood, and arterial oxygen saturation. Each of these components must be considered and optimized when addressing the resuscitation of patients who are in shock.

Early reassessment of the patient with purported hypovolemic shock after the initial resuscitation is extremely important. Concrete end points, such as increased BP and pulse pressure, improved capillary refill, urine output, and mental status, should be sought. The absence of a response suggests that the volume challenge may not be adequate. Careful and repeated searches for signs of volume overload (ie, new gallop or extra heart sounds, and pulmonary edema) should be performed as the resuscitation is ongoing.

If the patient remains in shock despite adequate volume resuscitation, support with vasoactive drugs is appropriate. Occasionally, vasoactive drugs must be started "prematurely" when volume resuscitation needs are large. When severe hypotension and hypovolemia are present, this approach is occasionally needed to "buy time" as volume resuscitation is ongoing. This strategy is occasionally necessary but should only be instituted temporarily until volume resuscitation is accomplished. When resuscitating a patient with hypovolemic shock, the use of evidence-based end points is recommended, as is outlined in the Hemodynamic Monitoring chapter. It is important to remember that vasoactive drugs may obscure hypovolemic shock by increasing BP despite a low CO state.

Once intravascular volume has been restored, patients who remain in shock may benefit from therapy with vasoactive drugs. These drugs should be titrated to end-organ perfusion, rather than to an arbitrary BP value. Accordingly, mental status, urine output, lactic acidosis, capillary refill and skin temperature, and venous oxygen saturation are reasonable end points to target in these patients. If the objective information obtained by physical examination is unclear or ambiguous, additional information obtained by more monitoring (eg, echocardiography, arterial catheter, central venous catheter) may be useful. Echocardiography is a useful adjunct or even replacement to invasive pressure measurements and can be used to distinguish poor ventricular pumping function from hypovolemia. The study can exclude or confirm tamponade, pulmonary hypertension, or significant valve dysfunction, all of which influence therapy and may supplement or replace the more invasive right heart catheterization.

Cardiogenic Shock

The model of the heart as a pump is useful in considering cardiogenic shock. By definition, pump failure is seen when CO is inappropriately low despite adequate input in the form of venous return (determined by right atrial pressure). The specific cause of decreased pump function must be considered. Left ventricular (LV) and/or right ventricular (RV) dysfunction may occur due to decreased systolic contractility, impaired diastolic relaxation, increases in afterload, valvular dysfunction, or abnormal heart rate and rhythm.

LV Failure

Systolic Dysfunction: This is the classic example of cardiogenic shock. When LV systolic function is impaired, the reason may be acute coronary ischemia. The result is a reduction of

CO relative to the increases in preload. Compensation for this impaired pump function occurs through the Frank-Starling mechanism, as well as by fluid retention by the kidneys and by increased venous tone mediated by the sympathetic nervous system. Patients present with reduced CO and a resulting increased oxygen extraction ratio by the peripheral tissues. The resulting low venous oxygen saturation may exacerbate hypoxemia, especially in patients with pulmonary edema with its resulting intrapulmonary shunt physiology. As mentioned, acute myocardial infarction or ischemia is a common cause of LV failure leading to shock. Cardiogenic shock is reported to complicate up to 10% of acute myocardial infarctions,[14] particularly with anterior infarctions.[15] Typically there is a substantial fraction of dysfunctional myocardium, which may recover with early revascularization. Evidence[4] supports the use of early aggressive revascularization using angioplasty or coronary artery bypass grafting in patients with cardiogenic shock. A survival benefit was seen in patients subjected to this strategy compared with the medical management of cardiogenic shock, including those patients to whom thrombolytic therapy was administered. The treatment of cardiogenic shock due to systolic dysfunction includes the judicious administration of IV crystalloid if hypovolemia is present. A more precise characterization of the circulation can be obtained with the use of echocardiography and/or pulmonary artery catheterization, topics that are discussed in more detail in another chapter of the book. Inotropic support includes the use of agents such as dobutamine or milrinone. Intra-aortic balloon counterpulsation may be used to support the circulation as a bridge to coronary artery revascularization.

Diastolic Dysfunction: Increased LV diastolic chamber stiffness and impaired LV filling can occur as a result of myocardial ischemia, LV hypertrophy, or restrictive myocardial diseases. Patients usually present with increased cardiac filling pressures despite a small LV end-diastolic volume, as documented by echocardiography (usually best seen in the short-axis view at the level of the papillary muscles). Aside from the management of acute ischemia, this condition may be difficult to treat. Volume administration can be considered, although sometimes there are only further increases in diastolic pressure with little change in diastolic volume or CO. Accordingly, objective measures of fluid responsiveness are recommended. Therapy with inotropic agents is usually ineffective. The aggressive management of tachycardia with volume administration and the cautious use of negative chronotropic agents is a rational approach to therapy. Because very little ventricular filling occurs late in diastole in these patients, a very low heart rate (eg, sinus bradycardia) may be detrimental. Often, the careful titration of chronotropic agents to achieve the "optimal" heart rate that maximizes CO is necessary. The maintenance of a normal sinus rhythm is important to maximize ventricular filling.

Valvular Dysfunction: The management of valvular disease contributing to cardiogenic shock is guided by interventions to counter the specific pathophysiologic status. Accordingly, aortic stenosis is managed by efforts to decrease heart rate while maintaining sinus rhythm when possible. Preload should be maintained, and afterload must not be reduced, as the fixed afterload imposed by the aortic stenosis may not tolerate further reductions in afterload by arteriolar dilation. One study[16] reported that afterload reduction with nitroprusside improved cardiac function in critically ill patients with decompensated heart failure due to severe LV systolic dysfunction and severe aortic stenosis; however, hypotensive patients were not included in the study. Surgical evaluation, transcatheter aortic valve implantation,[17] or palliative valvuloplasty are other important considerations in patients with cardiogenic shock complicated by aortic stenosis. Cardiogenic shock due to aortic insufficiency may present acutely and may require urgent surgical repair. Medical management includes the use of chronotropic agents to decrease regurgitant filling time and afterload-reducing agents to facilitate forward flow. Mitral regurgitation may occur acutely as a result of ischemic injury to papillary muscles. Medical management includes attempts to establish and maintain sinus rhythm, as well as afterload reduction to decrease the percentage of regurgitant blood flow. This may be accomplished with

medications, such as nitroprusside, or intra-aortic balloon counterpulsation as a bridge to mitral valve repair or replacement. Recently, percutaneous mitral valve repair has become an option for patients with mitral regurgitation,[18] although the experience with this procedure in patients with shock is limited. Mitral stenosis contributing to cardiogenic shock is managed by negative chronotropic agents, which seek to maximize diastolic filling time across the stenotic valve. Hypertrophic cardiomyopathy may contribute to cardiogenic shock. This lesion is managed by the maintenance of preload with volume administration and therapy with negative inotropic and chronotropic agents, which serve to decrease the obstruction of the LV outflow tract during systole. Rarely, acute obstruction of the mitral valve by left atrial thrombus or myxoma may also result in cardiogenic shock. These conditions generally require acute surgical interventions.

Cardiac Arrhythmias: Dysrhythmias may exacerbate shock in critically ill patients. A detailed discussion on the management of dysrhythmias is beyond the scope of this chapter, and the reader is referred to other chapters of the book for further discussion of this topic.

RV Failure

RV failure resulting in cardiogenic shock is typically associated with increased right atrial pressure and reduced CO.[19] Although the most common reason for RV failure is concomitant LV failure, this section will discuss the management of isolated RV failure. RV infarction may result in RV failure, usually accompanied by inferior myocardial infarction. Elevated jugular venous pressure in the presence of clear lungs is the classic physical finding seen in patients with acute RV infarction. It is important to distinguish RV infarction from cardiac tamponade. Echocardiography may be helpful in making this distinction (discussed later). Therapy includes careful volume administration to maintain preload; however, volume overload is common with RV failure, and RV dilation may increase tricuspid regurgitation, leading to worsening hepatic and renal congestion. Therapy with dobutamine or dopamine may be used to increase RV inotropy,[20] and therapy with norepinephrine or phenylephrine may improve RV endocardial perfusion. RV failure as a result of increases in right heart afterload may be due to pulmonary embolism, ARDS, and other causes of alveolar hypoxia, hypercapnia, and metabolic acidosis. Management is focused on treating the underlying physiologic derangement, with circulatory support as noted.[21,22] The treatment of RV failure is complicated, as volume administration may result in worsening RV function by causing mechanical overstretch and/or by reflex mechanisms that depress contractility.[23] However, some investigators[24] have found volume administration to result in favorable hemodynamics in patients with acute RV failure due to increased RV afterload. Optimal management is often facilitated by echocardiographic or pulmonary artery catheter-directed therapy. Thrombolytic therapy for acute pulmonary embolism complicated by cardiogenic shock has been shown to improve survival[25] and is currently accepted as a recommended strategy. Hypoxic pulmonary vasoconstriction may be reduced by improving alveolar and mixed venous oxygenation with the administration of supplemental oxygen. More aggressive correction of hypercapnia and acidemia may be necessary in patients with acute right heart syndromes. Pulmonary vasodilator therapy (eg, inhaled nitric oxide and prostaglandin E_1) may be considered, although outcome benefits in the acute setting are largely lacking.

Pericardial Tamponade and Other Syndromes Causing External Compression of the Heart

Cardiac tamponade impairs diastolic filling, resulting in shock. The diagnosis is established by the presence of elevated jugular venous pulse with Kussmaul sign and pulsus paradoxus. Pulmonary artery catheterization may reveal a decreased CO with equalization of right atrial, left atrial (ie, pulmonary capillary wedge pressure), and RV diastolic pressures. Echocardiography reveals pericardial fluid with diastolic collapse of the atria and RV, and right-to-left septal shift during inspiration. Other causes of external cardiac compression include tension pneumothorax and elevated intraabdominal pressure (ie, abdominal compartment syndrome). Medical

management of the circulatory pathophysiologic condition of tamponade includes the use of aggressive volume administration as well as inotropic and chronotropic support to increase heart rate and thus maintain forward flow. Definitive treatment is focused at the underlying cause and includes pericardial drainage with a catheter or surgical "window" in the case of pericardial tamponade. In unstable patients, drainage of the pericardial sac with a needle may be necessary. Ultrasound guidance should be used in circumstances where such drainage is performed; in abdominal compartment syndrome, treatment includes drainage of peritoneal fluid, decompression of the GI tract, and surgical decompression.

Decreased Venous Return (The "Empty" Heart)

Hypovolemia is the most common cause of shock due to decreased venous return. The venous circuit has tremendous capacitance potential, and venoconstriction in response to hypovolemia can compensate for the initial decreases in intravascular volume. Orthostatic changes in BP and heart rate may be seen early in patients in hypovolemic shock.[24] At a level of approximately 40% loss of intravascular volume, venoconstriction driven by the sympathetic nervous system can no longer maintain venous return and mean arterial BP.

In patients with hypovolemic shock, tissue injury (especially gut ischemia) and the resulting systemic inflammation may lead to ongoing shock despite the replacement of volume losses. This is particularly relevant if resuscitation is delayed and underscores the importance of early aggressive resuscitation in patients with hypovolemic shock. The phenomenon of systemic inflammation as it pertains to shock will be discussed in more detail in the section on septic shock.

Other causes of shock due to decreased venous return include severe neurologic damage or drug exposure resulting in hypotension due to a loss of venous tone. The prototypical example of loss of venous tone due to drug exposure is anaphylaxis. This unregulated immunologically mediated release of histamine can result in profound shock requiring aggressive catecholamine support (epinephrine is the drug of choice). An elevated tryptase level is seen within minutes after exposure to the anaphylactic agent. Septic shock is a common cause of shock due to decreased venous tone and is discussed separately in the next section. All of these processes result in decreased venous tone and impaired venous return, resulting in decreased CO and BP. The obstruction of veins due to compression (eg, pregnancy or intraabdominal tumor), thrombus formation, or tumor invasion increases the resistance to venous return and may occasionally result in shock.

The principal therapy of hypovolemic shock and other forms of shock due to decreased venous return is aggressive volume resuscitation while attempting to reverse the underlying problem driving the pathophysiologic condition. This has been described in more detail previously. In patients with hemorrhagic shock, resuscitation with packed RBCs should be performed through a blood warmer. The optimal hemoglobin concentration is controversial, and transfusion should be paced by the extent of ongoing blood loss. After large-volume RBC transfusions, dilutional thrombocytopenia and reduction in clotting factors should be anticipated, sought out, and corrected with platelet and plasma product transfusions, as directed by the findings of a platelet count and coagulation assays.

High CO Hypotension

Septic Shock

Septic shock is the most extreme presentation of a spectrum of pathophysiologic responses to an infectious insult. Sepsis is defined by the presence of SIRS with known or suspected infection.[2] Severe sepsis occurs when patients with sepsis accrue one or more organ failures. Septic shock is seen in patients with severe sepsis who manifest shock, as described previously. Any infectious organism may result in sepsis and septic shock, including all bacteria, fungi, viruses, and parasites. As noted, patients typically present with evidence of high CO (assuming hypovolemia has been resuscitated). These patients have a widened pulse pressure, warm extremities, brisk capillary refill, and a reduced diastolic and mean BP. A subgroup of patients with septic shock may

present with depressed cardiac function. Circulating myocardial depressant factors have been identified in some septic patients,[26,27] but the reason that only a small subgroup of patients manifest overt cardiac depression is not well understood.

Sepsis is a significant problem in the care of critically ill patients. It is a leading cause of death in noncoronary ICUs in the United States, with estimates suggesting that >750,000 patients are affected each year.[28] These numbers are expected to increase in the coming years as the population continues to age and a greater percentage of people who are vulnerable to infection seek medical care.

Decades of research have focused on modifying the pathophysiologic responses of the body to severe infection. For years, an unregulated proinflammatory state was thought to be the driving force behind severe sepsis and septic shock. Numerous trials[29] attempting to block a particular inflammatory pathway were conducted without any survival benefits noted. Recently the pathophysiology behind severe sepsis has become better understood. Currently, the pathophysiology of severe sepsis is thought to be driven by unregulated inflammation (by cytokines such as IL-6 and tumor necrosis factor) coupled to a hypercoagulable state favoring microvascular coagulation and impaired fibrinolysis. Such unregulated microvascular coagulation is thought to lead to impaired tissue perfusion and to predispose patients to the multiple organ dysfunction syndrome that is commonly observed in patients with severe sepsis.[30]

The mainstay of therapy for septic shock is aggressive supportive care. This includes early identification of the source of infection with eradication by surgical or percutaneous drainage, if possible. In addition, early broad-spectrum antibiotic therapy is mandatory. Many patients with severe sepsis will require ventilatory support for respiratory failure, which should be instituted early for the reasons outlined earlier in this chapter. Circulatory failure is supported with aggressive volume administration to correct any component of shock that is fluid responsive. Objective monitoring using echocardiography and invasive monitoring should be used early to guide therapy. Vasoactive support is directed by the underlying circulatory derangement. As noted, the early institution of broad-spectrum antibiotic therapy focused on potential pathogens has been shown to improve survival.[31,32] Acute renal failure in patients with septic shock carries a poor prognosis. The use of low-dose dopamine as a renal protective strategy has been found[33] to be of no benefit in preventing acute tubular necrosis in patients with SIRS and acute renal insufficiency. Other therapeutic interventions in patients with severe sepsis await further evaluation. Early trials evaluating the usefulness of very high-dose corticosteroids in patients with septic shock have failed to demonstrate a survival benefit.[34,35] Corticosteroid therapy remains controversial, and further studies are needed before it can be recommended for widespread use. Some data[36] suggest that the response to an adrenocorticotropic hormone stimulation test may have important prognostic implications. A 2002 multicenter trial[37] found that a combination of low-dose hydrocortisone and fludrocortisone improved survival in patients with septic shock who had relative adrenal insufficiency. However, a more recent trial[38] failed to reproduce these findings.

Other Types of Shock

Adrenal insufficiency is often viewed as a rare occurrence in critically ill patients. However, one study[39] has reported a 54% incidence of blunted adrenal response to adrenocorticotropic hormone in patients with septic shock. This number may be a generous estimate as the parameters for defining adrenal insufficiency have not been universally agreed on[39]; nevertheless, adrenal insufficiency may not be as rare as previously thought.

Neurogenic shock typically occurs as a result of severe injury to the CNS. The loss of sympathetic tone results in venodilation and venous blood pooling. The mainstays of therapy include volume repletion and vasoactive support with drugs that have venoconstricting properties.

Severe hypothyroidism or hyperthyroidism may result in shock. Myxedema presenting as shock should be treated with the administration of IV thyroid hormone. One should watch carefully for myocardial ischemia and/or infarction, which

may complicate aggressive thyroid replacement. Thyroid storm requires urgent therapy with Lugol solution, propylthiouracil or methimazole, steroids, propranolol, fluid resuscitation, and the identification of the precipitating cause. Pheochromocytoma often presents with a paradoxical hypertension despite a state of shock and impaired tissue perfusion. Intravascular volume depletion may be masked by extreme venoconstriction. The increase in afterload caused by endogenous catecholamines may also precipitate a shocklike state. Treatment includes aggressive volume replacement as well as α-adrenergic and β-adrenergic blockades. A search for the location of the pheochromocytoma with subsequent surgical removal is indicated.

Vasoactive Agents

The choice of vasoactive medications should be based on the underlying pathophysiology of the circulation as gleaned by the physical examination and supplemented by more sophisticated measurements. The most commonly used vasoactive agents are outlined.

Dobutamine

Dobutamine is a powerful inotrope that stimulates both β_1 and β_2 receptors. The end result is typically an increase in CO with diminished SVR. This reduction in afterload may benefit patients with LV systolic dysfunction.

Milrinone

Milrinone is an inotropic agent that induces a positive inotropic state through phosphodiesterase inhibition. It has potent vasodilating properties that decrease both systemic and pulmonary vascular resistance. One study of patients with acute exacerbations of congestive heart failure did not demonstrate a benefit with regard to the number of days hospitalized for cardiovascular causes, the in-hospital mortality rate, the 60-day mortality rate, or the composite incidence of death or hospital readmission. Rather, hypotension and new atrial arrhythmias were found to occur more frequently in patients who received milrinone compared to placebo.[40]

Dopamine

Dopamine is purported to have varying physiologic effects at different doses. Classically, "low-dose" dopamine (1–3 μg/kg/min) is thought to stimulate dopaminergic receptors and to increase renal and mesenteric blood flow. As noted, this notion has been disproven. There is evidence that dopamine may impair mesenteric perfusion to a greater degree than norepinephrine.[41] Because data are accumulating that report the ill effects of dopamine in patients with shock, this agent has fallen out of favor in the view of many clinicians, with other agents, such as norepinephrine, being more widely used (see next section). A recent randomized study comparing dopamine to norepinephrine in critically ill patients with shock of all types reported no difference in survival, although there was a trend favoring norepinephrine ($P = .10$). Furthermore, in subgroup analyses, survival in those patients with cardiogenic shock was better with the use of norepinephrine. Patients taking norepinephrine had 50% fewer dysrhythmias when compared to dopamine.[42]

Norepinephrine

Norepinephrine stimulates β_1-receptors as well as α-receptors. Data are now accumulating suggesting that norepinephrine may be a preferred drug in the treatment of septic shock and other vasodilatory types of shock. It appears to have a lesser propensity to cause renal injury[43] and provides a more reliable increase in BP compared with dopamine.[44] A prospective observational cohort study[45] found a significant reduction in mortality when compared with therapy with dopamine and/or epinephrine in patients with septic shock.

Phenylephrine

Phenylephrine is a pure α_1-agonist, which results in venous and arteriolar constriction. It often elicits a reflex bradycardia that is mediated by baroreceptors. This may prove useful in patients with tachydysrhythmias accompanied by hypotension. In a prospective observational study[46] of patients with septic shock, phenylephrine was found to increase BP, SVR, and cardiac

index when added to low-dose dopamine or dobutamine after volume resuscitation. There is a theoretical concern that α-agonism may precipitate myocardial ischemia, although there are few objective data to support or refute this concern.

Epinephrine

Epinephrine has both β-agonist as well as α-agonist properties. It has potent inotropic as well as vasoconstricting properties. It appears to have a higher propensity toward precipitating mesenteric ischemia,[47] a property that limits its usefulness as a first-line agent for the management of shock, regardless of the underlying etiology.

Vasopressin

The use of vasopressin as a vasoactive agent has increased tremendously in the past few years. Patients who present with septic shock or late phase hemorrhagic shock have been shown to have a relative deficiency of vasopressin. One study[48] found that patients with septic shock demonstrate an increase in BP and urine output without evidence of impaired cardiac, mesenteric, or skin perfusion when treated with "low-dose" (ie, 10–40 mU/min) vasopressin. Another large study compared vasopressin to norepinephrine in those with septic shock. All patients were required to be receiving at least 5 μg per minute of norepinephrine. There was no difference in survival between the two drugs; however, those patients with "less severe" septic shock (ie, treatment with 5–14 μg of norepinephrine or the equivalent per minute) had improved survival.[49] The exact role of vasopressin in the treatment of patients who are in various shock states requires further investigation.

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Notes

Chapter 24. Coagulopathies, Bleeding Disorders, and Blood Component Therapy

Karl W. Thomas, MD, FCCP

Objectives:

- Discuss the incidence and clinical significance of thrombocytopenia and coagulopathy in the critically ill patient population.
- Distinguish and initiate appropriate treatment for common causes of thrombocytopenia including heparin-induced thrombocytopenia, thrombotic thrombocytopenic purpura, and immune thrombocytopenic purpura.
- Identify and determine clinical response to common ICU clotting factor coagulopathies including disseminated intravascular coagulation and liver disease.
- Discuss the clinical monitoring and management of patients with coagulopathy of massive transfusion.
- Determine the appropriate clinical use and dose range for platelets, fresh-frozen plasma, and cryoprecipitate.
- Discuss briefly the role of blood substitutes and adjunctive treatments including desmopressin acetate, prothrombin complex concentrates, and recombinant activated factor VII.

Key words: coagulopathy; disseminated intravascular coagulation; hemolysis; hemolytic-uremic syndrome; heparin-induced thrombocytopenia; immune thrombocytopenic purpura; massive transfusion; thrombocytopenia

Synopsis:

Anemia, thrombocytopenia, and combined coagulopathies are common in patients in the ICU. These disorders rarely occur in isolation and are directly related to ICU outcomes. Rapid and efficient recognition of these disorders is essential to the provision of timely and appropriate care. These disorders require a systematic clinical approach based on examination of platelets and coagulation factor parameters. This chapter will review and apply basic laboratory testing including examination of coagulation times, fibrin levels, D-dimer levels, peripheral blood smear, and platelet count. Thrombocytopenias, disseminated intravascular coagulation, immune thrombocytopenic purpura, thrombotic thrombocytopenic purpura, heparin-induced thrombocytopenia, and massive transfusion will be reviewed with a focus on key identifying features. Finally, this chapter will review use of blood components including platelet, plasma, cryoprecipitate, and other blood products.

Incidence and Clinical Significance of Thrombocytopenia

A wide range for the rate of thrombocytopenia in acutely ill patients has been reported. The prevalence of thrombocytopenia in patients admitted to the ICU ranges from 8% to 67%, whereas the incidence of new thrombocytopenia after admission ranges from 13% to 44%.[1,2] The most commonly used platelet concentration for the definition of thrombocytopenia is less than 150,000/μL. However, some investigators use a cutoff of less than 100,000/μL, or less than 50,000/μL. For patients in the ICU multiple observational studies have associated thrombocytopenia with increased mortality, major bleeding, and increased blood product transfusion requirements. Thrombocytopenia is consistently associated with high illness severity, sepsis, and high rates of organ dysfunction.[2]

The platelet concentration in patients in the ICU changes over time. Both the degree and the duration of thrombocytopenia are clinically relevant. For medical and surgical patients in the ICU, platelet counts typically decrease and reach a nadir by days 3 to 4 of the ICU stay. Although ICU survivors typically have return of platelet counts back to baseline or above, nonsurvivors more frequently have persistent thrombocytopenia or a blunted increase in platelet count.[1,3–5] Thus, the dynamic changes of the platelet count are related to outcome and persistent thrombocytopenia has a negative prognostic value.

In the absence of other coagulopathies, significant bleeding is unlikely for patients undergoing surgery until the platelet count is less than 50,000/μL. Spontaneous bleeding from superficial cuts or mucosal surfaces is unlikely until the platelet count decreases below 10,000 to 20,000/μL.

Etiology of Thrombocytopenia

Thrombocytopenia may result from decreased production, increased destruction, or from distribution/dilution effects (Table 1). Causes of decreased platelet production include

Table 1—*Causes and Contributing Factors for Thrombocytopenia*

Decreased Platelet Production
Viral infection (Epstein-Barr virus, parvovirus, HIV)
Drugs and toxins
Alcohol
Cancer chemotherapy
Heparins (HIT)
Antiepileptics (phenytoin, carbamazepine, valproate)
Antibiotics (penicillin, meropenem, vancomycin)
Salicylates and glycoprotein IIb/IIIa inhibitors (aspirin, abciximab, clopidogrel)
Histamine 2 receptor blockers (ranitidine, cimetidine)
Nutritional deficiency (folate, B12)
Myelodysplastic syndromes
Increased platelet destruction
Sepsis
DIC
TTP
ITP
Posttransfusion purpura
Antiphospholipid antibody syndrome
HELLP syndrome
Abnormal distribution and dilution
Hypersplenism
Massive blood transfusion

HIT = heparin-induced thrombocytopenia; DIC = disseminated intravascular thrombocytopenia; TTP = thrombotic thrombocytopenic purpura; ITP = immune thrombocytopenic purpura; HELLP = hemolytic anemia, elevated liver function tests, low platelet count.

infections (eg, parvovirus, Epstein Barr virus, HIV), drugs and toxins (eg, heparin, antibiotics, chemotherapy, alcohol), nutritional deficiencies (eg, folate, cobalamin), and bone marrow diseases including myelodysplastic and myeloproliferative syndromes.

Increased platelet destruction and shortened platelet survival may result from either nonimmune or immune-mediated processes. Infection, sepsis, septic shock, and chronic liver disease are the underlying disorders in about half of all patients with thrombocytopenia in the ICU.[5] The mechanism for thrombocytopenia in sepsis is likely multifactorial and includes immune-mediated platelet destruction, hemophagocytic histiocytosis, and disseminated intravascular coagulation (DIC).[6]

Common immune-mediated disorders of thrombocytopenia include heparin-induced thrombocytopenia (HIT), thrombotic thrombocytopenic purpura (TTP), and immune thrombocytopenic purpura (ITP). Each of these disorders is associated with a specific antigen–antibody reaction leading to platelet activation and/or destruction.

Distributional thrombocytopenia has been attributed to hypersplenism and splenic sequestration resulting from portal hypertension. Dilutional thrombocytopenia commonly occurs in patients receiving massive blood transfusions on the order of 15 to 20 units of packed RBC/24 h.

Specific Disorders Associated With Thrombocytopenia

HIT

Heparin has been associated with two distinct syndromes of thrombocytopenia. Heparin may cause a transient, clinically insignificant thrombocytopenia immediately after exposure. This thrombocytopenia is usually transient and has been termed type I HIT. Type I HIT is not immune-mediated. In distinction, type II HIT results in increased morbidity and mortality, is immune mediated, occurs only after days of exposure, and requires treatments including discontinuation of heparin and initiation of alternative anticoagulation. The overall risk for development of type II HIT for general hospitalized patients ranges from 0.2% to 5%, but for patients in the ICU, the rate is $<1\%$. The prevalence of thrombotic complications including venous and arterial emboli is 30% to 70% of cases.[7–9] The remainder of this chapter will discuss type II HIT.

HIT is a clinical syndrome characterized by thrombocytopenia and thrombosis that results from an immune reaction. Specifically, HIT results from the generation of antibody formation to complexes of heparin and platelet factor 4 (PF4). These complexes bind to the surface of platelets on immunoglobulin Fc receptors. The binding of heparin, PF4, and antibody to the Fc receptor results in platelet activation characterized by release of platelet granules and platelet aggregation. The activated and aggregated platelets are thrombogenic (leading to arterial and venous thrombosis) and removed from the circulation (leading to thrombocytopenia).[10]

Table 2—*Patient and Clinical Risk Factors for HIT*

Patient Population at Risk for HIT
1. Female patients > male patients
2. Surgical patients > medical patients > obstetric patients
3. Highest risk in cardiac and orthopedic surgery
Exposure-related risk
1. Unfractionated heparin > low-molecular-weight heparin
Clinical features associated with highest risk 4 Ts stratification (Lo et al.[12])
1. Thrombocytopenia with platelet count fall >50% and nadir >20,000/mL
2. Timing of platelet count decrease—clear onset between days 5 and 10
3. Thrombosis or other sequelae—venous or arterial embolism, skin necrosis occurring after heparin exposure
4. Other causes for thrombocytopenia excluded

HIT is a clinical diagnosis established in the setting of elevated pretest probability and supporting clinical findings. A significant difficulty in the clinical evaluation and treatment of patients with HIT results from the lack of a quick and highly specific test to confirm the diagnosis. Thrombocytopenia by itself is common in critically ill patients and is nonspecific. Antiplatelet or anti-PF4 antibodies may be found in patients without thrombosis or thrombocytopenia. The highly specific, functional platelet activation assays for HIT cannot be quickly obtained within the time frame necessary to provide diagnostic confirmation and initiation of treatment. Often platelet activation assays are used to confirm the diagnosis of HIT after the clinical diagnosis has been established and treatment initiated.

The pretest probability of HIT depends on the patient population and specific clinical findings. The patient population at highest risk for HIT include postoperative patients receiving unfractionated heparin. Women are at a higher risk than men.[11] Patients receiving unfractionated heparin are at higher risk than those receiving low-molecular-weight heparin. Patients who have undergone cardiac or orthopedic surgery have the highest risk.

Four clinical factors, described as the "4 Ts" Clinical Scoring System, are commonly used to further assess clinical probability of HIT (Table 2)[12]:

1. *Thrombocytopenia*—a 50% decrease from baseline platelet count
2. *Timing* of platelet count decrease—between 5 and 10 days after heparin exposure
3. *Thrombosis* or other sequelae—newly confirmed thrombosis or skin necrosis
4. *Presence of other causes* for thrombocytopenia—no other apparent etiology

The diagnostic approach to HIT should account for the pretest probability of the disease based on patient profile, timing, degree of thrombocytopenia, and detection of antibodies directed against heparin–PF4.[13] Other causes of thrombocytopenia must be sought and ruled out.

Two clinical variants of type II HIT have been described. Patients who have received heparin previously and have preformed antiheparin–PF4 antibodies may develop rapid decreases in platelet count within hours of the second heparin administration. Rarely, delayed-onset HIT may occur more than 10 to 14 days after initiation of heparin or even after heparin has been discontinued.

Treatment of HIT occurs in three phases: initial treatment, transition treatment, and maintenance.

Initiation of treatment must include immediate discontinuation of all forms of heparin and initiation of parenteral anticoagulation with a direct thrombin inhibitor or factor Xa inhibitor. Immediate initiation of a non-heparin anticoagulant is required as the risk of thrombosis remains significantly elevated after heparin is discontinued.[14] Patients receiving oral coumadin at the time of diagnosis should also have coumadin immediately discontinued due to the risk for precipitation of thrombosis. Argatroban infusion adjusted to an activated partial thromboplastin time (aPTT) of 1.5 to 3.0 times the patient's baseline level is commonly used for immediate treatment. Options for initial treatment include lepirudin, bivalirudin, and fondaparinux. Oral direct thrombin and Xa inhibitors (dabigatran, apixaban, rivaroxaban) have not been studied or approved for treatment of HIT. Parenteral anticoagulation should be continued until the platelet count has recovered and remains stable.

Transition treatment with combination of parenteral non-heparin anticoagulant and vitamin K antagonist (coumadin) is required for two reasons. Patients remain hypercoagulable for 30 days or longer.[15] Second, unopposed decreases in protein C concentration after vitamin K antagonist treatment may produce a hypercoagulable state resulting in arterial thrombosis and skin necrosis. Overlap of dual therapy should be continued for at least 5 days.

Maintenance therapy with coumadin/vitamin K antagonist should be continued for 3–6 months.

ITP

ITP is characterized by isolated thrombocytopenia in the setting of normal coagulation time measurements and absence of other RBC or WBC abnormalities. The peripheral blood smear should be carefully examined to exclude spurious thrombocytopenia (clumped or giant platelets not detected in automated counter) and microangiopathic hemolytic anemias (schistocytes and RBC fragments present). Drug-induced thrombocytopenia should be excluded from consideration in all patients. Clinical manifestations include petechiae, purpura, mucosal bleeding, menorrhagia, and epistaxis. GI hemorrhage may occur, but massive hemorrhage and intracranial hemorrhage are uncommon.

ITP results from autoantibodies directed against platelet glycoproteins. There are suggestions that autoantibodies to platelets may develop after viral infections (particularly in children) and in systemic autoimmune disease (systemic lupus, antiphospholipid antibody syndrome); however, no specific inciting event is found in many patients.

Treatment is indicated in all patients with ITP and increased risk for bleeding and those with severe thrombocytopenia, typically 30,000–50,000/μL.[16] First-line treatment for ITP is corticosteroids. Refractory cases may be treated with IV immunoglobulin or anti-Rh_o(D) immune globulin in patients who are Rh-positive. Platelet transfusions alone do not effectively increase the platelet count in ITP, but may be necessary in combination with pulse-dose corticosteroids or IV immunoglobulin if the patient experiences clinically significant bleeding (eg, intracranial hemorrhage). Second-line therapies used primarily for management of chronic refractory disease include splenectomy, rituximab (anti-CD-20 B-cell antibody), and eltrombopag (thrombopoietin receptor agonist).[17]

TTP and the Hemolytic Uremic Syndrome

TTP and the hemolytic uremic syndrome (TTP-HUS) comprise a thrombotic microangiopathy that results from the abnormal activation and intravascular aggregation of platelets accompanied by intravascular hemolysis. TTP-HUS is identified by the presence of hemolytic anemia and thrombocytopenia. Untreated, the mortality of TTP approaches 100%. Since the widespread use of plasma exchange, the mortality rate for TTP has fallen to 10% to 35%.[18,19] Epidemiologic data from the United States has demonstrated a higher rate of disease in women compared with men and a higher mortality rate in blacks compared with whites.[20]

Both TTP and HUS are thrombotic microangiopathies characterized by platelet activation, microvascular platelet thrombi, and microangiopathic hemolytic anemia. Traditional definitions of TTP and HUS are based on slightly different clinical presentations. TTP is characterized by the clinical pentad of hemolysis, thrombocytopenia, neurologic defects, fever, and renal dysfunction. TTP may be idiopathic, congenital, or occur secondarily in systemic infections. Neurologic defects tend to be more prominent in TTP and include a spectrum of manifestations from headache, mental status abnormalities, focal defects, seizures, or coma. Renal defects ranging from mild renal insufficiency to acute renal failure may be found in both TTP and HUS, but are more prominent in HUS. HUS has been described more frequently in childhood and younger adults and typically presents immediately after bacterial infection.

Common infection syndromes that precede thrombotic microangiopathy include gastroenteritis from enterotoxin-producing, enterohemorrhagic bacteria including *Escherichia coli* O157:H7, *E coli* O104:H4, or *Shigella,* and acute bacterial infection in patients with HIV disease.[21,22] TTP-HUS also occurs sporadically and has been

Table 3—*Distinguishing Features of Coagulopathies*

	PT, aPTT	Platelets	Fibrinogen	D-Dimer	Other Features
ITP	Normal	Decreased	Normal	Normal	Normal RBC
TTP-HUS	Normal	Decreased	Normal	Normal	Schistocytes
DIC	Prolonged	Decreased	Decreased	Elevated	Schistocytes
Liver disease	Prolonged	Normal to decreased	Normal to decreased	Normal to mild elevation	Stigmata of liver disease
Massive transfusion/ trauma	Prolonged	Decreased	Decreased	Normal	Hypothermia, acidosis

PT = prothrombin time; aPTT = activated partial thromboplastin time.

well described in postpartum patients, patients with recent viral infection including HIV, transplant patients receiving immunosuppression, patients with cancer receiving chemotherapy, and patients with collagen vascular disease. The underlying causes of TTP are congenital or acquired inhibition of the von Willebrand factor cleaving protease.[23,24]

The laboratory features of TTP-HUS include thrombocytopenia, anemia, and schistocytes on peripheral blood smear. The thrombocytopenia in TTP-HUS tends be severe with levels usually $<50{,}000/\mu L$. Additional features include elevations of lactate dehydrogenase and serum bilirubin levels, which result from hemolysis. Urinalysis may demonstrate decreased creatinine clearance, proteinuria, and hematuria. Unlike DIC and liver disease, TTP-HUS is not associated with consumption of coagulation proteins. In TTP-HUS the prothrombin time (PT), aPTT, and fibrinogen levels remain within the normal range. From a clinical standpoint, TTP-HUS may be distinguished from DIC by the absence of clinical syndromes of trauma, shock, and sepsis typically associated with DIC (see DIC section, discussed later; Table 3).

The treatment of TTP-HUS requires emergent initiation of plasma exchange. If diagnostic uncertainty exists, plasma exchange should be initiated until an alternative diagnosis is established. Plasma infusion alone is less effective and is limited by the volume of plasma required to produce a clinical effect.[18,19] Patients with TTP-HUS may develop shock, respiratory failure, or neurologic deterioration. Although plasma exchange may be performed through peripheral venous access, central venous hemodialysis catheters are often used. Treatment with daily plasma exchange is indicated until the patient has platelet counts $>150{,}000/\mu L$, resolving anemia, resolution of renal failure, and normalization of neurologic deficits. Other indicators of therapeutic response include decreases in serum lactate dehydrogenase values and resolution of the abnormal peripheral blood smear. Typically, patients will require 1 to 2 weeks of plasma exchange treatments tapered from daily treatments to every other day to every third day. Refractory cases, late-responding patients, and relapsed patients may require treatment for 4 to 6 weeks. Patients who fail to respond to plasma exchange should be considered for high-dose steroid therapy or splenectomy.

Complex Coagulopathies

Epidemiology and Outcomes of Coagulopathy in Patients in the ICU

Critical illness predisposes to coagulopathy by multiple mechanisms including activation and consumption of coagulation factors through inflammation and vascular disease; insufficient coagulation factor production; and preexisting nutritional, metabolic, and bone marrow disease. A single center study[25] of 1,923 patients admitted to the ICU showed 30% of patients developed abnormal international normalized ratio (INR) values >1.5. Risk factors for coagulopathy included male sex, liver disease, sepsis, prior coumadin use, renal disease, and RBC transfusion. Abnormal INR values were strongly correlated with increased ICU mortality.

DIC

DIC is characterized by systemic activation of the clotting cascade, fibrin deposition throughout

the microvasculature, fibrinolysis, and consumption of clotting factors. The primary pathophysiology of DIC is thrombosis and the secondary pathophysiology is bleeding from depletion of clotting components and active fibrinolysis. Organ damage and hemodynamic collapse occur as the result of ischemia from microvascular thrombosis and hemorrhage.

The final common pathway in the development of DIC is massive thrombin generation and diffuse intravascular fibrin formation. This occurs as the result of exposure of the blood to procoagulants such as tissue factor and tissue thromboplastins. Predisposing factors for DIC include massive tissue injury (eg, pancreatitis), extensive vascular endothelial injury, shock of any cause, amniotic or fat embolism, traumatic brain injury, malignancy, severe infection with exposure to endotoxin, and massive release of inflammatory cytokines. Systemic activation of thrombosis results in a state of fibrinolysis characterized by rapid lysis of thrombosis, multifocal sites of bleeding, and accumulation of plasma fibrin degradation products.

Clinical and laboratory features of DIC include abnormalities in all aspects of blood and coagulation including hemostasis, RBCs, platelets, coagulation factors (Table 3). Bedside findings include petechiae, ecchymosis, and bleeding from venipuncture sites, surgical wounds, and noninjured mucosal surfaces. Peripheral blood smear demonstrates microangiopathic hemolysis with schistocytes. Thrombocytopenia occurs through diffuse intravascular activation and consumption of platelets.

DIC is a clinical diagnosis established by the presence of the appropriate clinical condition, exclusion of other similar conditions, and consistent laboratory findings. The appropriate clinical conditions include sepsis, trauma, burns, massive surgery, severe toxic reactions, transfusion reactions, and conditions known to be associated with systemic inflammatory response. Similar conditions that must be ruled out include TTP-HUS, isolated thrombocytopenia, coagulopathy of liver disease, and drugs/medications including anticoagulants. Scoring systems have shown to correlate with the progression/natural history of DIC. These have been based on presence of systemic inflammatory response syndrome (SIRS) criteria, severity of thrombocytopenia, severity of PT/INR deviation, and elevation of fibrin degradation products (Table 4).[26,27] The aPTT and PT are prolonged and reflect consumption of clotting factors in the common, intrinsic, and extrinsic coagulation cascade. A characteristic of DIC is the presence of fibrin degradation products and elevated D-dimer levels. Because plasma fibrinogen is an acute phase reactant, patients with inflammation, pregnancy, or malignancy may have an elevated baseline fibrinogen level. Thus, fibrinogen alone has a poor discrimination value and patients with DIC may have normal or decreased fibrinogen level. Other markers of DIC include detectable plasma fibrin monomers, decreased plasma antithrombin activity, and decreased levels of individual clotting factors, particularly factor VIII.

The presence of DIC is associated with increased ICU mortality in all patient subgroups. A representative, prospective multicenter series[26] demonstrated a 21.9% mortality rate at 28 days. Furthermore, combined indexes for DIC, which include D-dimer, platelet count, PT, and fibrinogen levels, correlate well with acute physiology and chronic health evaluation-II score and are predictive of mortality in general ICU populations.[28] The treatment of patients with DIC is focused on treating the underlying disorder. The benefit of prophylactic transfusion of blood products for patients without active bleeding or with low risk for bleeding has not been established. High-risk patients or actively bleeding patients should receive platelets to maintain at least 20,000–50,000/μL and fresh-frozen plasma (FFP) and cryoprecipitate to maintain a reasonable PT and fibrinogen concentration >50 mg/dL. Heparin treatment is indicated for patients with DIC who develop clinically apparent thrombosis.

Combined Coagulopathy of Hepatic Disease

Acute liver failure and severe chronic hepatic disease are associated with multiple simultaneous defects in hemostasis and coagulation functions. The liver produces clotting factors including fibrinogen, prothrombin, as well as factors V, VII, IX, X, XII, and XIII. Liver disease may result in a deficient production of the vitamin K-dependent

Table 4—*Clinical Diagnosis of Disseminated Intravascular Coagulation and Clinical Scoring System*

Clinical Conditions Associated With DIC
Sepsis
Trauma, severe burns, major surgery
Vasculitis
Severe toxic or immunologic reactions (eg, transfusion reaction, snake bite)
Malignancy
Severe organ destruction including pancreatitis, fulminant hepatic failure
Fat and amniotic fluid embolism
Conditions that must be ruled out before diagnosis of DIC
TTP, HIT, ITP
Thrombocytopenia secondary to viral infection, drugs, myelodysplastic syndrome
Coagulopathy of liver disease/cirrhosis
Coagulopathy of massive transfusion
Scoring algorithm for DIC if clinical condition is associated with DIC present and other conditions are excluded
Systemic inflammatory response syndrome criteria (temperature, respiratory rate, heart rate, WBC)
1–3 or more points meet SIRS criteria
0–2 or fewer points meet SIRS criteria
Platelet count
3 points—<80,000/μL or >50% decrease/24 h
1 points—>80,000/μL < 120,000/μL or >30% decrease/24 h
0 points—>120,000/μL
Prothrombin time
1 point—INR ≥1.2
0 point—INR <1.2
Fibrin degradation products
3 points—> 25 mg/L
1 point —10–25 mg/L
0 point—<10 mg/L
Clinical diagnosis of DIC—sum of ≥4 points

Adapted from Gando et al.[26]

factors (II, VII, IX, and X), as indicated by prolonged PTs. Laboratory features of coagulopathy in liver disease include thrombocytopenia, prolonged PT and aPTT, and normal or low fibrinogen levels. Patients with liver disease may also develop primary fibrinolysis associated with mildly elevated D-dimer levels.

Although advanced liver disease would appear to result in a hypocoagulable state, this effect is counterbalanced by concurrent underproduction of the anticoagulants protein C and antithrombin. There is evidence that patients with liver disease are not protected against thrombosis such as portal venous thrombosis and deep venous thrombosis.[29] Furthermore, patients with advanced liver disease may retain significant ability to generate thrombin despite significantly prolonged abnormal PT and aPTT.[30] These observations suggest that despite the outward evidence of clinical bleeding and prolonged coagulation times, bleeding in patients with advanced liver disease may have other important causative factors such as portal hypertension, endothelial dysfunction, renal failure/uremia, and infection.[31]

In addition to coagulation proteins, the liver produces thrombopoeitin. For patients with advanced liver disease, thrombopoeitin deficiency in combination with portal hypertension/hypersplenism and toxic effects of viral hepatitis or alcohol on the bone marrow may combine to produce thrombocytopenia.

Coagulopathy associated with liver disease is distinguished from DIC by the presence of only small-to-moderate elevations in D-dimer levels and preservation of factor VIII levels (factor VIII is not synthesized in the liver and is consumed only in DIC) (Table 3). Treatment for patients with coagulopathy of liver failure includes prophylactic vitamin K supplementation and, if bleeding is present, platelet and FFP or cryoprecipitate

transfusions. The role of prophylactic plasma transfusion in patients with hepatic disease is debated. Several small studies have demonstrated a very small complication and hemorrhage rate with paracentesis in the setting of advanced liver disease.[32,33]

Heparin, Warfarin, Oral Thrombin, and Factor Xa Inhibitors

Heparin therapy produces a prolonged aPTT and thrombin time. If a patient requires invasive procedures while receiving heparin, it is recommended that unfractionated heparin be discontinued 6 h before the procedure and low molecular weight heparin be discontinued 12 to 24 h before the procedure. For patients who require urgent intervention, have had heparin overdoses, or who develop severe bleeding complications while receiving heparin, protamine sulfate may be administered to neutralize the effect of unfractionated heparin. Protamine is not labeled in the US by the Food and Drug Administration (FDA) for reversal of low molecular weight heparin. Protamine may cause hypersensitivity reactions and severe hypotension from anaphylactoid reactions.

Warfarin administration results in prolonged PT, which may persist for 2 to 5 days after its discontinuation. Clinical guidelines have been published on management of excessively prolonged INR with or without bleeding for patients taking coumadin.[34] Patients with mild elevations in INR (<5) and without evidence of bleeding should have their next warfarin dose held and be followed with more frequent PT monitoring. Patients with higher elevations of INR (>5) should be treated with 1–2 mg of oral vitamin K. Patients with extreme elevations in INR (>9) are at increased risk of life-threatening hemorrhage, should be hospitalized, and treated with 5 to 10 mg of oral vitamin K. Patients who develop severe, hemodynamically significant bleeding at any level of INR while receiving warfarin should be treated with 10 mg of slow-infusion IV vitamin K. These patients should also receive FFP. Consideration should be given to administration of prothrombin complex concentrate (PCC) or recombinant activated factor VIIa if hemorrhage persists.[34] However, these uses for PCC and activated factor VIIa are not labeled indications in the United States by the FDA.

Several newer oral anticoagulants may have increased use in patients with atrial fibrillation including dabigatran etexilate, a direct thrombin inhibitor, and rivaroxaban, a factor Xa inhibitor. Both agents have raised concerns about excess bleeding risk. At present there is no specific antidote for either agent. Bleeding complications in patients taking these medications should include supportive measures. Investigations have shown some efficacy of PCCs for reversal of rivaroxaban; however, this remains an unlabeled use for PCCs in the United States.[35]

Massive Transfusion and Coagulopathy of Trauma

Massive transfusion has been clinically defined as replacement of more than 50% of a patient's blood volume within 24 h. Alternative definitions range from replacement of 100% blood volume within 12 h to administration of more than 10 units of packed RBCs within 24 h. Risk factors for mortality in patients admitted to an ICU and receiving massive transfusion include coagulopathy on admission, metabolic acidosis, and number of RBC transfusions.[36,37]

The immediate cause of complex coagulopathy in patients receiving massive transfusion is dilution of coagulation factors by crystalloid and packed RBC solutions. Also, existing coagulation factors and platelets are consumed by the underlying massive tissue and vascular disruption. Hypothermia and metabolic acidosis may exacerbate the coagulopathy.

The coagulopathy of trauma and massive transfusion is characterized by bleeding from mucosal lesions, serosal surfaces, surgical wounds, and vascular access sites.[38] Risk factors for the development of severe coagulopathy in trauma include metabolic acidosis, hypothermia, hypotension, and severe injury.[39] Patients who require massive transfusion for treatment of hemorrhagic shock or major trauma are also at high risk for DIC. Thus, the distinction between coagulopathy associated with massive transfusion and DIC may be difficult to discern. In general, massive transfusion is not associated

with elevated D-dimers or decreased in factor VIII (Table 3).

The clinical approach to monitoring and treating a massive transfusion is focused on two main priorities: establishment of hemostasis and maintenance of adequate coagulation function. Hemodynamic stability must be established by control of the underlying bleeding source, replacement of adequate intravascular volume, and maintenance of adequate hemoglobin concentration to support tissue oxygenation. Coagulation factors and platelets may become rapidly diluted or depleted in patients receiving a massive transfusion. It is estimated that transfusion of approximately 10 units of RBCs in an average adult is associated with decreases in plasma coagulation proteins to 20% to 30% of baseline levels.

Resuscitation in massive transfusion should anticipate development of coagulopathy and close monitoring of the PT, aPTT, fibrinogen level, and platelet count. Platelet transfusion and replacement of coagulation proteins with FFP and cryoprecipitate should be guided by laboratory results obtained after transfusion of every 5 to 10 units of packed RBCs. Although transfusion protocols have been proposed for replacement of blood, plasma, and platelets in fixed ratios in major trauma victims, these protocols have not been systematically evaluated in general medical patient populations.[40] For trauma patients who receive less than 10 units of packed RBC per 24 h, administration of fixed ratios of plasma, platelets, and blood showed no benefit and suggested possible harm through increased ICU and ventilator days.[41] Despite the significant impact of transfusion practice on trauma outcomes, resuscitation of patients given massive transfusions should only be given in a fixed-ratio manner to patients with massive trauma who are anticipated to require more than 10 units RBCs during the initial resuscitation.[42,43]

A wide range of metabolic and electrolyte abnormalities require monitoring and treatment in patients given massive transfusions. Citrate used as an anticoagulant in packed RBCs may result in hypocalcemia through binding of serum calcium. Massively transfused patients should have monitoring of serum-ionized calcium at regular intervals and replacement with calcium gluconate, if necessary. Additional electrolyte disorders related to citrate and packed RBCs include metabolic alkalosis from metabolism of citrate to bicarbonate and hyperkalemia from the presence of excess extracellular potassium in stored blood. Patients with renal failure are at increased risk for these side effects and warrant frequent pH and potassium monitoring. As the result of refrigerated blood, below body temperature IV fluids, and exposure, many trauma/massive transfusion patients will develop clinically significant hypothermia. For patients who receive more than 3 to 4 units of blood, a blood warmer should be used.

Platelet Transfusion

Platelets are collected by centrifugation of fresh whole donated blood or by pheresis from a single donor. Generally, 1 pheresis unit of platelets contains five to six times the number of platelets from 1 unit of donated whole blood. The primary indication to use single donor pheresis platelets is to reduce the risk of immunization and platelet sensitization in recipients who are frequently exposed to transfusion. Although in adults random-donor platelets from donated blood must be pooled or combined for most clinical uses, these platelets are more widely available than pheresis units. Platelets should not be refrigerated and are stored up to 5 days from collection in plasma and electrolyte solutions in a volume of 250–350 mL. In comparison to RBC units, this short storage life is more likely to place constraints on the supply and availability of platelets, particularly in smaller institutions. Platelet transfusion does not require ABO matching. Nevertheless, many clinicians select ABO-matched products to reduce the risk of immune reactions and improve the platelet survival. RhD(–) women and girls should receive only RhD-negative platelets, but may receive RhD(+) platelets in combination with Rh immune globulin.

There are two main indications for platelet transfusion: controlling bleeding in patients who have thrombocytopenia and prevention of bleeding in patients with profound thrombocytopenia. Indications for platelet transfusion are related to the underlying disease process, presence or

Table 5—*Indications for Platelet Transfusion*

Clinical Characteristics	Transfusion Trigger (transfuse to maintain circulating platelet count at least)
Thrombocytopenia—acute or chronic	
No active bleeding	Observation only. Some investigators advocate transfusion threshold of 5,000/μL
Active bleeding present	50,000/μL
Leukemia and hematopoietic stem cell transplantation and patients receiving therapy for solid tumors	10,000/μL
Surgical and invasive procedures	
Preoperative	40,000–50,000/μL
Recent surgery or invasive procedure already performed	20,000–50,000/μL

Upwards adjustments must be considered as clinically indicated in the presence of concurrent coagulopathy or anticoagulant treatment. See Schiffer et al.[44]

absence of active bleeding, anticipation of invasive procedures, and platelet count. Indications for platelet transfusion are reviewed in Table 5.

In clinical practice, each unit of pooled, random-donor platelets increases the circulating platelet count by 5,000–10,000/μL in patients with average body size. In comparison, 1 pheresis platelet unit may increase the platelet count by 30,000–60,000/μL. Routine monitoring of platelet transfusion should include post-transfusion platelet count to determine transfusion responsiveness. Failure of the circulating platelet count to increase may result from destruction of the transfused platelets or consumption of the platelets at sites of injury or clot activation. Risks for ineffective platelet transfusion include ITP, presence of antiplatelet antibodies, DIC, drug-induced thrombocytopenia, and sepsis. Platelet transfusions are relatively contraindicated in TTP-HUS unless the patient has severe bleeding. In general, platelet transfusions are ineffective if the cause of thrombocytopenia is enhanced destruction of circulating platelets because the transfused platelets are destroyed through the same mechanism. In addition, patients with uremia or who are taking aspirin or clopidogrel are not likely to have significant benefit from platelet transfusion unless the medications are discontinued and the uremia corrected.

FFP

FFP is prepared by separating plasma from single units of donated whole blood. The plasma is frozen at −18° C within 8 h of collection and has a storage life of 1 year. Each unit of FFP must be thawed immediately before use. Delay in transfusion after thawing results in declines in factors V and VIII. FFP should be used within 24 h of thawing. Each unit of FFP contains 250 mL of volume, which is administered in IV bolus or rapid infusion. FFP must be matched to donor ABO blood group. Use of FFP is associated with the same risks for infection and transfusion-associated acute lung injury as packed RBCs.

FFP contains all of the coagulant factors and coagulation inhibitors in typical blood. By convention, 1 mL of FFP is equivalent to 1 unit of blood coagulation factor activity. Typical dosage of FFP is 10–15 mL/kg, which should restore coagulation factors to 25%–30% normal levels.[45] It has been suggested that this dosage level is inadequate and that 30 mL/kg is more likely to correct all coagulation factors.[46] An observational study[47] described the median dose of 17 mL/kg FFP in patients who achieved correction of INR compared with 10 mL/kg in patients who did not correct their PT INR.

The indications for FFP are listed in Table 6. FFP should not be used as a primary method for intravascular volume expansion. FFP should also not be used as a primary means of replacement of isolated factor deficiencies when concentrated single factor replacement products are available. For example, recombinant factor VIII concentrate rather than FFP should be used in patients with hemophilia A. The decision to use FFP should be guided by clinical bedside evidence of coagulopathy and by measurements

Table 6—*Indications for Fresh-Frozen Plasma*

Replacement of individual factor deficiencies if no purified fractionated product available
Reversal of warfarin in patients with bleeding or emergent surgery
Correction of multiple simultaneous factor deficiencies
Plasma replacement in thrombotic thrombocytopenic purpura
Treat coagulopathy of massive transfusion
Coagulopathy of liver disease if bleeding is present

of the PT, aPTT, and other coagulation assays. Approaches to FFP transfusion based on formulas such as 2 units of FFP per 4 units of RBC transfusion are not appropriate in most medical patients or in patients not receiving massive transfusion.

The effect of FFP on coagulation times, bleeding risk, and clinical outcomes may be significantly less than assumed. A systematic review[48] of 80 clinical trials of FFP in a wide range of clinical uses demonstrated no consistent evidence of significant clinical benefit for either prophylactic or therapeutic use. An important factor in reducing the potential benefit of plasma is the development of significant complications. Acute lung injury and ARDS occur more frequently in patients receiving blood products and this risk is greatest with FFP.[49]

Cryoprecipitate

Cryoprecipitate is the precipitate that remains after FFP is thawed to 4° C. Cryoprecipitate contains fibrinogen, fibronectin, von Willebrand factor XIII, and factor VIII. Cryoprecipitate may be reconstituted in very low volumes (10–15 mL) and thus has a significant advantage over FFP in volume overloaded patients. Each unit of cryoprecipitate contains the precipitate from the plasma of 1 donated blood unit. The primary indication for cryoprecipitate is replacement of fibrinogen in patients with hypofibrinogenemia caused by dilution or consumptive coagulopathy. The dose of cryoprecipitate should be titrated to maintain a target plasma level of fibrinogen at more than 100 mg/dL. This usually requires 5–10 units of cryoprecipitate for the initial dose. Fibrinogen levels should be reassessed frequently to determine optimal dose and dosing interval.

Correction of Thrombocytopenia and Coagulopathy for Routine Bedside Procedures

A consistent source of variation in clinical practice is the use of platelet and FFP transfusions before bedside procedures including central venous catheter (CVC) placement, thoracentesis, and paracentesis. In general, there is limited evidence to support routine preprocedure transfusion for patients with mild elevations in PT, aPTT, or thrombocytopenia. In a cohort[50] of 1,825 patients undergoing CVC placement, the rate of bleeding complications was 3 of 88 patients with uncorrected coagulopathy (range of platelet count 12,000–46,000/μL, and PT INR 1.1–1.5). There were no severe complications requiring transfusion or surgical intervention. Similarly, a cohort[51] of 76 patients with coagulopathy, thrombocytopenia, or both undergoing CVC placement had only one significant bleeding complication requiring blood product transfusion and 6.5% minor bleeding complications defined as oozing from the catheter insertion site. Finally, in a cohort[52] of 40 coagulopathic liver transplant patients (average PT 29% of control, average aPTT 92 s, average platelet count 47,000/μL) who underwent 259 catheterizations without corrective transfusions, there were no reported serious bleeding complications. The overall frequency of bleeding complications in a cohort of 608 consecutive patients having thoracentesis or paracentesis was 0.2%. The mildly coagulopathic group with average PT and aPTT less than twice normal and platelet count 50,000–100,000/μL did not have an increased risk of bleeding complications.[53] In summary, bedside line insertions, thoracentesis, and paracentesis appears to be safe without increased risk of bleeding complications in patients with mild coagulation abnormalities.

DDAVP, PCC, Activated Factor VII, and Other Hemostatic Agents

DDAVP is a synthetic vasopressin analogue that stimulates vascular endothelial cells to release von Willebrand factor and increases plasma factor VIIIc. DDAVP was initially estab-

lished for treatment of bleeding in patients with hemophilia and von Willebrand disease. There are no data to recommend routine DDAVP in the general population with bleeding. There may be a limited role for DDAVP in the treatment of patients with qualitative platelet defects such as those taking aspirin and patients with uremia.

Epsilon-aminocaproic acid and tranexamic acid inhibit the binding of plasmin to fibrin and thus inhibit fibrinolysis. As with DDAVP, there is no clinical evidence to support the routine use of these agents in the general ICU population. There is a limited role of these agents in patients with hemophilia and profound refractory thrombocytopenia who have active bleeding. The most significant side effect of epsilon-aminocaproic acid is an increased risk of thrombosis.

Recombinant activated factor VII was originally developed to provide specific factor replacement and hemostasis in patients with hemophilia and congenital factor VII deficiency. In the United States, the only FDA-approved indication for the drug is for treatment of bleeding in hemophiliac patients with antibody inhibitors to coagulation factors VIII and IX. Off-label uses appear in case report and case series literature and have included correction of bleeding associated with trauma, intracranial hemorrhage, coagulopathy of liver disease, and reversal of warfarin-associated bleeding. The use of recombinant factor VII in these clinical scenarios does not consistently show benefit in the reduction of bleeding or mortality. Systematic review[54] of available published evidence suggests no overall mortality reduction with recombinant activated factor VII use in these off-label indications. The use of recombinant activated factor VII is associated with increased risk for thrombosis and thromboembolic disease.

PCCs are manufactured either by fractionation of plasma cryoprecipitate or through recombinant factor production. These products contain concentrated or activated coagulation factors and are intended for use to correct bleeding in patients with known factor deficiency or factor inhibitors. Off-label use has included patients with trauma, bleeding in patients with liver disease, anticoagulation overdose, and massive hemorrhage. Recently, PCCs have been evaluated in the correction of coagulopathy secondary to use of oral direct thrombin and factor Xa inhibitors.[35]

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Chapter 25. Gastrointestinal Bleeding in the ICU

Nikhil R. Asher, MD; Kevin McGrath, MD; and Douglas B. White, MD, MAS

Objectives:

- Identify high risk patients presenting with acute GI bleeding (GIB); recognize patients in the ICU at highest risk of developing GIB.
- Develop an effective strategy for initial evaluation and management of patients with acute, severe GI hemorrhage.
- Recognize risk factors for recurrent upper GI hemorrhage and discuss management strategies to reduce risk of recurrent bleeding.
- Discuss therapeutic options for management of patients with lower GIB.
- Discuss appropriate stress ulcer prophylaxis in critically ill patients.

Key words: GI bleeding; peptic ulcer disease; resuscitation; stress ulceration; variceal hemorrhage

Synopsis:

GI bleeding (GIB) associated with high-risk features should be managed within an ICU setting. Patients presenting with GIB must have timely identification of high-risk features and appropriate management. Furthermore, patients already admitted to an ICU for an unrelated diagnosis are at risk for GIB. Critically ill patients at risk for GIB must receive appropriate prophylactic therapies. This review covers the key aspects of evaluation and management of patients with acute, severe GI hemorrhage and discusses risk-reduction strategies for GIB arising in ICU patients.

Incidence

The annual incidence of hospitalization for acute upper GI bleeding (GIB) is 1 in 1,000 people in North America.[1] Acute GI hemorrhage is associated with mortality as high as 7% to 10%.[2] Mortality risk is particularly pronounced in elderly patients and patients with multiple comorbid conditions. Critically ill patients that develop clinically significant bleeding in an ICU have mortality as high as 48% compared with 9% in ICU patients without bleeding.[3]

Evaluation

Patients presenting with acute, severe GIB should have a focused evaluation with initial emphasis on patient stabilization and appropriate triage. History should focus on bleeding acuity and severity, associated symptoms, past history of similar bleeding episodes (60% of upper GIB episodes are from the same lesion), liver disease, alcoholism, and recent use of medications such as nonsteroidal antiinflammatory drugs or anticoagulants. Vital parameters indicating significant blood volume loss are resting tachycardia, orthostatic hypotension, decreased urine output, tachypnea, and hypoxemia. Initial laboratory analysis may not reveal blood loss anemia, particularly in patients with acute hemorrhage. A urea to creatinine ratio of 100 or higher generally indicates an upper GI source of bleeding.[4]

Role of Nasogastric Lavage (NGL)

It is important to determine whether GIB is from an upper or lower GI source because of the different management implications. Traditionally, bleeding arising above the ligament of Treitz is classified as upper GIB (UGIB), whereas distal bleeding is classified as lower GIB (LGIB). Although certain clinical manifestations such as hematemesis and/or melena (passage of black, tarry stools) usually indicate an UGIB, these are not consistently present. Bright red blood per rectum is generally associated with a LGIB but may occur in patients with large quantity, brisk UGIB due to the rapid transit of blood through the GI tract. NGL aids in the identification of potential upper GI source of blood loss. NGL is associated with earlier time to endoscopy, and bloody nasogastric (NG) aspirates are indicative of high-risk lesions.[5] However, performing NGL does not affect mortality. In addition, a nonbloody NG aspirate does not rule out a duodenal ulcer bleed, as 10 to 15% of bleeding duodenal ulcers do not reflux blood into the stomach.

Risk Stratification

Clinically significant GIB is marked by any one of the following features within 24 h of onset (in the absence of obvious other causes):

1. Increase in resting heart rate by more than 20 beats per min
2. Spontaneous decrease of more than 20 mm Hg in systolic BP
3. Decrease in BP with change in position from supine to sitting up of more than 10 mm Hg
4. Decrease in hemoglobin level of more than 2 g/dL from baseline
5. Failure of hemoglobin to rise with blood transfusion

High-risk clinical criteria for recurrent bleeding are: age >65 years, comorbid conditions, low initial hemoglobin, melena, fresh blood on rectal exam, hematemesis, bloody NG aspirate, and transfusion requirements.

There is an increased risk of death in patients >60 years with comorbid conditions, patients presenting with shock, patients with continued bleeding or recurrent bleeding, and patients with onset of bleeding while hospitalized for another condition.[6,7]

Risk assessment must be performed to identify high-risk patients who require timely endoscopic management, and these patients should be monitored within an ICU setting.

General Management

Volume resuscitation is first priority in patients with acute severe GIB.

Vascular Access

Larger diameter, shorter IV catheters are most effective for resuscitation. Large-bore peripheral IV lines (preferably 18G or larger) are used for resuscitation and are generally more efficacious than a 15/20 cm, small-diameter central venous triple lumen catheter. This is because Poiseuille's law dictates that the velocity of blood passing through a tube is directly related to the internal radius of the tube and inversely related to its length. In patients that require massive transfusions and/or those who do not have adequate peripheral access, a short, large lumen, central venous catheter should be placed (eg, an introducer sheath). Flow rates with different gauge IV lines are shown in Table 1.

Table 1—*Blood Flow Rates Through IV Catheters With Different Lumen Sizes*

IV Gauge	Flow Rate, mL/min
22G	38
20G	63
18G	110
16G	215
Triple lumen catheter	98 (all three lumens combined)
16G	52
18G	22
18G	24
Introducer catheter 8.5F	600

Resuscitation

The decision to transfuse packed RBCs (pRBCs) to replace lost blood volume depends on several clinical factors such as presence of ongoing blood loss, high-risk clinical features discussed above, and presence of comorbid conditions. In select patients with self-limited bleeding and absence of high-risk features, blood loss anemia of hemoglobin 7 to 10 g/dL may be well tolerated without need for pRBC transfusion. However, it is important to note that patients with active GIB are not appropriate candidates for conservative transfusion thresholds and were excluded from studies assessing the safety of such thresholds.[8]

Patients with hemodynamic instability and ongoing severe bleeding will require immediate resuscitation with pRBC. Cross-matching of blood should not delay transfusion. For logistical reasons, fluid resuscitation with crystalloid solutions may often precede pRBC transfusion. For patients with life-threatening hemorrhage who have recently ingested antiplatelet agents such as aspirin or clopidogrel, pooled platelet transfusion should be considered. Attempts to rapidly correct preexisting coagulopathy must be undertaken. Furthermore, in patients requiring massive transfusions, fresh frozen plasma replacement should be undertaken at a ratio of 4:1 pRBC:FFP; albeit, recent evidence suggests that tighter ratios of

pRBC:FFP transfusion of 1:1 have improved outcomes in patients with traumatic hemorrhagic shock.[9]

UGIB

Peptic ulcer disease (PUD) accounts for about half of all patients with UGIB. Risk factors for PUD include *Helicobacter pylori* infection, use of nonsteroidal antiinflammatory drugs or aspirin, prior history of PUD, smoking, and alcoholism. The most common cause of UGIB arising in critically ill patients is stress mucosal ulceration, particularly in patients with respiratory failure. Other etiologies of UGIB are summarized in Table 2 below. Table 3 summarizes principal management strategies for UGIB.

Management of UGIB

General Management

Pharmacotherapy: Empiric initiation of proton pump inhibitors (PPIs) is recommended in all patients suspected to have UGIB, even before the etiology of the bleed is confirmed.[10] PPIs neutralize gastric acid leading to stabilization of clots and promote hemostasis. A prokinetic drug such as erythromycin prior to endoscopy in patients with UGIB improves endoscopic visibility by clearing fundal clot.[11]

Intubation to diminish risk of aspiration: Prophylactic tracheal intubation of patients with UGIB requiring esophagogastroduodenoscopy (EGD) does not significantly diminish the relatively high risk of acquired pneumonia or cardiopulmonary events. It may benefit select patients that are at risk of the rare fatal occurrence of massive aspiration.[12]

EGD: EGD is used first line in the confirmation of diagnosis and hemostatic management of UGIB. EGD should be performed within 24 h of presentation with UGIB, and sooner in patients with active blood loss.

Table 2—*Causes of Acute Upper GI Bleeding in Adults*

Etiologies of UGIB	% of all UGIB
Most common lesions	
1. Peptic ulcer disease	
Duodenal ulcer	30–37
Gastric ulcer	15–20
-*H pylori* associated	
-Drug-induced ulcers	
-Stress induced	
2. Varices	5–10
-Esophageal	
-Gastric	
3. Portal hypertensive gastropathy	5–10
4. Mallory-Weiss tear	3–7
5. Erosive esophagitis	2
Less common lesions	
1. Neoplastic lesions	1–4
2. Vascular malformations, eg, gastric antral vascular ectasia	0.5–2
3. Dieulafoy's lesion: aberrant large-caliber submucosal vessel eroding the overlying epithelium	1
4. Pill-induced esophagitis: alendronate, KCL	<1
5. Aortoenteric fistula	<1
6. Infectious esophagitis or gastritis, eg, herpes, CMV, HIV, *Candida*	

Infectious esophagitis: <1%.

PUD-Associated GIB

Randomized, controlled studies have shown superiority of high-dose PPIs in preventing further bleeding after endoscopic hemostasis for peptic ulcer bleeding.[13] Typical high-dose therapy would be an 80-mg bolus of pantoprazole followed by a continuous infusion of 8 mg/h for 72 h. *H. pylori* serology should be checked and treated if positive.

In patients with PUD, EGD findings facilitate risk stratification of recurrent bleeding as shown in Table 4.[14]

Finding of low-risk endoscopic stigmata is not an indication for endoscopic hemostatic therapy. An adherent clot in an ulcer bed warrants targeted irrigation in an attempt at dislodgement, with appropriate treatment of the underlying lesion. If the clot cannot be dislodged with irrigation, the endoscopist should consider suction, cold guillotine removal with a snare, or use of hydrogen peroxide.

Hemostatic therapy indicated for high-risk endoscopic stigmata consists of cautery with bipolar probes or mechanical therapy with hemostatic clips. Injection of dilute epinephrine may precede either modality. More recent literature suggests superiority of "hemoclips" in prevention of ulcer rebleeding.[15]

Table 3—*Overview of Management for Acute, Severe Upper GI Bleeding*

Management of Suspected Acute, Upper GI Bleeding
Hemodynamic assessment and resuscitation
Assess vital parameters for volume depletion or decreased perfusion
2 large-bore IVs; consider large lumen, shorter diameter central venous catheter
Blood transfusion for patients with large bleeds with comorbidities, active bleeding, or hemodynamic instability
Risk assessment to identify patients at high risk for rebleeding or death
Identify high-risk features such as advanced age, comorbid conditions, shock, continued bleeding, and transfusion requirements
Pre-endoscopic medical therapy
IV erythromycin 250 mg approximately 30 min prior to endoscopy
IV PPI; 80-mg bolus of pantoprazole followed by 8 mg/h infusion
EGD
Performed within 24 h of admission, within 12 h in presence of high-risk features
Endoscopic hemostatic management of high-risk PUD lesions
Variceal band ligation for esophageal varices

Patients with high-risk stigmata for recurrent bleeding (nonbleeding or actively bleeding vessel) require post-EGD ICU monitoring for at least 24 h. Most rebleeding episodes occur within 72 h of the initial episode.

Early surgical consultation must be obtained in patients with severe, acute UGIB who may have aortoenteric fistula based on clinical suspicion, or those at high risk of recurrent bleeding, if repeat endoscopy is unlikely to be successful.

Variceal Bleed

Patients with advanced liver disease commonly have esophageal and/or gastric varices. In patients with esophageal varices, the 1-year risk of first-time variceal hemorrhage is 12%, whereas the 1-year risk of recurrent hemorrhage is 60%.

Risk severity of acute variceal bleeding depends on the Childs stage of underlying end-stage liver disease and hepatic venous pressure gradient. Patients with Child A or B disease with hepatic venous pressure gradient <20 can often be managed with a combination of octreotride from the time of admission until 2 to 5 days after onset of bleeding, and endoscopic therapy (preferably less than 12 h from admission). Patients with variceal hemorrhage require the administration of antibiotic therapy for prophylaxis against spontaneous bacterial peritonitis, generally either a broad spectrum beta lactam or cephalosporin.

High-risk factors for mortality from variceal bleeding are Child C end-stage liver disease and hepatic venous pressure gradient >20. Emergent EGD is necessary to differentiate esophageal from gastric variceal bleeding. For esophageal variceal hemorrhage, endoscopic therapy is recommended and consists of variceal band ligation or sclerotherapy. Band ligation is preferred; sclerotherapy is used if the culprit varix cannot be localized due to poor visibility, or if the bands do not adhere (which occurs in the setting of scarring from previous band ligation).[16] Balloon tamponade is reserved for patients with acute, severe hemorrhage with rapid hemodynamic instability, allowing temporary stabilization until definitive treatment can be instituted.

A transjugular intrahepatic portosystemic shunt (TIPS) is generally reserved for failed endoscopic therapy or recurrent variceal bleed. However, recent randomized controlled trial evidence suggests that early decompression by TIPS placement within 24 to 48 h in high-risk patients is associated with reductions in treatment failure and in mortality.[17,18] TIPS is recom-

Table 4—*Risk of Recurrent UGIB Based on Index Endoscopy Findings*

EGD Feature	Risk of Recurrent Bleeding, %
Clean ulcer base	<5
Flat spot	10
Adherent clot	22
Nonbleeding visible vessel	45
Actively bleeding visible vessel	55

mended as primary therapy for gastric variceal hemorrhage.

Bleeding Associated With Mallory Weiss Tear

Mallory Weiss tear is a longitudinal mucosal laceration involving the distal esophagus and proximal stomach and is usually associated with forceful retching. Patients with a history of heavy alcohol consumption followed by vomiting are at increased risk of developing this condition. Although bleeding associated with a Mallory Weiss tear is generally self-limited, it can sometimes present with massive upper GI hemorrhage. Endoscopic hemostatic treatment is generally required only for actively bleeding lesions; lesions not actively bleeding but associated with high-risk features for rebleeding, such as coagulopathy, portal hypertension, or endoscopic high-risk stigmata, may require in-hospital observation for 48 h.

LGIB

LGIB can be characterized by the passage of maroon or bright red blood or blood clots per rectum. Many conditions may cause GIB arising below the ligament of Treitz, but the most common cause of LGIB is diverticulosis.

Younger patients generally have bleeding arising from angiodysplasia or inflammatory bowel disease. Older patients are at increased risk of bleeding related to neoplasm or mesenteric ischemia. In many patients, the source of LGIB may be difficult to identify at colonoscopy. Various sources of LGIB are listed in Table 5 below.

High-risk patients with LGIB are those with persistent bleeding, need for multiple transfusions, hemodynamic instability, and comorbidities.

Table 5—*Causes of Acute, Lower GI Bleeding in Adults*

Etiology of Lower GI Bleeding
1. Diverticulosis: most common etiology
2. Unknown cause: 6–20% of patients
3. Bowel ischemia: suspect in elderly patients with abdominal pain
4. Anorectal disorders: hemorrhoids, anal fissures
7. Neoplasia: 10% of patients age >50
8. Angiodysplasia: jejunal/ileal or colonic
9. Post polypectomy
10. Inflammatory bowel disease
11. Radiation colitis
12. Other colitis: infectious, antibiotic associated
13. Meckel's diverticulum

Treatment

Colonoscopy is the initial examination of choice. For patients in whom the possible source (UGIB vs LGIB) cannot be clearly ascertained on clinical assessment, EGD should precede colonoscopic evaluation for GIB. Purge preparation prior to colonoscopy involves the administration of 4 to 6 L of polyethylene glycol over 2 h, as tolerated by the patient. NG tube placement may be necessary to facilitate the bowel prep. Urgent colonoscopy after a purge is safe, effective, and often diagnostic.[19]

Among patients with severe hematochezia and diverticulosis, at least one fifth have definitive diverticular hemorrhage. Treatment of choice for these patients is the application of hemoclips if the bleeding vessel can be identified. Hemostatic treatment decreases incidence of recurrent bleeding and need for surgery. Other hemostatic modalities include epinephrine injection, bipolar coagulation, or both.

Patients with ongoing bleeding without an identifiable lesion at colonoscopy may require further diagnostic modalities for source localization. Radionuclide scanning with technetium-99m-labeled red cell scintigraphy is highly sensitive at detecting bleeding occurring at rates of 0.1 to 0.5 mL/min. However, it only localizes bleeding to a general area of the abdomen and has low specificity. Therefore, it has a limited diagnostic value, possibly only in the setting prior to angiography, to determine if bleeding is significant enough to be angiographically detected. Mesenteric angiography generally detects bleeding >0.5 mL/min. Although not highly sensitive, angiography is 100% specific, and a positive angiogram is often followed by selective embolization of the bleeding source. Surgical intervention (eg, colectomy) may be required to halt hemorrhage in patients with a rapidly declining clinical course (in spite of optimal resuscitation) and in cases of failed attempts at

hemostasis, signs of acute abdomen, or recent abdominal surgery with high clinical suspicion of surgical etiology of LGIB.

Prophylaxis of Stress Ulcer Bleeding in Critically Ill Patients

Indications for stress ulcer prophylaxis in critically ill patients are: [20]

1. Mechanical ventilation of >48 h duration
2. Coagulopathy
3. Two or more of the following: sepsis, ICU admission of >1 week, occult GIB >6 days, steroid therapy

The agent of choice for prophylaxis is famotidine, via IV or oral route. There is no convincing evidence that utilization of PPIs for stress ulcer prophylaxis results in a clinically relevant decrease in GIB.[21] On the other hand, there is some evidence that use of PPI increases risk of nosocomial pneumonia.[22] Prophylaxis should be discontinued when no further indications exist.

Nothing to Disclose

The authors have disclosed that no relationships exist with any companies/organizations whose products or services may be discussed in this chapter.

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Notes

Chapter 26. Nutrition

Brian K. Gehlbach, MD

Objectives:

- Prescribe a nutritional plan for the general medical ICU patient.
- Describe common complications of enteral and parenteral nutrition, and list strategies for minimizing them.
- Cite the differential diagnosis for diarrhea in the critically ill patient.

Key words: diarrhea; enteral nutrition; nutritional support; parenteral nutrition; refeeding syndrome

Synopsis:

It has been difficult to demonstrate either the benefit or the harm to most nutritional practices in the ICU. This is likely caused in part by methodological limitations in the existing literature; however, our understanding of the interaction between nutrition and critical illness is also inadequate. A few recommendations can be made. The intensivist should be aware of the potential complications of feeding, including overfeeding syndrome and the refeeding syndrome. Enteral feeding should be started whenever possible within 24 to 48 h of admission to the ICU. There presently is insufficient evidence to recommend the use of one enteral feeding tube or location over another. Patients should be fed with the head of bed elevated. The optimal dose of nutrition is not known; however, the practice of using parenteral nutrition to supplement enteral nutrition early in the course of critical illness has been shown to cause harm and should be avoided. At the present time, the use of immune-modulating enteral formulations, such as those enriched with omega-3 fatty acids and γ-linolenic acid, cannot be recommended for patients with acute lung injury. Various forms of GI intolerance, including constipation, abdominal distension, and diarrhea, are common in critically ill patients. Metoclopramide and erythromycin may be used to facilitate enteral feeding. Diarrhea has many potential causes, including infection with *Clostridium difficile* and numerous commonly used medications. When diarrhea appears to be caused by enteral feeding, switching from intermittent bolus feeding to continuous feeding may help, as may changing the formulation to one with a lower osmolality. The blood glucose target for critically ill patients is approximately 140 to 180 mg/dL.

Overview

It has been difficult to show either the benefit or the harm of different approaches to nutritional support in critically ill patients. This is somewhat surprising, given that (1) critical illness is metabolically costly, (2) nutrition can be difficult to administer, and (3) the potential harm from malnutrition seems obvious. It is likely that progress in this area has been constrained by the following:

1. Many prior studies in this area have been underpowered or had other serious limitations in study design.
2. Previous investigations have varied greatly in the dose, timing, and route of nutritional support, making comparisons among studies difficult.
3. Most prior studies have not utilized protocols for therapies that are likely to interact with feeding, such as the administration of sedatives.
4. Patient heterogeneity may make it difficult to demonstrate the benefit or harm of a "one size fits all" nutritional strategy.
5. The benefit of nutrition, or of certain levels of nutritional support, may in some cases by outweighed by its harm, as discussed below.
6. Our understanding of the host response to critical illness, and of the role played by nutrition in mediating this response, is inadequate.

The Metabolic Cost of Critical Illness

Sepsis, trauma, and other causes of critical illness are metabolically costly. Classic studies performed in the 1970s showed that critically ill patients experience a significant increase in resting energy expenditure and an increase in protein catabolism and nitrogen excretion. The potential complications of this hypercatabolic state include immune dysfunction, skeletal muscle atrophy, peripheral and central weakness (including diaphragmatic weakness), the development of various micronutrient deficiencies, and an impaired ability to rehabilitate during recovery. In this vein, studies of survivors of

critical illness by Herridge and coworkers[1] and other groups have identified weight loss, skeletal muscle atrophy, and reduced physical function as being among the most burdensome sequelae of critical illness.

Potential Harm From Nutritional Support

The effects of certain seemingly straightforward nutritional interventions may be more complex than previously anticipated. For instance, the benefit of a nutritional plan that aims to provide more calories may be offset by an increase in aspiration or decreased glucose tolerance. It is also possible that increased nutritional support suppresses autophagy, thereby interfering with the body's clearance of microorganisms and the products of cell damage. Specific potential complications of enteral and parenteral nutrition are listed in Table 1. Below we briefly discuss two well-established syndromes that may occur in the ICU setting: overfeeding syndrome and the refeeding syndrome.

Table 1—*Potential Complications of Nutrition*

Enteral	Parenteral
Aspiration	Catheter-related bloodstream infection
Pneumonia	Hyperglycemia, antioxidant depletion
Bowel ischemia	Thrombosis
Abdominal distension pain	Availability may distract from efforts to make the gut work
Respiratory compromise	
Diarrhea	Volume overload

Overfeeding Syndrome

This occurs in the setting of excessive (particularly parenteral) nutritional support. Clinical manifestations may include one or more of the following: azotemia from excessive protein administration, hepatic steatosis, hypertriglyceridemia, metabolic acidosis, hyperglycemia, and increased CO_2 production. The latter may complicate the patient's efforts to achieve spontaneous breathing.

Refeeding Syndrome

Patients with a history of malnourishment may develop life-threatening complications when provided with increased nutritional support. Notable and unfortunate examples of this condition occurred at the end of World War II, among recently liberated victims of concentration camps and in prisoners of war. An increase in caloric intake causes an increase in insulin secretion and the increased production of glycogen, protein, and fat. This causes potassium, phosphorus, and magnesium to move from the extracellular to the intracellular space. Because the total body stores of these electrolytes are diminished from prior malnutrition, this shift may result in some patients in life-threatening hypokalemia, hypophosphatemia, and hypomagnesemia. Respiratory failure, heart failure, and arrhythmias may result. Prevention of this complication involves (1) the identification of at-risk patients; (2) close monitoring of serum biochemistry values during the initial refeeding period, with appropriate repletion of electrolytes as necessary; and (3) the prescription of vitamin B complex, thiamine, and a multivitamin. Of note, such patients are also at increased risk for various manifestations of GI intolerance provoked by feeding, including cramping, regurgitation, and nausea.

Timing, Route, and Dose of Feeding

Enteral feeding preserves the structure and function of the GI tract, preventing atrophy of the intestinal villi and preserving its barrier function. Overall, enteral feeding has been shown to reduce infectious complications when compared with parenteral nutrition. The current consensus is to start enteral feeding within the first 24 to 48 h after ICU admission.[2] The optimal dose of nutritional support is not known. A number of studies have shown that a large number of critically ill patients receive many fewer calories than recommended by established guidelines. Historically, these guidelines have recommended the provision of approximately 25 to 30 kcal/kg/d to the typical ICU patient, including 1.2 to 2.0 g/kg/d of protein. However, Krishnan and coworkers found

in a prospective cohort study that those patients who had moderate caloric intake (33%–65% of target, or 9–18 kcal/kg/d) had better outcomes than those receiving higher levels of nutritional support.[3] Indeed, although a cluster randomized trial examining the impact of evidence-based feeding guidelines on mortality in critically ill patients caused guideline ICUs to reach nutritional targets more frequently, there was no difference in mortality between the two groups.[4]

Because many studies have shown that patients receiving enteral feeding frequently fall short of established guidelines for nutritional support, it was hypothesized by some that the early use of parenteral nutrition would eliminate this deficit and thereby improve outcomes.[4] However, a recent study that compared early versus late parenteral nutritional support in critically ill patients showed that late support was associated with faster recovery and fewer complications.[5] Based on this study and other data, it appears unwise to use parenteral nutrition early in the course of critical illness for any but the most exceptional reasons.

Recently, the ARDS Clinical Trials Network investigators tested the hypothesis that early trophic feeding may improve outcomes when compared with full enteral feeding in patients with acute lung injury[6]: essentially, a "less is more" approach. The EDEN trial randomized patients to receive either trophic of full enteral feeding for the first 6 days. The full feeding group received approximately 1,300 calories/d whereas the trophic feeding group received approximately 400 calories/d during this period. There were no differences in ventilator-free days, 60-day mortality, or infectious complications between the two groups. The trophic group did experience less GI intolerance in the way of elevated gastric residual volumes, vomiting, and constipation; and received fewer prokinetic agents than the full-feeding group. The full-feeding group had higher mean plasma glucose levels and required more insulin administration.

The EDEN study did not control the location of the enteral feeding tube (more than 85% were initially fed using a gastric rather than a post-pyloric tube) or the composition of the enteral formulation. In general, there is insufficient evidence to recommend the routine use of nasojejunal tubes in critically ill patients, although they may be considered in selected patients. All patients should be fed with the head of bed elevated.

Immune Modulating Enteral Formulations

Enthusiasm for the use of so-called immune modulating formulations in critically ill patients has been tempered by the results of a randomized controlled trail conducted by the Acute Respiratory Distress Syndrome Clinical Trials Network.[7] In this study, twice-daily administration of enteral omega-3 fatty acid, γ-linolenic acid, and antioxidants did not improve clinical outcomes in patients with acute lung injury. The study was stopped for futility, but the results suggested the possibility of harm with this approach. It is of course possible that a benefit to the "immune modulating" approach to nutritional support may be achieved using different approaches or formulations in different subsets of patients; however, further study is required.

GI Intolerance of Feeding

Critically ill patients may experience a variety of symptoms while receiving enteral feeding, including abdominal distension, bloating, constipation, diarrhea, and regurgitation. Gastric residual volumes are frequently monitored in an effort to reduce the development of such complications. However, gastric residual volumes correlate poorly with gastric emptying, and with regurgitation. It is increasingly evident that the interruption of enteral feeds for relatively low gastric residual volumes (eg, $<$400 mL) is inappropriate. The feeding protocol utilized in the EDEN trial[6] resulted in a low rate of GI overall and may serve as a model for the administration of enteral feeding. Prokinetic agents such as metoclopramide or erythromycin should be considered in patients with intolerance of feeding.

Diarrhea is a fairly common occurrence in an ICU, although the precise incidence is unknown. The differential diagnosis for diarrhea is quite broad. *Clostridium difficile* infection should always be considered. Frequently, however, medications may be responsible.[8] A large number of com-

Table 2—*Approach to Diarrhea in the Critically Ill Patient*

Consider *Clostridium difficile* Infection
Examine the medication list for potential causative agents. These include hyperosmolar agents (hypertonic elixirs, sorbitol-containing medications), antibiotics, and numerous other medications
Try continuous instead of bolus feeding
Try an enteral formulation with a lower osmolality
Consider soluble fiber-containing or small peptide formulations, but avoid this approach if the patient is at high risk for bowel ischemia or severe dysmotility. DO NOT use insoluble fiber!

monly administered medications contain sorbitol. Sometimes a different formulation, one that does not contain sorbitol, may be used in cases where the continuation of the medication is desired. Consultation with a pharmacist can be very helpful when medication-induced diarrhea is suspected. Table 2 lists potential solutions to the problem of diarrhea in the critically ill patient.

Glucose Control

The optimal target for blood glucose in critically ill patients has been intensely investigated over the past decade. A detailed review of this topic is beyond the scope of this chapter. The Normoglycemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study, a multicenter study performed in more than 6,000 critically ill adult subjects, is the most important study performed on this subject to date.[9] The investigators found that intensive glucose control, targeting a blood glucose level of 80 to 108 mg/dL, increased mortality when compared with a blood glucose target of 180 mg or less. The American Association of Clinical Endocrinologists and the American Diabetes Association support a blood glucose target of 140 to 180 mg/dL for ICU patients[10]; the American College of Physicians recommends a similar, but slightly higher, blood glucose range of 140 to 200 mg/dL.[11]

Conclusions

Ultimately, efforts to improve outcomes through the provision of nutritional support will require an improved understanding of the interaction between nutrition and the host response to critical illness. Until then, the following recommendations seem sensible:

- Use the gut, and give it a hand!
- Start enteral nutrition within the first 48 h after ICU admission.
- Utilize sedation protocols/daily interruption to prevent drug accumulation.
- Mobilize patients as early as feasible.
- Use prokinetics (metoclopramide and erythromycin) in patients with intolerance of feeding.
- Watch fluid balance to avoid gut edema.
- Minimize time nils per os.
- DON'T hold tube feeds for residuals <400 mL if feeding is otherwise well tolerated. Try to keep at least some foods going ("trickle feeds").
- Elevate the head of bed.
- Have a slow hand where parenteral nutrition is concerned. Wait at least a week before even considering its use, except in highly unusual circumstances.

Nothing to Disclose

The author has disclosed that no relationships exist with any companies/organizations whose products or services may be discussed in this chapter.

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Notes

Chapter 27. Resuscitation: Cooling, Drugs, and Fluids

Brian K. Gehlbach, MD

Objectives:

- Discuss the evidence supporting the use of crystalloids over colloids in critically ill patients.
- Describe hemostatic resuscitation.
- Cite appropriate endpoints for resuscitation in the management of septic shock.
- Describe the use of arterial pulse pressure variation, inspiratory changes in central venous pressure, and ultrasonographically assessed respiratory changes in inferior vena cava diameter in determining fluid responsiveness.
- Describe the uses of waveform capnography during advanced cardiac life support.
- Describe the use of therapeutic hypothermia following cardiac arrest.

Key words: cardiac arrest; induced hypothermia; resuscitation; septic shock; trauma

Synopsis:

This chapter reviews selected concepts related to resuscitation. In most ICU settings, there is no advantage to the use of colloids over crystalloids. Contemporary management of traumatic hemorrhage involves the transfusion of red blood cells, plasma, and platelets in a 1:1:1 ratio. Resuscitation of septic shock should be accomplished early and should target the restoration of an adequate intravascular volume, an adequate ($\geq$65 mm Hg) mean arterial pressure, an adequate urine output ($\geq$0.5 mL/kg/h), and either a central venous saturation >70% or a lactate clearance of at least 10% within the first 6 h. Fluid responsiveness in septic shock may be assessed through the assessment of arterial pulse pressure variation in mechanically ventilated patients, the identification of an inspiratory fall in central venous pressure in spontaneously breathing patients, or through the use of bedside ultrasound to assess respiratory changes in inferior vena cava diameter. The best vasoactive drug for shock depends on indication; in general, however, norepinephrine is superior to dopamine for the treatment of shock. The 2010 advanced cardiac life support (ACLS) guidelines emphasize the use of waveform capnography for the confirmation of endotracheal tube position to ensure the quality of CPR and to detect return of spontaneous circulation. Therapeutic hypothermia should be at least considered for all survivors of cardiac arrest. Neurologic prognostication should be more conservative in patients who have been treated with therapeutic hypothermia.

Colloids or Crystalloids?

Numerous studies have compared the use of colloids and crystalloids in the management of a variety of conditions in critically ill patients. The largest of these, the Saline versus Albumin Fluid Evaluation (SAFE) study,[1] randomized 6,997 patients in 16 ICUs in Australia and New Zealand to receive either 4% albumin or normal saline solution for intravascular fluid resuscitation for the following 28 days. There was no difference in 28-day mortality or in any meaningful clinical outcome. In a post hoc analysis of the subset of patients with traumatic brain injury,[2] mortality was higher with albumin than with saline solution. Recent Cochrane reviews of the use of albumin versus crystalloids[3] and colloids vs crystalloids[4] generally concluded there was no evidence from randomized controlled trials that colloids were superior to crystalloids in critically ill patients. Although there may be a benefit to the use of colloids in highly specific settings—for instance, the administration of albumin to patients with high-risk spontaneous bacterial peritonitis[5]—there is presently no evidence to support their use in the general management of critically ill patients.

Resuscitation of Traumatic Hemorrhage

The management of traumatic hemorrhage has continued to evolve based on recent combat experiences, although aspects of this approach remain controversial.[6] This approach incorporates a number of concepts that are beyond the scope of this chapter, including rapid surgical control, hypotensive resuscitation, and the prevention and treatment of acidosis and hypothermia. A central tenet of this approach is the concept of hemostatic resuscitation. This involves the transfusion of red blood cells, plasma, and platelets in a 1:1:1 ratio. Conclusive evidence to

support the foregoing concepts is difficult to gather given the challenges of conducting methodologically rigorous clinical studies in the trauma setting. However, there is some evidence to support the hemostatic resuscitation approach in patients with significant traumatic hemorrhage. Although the optimal ratio of plasma to blood transfusion may be debated, the need to replace factors and platelets in patients bleeding whole blood cannot be disputed and the importance of preventing the development of a cold coagulopathy cannot be overemphasized.

Overall Approach and Endpoints for Resuscitation in Septic Shock

In 2001 a study by Rivers and coworkers[7] compared usual care of patients with severe sepsis and septic shock to an early, goal-directed therapy (EGDT) approach. Patients receiving EGDT were managed in the ED with an algorithm designed to achieve four goals within the first 6 h of resuscitation: a central venous pressure (CVP) of 8 to 12 mm Hg, a mean arterial pressure $\geq$65 mm Hg (and $\leq$90 mm Hg), a central venous saturation $\geq$70%, and a urine output of $\geq$ 0.5 mL/kg/h. In-hospital mortality was significantly reduced (30.5% vs 46.5%) in the EGDT group when compared with the usual-care group. The specific endpoints used in this study can (and have) been debated. In general, however, it seems reasonable to promptly restore intravascular volume in the setting of functional hypovolemia from venodilation and capillary leak to achieve a mean arterial pressure that is adequate for perfusion and to assess the overall adequacy of the circulation by examining organ function (urine output) and/or a measure of the balance between oxygen delivery and consumption (central venous saturation). Another method of determining the adequacy of the circulation is to examine the effect of resuscitation on lactate clearance. Jones and colleagues[8] recently randomized 300 patients with septic shock to either lactate clearance of at least 10% or central venous saturation of at least 70% as the goals of therapy. Both groups were resuscitated to a CVP of 8 mm Hg or higher and a mean arterial pressure of 65 mm Hg or higher, similar to the Rivers study. There was no difference in in-hospital mortality between the two groups.

Overall, the following is a reasonable approach to the resuscitation of patients with septic shock:

1. Administer normal saline solution to restore intravascular volume. This may be done most rationally using dynamic indices of fluid responsiveness (see below). Absent these measures, a CVP of 8 to 12 mm Hg is a reasonable target in many patients.
2. The adequacy of perfusion may be assessed by clinical criteria—mentation, urine output, peripheral extremity warmth, capillary refill, and blood pressure—and by achieving, within the first 6 h of resuscitation, either a central venous saturation of >70% or a lactate clearance >10%.
3. Hypotension that persists despite adequate intravascular volume is treated as follows:
   a. If the cardiac output and/or central venous saturation are judged to be low, the presence of cardiac dysfunction should be considered and echocardiography is indicated. Dobutamine (for left ventricular or global dysfunction) or norepinephrine (for right ventricular failure) may be useful.
   b. If the cardiac output and/or central venous saturation are judged to be adequate, then a vasopressor (norepinephrine or vasopressin, see below) should be administered.
4. Intubation and mechanical ventilation will be indicated in many patients and may be particularly useful when the targets of EGDT are unable to be achieved despite modest levels of circulatory support and when the work of breathing is elevated.

Determining Fluid Responsiveness in Septic Shock

Although many questions have been raised by the EGDT study, most authorities believe that the better outcomes in the EGDT group were at least in part attributable to the fact that they received more aggressive volume resuscitation: nearly 5 L within the first 6 h vs approximately 3.5 L in the control group. Unfortunately, fluid administration has a cost as well. In the Fluid and Catheter Treatment Trial, patients managed with

a liberal (as opposed to conservative) approach to fluids after achieving hemodynamically stability spent more time mechanically ventilated.[9] Fluid accumulation has also been associated, in retrospective analyses,[10] with increased mortality in critically ill patients. Fluid accumulation may result in pulmonary and gut edema, skin breakdown, increased cardiac stress, hemodilution and electrolyte abnormalities, and cerebral edema. In short, fluids should be administered when they are needed, and avoided when they are not. The determination of fluid responsiveness—whether a patient's cardiac output will increase in response to a fluid bolus—is useful at separating those patients who may benefit from a fluid bolus from those who may only be harmed.

Static measurements of intravascular pressure such as the CVP or the pulmonary capillary wedge pressure are poor predictors of fluid responsiveness. In contrast, so-called dynamic indices of fluid responsiveness (also called preload reserve), take advantage of the fact that the heart and great vessels reside within a chamber—the thorax—in which the pressure changes with respiration, whether the patient is breathing spontaneously or receiving positive pressure ventilation. These pressure changes in turn affect right and left ventricular preload and afterload in a cyclical manner. Empirical data indicate that the presence of preload reserve can be inferred from the physiologic responses to these respiratory changes. A detailed discussion of hemodynamic monitoring is beyond the scope of this review. Below are highlighted selected parameters.

Inspiratory Fall in CVP

Normal inspiration decreases pleural pressure and, consequently, right atrial pressure. This increases the driving pressure for venous return and thereby right ventricular preload. In the hypovolemic (or even euvolemic) patient, the fall in right atrial pressure is not overcome by the resulting increase in venous return. In such a patient, the administration of a fluid bolus will increase the cardiac output. This was confirmed by Magder and colleagues in a small study[11] performed in spontaneously breathing patients, in which an inspiratory fall in the CVP of greater than 1 mm Hg indicated preload reserve.

Arterial Pulse Pressure Variation

Mechanical ventilation provokes cyclic changes in left ventricular (LV) stroke volume, and therefore in arterial pulse pressure, in patients with septic shock and preload reserve. Mechanical insufflation increases LV ejection (by increasing LV preload and decreasing LV afterload), but decreases RV ejection (by decreasing RV preload and increasing RV afterload). The latter effect reduces LV preload several beats later. Passive expiration has the opposite effects. As a result of these cyclic changes, the pulse pressure is greatest during mechanical insufflation and least during expiration. Hypovolemia exaggerates these effects. In mechanically ventilated, sedated patients in sinus rhythm who are passive on the ventilator and receiving a tidal V_T of 8 mL/kg, a change in arterial pulse pressure of $\geq$13% predicted preload reserve (defined as an increase in cardiac index by at least 15% with volume expansion) with a sensitivity of 94% and a specificity of 96%.[12] Lower V_T (for instance, 6 mL/kg ideal body weight) somewhat reduces the sensitivity for predicting preload reserve.

$$\Delta Pp(\%) = \frac{(Ppmax - Ppmin)}{(Ppmax + PPmin)/2} \times 100$$

where Pp = pulse pressure, Ppmax = maximal pulse pressure, and Ppmin = minimum pulse pressure.

It is important to note that the identification of preload reserve in a patient does not necessarily mean that the patient will benefit from a higher cardiac output. Normal, healthy individuals also have preload reserve. Table 1 summarizes important caveats regarding the use of arterial pulse pressure variation as a guide to fluid resuscitation.

Ultrasound-Guided Volume Resuscitation

Clinician-performed ultrasonography has increased dramatically. Intensivists are also learning to conduct limited echocardiography. It is therefore noteworthy that respiratory changes in inferior vena cava diameter have been shown to predict fluid responsiveness in mechanically

Table 1—*Important Considerations When Analyzing Arterial Pulse Pressure Variation*

Arrhythmias invalidate its use
The patient should be passive on the ventilator
The sensitivity for predicting fluid responsiveness is reduced in patients receiving low V_T ventilation
If the patient is fluid responsive, will the patient also *benefit* from an increased cardiac output?

ventilated patients.[13,14] This parameter may be less useful in patients with elevated intraabdominal pressure and may be difficult to assess in patients with obesity. A discussion of these approaches is beyond the scope of this review.

Vasoactive Drugs in Shock

It is difficult to rigorously study the use of vasoactive drugs in shock, and most head-to-head studies of different drugs have not shown large (or even any) differences in clinical outcomes. In general, the choice of agent is probably less important than how it is used. However, a few general comments can be made. Taken together, the available literature suggests that dopamine tends to cause more arrhythmias than norepinephrine. The SOAP II Investigators compared dopamine and norepinephrine in the treatment of shock in a multicenter double-blind randomized controlled trial[15] in 1,679 patients. Overall, there was no difference in mortality although there were more arrhythmias with dopamine and more deaths with dopamine in patients with cardiogenic shock. Two meta-analyses[16,17] have confirmed the relative increase in arrhythmias with dopamine compared with other agents. The study by Havel and colleagues[16] found no clear winner among the six vasoactive drugs studied, but there was a trend toward a mortality benefit with norepinephrine when compared with dopamine (relative risk of death 0.95; 95% CI: 0.87–1.03). In the metaanalysis by Vasu and colleagues,[17] there was a slight mortality advantage to norepinephrine when compared with dopamine. The vasopressin and septic shock trial study[18] comparing low-dose vasopressin with norepinephrine showed no difference in 28-day mortality. However, vasopressin was superior to norepinephrine in the predefined stratum of less severe septic shock. Taken together, these and other studies suggest that:

1. Dobutamine is generally the agent of choice for cardiogenic shock with an adequate blood pressure.
2. Cardiogenic shock with hypotension is best treated with norepinephrine alone or in combination with dobutamine. Norepinephrine is particularly useful for patients with acute right-sided heart syndromes.
3. Septic shock may be treated with norepinephrine +/− low-dose vasopressin; dobutamine may be added when concomitant cardiac dysfunction exists. Phenylephrine may be considered for septic shock complicated by tachyarrhythmias.

ACLS: The Role of Waveform Capnography

A comprehensive review of the 2010 Advanced Cardiac Life Support guidelines is beyond the scope of this review. The authors continue to emphasize the importance of performing effective CPR. Continuous waveform capnography is recommended during ACLS for three reasons:[19]

1. To confirm and continuously monitor the position of the endotracheal tube. The absence of an end-tidal CO_2 waveform suggests tube malposition.
2. To monitor the quality of CPR. If the end-tidal CO_2 is <10 mm Hg, attempts to improve CPR quality should be made.
3. To detect the return of spontaneous circulation. This is typically heralded by an abrupt and sustained increase in end-tidal CO_2 (typically ≥ 40 mm Hg).

Therapeutic Hypothermia After Cardiac Arrest

Mild therapeutic hypothermia (TH) has been shown to improve long-term survival and neurologic outcomes in comatose adult survivors with return of spontaneous circulation after out-of-hospital arrest because of ventricular fibrillation.[20]

As a result, TH is recommended for this indication. TH may also be considered for the unconscious adult patient with return of spontaneous circulation after nonventricular fibrillation arrest or following an in-hospital arrest. In general, patients with active bleeding, significant bradycardia, and severe hemodynamic instability are excluded from receiving TH. A core body temperature of 32° to 34° C is targeted for 12 to 24 h. This may be achieved using commercially available devices with a computerized temperature management system that circulate chilled water in pads placed on the patient's skin. Endovascular devices and cooled fluids may also be used. Protocols vary as to the approach to sedation and/or paralysis. TH is more readily and effectively administered when done frequently and with the aid of a protocol.

Intensivists are frequently involved in neurologic prognostication after cardiac arrest. It is therefore worth noting that most of the literature that guides this practice comes from the pre-TH era. Limited studies[21] performed in patients treated with TH suggest that certain findings are not as reliable in patients treated with hypothermia.

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The author has disclosed that no relationships exist with any companies/organizations whose products or services may be discussed in this chapter.

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Chapter 28. Ethical Issues in Intensive Care Medicine

Douglas B. White, MD, MAS

Objectives:

- Describe the standards of surrogate decision making.
- Review the concept of shared decision making.
- Discuss whether there is an ethical distinction between withholding and withdrawing life support.
- Highlight the important of the principle of double effect to end-of-life care.
- Define futile and potentially inappropriate treatment and present a strategy for managing intractable clinician-family conflicts.

Key words: futile and potentially inappropriate treatment; principle of double effect; surrogate decision making

Synopsis:

This chapter is organized around the incremental presentation of a clinical case. The goal is to use the case to summarize key concepts related to ethical issues in ICUs. In the first section, the case is introduced, and each subsequent section provides additional case information that informs the discussion of the next topic.

The Case of Mr. Paul

Mr. Paul is a 72-year-old man with history of coronary artery disease, status post–coronary artery bypass graft admitted with pneumonia. He develops sepsis, multisymptom organ failure, and is intubated, ventilated, and treated with pressors and antibiotics. After 3 days in the ICU, Mr. Paul is clinically unchanged, except for worsening renal function. In meeting with the family, they ask you, "*How are we supposed to decide whether to keep going with intensive treatment?*"

Surrogate Decision Making

Because most patients with advanced critical illness lack decision-making capacity, other individuals—generally close family members—are asked to make decisions on their behalf.[1] In general, physicians are not authorized to unilaterally make major medical decisions for incapacitated patients, such as decisions to withdraw life support or decisions to undergo surgery. Instead, the norm in American medicine is that physicians must involve surrogates to make decisions that most respect patient's interests and preferences. Underlying this rule is a belief that family members—rather than physicians—are better positioned to select which available treatment plan most promotes the patient's interests.[2] In all 50 states, surrogates have the authority to withdraw life support, including artificial nutrition and hydration.

There are three hierarchically ordered standards that should generally guide the decisions surrogates make for patients.[3] The first standard is the *known wishes standard*. This applies when the patient has expressed clear wishes about his medical treatment that apply to the medical situation at hand. When present, these wishes should generally be followed, assuming that they are within the boundaries of acceptable medical practice. For example, if a patient completed an advance directive indicating he does not wish to receive prolonged mechanical ventilation in the event of a terminal illness, this decision should be respected. If it is not possible to use the known wishes standard (eg, because the patient has not articulated clear treatment preferences), then surrogates should make decisions according to the *substituted judgment standard*: In the surrogate's judgment, what decision would the patient make for himself if he were able? If this is not known, surrogates should make decisions according to the *best interests standard*: What treatment decisions will most advance the patient's interests?

Another important conceptual point is that it is the *patient's* values that should predominantly guide decision making rather than the *surrogate's* values or the *doctor's* values.[4] Consider the following situation: an incapacitated patient with a life-threatening GI bleed requires a blood transfusion to survive. It appears that the patient has no beliefs that would contraindicate a blood transfusion. However, the surrogate is a Jehovah's Witness and is opposed to transfusions on religious grounds. In this circumstance, the

physician should instruct the surrogate to use the patient's values to inform decisions rather than the surrogate's own values. Decisions by surrogates that do not comport with patients' values should be challenged, such as through the involvement of a hospital ethics committee.

Shared Decision Making

Case: During a family meeting about whether to continue life support, Mr. Paul's surrogate asks you who is supposed to ultimately make decisions about the ongoing use of life support.

The paternalistic approach in which physicians make decisions without consulting the surrogate has given way to a focus on shared decision making. Shared decision making is defined as a collaborative process between clinicians and patients/surrogates in which decisions are informed by the best available evidence and the values of the patients.[5]

The four major European and American critical care societies issued a policy statement supporting shared decision making: "We advocate a shared approach to end of life decision making, with responsibility for the decision shared between the caregiver's team and the patient's surrogate."[6(p1781)]

Shared decision making can be conceptualized as having three steps (Table 1): information exchange, deliberation, and deciding. The first step of shared decision making is the exchange of information between the clinicians and surrogate in which the physician explains the disease, treatment options, and the prognosis. The surrogate provides information about the patient's values and treatment preferences. On this view, neither the doctor nor the surrogate independently possesses all of the information needed to make a good decision. The crux of shared decision making is that the physician and surrogate together deliberate about the best treatment decision and arrive at a shared agreement about the best course of action. This is to be contrasted with the informed consent model in which only the surrogate deliberates (after receiving information from the physician) and the paternalistic model in which only the physician deliberates. The vast majority of surrogates prefer a shared approach to decision making rather than an informed consent or paternalistic approach.[7]

Withholding and Withdrawing Life-Sustaining Treatment

Case: Mr. Paul develops acute renal failure. Hemodialysis is initiated. Despite aggressive intensive care, his condition deteriorates. He now has ARDS, persistent shock, and is completely unresponsive. In light of his worsening status in the face of maximal treatment, the family raises the possibility of stopping dialysis and transitioning to a plan of care focused on keeping the patient comfortable as he dies. However, one family member states that although it would have been legal and ethical not to begin dialysis, once initiated, it is illegal to stop. Is it ethically and legally acceptable to withdraw dialysis?

Withholding treatment is refraining from starting a therapy. Withdrawing treatment is stopping a therapy that already has been initiated. From the standpoint of US law and bioethics, there is not an ethically meaningful distinction between withholding and withdrawing life-sustaining treatment. Both are permitted when doing so and reflects an informed decision by the patient or the patient's surrogate to refuse ongoing life-prolonging treatment. The US Supreme Court reaffirmed this in the Cruzan decision, articulating that it is legally and ethically permissible to withhold *or* withdraw any medical intervention, including nutrition and hydration.[8] Roughly 60% to 90% of deaths in ICUs are preceded by some form of limitation of life-prolonging treatment.[1,9]

What would be the consequences to patients if withholding treatment was permitted but withdrawing treatment was not? Most importantly, patients/surrogates would not be permitted to request a time-limited trial of intensive care and instead would be required to make an "all-or-nothing" decision either to not initiate life support or to agree to indefinite use of life support. This would be problematic because it would likely result in patients foregoing an opportunity for survival (via a time-limited trial) out of fear of being kept alive indefinitely attached to invasive life support, a condition that some patients view as a "state worse than death."[10]

Table 1—*Different Models of Medical Decision Making*

Dimensions of Decision Making	Informed	Shared	Paternalistic
Information Exchange			
MD provides medical information	x	x	x (minimal)
MD elicits patient values		x	
Who deliberates?	Family	Physician and family	Physician
Who decides?	Family	Physician and family	Physician

The Doctrine of Double Effect and End-of-Life Care

Case: After the clinical team and family together decided to withdraw life support, mechanical ventilation and hemodialysis are discontinued. Three hours later on a relatively low-dose narcotic infusion, Mr. Paul is unresponsive but has an elevated respiratory rate and signs of air hunger.

In this setting, is it ethically acceptable to increase the opioids, even though it may lead to a hastened death?

It is ethically permissible to treat pain and other symptoms in a dying patient even if doing so might hasten the patient's death. This is generally justified by the doctrine of double effect (DDE). The DDE[11,12] has been developed over the past several centuries as a way to evaluate the ethical acceptability of actions that result in both good and bad outcomes. It is relevant in this context because administration of narcotics and sedatives prior to ventilator withdrawal will make the patient comfortable (the good effect), but in some cases will also hasten the patient's death (the bad effect). According to the DDE, it is permissible to administer narcotics to a dying patient if the intended effect is to treat symptoms, even if hastened death is a foreseeable but unintended consequence.

In contrast, according to the DDE, if the patient had no clear signs of pain or distress, it would be ethically problematic to increase the narcotic dose (eg, if the family requested a quick death for the patient). This is because, in such circumstances, the administration of additional narcotics could not be viewed to be as *intended* to relieve symptoms. Instead, the intended effect would be death, rather than symptom control, and as such, the additional administration would be intended to be active euthanasia, a practice that is illegal in all 50 states.

As a general rule, legal views in the United States accord with the DDE. For example, in *Vacco v Quill,* former Chief Justice William Rehnquist wrote: "It is widely recognized that the provision of pain medication is ethically and professionally acceptable even when the treatment may hasten the patient's death if the medication is intended to alleviate pain and severe discomfort, not to cause death."[13]

Futile and Potentially Inappropriate Treatment

Case: Imagine that instead of requesting the withdrawal of life-sustaining treatments, Mr. Paul's family requests full use of life support because they believe that he would want everything possible to extend his life at all, even if he were unconscious in an ICU. As the attending physician, you think his survival to hospital discharge is highly unlikely (eg, 1%–5% chance of survival). In light of his prognosis, is ongoing treatment in an ICU futile?

Currently, the only widely accepted definition of futility is that "the intervention cannot accomplish the intended goal."[14] In Mr. Paul's case above, the patient's goal appears to be any increase in the duration of life, regardless of its quality; the clinician judges this to be unlikely but not impossible. Therefore, the treatments requested are not strictly futile. This case illustrates that cases of strict futility are quite rare and generally occur late in a disease trajectory. Therefore, futility policies are unlikely to result in substantial cost savings to the health-care system.[15]

Contemporary professional society policies, such as the Society of Critical Care Medicine guidelines, note that the more common clinical dilemma is that surrogates request treatments that, although not strictly futile, may nonetheless be inappropriate.[14] Examples include requests for treatment that are extremely unlikely to achieve the intended outcome, that are extremely expensive, or that may achieve a goal of controversial benefit (eg, extending the life of an actively dying, unconscious patient by several hours through ongoing use of life support).

The guidelines recommend that clinician-family disputes about potentially inadvisable treatment should be resolved through a fair process rather than through unilateral decision making by clinicians. The American Medical Association (AMA) recommends several steps that are aimed first at conflict resolution through intensive communication between surrogates, providers, and ethics or palliative care consultants.[16] If these steps do not result in consensus, there should be attempts to transfer the patient to another provider at the same institution and, if this fails, to another institution. Attempting to transfer the patient is ethically important because it allows the decision to reflect the input of multiple clinicians at different institutions. As noted in the AMA policy, "If transfer is not possible. . .it may be because the request is considered offensive to medical ethics and professional standards in the eyes of a majority of the health care profession." In such cases, the AMA recommends that the treatments in question need not be provided, but also notes that the legal ramifications of such actions by physicians is uncertain.

There is widespread agreement that adversarial or unilateral approaches to resolve conflicts are harmful to clinicians and families. Such approaches should be used as a last resort only after all other available approaches to find a solution have been unsuccessful.

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The author has disclosed that no relationships exist with any companies/organizations whose products or services may be discussed in this chapter.

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Notes

Chapter 29. Interpreting Clinical Research and Understanding Diagnostic Tests in Critical Care Medicine

Douglas B. White, MD, MAS

Objectives:

- Summarize important elements of clinical research study design and interpretation.
- Explain the common measures of association used in clinical research studies.
- Describe concepts of statistical testing relevant to research in ICUs.
- Explain basic elements of interpreting diagnostic tests in medicine.

Key words: biostatistics; clinical research design; confidence interval, 95%; *P* values; sensitivity; specificity

Synopsis:

In order to apply existing research evidence to patient care, clinicians must be able to critically appraise the literature. Doing so requires understanding of the strengths and weaknesses of various research designs, as well as biases that can occur in the collection and analysis of data. In addition, clinicians should be able to understand and apply basic concepts of diagnostic testing such as sensitivity, specificity, and positive predictive value in order to fully appreciate the meaning of the tests they order for their patients. These topics are reviewed.

Interpreting Clinical Research

Observational Studies

Observational studies include case series, case-control studies, prospective cohort studies, and cross-sectional studies. Observational studies involve measuring the results of a subject's exposure to an intervention or medication that was introduced independent of a research protocol. Observational studies are by definition nonexperimental. Although observational studies can help identify associations between interventions and outcomes, they generally cannot be used to establish a causal link between the predictor and outcome of interest.[1]

Sometimes observational studies suggest a causal link between the exposure and outcome that is subsequently disproven in experimental studies. For example, early observational studies suggested that hormone replacement therapy was protective against coronary artery disease,[2] but subsequent randomized trials suggest no benefit and potential harm from the therapy.[3,4]

The results of observational studies are vulnerable to confounding and bias. A confounding variable is one that is associated with the predictor variable and a cause of the outcome variable. For example, it was once claimed that carrying matches was a cause of lung cancer. In fact, this is because cigarette smokers tended to carry matches and cigarette smokers are at increased risk of lung cancer from smoking. In this example, the relationship between matches and lung cancer is confounded by cigarette smoking. Cigarette smoking is the confounding variable that is the actual cause of lung cancer.

Bias results from systematic errors in the design or conduct of a study.[5] There are two general categories of bias: selection bias and information bias. Selection bias occurs when subjects have differing probabilities of being included in the study sample based on a factor that is relevant to the study design. Information bias results in systematic misclassification of participants in a study based on a variety of sources of misinformation, such as recall bias.[6] For example, if a research participant in a study about environmental exposures is aware that he has contracted a disease caused by toxic environmental exposures, he may be more likely to recall incidences of environmental exposures in his life compared with someone without such a disease.

Randomized Controlled Trials

Randomized controlled trials are an important experimental design to establish a causal link between an intervention and health outcomes. Subjects are randomly assigned to either

the treatment or control arm. Randomization is important because it increases the likelihood that both known and unknown confounders will be equally distributed between the two groups. This in turn minimizes the risk that a treatment is erroneously judged to be effective when the outcome differences between groups are actually due to measured or unmeasured differences in the patients in the two study arms.

Assessing the Quality of a Randomized Controlled Trial

Below are a series of questions physicians should ask before deciding whether the results of the trial are valid

Did Randomization Occur and Was It Successful? As noted above, the goal of randomization is to balance the distribution of known and unknown confounders between study arms. Readers should inspect the characteristics of the control and treatment groups at baseline to ensure that potential confounders were successfully balanced. Especially in small studies, randomization does not always result in the desired balanced distribution.

Were Researchers and Participants Blinded? Blinding is the process by which study subjects and/or investigators are prevented from knowing to which study group subjects have been assigned. Blinding of the subject is especially important for subjective outcome measures, such as a self-reported measure of quality of life. Blinding of investigators prevents bias in how investigator-measured outcomes are determined. Double-blind studies are those in which both the investigator and the research subject are unaware of the group to which the subject was randomized.

Was There Minimal Loss to Follow-up? Loss to follow-up can lead to biased study results. Nondifferential loss to follow-up involves loss of subjects with similar outcomes to those for whom follow-up data are obtained. Therefore, nondifferential loss generally results in a loss of study power and increased risk of a falsely negative trial. Differential loss to follow-up occurs when those who are lost to follow-up differ in important ways from those in whom follow-up occurs. Differential loss results in potential bias in the findings due to uncontrolled confounders. For example, if more patients in the intervention group were lost to follow-up, this could be because they died from the intervention. Their omission from the analysis may make it appear that the intervention is actually beneficial rather than harmful.

Surrogate Outcomes Measures

Critical care research often relies on surrogate endpoints, which allow demonstration of treatment effect with fewer patients over less time. Surrogate endpoints for studies of mechanical ventilation include measures such as improvement in oxygenation, time to extubation, or ICU length of stay. Some surrogate endpoints have some importance to patients, but, quite often, they do not represent what is most important to most patients (ie, hospital survival and good long-term functional status).

Trials using surrogate endpoints should be interpreted with great caution because many surrogate endpoints do not reliably track with important patient-centered outcomes.[6] For example, some studies of partial liquid ventilation for ARDS demonstrated significant improvements in oxygenation,[7] a finding which some took to mean that the treatment was beneficial for patients. Subsequent studies showed that, despite improvement in oxygenation, the treatment had no impact on mortality and may, in fact, be harmful.[8,9]

Measures of Association

Two main measures of association used in clinical research are the relative and absolute risk reduction that occurs due to an intervention.

Relative Risk: The relative risk, also called the risk ratio, is calculated by dividing the risk in the treatment group by the risk in the placebo group. The relative risk reduction is calculated by subtracting the relative risk from 1. The following hypothetical example illustrates these concepts:

A trial enrolls 400 patients to receive antibiotics or placebo to determine whether the antibiotic decreases the incidence of ventilator-associated pneumonia (VAP). Two hundred patients are assigned to receive antibiotics, and

200 are assigned to receive placebo. Ten patients in the antibiotic group and 15 in the placebo group get VAP. Therefore:

Group	Risk
Antibiotics	$10/200 = 0.050$
Placebo	$15/200 = 0.075$

And the relative risk is:

$$\frac{\text{Risk in intervention group}}{\text{Risk in control group}} = \frac{0.050}{0.075} = 0.67$$

The relative risk reduction is $1 - 0.67 = 0.33$ or 33%.

The absolute risk reduction is calculated by subtracting the risk in the control group from the risk in the intervention group. In this example, the absolute risk reduction is $0.075 - 0.05 = 0.025$ or 2.5%.

Quantifying Effect Size

Number Needed to Treat (NNT): NNT is the number of patients that must receive the intervention in order to prevent one occurrence of the outcome being studied. Knowing the absolute risk reduction allows the calculation of the NNT.[10] NNT is calculated as 1 divided by the absolute risk reduction. In the example above, the NNT tells us how many patients would need to be treated with antibiotics in order to avoid one episode of VAP. In this example, the $\text{NNT} = 1/(0.075 - 0.05) = 40$.

Calculating the NNT highlights that the risk ratio can be a misleading measure of association. For example, if there were 20,000 patients in each group, rather than 200, and there were 100 cases of VAP in the antibiotic group and 150 cases in the placebo group, the risk ratio would be the same:

Group	Risk
Antibiotics	$100/20{,}000 = 0.0050$
Placebo	$150/20{,}000 = 0.0075$

And the relative risk is:

$$\frac{\text{Risk in intervention group}}{\text{Risk in control group}} = \frac{0.0050}{0.0075} = 0.67$$

The relative risk reduction in this example would still be 0.33 or 33%. However, the absolute risk reduction is much smaller (0.25% instead of 2.5%). Despite an identical risk ratio, the NNT is $1/(0.0075 - 0.005) = 400$, or 10 times higher.

P values and Confidence Intervals

P values and confidence intervals (CIs) are statistical measures to aid the assessment of whether observed differences in outcomes between groups are true differences or are simply due to chance.

The *P* value is the probability of obtaining the given study results or something more extreme if there is truly no difference between the groups.[11] By convention, a *P* value of $<.05$ is considered statistically significant.

Another common approach to quantifying the possibility of random error is to calculate 95% CIs. The 95% CI includes the point estimate and is best defined as the range of values consistent with the findings observed in the study.[11] CIs aid in the interpretation of the precision with which a given outcome is determined. Narrower CIs indicate a more precise measurement of the effect size. In general, if the 95% CI of a risk ratio includes 1, the study did not demonstrate a statistically significant difference in risk between the two groups. Even if the CI does not cross 1, a wide CI indicates substantial uncertainty about the actual effect size of an intervention.

The power of a study is the likelihood of correctly finding a difference when one exists. A study's power is, in large part, a function of both the sample size and the magnitude of the difference between the groups that the investigator is attempting to detect. The larger the sample size, the smaller a difference one will be able to detect, and the larger the difference between the groups, the smaller the sample size needed to detect that difference.

Diagnostic Tests: Sensitivity, Specificity, and Beyond

To interpret diagnostic tests, one must understand how well that test reflects the actual presence or absence of disease in any given patient. The sensitivity and specificity of a given test measure the ability of a test to measure

patients' true disease state status. In order to evaluate the sensitivity and specificity of a diagnostic test, it must be tested against a "gold standard." Sensitivity and specificity are best visualized, understood, and calculated using a 2×2 table, as shown in the example below.

Sensitivity: The sensitivity of a test is the proportion of people with the disease who have a positive test result. A highly sensitive test will identify the majority of patients who actually have that disease and will yield very few false negative results.

Specificity: The specificity of a test is the proportion of people without the disease that have a negative test. A highly specific test will identify the majority of those who do not have the disease and will have very few false-positive results.

Example:

A company markets their "PE-Finder," a noninvasive test for pulmonary embolism (PE) highly accurate in diagnosis acute PE. You study 2,000 patients using both the PE-Finder and pulmonary angiogram (the gold standard); 800 patients have a PE diagnosed via angiogram, of whom 400 have a positive PE-Finder test. Among those with a negative angiogram, 300 have a positive PE-Finder. What are the sensitivity and specificity of the PE-Finder?

Using a 2×2 table we see:

	PE by angiogram (gold standard)	
PE-Finder Test Result	Positive	Negative
Positive	400 (a)	300 (b)
Negative	400 (c)	900 (d)
Total	800	1200

The sensitivity, which is the proportion of patients with the disease (800) who have a positive test (400), is $400/800 = 0.5$, or 50%. The specificity is the proportion of patients without a PE on angiogram who have a negative PE-Finder test, in this case $900/1{,}200 = 0.75$, or 75%.

Positive Predictive Value (PPV): A test's PPV is the proportion of those who test positive who actually have the disease. The PPV is calculated by dividing the number of true-positives by the total number of people who tested positive $[a/(a + b)]$. In the example above, the PPV of the PE-Finder is $400/700 = 57\%$.

Negative Predictive Value: The negative predictive value is the proportion of those whose test result is negative who are actually disease-free. The negative predictive value is calculated by dividing the number of true negative test (d) results by the total number of patients testing negative $[d/(d + c)]$.

The predictive value of a test is influenced by the prevalence of the disease in the population being tested. In a population in which the disease is rare, the predictive value will be much lower than in a population in which the disease is more common.

Nothing to Disclose

The author has disclosed that no relationships exist with any companies/organizations whose products or services may be discussed in this chapter.

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Notes

Chapter 30. Imaging

Brian K. Gehlbach, MD

Objectives:

- Describe how to evaluate suspected pulmonary embolism in pregnancy using the American Thoracic Society/Society of Thoracic Radiology Clinical Practice Guideline.
- Describe the uses and limitations of bedside ultrasonography.
- Describe the evidence supporting the use of an on-demand strategy to chest radiography in ICU patients.
- Describe the advantages and disadvantages of different approaches to the diagnosis of suspected esophageal perforation and suspected aortic dissection.
- Cite risk factors for the development of contrast nephropathy and nephrogenic systemic fibrosis and list strategies for their prevention.

Key words: acute kidney injury; diagnostic imaging; nephrogenic fibrosing dermopathy; pulmonary embolism; ultrasonography

Synopsis:

The practice of critical care relies heavily on imaging. As a result, the intensivist needs to be familiar with the indications, advantages, disadvantages, and potential toxicities of a wide variety of imaging modalities, regardless of whether the practitioner personally interprets all of them. This chapter summarizes recent evidence-based practices related to the safe and effective use of different imaging modalities, including the following: (1) The approach to evaluating suspected pulmonary embolism in pregnancy. (2) The uses and limitations of bedside ultrasonography. (3) The evidence supporting the adoption of an on-demand strategy to chest radiography in the ICU. (4) The pros and cons to different approaches to the diagnosis of esophageal perforation and aortic dissection. (5) The prevention of contrast nephropathy and nephrogenic systemic fibrosis.

Overview

Critical care imaging is obviously a very broad topic. The lecture on this topic will include specific examples of imaging. This chapter will concentrate on evidence-based strategies for the safe and effective use of different imaging modalities.

Evaluation of Suspected Pulmonary Embolism in Pregnancy

The evaluation of pulmonary embolism (PE) in pregnancy can be difficult. On the one hand, the incidence of PE is increased in pregnancy and PE is a leading cause of maternal mortality. On the other hand, pregnant patients may have signs or symptoms compatible with venous thromboembolic disease that are attributable to another cause or even to normal pregnancy. Given the potential risks of radiation to the patient and to the fetus, it is desirable to safely exclude PE while exposing the patient and fetus to the least amount of radiation possible. Unfortunately, there is a dearth of high-quality evidence regarding the evaluation of venous thromboembolic disease in pregnancy. The American Thoracic Society and the Society of Thoracic Radiology[1] have recently published a clinical practice guideline for the evaluation of suspected PE in pregnancy. This guideline has also been officially endorsed by the American College of Obstetricians and Gynecologists. It should be emphasized that *in situations in which the patient is unstable or in which certain studies may be unavailable or impractical, empiric therapy or alternative diagnostic approaches may be indicated*.

Before considering the guidelines themselves, it should be noted that (1) there is no consensus as to whether lung scintigraphy ($\dot{V}/\dot{Q}$ scans) or computed tomographic pulmonary angiography (CTPA) deliver a lower fetal dose of radiation; (2) maternal radiation exposure is lower with a $\dot{V}/\dot{Q}$ scan than with CTPA; (3) the principal risks to both mother and fetus from ionizing radiation is thought to be carcinogenesis (in the mother, lung and breast tissue are most at risk); (4) techniques for minimizing nondiagnostic studies and for also minimizing radiation exposure are available for both CTPA and lung scintigraphy; and (5) the lack of demonstrated superiority for any one diagnostic test in this setting means that the

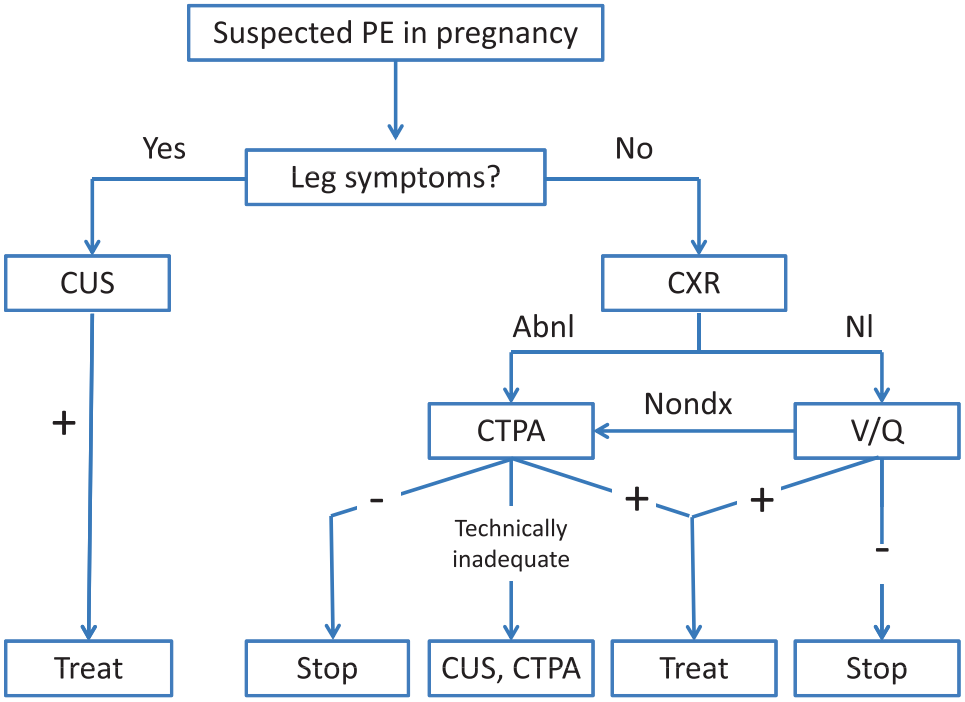

Figure 1. Diagnosis of suspected PE in pregnancy. CUS = bilateral compression ultrasonography; CTPA = computed tomographic pulmonary angiography; Abnl = abnormal; Nl = normal; Nondx = nondiagnostic. Adapted from Leung et al.[1]

values and preferences of the patient and physician may influence decision-making in individual cases.

Below is a brief summary of the guidelines:

1. Although certain risk factors have been identified, there are no validated clinical rules for determining pretest probability in the pregnant patient (eg, there is no Wells score for this situation). Accordingly, physicians must rely on their own clinical judgment along with a high index of suspicion.
2. The panel recommends that the D-dimer should not be used to exclude PE in pregnant patients based on limited studies that show reduced sensitivity in this population.
3. Patients with suspected PE and signs or symptoms of DVT should undergo bilateral compression ultrasound first (assuming patient stability and that this test is readily available).
4. Patients with suspected PE and no signs or symptoms of DVT should undergo studies of the pulmonary vasculature first.
5. In patients with suspected PE, the chest radiograph (CXR) is recommended as the first radiation-associated procedure in the diagnostic workup. This test has minimal radiation, may occasionally reveal an alternative diagnosis, and helps direct further imaging of the pulmonary vasculature.
6. In patients with suspected PE and a normal CXR, the next test is lung scintigraphy.
7. In patients with suspected PE and a nondiagnostic $\dot{V}/\dot{Q}$ scan, CTPA is recommended over pulmonary angiography.
8. In patients with suspected PE and an abnormal CXR, CTPA is recommended over lung scintigraphy.

Figure 1 provides a diagnostic algorithm for the diagnosis of suspected PE in pregnancy.

Clinician-Performed Ultrasonography

Ultrasound (US) is a simple, rapid, repeatable test that is being rapidly adopted by clinicians at the bedside in the emergency department, the ICU, and the general hospital ward. Although the penetration of US into the ICU is certainly not complete, its increasing use and rapid growth mean that clinicians should have a basic understanding of its uses and limitations. The review below will focus on these principles.

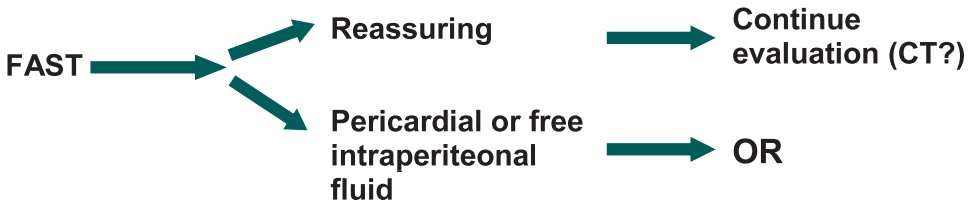

Figure 2. Use of FAST in the trauma patient.

Focused Assessment With Sonography for Trauma

The origins of clinician-performed US can be traced clearly to its use in the setting of trauma. Focused Assessment with Sonography for Trauma, otherwise known as FAST, examines the trauma patient for evidence of free intraperitoneal and/or intrapericardial fluid. In most centers, FAST has replaced diagnostic peritoneal lavage as the initial screening test for severe abdominal trauma, and the exam has been taught in the Advanced Trauma Life Support course for some time. Four areas are examined: the perihepatic and hepatorenal space, the perisplenic space, the pelvis, and the pericardium. The FAST exam is highly operator-dependent and may be further limited when evaluating patients with obesity or subcutaneous emphysema. FAST may miss injuries that are not associated with free fluid, such as intraparenchymal solid organ injuries, and, overall is less sensitive than CT for the detection of injuries.

FAST is most valuable for the clinician in the rapid evaluation of unstable, hypotensive patients with trauma.[2] Used in this way as part of the initial survey, FAST may facilitate early operative or bedside intervention (eg, pericardiocentesis). It is generally accepted that a negative FAST examination should not provide false reassurance when the suspicion for solid organ or other significant injury is high. A summary of this approach is provided in Figure 2. More recently, FAST has been extended to the detection of pneumothoraces, massive hemothoraces, and rib fractures.

Pulmonary and Pleural Imaging

With the caveat that the effective use of clinician-performed US requires training and experience, several studies have reported that bedside US is more sensitive, and certainly much faster, than chest radiography for the detection of pneumothorax. Bedside US is also very sensitive at detecting pleural effusions; this skill is readily acquired by clinicians. More recent studies[3] have shown that clinician-performed US can be useful in diagnosing lung consolidation, pulmonary edema, lung fibrosis, masses, and the extent of lung aeration in patients with acute lung injury.

US-Guided Procedures

Real-time US guidance of central venous catheter insertion has been shown to increase the rate of successful cannulation while reducing complications. In contrast, there appears to be no advantage to the use of US over landmark techniques when the US is only used to locate and visualize the vessel prior to the performance of the procedure. US has showed similar efficacy for the performance of thoracentesis and paracentesis, increasing the rate of success and decreasing the rate of complications associated with these procedures.

Selected Topics in Thoracic Imaging

Routine Daily vs On-Demand Chest Radiograph Strategies in the ICU

Many ICUs perform chest radiographs daily on patients receiving mechanical ventilation. Historically, opinions have varied as to whether this is necessary. Several recent studies have compared the routine daily CXR strategy with an on-demand strategy. Hejblum et al[4] randomly allocated 21 ICUs to either a routine strategy (11 ICUs) or an on-demand strategy (10 ICUs). They found that the on-demand strategy was associated with a 32% reduction in the total number of CXR obtained, with no differences between the two groups in days of mechanical ventilation, length of stay, or mortality. The number of chest films that led to or contributed to a therapeutic or

diagnostic intervention was similar between the two groups. Similarly, a recent meta-analysis by Oba and Zaza[5] of eight studies comprising a total of 7,078 patients found no difference in hospital or ICU outcomes between the two approaches. Conceivably, subgroups of patients receiving mechanical ventilation may benefit from routine daily chest films, and routine films may still be advantageous in situations where chest radiography and/or bedside US cannot be rapidly performed, or in the case of particular (as opposed to all) indwelling medical devices. However, there appears to be no benefit to the practice of routinely ordering a daily CXR on every patient receiving mechanical ventilation.

Diagnosing Esophageal Perforation

Esophageal perforation is caused by a number of diseases but is increasingly iatrogenic. Chest radiographic abnormalities are frequent in the setting of esophageal perforation but may be nonspecific, depending on the timing of the exam relative to the injury and the nature of the perforation. Early worrisome signs include pneumomediastinum and subcutaneous emphysema. Later signs may include pleural effusions (especially left-sided), free air under the diaphragm, pneumothorax, hydropneumothorax, and the presence of mediastinal air-fluid levels. Patients with suspected perforation should undergo a contrast esophagogram, first with a water-soluble contrast agent and then with barium if necessary. The water-soluble agents have a lower sensitivity but are better tolerated than barium, which may evoke a severe inflammatory response (including mediastinitis) in some patients. A contrast-enhanced CT of the chest is also a useful imaging modality in this setting[6] and should be performed if it is not possible to obtain a contrast esophagogram, if the esophagogram is negative but clinical suspicion persists, or to evaluate alternative diagnoses along with esophageal perforation.

Diagnosing Aortic Dissection

CT angiography (CTA) of the chest and abdomen, magnetic resonance angiography (MRA) of the chest and abdomen, and transesophageal echocardiography have similar accuracy for the diagnosis of aortic dissection when performed in centers with expertise in these modalities. CT angiography is readily available at most centers on a 24-h basis, involves little in the way of patient discomfort, and evaluates the aorta and branch vessels in their entirety. It is often, therefore, the initial test of choice for patients presenting to the ED with concerning signs and symptoms. Transesophageal echocardiography provides information that CTA does not, including the presence or absence of aortic insufficiency. MRA is a useful alternative to CTA when the patient shows no signs of hemodynamic instability and when there are concerns regarding contrast administration or the patient has had prior unrevealing CTA for similar symptoms. Angiography is now rarely performed except when definitive evaluation of the coronary arteries is required. The American College of Radiology[7] has issued Appropriateness Criteria and a summary statement regarding the evaluation of suspected aortic dissection.

Avoiding Complications Associated With Imaging

Preventing Contrast Nephropathy

Contrast nephropathy is associated with an increased risk of in-hospital and long-term mortality as well as with accelerated progression of chronic kidney disease.[8] The major risk factors for this condition include (1) acute or chronic kidney disease or single kidney, (2) diabetes mellitus, (3) intravascular volume depletion, and (4) congestive heart failure. The risk of contrast nephropathy is proportional to the volume of contrast used and is higher with intra-arterial (as opposed to IV) administration. Nonsteroidal antiinflammatory medications and selective cyclooxygenase-2 inhibitors may also increase risk. When it is not possible or desirable to obtain a noncontrast study or to use an alternative imaging modality, the following strategies for preventing contrast nephropathy are recommended when feasible:

1. Nonsteroidal antiinflammatory medications and cyclooxygenase-2 inhibitors should be

discontinued the day prior to the procedure and held for several days thereafter.
2. Metformin should be held the day of the procedure and restarted when renal function is known to be stable.
3. IV normal saline should be administered prior to and following contrast administration. A standard protocol for hospitalized patients is 1 mL/kg/h for 12 h prior to and 12 h following the procedure. The superiority of sodium bicarbonate over isotonic saline has not been conclusively demonstrated.
4. The lowest possible dose of contrast should be used. Hyperosmolar contrast should not be used.
5. N-acetylcysteine, 1,200 mg orally twice daily, may be given the day before and the day of the procedure. The benefit of this approach is unclear; however, the drug has minimal toxicity and is inexpensive. It does not have the same level of evidence to support its use as volume administration.
6. Follow-up testing of renal function is recommended in at-risk individuals.

Preventing Nephrogenic Systemic Fibrosis

Nephrogenic systemic fibrosis is a relatively recently described condition that develops in patients with acute or chronic kidney disease who are exposed to gadolinium-based contrast.[9] Clinical manifestations vary widely, ranging from a small, isolated plaque on an extremity to visceral involvement and death. The initial symptoms typically present within 2 months of gadolinium exposure and include sharp pain, burning, tingling, and tightening of the skin, along with redness and swelling. Generally, the dependent extremities are most involved. Subsequently, the patients may develop plaques and nodules that have a woody or fibrotic character. Patients may develop contractures and involvement of the viscera, including the heart, diaphragm, and lung, has been described.

Avoidance of gadolinium-based contrast (GBC) administration to high-risk patients is the cornerstone of prevention. GBC is considered to be contraindicated except in unusual circumstances (see below) in patients on dialysis. GBC should also be avoided in patients with estimated glomerular filtration rate <30 mL/min. The latter circumstance should generally be assumed in patients with a rising creatinine (acute kidney injury). The modification of diet in renal disease formula may overestimate glomerular filtration rate in patients with chronic liver disease and in those who are underweight or malnourished. If time permits, it may be useful to perform 24-h urine collection for creatinine clearance to directly measure renal function. GBC should be administered with caution to patients with chronic kidney disease 3 (glomerular filtration rate 30–59 mL/min). Consultation with a radiologist is recommended if administration of GBC is considered in the above groups. Frequently, the necessary diagnostic information can be obtained without the use of GBC by relying on a noncontrast study, by administering an alternative contrast agent, or through the selection of a different imaging modality. If GBC administration is considered to be necessary, the lowest possible dose of a macrocyclic chelate (a particular kind of gadolinium contrast) should be used. In such cases, temporary catheter placement and hemodialysis should be considered to accelerate removal of gadolinium, particularly in patients with chronic kidney disease stage 4 or stage 5 or in those with acute kidney injury.

Nothing to Disclose

The author has disclosed that no relationships exist with any companies/organizations whose products or services may be discussed in this chapter.

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Chapter 31. Approach to Acid-Base Disorders

Harold M. Szerlip, MD, MS, FCCP

Objectives:

1. Understand a systematic approach to acid-base disorders.
2. Identify simple and mixed acid-base disturbances.
3. Be able to apply compensation rules.
4. Recognize the etiology of the acid-base disorder.
5. Be able to treat the identified disorder.

Key words: anion gap; metabolic acidosis; metabolic alkalosis; mixed acid-base disorders; respiratory acidosis; respiratory alkalosis; simple acid-base disorders

Synopsis:

Acid-base disorders are extremely common in critically ill patients. Metabolism of fats, carbohydrates, and proteins produces both volatile carbon dioxide (CO_2) and nonvolatile acids. CO_2 is eliminated through the respiratory tract while nonvolatile acids are excreted by the kidneys. Acid-base disturbances can be caused by pathologic conditions that increase or decrease alveolar ventilation and by metabolic disorders in which there is either excessive production of nonvolatile acids or an inability of the kidney to excrete acid or reclaim filtered bicarbonate. Using a stepwise systematic approach, the clinician should be able to identify both simple and mixed acid-base disorders. Once the disturbance is identified, appropriate therapeutic measures can be initiated.

Because of the nature of the ICU, it is understandable that both simple and mixed acid-base disturbances are commonly encountered. Hypotension, sepsis, renal failure, drug overdose, diabetes, renal failure, and hepatic dysfunction all perturb acid-base homeostasis. In addition, the diagnostic and therapeutic interventions used in the critical care setting further complicate acid-base equilibrium. Timely and accurate characterization of these disturbances is therefore an essential component of critical care medicine and is often a means of assessing the severity of the underlying disease process. Identification of an acid-base disturbance should prompt a search for the cause of the disturbance itself. A thoughtful evaluation of all acid-base disturbances is of primary importance, and efforts to normalize pH should be cause-specific and based on therapeutic efficacy.

Acid-Base Homeostasis

To maintain extracellular pH within narrow normal limits (36–44 nm/L, pH 7.36–7.44), the daily production of acid must be excreted from the body (Fig 1). The majority of the acid production comes from the metabolism of dietary fats and carbohydrates. This metabolism produces approximately 15,000 mmol of CO_2 each day that are rapidly excreted by ventilation through the lungs and are known as volatile acids. As long as ventilatory function remains normal, this acid production does not produce changes in acid-base balance. The metabolism of sulfate-containing and phosphorus-containing amino acids along with incomplete metabolism of carbohydrates and fats contributes 1 to 1.5 mEq/kg of nonvolatile acids each day. These nonvolatile acids are excreted by the kidney. In addition, the kidney must reclaim all the bicarbonate that is filtered. Acid-base imbalance will occur if there is (1) a change in ventilation, (2) a significant increase in nonvolatile acid production, (3) a renal disorder affecting the kidneys ability to excrete acid or reclaim bicarbonate, or (4) an increased loss of acid or base through the GI tract.

When the pH is less than 7.35, an acidemia is present. When the pH is greater than 7.44, an alkalemia is present. An acidosis is the process causing the increase in protons while an alkalosis is the process causing a decrease in protons. Both of these processes can coexist and are therefore independent of pH. It is therefore important to apply a stepwise systematic approach to acid-base disorder to correctly identify the underlying disturbance.

Approach to Acid-Base Disorders

There are two main diagnostic approaches to disorders of acid-base balance: The "traditional" Henderson-Hasselbalch/anion gap method[1] and

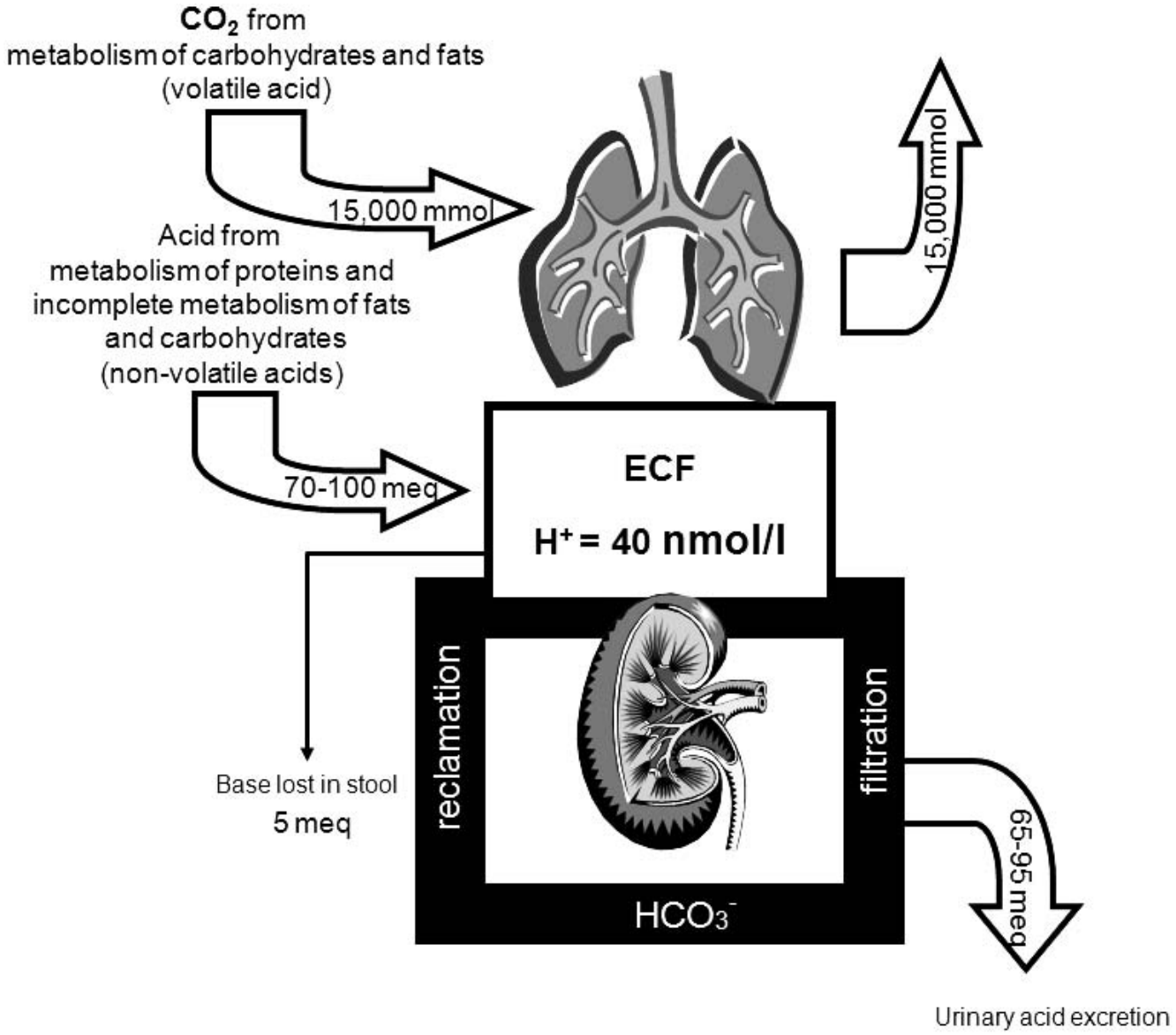

Figure 1. Acid-base homeostasis. Maintenance of acid-base homeostasis requires that the addition of acid to the body is balanced by excretion of acid. Metabolism of fats and carbohydrates produce volatile CO_2 that is excreted through the lungs. Production of fixed nonvolatile acid is mainly through the metabolism of proteins and incomplete metabolism of carbohydrates and fats. Nonvolatile acids are excreted by the kidney through the secretion of H+ buffered by titratable acids and NH_3. Normally, bicarbonate filtration and reclamation by the kidney is a neutral process. As long as both systems function, pH is tightly regulated.

the "modern" strong ion difference (Stewart) approach.[2,3] In the traditional approach, analysis of the acid-base disturbance depends on the pH, partial pressure of carbon dioxide (P_{CO_2}), bicarbonate (HCO_3^-), and the anion gap. It should be emphasized that this approach does not imply what are the independent variables affecting hydrogen ion concentration, nor does it suggest that the bicarbonate buffer system is the most important. This traditional approach defines four major acid-base disturbances: (1) metabolic acidosis, (2) metabolic alkalosis, (3) respiratory acidosis, and (4) respiratory alkalosis. Metabolic acidosis is further divided into an anion gap metabolic acidosis and a non-anion-gap or hyperchloremic metabolic acidosis (HCMA). The strong ion methodology is based on the physical chemical principle that the hydrogen ion concentration of a biologic solution is determined by the dissociation of water ($H^+ + OH^-$). This dissociation is dependent on the difference between strong cations and strong anions: the strong ion difference (strong ions are those that completely dissociate – NaCl), the total weak

acids (mainly proteins and phosphorous), and the P_{CO_2}. Using the strong ion approach, there are six major acid base disorders: (1) strong ion acidosis, (2) strong ion alkalosis, (3) weak acid acidosis, (4) weak acid alkalosis, (5) respiratory acidosis, and (6) respiratory alkalosis.

Although the Stewart approach is based on sound principles and provides insight into certain acid-base disturbances, its complexity adds little to the clinical understanding of acid-base disorders. Furthermore, it ignores the fact that living organisms have evolved specific transport mechanisms for H^+ and HCO_3^- to help maintain physiologic pH. When comparing the traditional approach with the modern approach, as long as the anion gap is corrected for the albumin concentration,[4] minimal differences have been found.[5–7] For that reason, in the remainder of this chapter the traditional approach to acid base disturbances will be used.

Traditional Approach to Acid-Base Disorders

The traditional method of appraising an acid-base disorder follows a systematic stepwise approach. This begins by evaluating a blood gas either on a venous or arterial blood specimen. Because there are only minor differences between arterial and venous specimens, they can be used interchangeably.[8,9] Next, apply compensation rules (Table 1). Then, calculate the anion gap. Finally, it is essential to see if the change in the anion gap and the change in the bicarbonate are equivalent.

Evaluation of the Blood Gas

1. Use the Henderson equation: $[H^+] = 24(P_{CO_2}/HCO_3^-)$ to make sure that the obtained values are consistent. Remember a pH of 7.40 = [H+] of 40 nm/L, 7.3 = 50 nm/L, and 7.5 ≈ 30 nm/L.
2. Look at the pH. If the pH is less than 7.35, there is an acidemia, and if it is greater than 7.44, there is an alkalemia.
3. Determine if the abnormal pH is caused primarily by a respiratory disturbance or a metabolic disturbance. This is done by looking at the P_{CO_2}. If there is an acidemia and the P_{CO_2} is high, a respiratory acidosis is present, and if the P_{CO_2} is low, a metabolic acidosis is present. For an alkalemia, a low P_{CO_2} indicates a respiratory alkalosis and an elevated P_{CO_2} indicates a metabolic alkalosis. If the pH is normal and the P_{CO_2} or HCO_3^- is abnormal, there must be a mixed acid-base disorder.

Table 1—*Compensation Rules*

Metabolic Acidosis
$P_{CO_2} = 1.5(HCO_3^-) + 8 \pm 2$ or
P_{CO_2} = last 2 digits of pH or
$P_{CO_2} = HCO_3^- + 15$
Metabolic Alkalosis
P_{CO_2} ↑ by 0.5-0.7 for each 1 mEq ↑ HCO_3^- (usually not >55–60 mm Hg)
Respiratory Acidosis
Acute—1 mEq ↑ in HCO_3^- for every 10 mm Hg ↑ P_{CO_2}
Chronic—3.5 mEq ↑ in HCO_3^- for every 10 mm HG ↑ P_{CO_2}
Respiratory Alkalosis
Acute—2 mEq ↓ in HCO_3^- for every 10 mm Hg ↓ P_{CO_2}
Chronic—5 mEq ↓ in HCO_3^- for every 10 mm Hg ↓ P_{CO_2}

Compensation Rules

Whenever there is a change from normal in the extracellular pH, the homeostatic response is to correct the pH back toward normal (Table 1). In a metabolic acidosis, the fall in pH activates chemoreceptors that increase ventilation and lower P_{CO_2}. The opposite occurs with a metabolic alkalosis. This response occurs within minutes. For respiratory disturbances, there is an initial acute change in the HCO_3^- because of the biochemical shift in the buffer-base equilibrium. This is followed in 1 to 2 days by renal compensation. Hypercarbia augments renal bicarbonate reabsorption, increasing the serum bicarbonate, and a decrease in P_{CO_2} decreases bicarbonate reabsorption, with a resultant decrease in the serum bicarbonate. Be aware that compensation never brings the pH back to normal, but only toward normal. If compensation is too much or too little, there must be an additional primary disturbance.

Anion Gap

The anion gap is the difference between the measured cation Na^+ and the measured anions Cl^- and HCO_3^-: Anion gap = $Na^+ - (Cl^-$ and $HCO_3^-)$ (Fig 2).[10] Because electrical neutrality

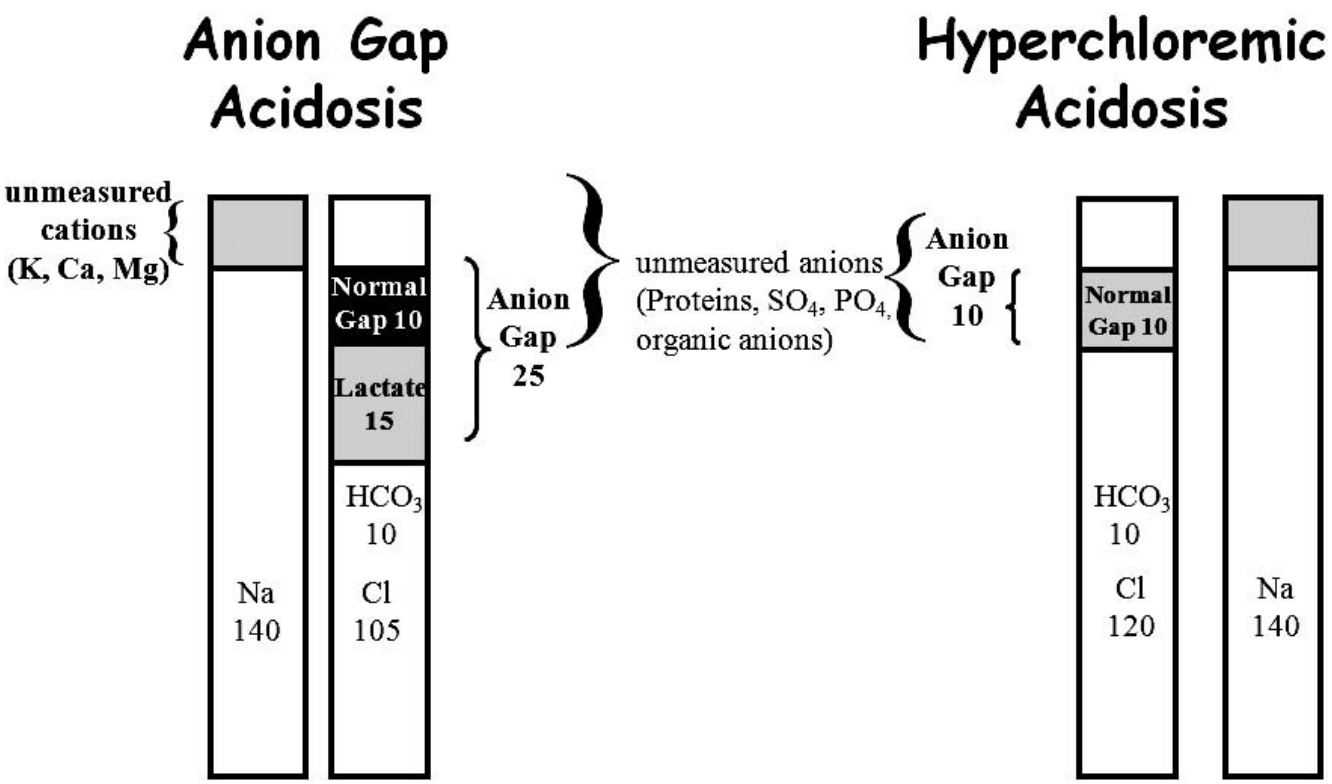

Figure 2. The anion gap is equal to $[Na^+] - [Cl^- + HCO_3^-]$. Because electrical neutrality must be maintained and there are more unmeasured anions than unmeasured cations, the anion gap is positive. In an anion gap metabolic acidosis, there is a decrease in the HCO_3^- and an increase in organic anions. In a hyperchloremic metabolic acidosis, there is a decrease in HCO_3^- and an increase in Cl^-.

must be satisfied, the anion gap represents the fact that there are more unmeasured anions than there are unmeasured cations. Although the normal anion gap is approximately 10 ± 2, this can vary between individuals and laboratories. If possible, it is recommended that what constitutes a normal gap for an individual be based on previous labs. The vast majority of the anion gap is made up by the negative charge on albumin. It is therefore important to correct the anion gap in cases of hypoalbuminemia: for every gram the serum albumin falls, 2.5 should be added to the anion gap.[4] An increase in anion gap is almost always caused by an increase in organic acids. This is especially true whenever the anion gap is greater than 18. Therefore, an elevated anion gap indicates the existence of a metabolic acidosis even if the pH is normal or high.

Delta Anion Gap: Delta Bicarbonate

Assuming that bicarbonate is the major buffer, for every milliequivalent increase in the anion gap, there should be a milliequivalent decline in the serum bicarbonate. Thus, the ratio of the change in anion gap from normal to the change in bicarbonate from normal [(anion gap − normal anion gap)/(bicarbonate − normal bicarbonate)], the so-called "delta:delta" (Δ/Δ), should be approximately 1. A Δ/Δ greater than 1 points to the existence of a concurrent metabolic alkalosis because when corrected for the increase in anion gap, the bicarbonate must have been elevated. A Δ/Δ less than 1 suggests that in addition to the anion gap metabolic acidosis, there is also a non-anion-gap metabolic acidosis.

Simple Acid-Base Disorders

A simple acid-base disorder is one in which there is only a single disturbance and compensation is normal. Simple acid base disturbances are characterized by the P_{CO_2} and the HCO_3^- moving in the same direction. An increase in both P_{CO_2} and HCO_3^- is seen in a simple respiratory acidosis or metabolic alkalosis depending on the pH. A decrease in both points to a simple respiratory alkalosis or metabolic acidosis.

Table 2—*Clues on the History and Physical Examination to Acid-Base Disturbances*

1. Vomiting—metabolic alkalosis
2. History of diabetes—metabolic acidosis
3. History smoking/COPD—respiratory acidosis
4. History of liver disease—respiratory alkalosis
5. Recent binge drinking—metabolic acidosis
6. Diarrhea—metabolic acidosis
7. Tachypnea—respiratory alkalosis
8. Hypotension—metabolic acidosis
9. Aspirin ingestion—mixed respiratory alkalosis and metabolic acidosis

Mixed Acid-Base Disorders

It is important to be able recognize mixed acid-base disorders (Table 2). Clues to their existence are often found in the history and physical examination. Mixed acid-base disturbances can exist as combined metabolic acidosis and metabolic alkalosis (eg, vomiting and hypotension); mixed metabolic and respiratory disturbances (eg, somnolence and hypotension or salicylate toxicity); and mixed metabolic acidosis, metabolic alkalosis, and respiratory disturbance (eg, alcohol binge, liver disease, and vomiting). In addition to the clues in the history and physical examination, mixed disturbances need to be considered (1) whenever the P_{CO_2} and the HCO_3^- move in opposite directions, (2) when the pH is normal but there is abnormal P_{CO_2} or HCO_3^-, (3) when the pH is normal or high and there is an elevated anion gap, and (4) when the delta gap is greater than 1.

Complications of Acid-Base Disorders

Although it had been accepted that a decrease in extracellular pH has detrimental effects on numerous physiologic parameters and should be aggressively treated, there are little convincing data to support this dogma. It has been argued that acidemia depresses myocardial contractility, blocks adrenergic receptor activation, and inhibits the function of key enzymes. Uncontrolled studies are challenging to interpret because of the difficulties in separating the effects of the underlying disease from the effects of the acidemia. Most of the experimental studies have been conducted in isolated cells or organs. The effects of acidemia on whole-body physiology are less clear. Data on the effects of acidemia on cardiac function have been conflicting. Cardiac output is influenced by multiple components, and it is the sum of the effects on these individual components that determines the overall effect of acidemia on cardiac output. Because of the differing effects of acidosis on contractile force, vascular tone, and sympathetic discharge, it is difficult to predict what happens in vivo from studies of isolated organs. In patients with diabetic ketoacidosis who have pH below 7.0, echocardiographic assessment of ejection fraction has demonstrated hyperdynamic cardiac function and not cardiac depression.[11] Although intuitively it makes sense that acidemia should adversely effect cellular function, evidence supporting this is difficult to find. Because intracellular and mitochondrial pH maybe more tightly defended, the effects of extracellular pH on cellular processes may be mitigated.

The effects of metabolic alkalosis are far less documented. Alkalosis has been associated with confusion, obtundation, lowered seizure threshold, arrhythmias, and tetany. As pH rises there is an increase in the binding of calcium to albumin resulting in a decrease in ionized calcium. There is frequently an increase in lactic acid production caused by enhanced glycolysis. Both hypokalemia and hypophosphatemia are often present in cases of metabolic alkalosis and contribute to the adverse effects.

Anion Gap Metabolic Acidosis

As already described, an elevated anion gap implies the existence of an organic acidosis. The presence of an elevated anion gap requires a

Table 3—*Cause of an Anion Gap Acidosis*

G lycols—ethylene glycol, propylene glycol
O xoproline—acetaminophen-induced pyroglutamic acid (5-oxoproline)
L actic acidosis—L-lactate and D-lactate
D iabetic ketoacidosis
M ethanol
A spirin
R enal failure
K etoacidosis—diabetic and alcoholic

search for its cause. The common causes of an anion gap are listed in Table 3 and are best remembered by the new mnemonic: GOLD-MARK[12] (Table 3). Interestingly, the exact organic acids that account for the majority of an elevated gap have not been well identified.[13]

Lactic Acidosis

Lactic acidosis is a common anion gap acidosis and it is by far the most serious of all the anion gap acidoses. Extramitochondrial metabolism of glucose is an anaerobic process that produces pyruvate. If this were the end of the glycolytic process, there would be a net production of two protons and a metabolically unsatisfactory reduction of nicotinamide adenine dinucleotide (NAD) to nicotinamide adenine dinucleotide dehydrogenase (NADH). However, pyruvate rapidly undergoes one of two metabolic fates: (1) under anaerobic conditions, because of the high NADH/NAD ratio, pyruvate is quickly reduced to lactate and in the process produces energy, consumes a proton, and decreases the NADH/NAD ratio, thereby allowing continued glycolysis; or (2) in the presence of oxygen, pyruvate diffuses into the mitochondria and after oxidation by the pyruvate dehydrogenase complex enters the tricarboxylic acid cycle, where it is metabolized to CO_2 and water. Neither of these processes produces protons. During glycolysis, however, glucose metabolism produces two molecules of lactate and two molecules of ATP. It is the hydrolysis of ATP that releases protons ($ATP \rightarrow ADP + H^+ + P_i$). Therefore, acidosis does not occur because of the buildup of lactate but because, under hypoxic conditions, the hydrolysis of ATP is greater than ATP production. Lactate accumulation is consequently a surrogate marker for ATP consumption under hypoxic conditions.

Although normal lactate production averages approximately 1,300 mmol/day, serum lactate levels are usually less than 1 mmol/L because lactate is either reoxidized to pyruvate after which it enters the tricarboxylic acid cycle or is converted back to glucose in the liver and kidney via the Cori cycle. Increased lactate can result from decreased oxidative phosphorylation, increased glycolysis, or decreased gluconeogenesis. Lactate levels are frequently between 2 to 3 mmol/L in hospitalized patients. Some of these patients will develop frank acidosis, but others will have no adverse effects. Lactic acidosis is defined as a lactate level greater than 5 mmol/L.

Lactate levels greater than 5 mmol/L are associated with increased mortality and have been equated as being equivalent to shock in patients with sepsis.[14–16] It remains unclear, however, whether blood lactate level is an independent contributor to mortality or just a surrogate marker for the underlying severity of the illness. Equally as important as the lactate level is the body's ability to clear lactate. Patients able to clear their elevated lactate level have a far better survival than those who cannot.[17,18] Unfortunately, there is a poor correlation among pH, serum AG, and serum lactate levels. Approximately 25% of patients with serum lactate levels between 5 and 9.9 mmol/L have a pH greater than 7.35, and as many as half will have an AG less than 12.[19] Because of this, it is wise to measure serum lactate levels in critically ill patients and not rely on the pH or anion gap.

Lactic acidosis has been traditionally divided into type A, in which there is a clear imbalance between oxygen delivery and oxygen demand, and type B, in which oxygen delivery is normal (Table 4). Type B lactic acidosis is often caused by inborn errors of metabolism, toxins, or drugs. Many times, however, lactic acidosis is caused by hypoxic and nonhypoxic factors. In patients with partial defects in mitochondrial metabolism or age-related declines in cytochrome IV complex activity, lactic acidosis may result with lesser degree of hypoxia than in patients without such defects. Even in shock, where there is a clear decrease in oxygen delivery, some of the increase in lactate levels is not only the result of increased production but also the result of reduced lactate clearance by the liver. In sepsis, there is increased lactate production due both to regional areas of hypoperfusion and increased production from hypermetabolism.[20] In addition, in sepsis there appears to be a decreased ability to utilize oxygen. Administration of dichloracetate, which increases activity of the pyruvate dehydrogenase complex, decreases lactate levels, thus showing that oxygen delivery is not the limiting factor.[21]

Table 4—*Causes of Lactic Acidosis*

Type A
Generalized seizure
Extreme exercise
Shock
Cardiac arrest
Low cardiac output
Severe anemia
Severe hypoxemia
Carbon monoxide poisoning
Type B
Sepsis
Thiamine deficiency
Uncontrolled diabetes mellitus
Malignancy
Hypoglycemia
Respiratory or metabolic alkalosis
Drugs/toxins
Ethanol
Propylene glycol
Metformin
Zidovudine
Diadanosine
Stavudine
Lamivudine
Zalcitabine
Salicylate
Propofol
Niacin
Isoniazid
Nitroprusside
Cyanide
Catecholamines
Cocaine
Acetaminophen
Streptozotocin
Pheochromocytoma
Sorbitol/fructose
Malaria
Inborn errors of metabolism
Other
Hepatic failure
D-Lactic acidosis

Treatment of Lactic Acidosis: The treatment of lactic acidosis is extremely controversial. Obviously, the best therapy is treatment of the underlying disorder. Optimizing cardiac output and oxygen delivery using supportive measures is of utmost importance. Initiation of mechanical ventilation will reduce the work of breathing and reduce lactate production. Many clinicians become concerned, however, when the pH drops below 7.1 and will turn to the use of alkalinizing agents. Increasing pH may not be the panacea that some believe.[22,23] Raising pH may actually increase lactate production by stimulating glycolysis. As pH rises, ventilation, if not mechanically controlled, will decrease, causing a rise in P_{CO_2} with resultant intracellular acidification. In addition, the improvement in pH will shift the oxyhemoglobin dissociation curve to the left, increasing the affinity of oxygen to hemoglobin, thus worsening tissue hypoxemia.

Although there are several alkalinizing agents, only two are available in the United States: sodium bicarbonate and tromethamine (Tham). If sodium bicarbonate is used, it should be infused as an isotonic solution to avoid hypertonicity. The metabolism of bicarbonate increases CO_2 production and raises mixed venous P_{CO_2} levels. With depressed cardiac output or inadequate ventilation, CO_2 can build up in the venous circulation, causing intracellular acidosis and worsening cardiac output. There are no studies that have demonstrated a positive effect of sodium bicarbonate on hemodynamic function or outcomes in critically ill patients.[23,24] In patients with congestive heart failure, the use of sodium bicarbonate actually further depresses cardiac function.[25] Dialysis or hemofiltration using high bicarbonate concentrations in the dialysate or replacement fluid have been reported in anecdotal case reports to successfully improve pH. Unfortunately, no randomized studies examining outcomes exist. Tham is an amino alcohol that buffers both protons and CO_2 and, unlike bicarbonate, does not require an open system to exert its effects. Protonated Tham is excreted by the kidneys. Therefore, its use should be avoided in patients with renal insufficiency. Adverse effects include hyperkalemia, hypoglycemia, and respiratory depression. Despite its ability to improve pH, there are no studies that have demonstrated an improvement in survival.

Drug-Induced Lactic Acidosis: The list of drugs that can cause lactic acidosis is quite large (Table 4). Many of the antiretroviral drugs including stavudine, zidovudine, didanosine, and lamivudine inhibit mitochondrial DNA and increase lactate levels. The biguanide, phenformin, clearly impaired mitochondrial function and was withdrawn from the market because of the resulting lactic acidosis. Although metformin has been implicated as a cause of lactic acidosis, the number of adjudicated cases in which metformin was truly the cause is extremely small.[26]

Critical care practitioners need to be knowledgeable of the lactic acidosis associated with propylene glycol.[27] Propylene glycol is a common vehicle used to solubilize medications such as diazepam, lorazapam, etomidate, and nitroglycerin among others. Propylene glycol is metabolized to lactate, and when these medications are used in high doses, a significant lactic acidosis can result. Because these patients often may have other causes for their lactic acidosis, it is important to be aware of this entity. The clue to this will be a concomitant increase in the osmolal gap caused by the propylene glycol. High-dose propofol infused for prolonged periods can also be associated with lactic acidosis. Most of the reported cases have been in children.

Toxins

Ingestion of ethylene glycol and methanol are both associated with a high-anion-gap metabolic acidosis.[28] Ethylene glycol is metabolized by alcohol dehydrogenase to glycolic acid and subsequently oxalic acid. Methanol is similarly metabolized to formic acid. In the metabolic process, NADH is generated, which favors the accumulation of lactate. Early after ingestion, these osmotically active small-molecular-weight alcohols contribute to an increase in serum osmolality. An osmolar gap (measured osmolality – calculated osmolality $[2 \times Na^{+} + BUN/2.8 + glucose/18 + ethanol/4.6]$) greater than 15 mOsm/kg in the presence of an anion gap acidosis should suggest the ingestion of one of these alcohols. Metabolism of these alcohols will result in a decline in the osmolar gap and an increase in the anion gap.[29] Calcium oxalate crystals are frequently noted on urinalysis after the ingestion of ethylene glycol. Methanol toxicity is associated with blurry vision and edema of the optic nerve.

Treatment of Toxic Alcohol Ingestion: The key to treatment of toxic alcohol ingestions is early recognition. Therapy should be begun in all suspected cases prior to their laboratory confirmation. Treatment consists of blocking the metabolism of these toxins by alcohol dehydrogenase. Fomepazole, a potent inhibitor of alcohol dehydrogenase, has replaced ethanol as the treatment of choice. In addition, depending on the severity of the ingestion and the degree of renal insufficiency, hemodialysis can be initiated to remove the alcohol and correct the pH.

Ketoacidosis

Both diabetic ketoacidosis and alcoholic ketoacidosis (AKA) result from a state of low insulin with a relative excess of counter-regulatory hormones. In diabetic ketoacidosis acidemia is always present whereas patients with AKA frequently have a concomitant metabolic alkalosis from vomiting that may mask the acidemia. Although ketonemia is the hallmark of these two disorders, because of the increased NADH/NAD ratio, acetoacetate, which is measured by the routine serum test for ketones, will shift to β-hydroxybutyrate, which is not measured. This may give the false impression that ketones are not present.

Treatment of Ketoacidosis

Because patients with diabetic ketoacidosis have significant volume depletion from the hyperglycemia-induced osmotic diuresis, the first step in treatment is adequate volume resuscitation with isotonic saline. If insulin is given prior to volume expansion, cardiovascular collapse may occur, as glucose along with water moves out of the extracellular fluid space into cells. After fluid resuscitation, treatment with insulin is essential to turn off ketogenesis. With restoration of the glomerular filtration rate, ketones will be rapidly excreted by the kidney. This occurs prior to the regeneration of bicarbonate. Thus, what was an anion gap acidosis converts to a hyperchloremic metabolic acidosis during the recovery phase. In patients with AKA, therapy consists of correction of the concurrent electrolyte abnormalities (hypokalemia, hypophosphatemia, and hypomagnesemia) and administration of glucose-containing fluids, which will turn on insulin secretion and abrogate the ketogenesis.

Pyroglutamic Acidosis

A recently recognized and likely underdiagnosed cause of an anion gap acidosis is pyroglutamic (5-oxoproline) acidosis. This acidosis occurs

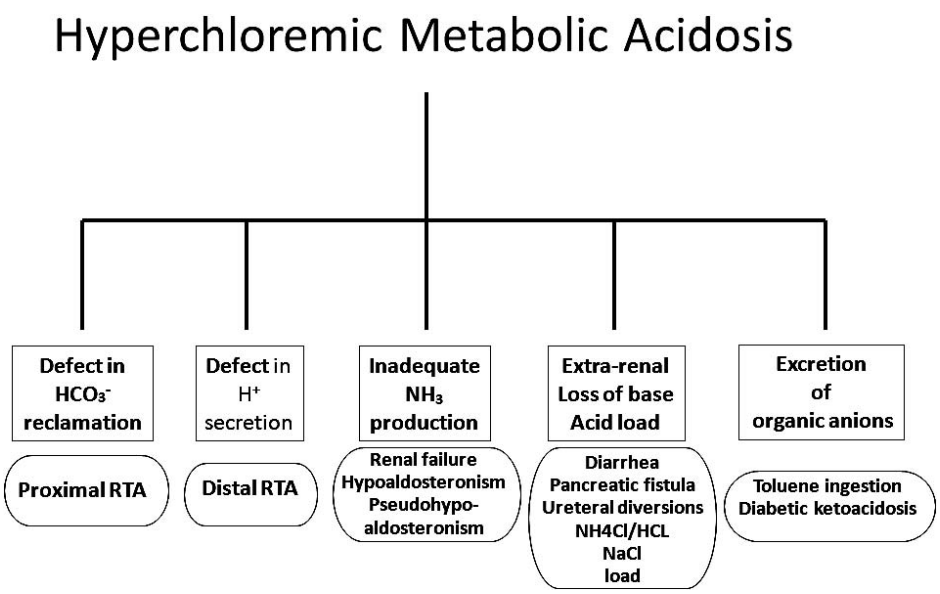

Figure 3. Causes of a hyperchloremic metabolic acidosis.

in patients who usually have an underlying chronic disease and ingest acetaminophen.[30] Acetaminophen causes glutathione depletion, which results in loss of feedback inhibition of γ-glutamylcysteine synthetase with an increase in 5-oxoproline (pyroglutamic acid). Treatment consists of discontinuation of the acetaminophen. Repletion of glutathione stores with *N*-acetylcysteine may be beneficial.

Hyperchloremic Metabolic Acidosis

Hyperchloremic metabolic acidoses (HCMA) are divided into renal and nonrenal causes (Fig 3). Renal causes of HCMA can be a result of a defect in proximal tubule bicarbonate reabsorption (proximal or type 2 renal tubular acidosis [RTA]), inability of the distal tubule to secrete H^+ (distal or type 1 RTA), or an ammoniagenesis defect (type 4 RTA or kidney disease). Extrarenal causes result from loss of bicarbonate such as occurs with diarrhea or the gain of acid such as seen with infusion of isotonic saline. Both proximal and distal RTAs can be secondary to medication or disease (Table 5). As renal function declines, the production of ammonia decreases, limiting the kidney's ability to excrete an acid load. Patients with chronic kidney disease will often have a mild HCMA. Critically ill patients frequently receive large volumes of IV saline. The subsequent increase in the chloride concentration is balanced by an increase in the dissociation of protons from water. In contrast to the treatment of anion gap acidosis, most cases of HCMA can be easily treated with supplemental base.

Metabolic Alkalosis

Although less worrisome than metabolic acidosis, metabolic alkalosis is commonly seen in critically ill patients (Table 6). Metabolic alkalosis is characterized by an increase in bicarbonate in the absence of a primary respiratory process. Because under normal circumstances the kidney has enormous capacity to excrete excess bicarbonate, a sustained rise in bicarbonate can only occur if renal excretion becomes limited. Therefore, a metabolic alkalosis requires a generation phase in which bicarbonate is gained and a maintenance phase during which the kidney cannot excrete the excess bicarbonate. The increase in bicarbonate can be secondary to a gain of base as occurs with administration of exogenous bicarbonate or loss of acid as occurs with vomiting. Normally, this excess bicarbonate would promptly be excreted by the kidney; however, in the face of volume/chloride depletion,[31] hypokalemia,[32]or hyperaldosteronism, not only is bicarbonate excretion reduced, but bicarbonate reabsorption is enhanced.

A common cause of metabolic alkalosis is vomiting or nasogastric suction. The loss of acid produces the alkalosis, which is maintained by chloride depletion. The use of proton pump

Table 5—*Causes of Renal Tubular Acidosis*

Proximal Renal Tubular Acidosis
Idiopathic
Genetic
Cystinosis
Tyrosinemia
Galactosemia
Wilson disease
Sporadic (may be transient in children)
Acquired disorders
Multiple myeloma
Vitamin D deficiency
Toxins and drugs
Heavy metals—lead, copper, cadmium, mercury
Acetazolamide
Topiramate
Sulfamylon
Ifosfamide
Cidofovir
Distal Renal Tubular Acidosis With Hypokalemia
Idiopathic
Genetic
Familial
Ehler-Danlos syndrome
Wilson disease
Marfan syndrome
Nephrocalcinosis
Hypergammaglobulinemic states
Drugs and toxins
Amphotericin B
Aminoglycosides
Ifosfamide
Analgesics
Vanadate
Lithium carbonate
Toluene
Autoimmune disease
Sjogren syndrome
Rheumatoid arthritis
Thyroiditis
Chronic active hepatitis
Primary biliary cirrhosis
Cirrhosis
Medullary sponge kidney
Renal transplantation
Distal Renal Tubular Acidosis With Hyperkalemia
Sickle cell anemia
Urinary tract obstruction
Systemic lupus erythematosus
Renal transplantation
Type IV Renal Tubular Acidosis
Aldosterone deficiency
Adrenal insufficiency
Hyporenin-hypoaldosteronism
Drugs
Angiotensin-converting enzyme inhibitors
Angiotensin receptor blockers
Nonsteroidal antiinflammatory drugs
Heparin
Aldosterone resistance
Drugs
Spironolactone
Pentamidine
Trimethoprim
Amiloride
Gordon syndrome (chloride shunt)

inhibitors or H_2-receptor antagonists can help to prevent the metabolic alkalosis in this setting. Another frequent cause of metabolic alkalosis is aggressive diuresis, with a decrease in serum chloride and a subsequent increase in bicarbonate. In patients who require massive transfusions, citrate, used as an anticoagulant in blood products, is metabolized to bicarbonate, resulting in a metabolic alkalosis. Because patients with chronic hypercapnia have a compensatory increase in their serum bicarbonate, rapid correction of the hypercapnia by mechanical ventilation produces a metabolic alkalosis. This posthypercapneic metabolic alkalosis can be avoided if the respiratory acidosis is corrected more slowly. Occasionally, patients who free-base cocaine, which is made by adding bicarbonate or sodium hydroxide to cocaine, will present to the ICU with a metabolic alkalosis. Because albumin is a weak acid, hypoalbuminemia can cause a mild metabolic alkalosis.

Metabolic alkaloses are divided into those that are responsive to treatment with chloride-containing fluid and those that are chloride

Table 6—*Causes of Metabolic Alkalosis*

Vomiting
Nasogastric suction
Diuretics
Congenital chloridorrhea
Refeeding after starvation
Bartter syndrome
Gitelman syndrome
Excess bicarbonate intake (usually requires renal insufficiency)
Free-base cocaine
Citrate in blood products
Primary hyperaldosteronism
Posthypercapnic states
Recovery phase of diabetic ketoacidosis
Syndromes of apparent mineralocorticoid excess
11 β-hydroxysteroid dehydrogenase deficiency
Liddle syndrome
Licorice
Hypokalemia
Hypoproteinemia

Table 7—*Causes of Respiratory Acidosis*

Central Respiratory Depression
Primary hypoventilation
Drug overdose
Cerebrovascular accident
Brain tumor
Head trauma
Encephalitis, meningitis
Musculoskeletal
Scoliosis
Chest wall deformities
Muscle paralysis
Myasthenia gravis
Poliomyelitis
Guillain-Barre syndrome
Hypokalemia
Hypophosphatemia
Paralytic drugs
Pulmonary
Chronic obstructive lung disease
Acute asthma
ARDS
Obstructive sleep apnea
Ventilator malfunction

unresponsive. They can be distinguished by the fractional excretion of chloride (FE_{Cl}) = (Serum creatinine × Urine chloride) / (Serum chloride × Urine creatinine). A FE_{Cl} less than 1% suggests chloride depletion. Infusion of chloride will allow the kidney to excrete the excess bicarbonate and promptly correct the alkalosis. Patients with a FE_{Cl} greater than 1% will not respond to chloride infusion. Chloride resistance alkalosis is seen in patients with severe potassium depletion or with primary hyperaldosteronism. In those cases, treatment is aimed at correction of the hypokalemia or by administration of an aldosterone antagonist. When volume expansion is not desirable, metabolic alkalosis can be treated with a carbonic anhydrase inhibitor (acetazolamide) or by infusion of 0.1 N HCL through a central vein.

Respiratory Acidosis

Inadequate ventilation will raise the P_{CO_2} and result in a respiratory acidosis. Decreased ventilation can be secondary to numerous disease processes, from depressed level of consciousness to primary pulmonary disorders to neuromuscular diseases (Table 7). Because of the neuromuscular and pulmonary diseases that are common in critically ill patients, respiratory acidosis is one of the most frequent acid-base disorders encountered in the ICU. With the use of low tidal volume, ventilation respiratory acidosis is becoming even more common.

Acute increases in the P_{CO_2} may be associated with confusion, anxiety, and seizures. Hypercarbia results in cardiac depression increase in pulmonary vascular resistance and increased cerebral blood flow. An elevated P_{CO_2}, as predicted by the alveolar air equation, will cause the alveolar oxygen pressure to fall. Chronic increases are usually well tolerated.

Treatment of acute respiratory acidosis requires noninvasive or invasive ventilation. Rapid falls in the P_{CO_2} need to be avoided. In chronic CO_2 retainers, the aim is not to bring the P_{CO_2} back to normal. This will lead to unnecessary prolonged period of ventilatory support. In cases of permissive hypercapnia, in which ventilation cannot be increased, the goal is to maintain the pH above 7.1. The precise degree of acidosis that is tolerated is highly dependent on the clinician. Many clinicians will use alkalinizing agents in the face of severe acidosis although there is no evidence to support their use. In fact, in animal studies, the use of buffering agents has been demonstrated to worsen lung injury.[33]

Respiratory Alkalosis

Respiratory alkalosis is characterized by a low P_{CO_2} in the absence of a primary metabolic disturbance. It is caused by an increase in alveolar ventilation. This often results from an increase in central respiratory drive. This may be secondary to direct stimulation of the respiratory center or through stimulation of mechanoreceptors within the thorax or chemoreceptors located in the aortic arch or carotid bodies. Common causes of respiratory alkalosis include hypoxemia, fever, salicylates, early sepsis, and CNS disorders (Table 8). The treatment of a respiratory alkalosis is aimed at removing the stimulus that increased the respiratory drive.

Relationship Disclosed

The author has disclosed the following relationships: Grant monies (from industry related

Table 8—*Causes of Respiratory Alkalosis*

Hypoxemia
Stimulation of pulmonary or pleural receptors
Pneumonia
Pulmonary embolism
Pulmonary edema
Asthma
Psychogenic hyperventilation
Medications
Theophylline
Catecholamines
Salicylates
Progesterone
CNS disorders
Subarachnoid hemorrhage
Cheyne-Stokes respirations
Increased intracranial pressure
Fever
Early sepsis
Increased minute ventilation secondary to ventilator management

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Notes

Chapter 32. Severe Pneumonia

Michael S. Niederman, MD, MS, FCCP

Objectives:

- Define the epidemiology of severe community-acquired pneumonia (CAP), hospital acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP), and health-care-associated pneumonia (HCAP) and risk factors for mortality.
- Discuss the common etiologic pathogens and therapy of severe CAP, HAP/VAP, and HCAP, including the impact of atypical pathogens, multidrug-resistant gram-negative, methicillin-resistant *Staphylococcus aureus* (MRSA), and penicillin-resistant pneumococcus.
- Describe the pathogenesis of severe pneumonia.
- Outline therapies and prevention strategies for severe pneumonia.

Key words: adequate therapy; antibiotic therapy; community acquired; drug-resistant pneumococcus; health-care-associated pneumonia; methicillin-resistant *S aureus*; multidrug-resistant pathogens; nosocomial; pneumonia

Synopsis:

Severe pneumonia can occur in patients with all forms of lung infection, including community-acquired pneumonia (CAP), nosocomial pneumonia, ventilator-associated pneumonia (VAP), and health-care-associated pneumonia. Patients who acquire severe pneumonia often have an excessive immune response to infection that is not localized to the initial site of lung infection. In patients with CAP, early recognition of severe illness can reduce mortality, and delayed transfer to the ICU may be a predictor of poor outcome. Scoring systems such as the Pneumonia Severity Index, CURB-65, and SMART-COP are adjunctive tools that can help identify CAP patients with severe illness. Once recognized, severe pneumonia should be treated promptly, and delays in therapy increase mortality, as does inappropriate therapy, which is more likely to occur when patients are infected with multidrug-resistant (MDR) bacteria. For patients with severe CAP and for those with VAP who are at risk for MDR pathogens, initial therapy should be with a combination of agents. In severe CAP, combination therapy provides coverage of multiple organisms, including atypical pathogens. In VAP, combination therapy increases the likelihood of covering MDR pathogens and can provide coverage for mixed infection involving gram-negatives and methicillin-resistant *Staphylococcus aureus*. Prevention of severe CAP is focused on smoking cessation and vaccination (pneumococcal and influenza), while VAP prevention involves multiple interventions, often combined into a "ventilator bundle."

Together, influenza and pneumonia are the eighth-leading cause of death in the United States and the number one cause of death from infectious diseases. The patient with pneumonia is managed in the ICU when severe forms of community-acquired pneumonia (CAP) are present, when a patient with health-care-associated pneumonia (HCAP) presents with severe illness, or when a hospitalized patient develops a life-threatening nosocomial pneumonia. HCAP is a relatively new terminology that refers to infection arising in patients who have been in contact with environments (nursing homes, hemodialysis centers) prior to admission to the hospital that expose them to the same multidrug-resistant (MDR) bacteria that are present in the hospital, and these patients frequently develop severe pneumonia.[1,2] In the ICU, almost 90% of episodes of nosocomial pneumonia occur in patients who are being mechanically ventilated for other reasons, and this is termed ventilator-associated pneumonia (VAP) if the pneumonia develops after at least 48 h supported by mechanical ventilation. The elderly account for a disproportionate number of critically ill patients with all forms of pneumonia, often because they commonly have comorbid illness that predisposes them to more severe forms of infection and their short- and long-term mortality is higher than that of younger patients.[3] In all forms of severe pneumonia, antibiotic resistance is an increasing problem, especially among pneumococci in CAP and with *Pseudomonas aeruginosa*, *Acinetobacter* spp, extended-spectrum β-lactamase-producing gram-negatives, and methicillin-resistant *Staphylococcus aureus* (MRSA) in VAP, CAP, and HCAP.[1,2] Although patients with HIV infection and those with other immunocompromising diseases commonly develop pneumonia, the approach to managing these patients is specific to the immune impairment, and these populations have specific management that is not discussed here. Pneumonia remains a controversial illness because of difficulties in diagnosis and in establishing an etiologic pathogen.[4,5] Recently,

Table 1—*Risk Factors for Developing Severe CAP*

Advanced age (>65)
Delay in seeking medical attention
Nonrespiratory presentation
Comorbid illness
Chronic respiratory illness (including COPD), cardiovascular disease, diabetes mellitus, neurologic illness, renal insufficiency, malignancy (especially if active)
Cigarette smoking (risk for pneumococcal bacteremia)
Alcohol abuse
Absence of antibiotic therapy prior to hospitalization
Inappropriate initial therapy
Infection with specific pathogens: community-acquired MRSA, influenza, *Legionella*, type 3 pneumococcus
Failure to contain infection to its initial site of entry
Immune suppression (role of prior corticosteroids uncertain)
Genetic polymorphisms in the immune response

the problem of VAP has become controversial since many believe that with simple prevention measures, the disease can be eliminated, with the result being "zero VAP."[6]

Definitions of Severe Pneumonia, Risk Factors, and Prognosis

Among patients with CAP admitted to the hospital, 10% to 20% require care in the ICU, and the rates are higher in elderly patients. It is important to define the need for ICU admission as soon as possible since patients who are admitted in a delayed fashion, after first being admitted to a medical floor, have a worse prognosis than those directly admitted to the ICU.[1] In the latest IDSA/ATS guidelines, the ICU is recommended for patients needing mechanical ventilation or those in septic shock. In addition, the ICU should be used for patients with at least three of the following minor criteria: Pa_{O_2}/F_{IO_2} ratio <250, respiratory rate >30/min, confusion, multilobar infiltrates, systolic BP <90 mm Hg despite aggressive fluid resuscitation, BUN >20 mg/dL, leukopenia (<4,000 cells/μL), thrombocytopenia (<100,000 cells/μL), and hypothermia (<36°C).[1] Other findings in severe pneumonia are hyponatremia (<130 mEq/L) and an arterial pH <7.3, the latter being one of the most important indicators of need for ICU admission. Recent data suggest that the presence of four minor criteria may be a better predictor of the need for ICU admission than three criteria.[7]

The mortality rate for CAP patients admitted to the ICU is 35% to 40%, but higher rates have been observed if the majority of ICU-admitted patients are mechanically ventilated, implying that the prognosis is worse if ICU care is first provided late in the course of illness Based on a number of studies, a reasonable benchmark is that about 60% of all ICU CAP patients will be mechanically ventilated at the time of admission.[8,9]

The mortality rate of VAP can be as high as 50% to 70%, and case-control studies have documented mortality directly attributable to the presence of pneumonia, although not all studies have accepted that this illness adds to the mortality risk of critically ill patients.[10] The presence of MDR bacteria adds to mortality, most likely because these organisms are often not anticipated and, when present, are often initially treated with ineffective antibiotic regimens.[11] Some patients with HCAP are at risk for infection with MDR pathogens, and in general HCAP patients have a higher mortality than CAP patients because they have more serious underlying illness. Risk factors for HCAP include a history of: hospitalization in the past 3 months, admission from a long-term care facility, need for dialysis or home infusion therapy, home wound care, or antibiotic therapy in the past 3 months.[2] While not all HCAP patients are at risk for MDR pathogens, those who are have multiple risk factors, particularly severe illness, as well as poor functional status, recent hospitalization, recent antibiotic therapy, and immune suppression.[12]

Risk Factors for Severe CAP

Coexisting illness is present in most patients with severe CAP (45% to 65%) and in those with a complicated pneumonic illness[1,13] (Table 1). The most common chronic illnesses in these patients are respiratory disease, such as chronic obstructive lung disease (COPD), cardiovascular disease, and diabetes mellitus. In addition, certain habits, such as cigarette smoking and alcohol abuse, are common, with cigarette smoking being a risk factor for bacteremic pneumococcal infection.[14] Even milder forms of pneumonia may be more severe on presentation

if the patient has not received antibiotic therapy prior to hospital admission. Recently, it has become clear that certain genetic differences in the immune response may predispose certain individuals to more severe forms of infection and adverse outcomes and may be reflected by a family history of severe pneumonia or death from infection.[15]

Risk Factors for Mortality From CAP

Clinical features that predict a poor outcome (Table 2) include advanced age (>65 years), preexisting chronic illness of any type, the absence of fever on admission, respiratory rate ≥30/min, diastolic or systolic hypotension, elevated BUN (>19.6 mg/dL), profound leukopenia or leukocytosis, inadequate antibiotic therapy, need for mechanical ventilation, hypoalbuminemia, and the presence of certain "high-risk" organisms (type III pneumococcus, *S aureus*, gram-negative bacilli, aspiration organisms, or postobstructive pneumonia).[1,16] Delay in the initiation of appropriate antibiotic therapy of more than 4 h is also a mortality risk.[1,17]

Scoring systems have been used to predict mortality in CAP, and commonly used tools include CURB-65, the Pneumonia Severity Index (PSI), SMART-COP, and the CUR-XO system.[18–20] The PSI is a complex scoring system that places patients into one of five risk groups for death, based on age and the presence of male sex, comorbid illness, and certain laboratory and physical findings. This tool heavily weights age and comorbidity but does not place a heavy emphasis on evaluation of vital signs unless they exceed a relatively high threshold. On the other hand, the CURB-65 approach assesses the presence of confusion, elevated blood urea nitrogen, respiratory rate ≥30/min, low blood pressure (either systolic ≤90 mm Hg or diastolic ≤60 mm Hg), and whether the patient is at least 65 years old. If three of these five criteria are present, the predicted mortality rate is >20%.[19,20]

None of the prognostic tools can specifically define the need for ICU care. The PSI can predict mortality, but nearly 40% of those admitted to the ICU fall into low mortality risk groups, while not all those in high mortality risk categories need ICU care.[20]

Table 2—*Risk Factors for a Poor Outcome From CAP*[a]

Patient-related factors
Male sex
Absence of pleuritic chest pain
Nonrespiratory clinical presentation
Neoplastic illness
Neurologic illness
Age >65 years
Family history of severe pneumonia or death from sepsis
Delay in seeking therapy
Coexisting decompensation of comorbid illness
Multiple system organ failure
Abnormal physical findings
Respiratory rate >30/min on admission
Systolic (<90 mm Hg) or diastolic (<60 mm Hg) hypotension
Tachycardia (>125/min)
High fever (>40°C) or Hypothermia (<36°C)
Confusion
Laboratory abnormalities
BUN >19.6 mg/dL
Leukocytosis or leukopenia
Multilobar radiographic abnormalities
Rapidly progressive radiographic abnormalities during therapy
Bacteremia
Hyponatremia (<130 mmol/L)
Thrombocytopenia (<100,000/mm^3)
Leukopenia (<4000 cells/mm^3)
Renal failure
Respiratory failure
Hypoalbuminemia
Arterial pH <7.35
Pleural effusion
Pathogen-related factors
High-risk organisms
Type III pneumococcus, *S aureus*, gram-negative bacilli (including *P aeruginosa*), aspiration organisms, epidemic viral pneumonia
High levels of penicillin resistance (minimum inhibitory concentration of at least 4 mg/L) in pneumococcus
Therapy-related factors
Delay in initial antibiotic therapy (more than 4 to 6 h)
Delay in admission to the ICU (initially admitted to a medical ward)
Initial therapy with inappropriate antibiotic therapy
Failure to have a clinical response to empiric therapy within 72 h
Use of too low a dose of the right antibiotic

Adapted from Mandell et al.[1]
[a]Many are included in current prognostic scoring tools (PSI, CURB-65, SMART COP; see text).

The SMART-COP tool has focused on defining which patients will need intensive respiratory or vasopressor support (IRVS).[21] The acronym "SMART-COP" refers to systolic blood pressure <90 mm Hg, multilobar infiltrates, albumin value

<3.5 g/dL, respiratory rate elevation (≤25 for those age ≤50 and ≥30 for those age >50), tachycardia (>125/min), confusion, low oxygen (<70 mm Hg if age ≤50 or <60 mm Hg if age >50), and arterial pH <7.35. The abnormalities in systolic blood pressure, oxygenation, and arterial pH each received 2 points, while the five other criteria received 1 point each, and with this system, the need for IRVS was predicted by a SMART-COP score of at least 3 points. Using this cutoff, the sensitivity for need for IRVS was 92.3% and the specificity 62.3%, with a positive and negative predictive value of 22% and 98.6%, respectively. The PSI and CURB-65 did not perform as well overall.[21]

Therapy factors can increase mortality, with delay in starting therapy, particularly with septic shock, increasing mortality in a linear fashion for each hour that therapy is not started. Ineffective initial empiric therapy is also a predictor of death in all forms of pneumonia, including severe CAP, and recent data have suggested that with pneumonia and septic shock, the use of dual effective therapy leads to better outcome than single effective therapy.[22] In patients with CAP and pneumococcal bacteremia, this is particularly true if the second agent used with a β-lactam is a macrolide.[23]

In severe CAP, another important prognostic finding is clinical evolution, as reflected by radiographic progression during therapy.[1] The elderly with CAP often have a higher risk of dying than other populations, and in one series, the mortality rate of nursing home-acquired pneumonia was 32%, compared with a mortality rate of 14% in other patients with CAP.[24] One factor that may explain this finding is that older patients often have atypical clinical presentations of pneumonia, which may lead to their being diagnosed at a later, more advanced stage of illness, resulting in an increased risk of death.[25]

Risk Factors for VAP

Mechanical ventilation (for >2 days) is the most important risk factor for nosocomial pneumonia, and the use of noninvasive ventilation can reduce the risk of nosocomial respiratory infection. Other risk factors are age >60, malnutrition (serum albumin value <2.2 g/dL), acute lung injury (ARDS), coma, burns, recent abdominal or thoracic surgery, multiple organ failure, transfusion of >4 units of blood, transport from the ICU, prior antibiotic therapy, elevation of gastric pH (by antacids or histamine type 2 blocking agents), large-volume aspiration, use of a nasogastric tube (rather than a tube placed in the jejunum or a tube inserted through the mouth), use of inadequate endotracheal tube cuff pressure, prolonged sedation and paralysis, maintaining patients in the supine position in bed, use of total parenteral nutrition feeding rather than enteral feeding, and repeated reintubation.[2] When a patient is mechanically ventilated, the risk of pneumonia is greatest in the first 5 days (3% per day) and declines thereafter to a risk of 2% per day for days 6 to 10 and to a rate of 1% per day or lower after this.[26] Recent studies[6] have shown a marked decline in the incidence of VAP, compared to in the past, and this has been attributed to successful prevention by the use of ventilator "bundles."

Risk Factors for Mortality From VAP

Therapy is a major determinant of attributable mortality, with the risk of death rising with the use of the wrong therapy, of delayed therapy, of the correct therapy at too low a dose, or of an agent that does not penetrate to the site of infection.[2] Initial appropriate therapy (using an agent to which the etiologic pathogen is sensitive) can reduce mortality, but administration of correct therapy at a later date, after initially incorrect therapy, may not effectively correct such a mistake.[27] The benefit of accurate empiric therapy may be greatest for those infected with *P aeruginosa* or *S aureus* and for those without the most severe degree of multiple organ dysfunction at the time of therapy.[28] The practice of "deescalation," or decreasing the number and/or spectrum of antimicrobial therapy once culture data become available, is associated with a lower mortality compared to escalation or therapy or compared to a strategy of making no effort to reduce antibiotic therapy.[29]

Other risk factors for mortality include prolonged duration of ventilation, coma on admission, creatinine value >1.5, transfer from another ward to the ICU, the presence of certain

"high-risk" pathogens (particularly an antibiotic resistant organism such as *P aeruginosa*, *Acinetobacter* spp, or *S aureus*), bilateral radiographic abnormalities, age >60 years, ultimately fatal underlying condition, shock, prior antibiotic therapy, multiple system organ failure, nonsurgical primary diagnosis, or a rising Acute Physiology and Chronic Health Evaluation score during pneumonia therapy (Table 3).[2,30] Superinfection, as opposed to a primary nosocomial pneumonia, is associated with a higher mortality, emphasizing that prior therapy may lead to a worse outcome by predisposing to infection with a pathogen resistant to usual therapy.[31]

Table 3—*Risk Factors for Mortality From Nosocomial Pneumonia*

Physiologic findings
Respiratory failure
Coma on admission
Multiple system organ failure
Acute Physiology and Chronic Health Evaluation II score rising to greater than 20 at 72 h after diagnosis
Worsening hypoxemia in the first 3 days
Laboratory findings
Creatinine value >1.5 mg/dL
Gram-negative pneumonia, especially *Pseudomonas* or *Acinetobacter* infection
Infection with any drug-resistant pathogen, including MRSA
Bilateral radiographic abnormalities
Fungal pneumonia
Polymicrobial infection
Superinfection as the cause of pneumonia
Risking Clinical Pulmonary Infection in the first 3 days of therapy
Historical data
Prior antibiotic therapy
Age >60 years
Underlying fatal illness
Prolonged mechanical ventilation
Inappropriate initial antimicrobial therapy

Pathogenesis

General Overview

Pneumonia results when an infectious pathogen (bacteria, virus, fungus, protozoa) overwhelms host defenses. This may occur because the patient has an inadequate immune response, often as the result of underlying comorbid illness, because of anatomic abnormalities (endobronchial obstruction, bronchiectasis), or because of therapy-induced dysfunction of the immune system (corticosteroids, endotracheal intubation).[2,32] In addition, there are genetic variations in the immune response, making some patients prone to overwhelming infection due to an inadequate response and others prone to acute lung injury due to an excessive immune response.[15,33] The normal host response to pneumonia is to localize inflammation to the site of infection, but when it spills over to the other lung, ARDS may occur, and if it spills over to the systemic circulation, the result can be septic shock.[33] Pneumonia can also occur if, an even adequate host defense system is overwhelmed by a large inoculum of bacteria (massive aspiration) or by a particularly virulent organism to which the patient has no preexisting immunity (epidemic virus) or to which the patient has an inability to form an adequate immune response. With this paradigm in mind, it is easy to understand why previously healthy individuals develop infection with virulent pathogens such as viruses (influenza), *Legionella pneumophila*, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and *Streptococcus pneumoniae*. However, for chronically ill patients, it is possible for them to be infected not only by these virulent organisms but also by less virulent organisms that can first colonize the respiratory tract. These organisms include enteric gram-negative bacteria (*Escherichia coli*, *Klebsiella pneumoniae*, *P aeruginosa*, and *Acinetobacter* spp), gram-positives (MRSA), and fungi (*Aspergillus* and *Candida* spp).

Bacteria can enter the lung via several routes, but aspiration from a previously colonized oropharynx is the most common pathway. Patients can also aspirate large volumes of bacteria if they have impaired neurologic protection of the upper airway (stroke, seizure) or if they have gastrointestinal illnesses that predispose to vomiting. Other routes of entry include inhalation, which applies primarily to viruses, *L pneumophila*, and *Mycobacterium tuberculosis*; hematogenous dissemination from extrapulmonary sites of infection (right-sided endocarditis); and direct extension from contiguous sites of infection. In critically ill hospitalized patients, bacteria can also enter the lung from a colonized stomach (spreading retrograde to the oropharynx, followed by aspiration), from a colonized or

infected maxillary sinus, or from colonization of dental plaque, or they can enter the lung directly via the endotracheal tube (from the hands of staff members). The use of nasal tubes (into the stomach or trachea) can predispose to sinusitis and pneumonia, although a gastric source of pneumonia pathogens in ventilated patients is not common.[2,34]

The Role of Respiratory Therapy Equipment and Endotracheal Tubes

The endotracheal tube bypasses the filtration and host defense functions of the upper airway and can act as a conduit for direct inoculation of bacteria into the lung. This route may be particularly important if bacteria colonize the inside of the endotracheal tube itself in the form of a biofilm and then get dislodged with suction catheters.[35,36] In spite of this biofilm, reintubating patients with a fresh tube is not recommended because reintubation is itself a risk factor for VAP.[2] In an effort to minimize the role of the endotracheal tube in pneumonia pathogenesis, efforts are being made to develop new endotracheal tube materials (silver-coated tube) or new tube-cleaning devices (the mucus shaver). In addition, there has been renewed attention to the endotracheal tube cuff, with prevention efforts focused on using polyurethane (rather than polyvinylchloride) materials for a high-pressure, low-volume cuff, that does not easily form folds that allow oral secretions to reach the trachea. Efforts are also being focused on maintaining endotracheal tube cuff pressures continuously above 20 to 25 cm H_2O and on considering the use of a tapered cuff shape.[37]

Respiratory therapy equipment and ventilator circuits can contribute to VAP,[37,38] particularly if the heavily colonized condensate in the tubing is inadvertently inoculated into the patient because it was not handled carefully. Tubing changes every 24 h (rather than every 48 h served as a risk factor for pneumonia.[39] Although most patients have ventilator tubing changed every 48 h, several studies have shown no increased risk of infection if tubing is never changed or is changed infrequently.[40] The use of heat moisture exchangers may be one way to avoid this problem, but they have had an inconsistent effect on preventing VAP, but frequent changes of heat moisture exchangers (ie, every 24 h) have not been shown to have an impact on the incidence of VAP, and heat moisture exchangers should be changed no more frequently than every 48 h.[41]

Clinical Features of Pneumonia

Historical Information

When CAP develops in a patient with an intact immune system, classic pneumonia symptoms are present (fever, cough, sputum production, dyspnea, pleuritic chest pain), but the elderly patient can have a nonrespiratory presentation with symptoms of confusion, falling, failure to thrive, altered functional capacity, or deterioration in a preexisting medical illness, such as congestive heart failure.[42]

The absence of clear-cut respiratory symptoms and an afebrile status have themselves been predictors of an increased risk of death. Pleuritic chest pain is a common symptom, and in one study, its absence was also identified as a poor prognostic finding.[43]

There are certain clinical conditions associated with specific pathogens in patients with CAP, and these associations should be evaluated when obtaining a history (Table 4).[1] For example, if the presentation is subacute, following contact with birds, rats, or rabbits, then the possibility of psittacosis, leptospirosis, tularemia, or plague should be considered. *Coxiella brunetti* (Q fever) is a concern with exposure to parturient cats, cattle, sheep, or goats; *Francisella tularensis* with rabbit exposure; hantavirus with exposure to mice droppings in endemic areas; *Chlamydophila psittaci* with exposure to turkeys or infected birds; and *Legionella* with exposure to contaminated water sources (saunas). Following influenza, superinfection with pneumococcus, *S aureus* (including MRSA), and *H influenzae* should be considered. With travel to endemic areas in Asia, the onset of respiratory failure after a preceding viral illness should lead to suspicion of a viral pneumonia, which could be influenza or avian influenza.[44] Endemic fungi, (coccidioidomycosis, histoplasmosis, and blastomycosis) occur in well-defined geographic areas and may present with symptoms that overlap with acute bacterial pneumonia.

Table 4—*Likely Microbiologic Etiology and Host Epidemiology of CAP and NP/VAP*

Epidemiology	Suspected Pathogen
Community-acquired	
Alcoholism	Pneumococcus (including drug-resistant organisms), anaerobes, *H influenzae*, *K pneumoniae*, TB
Splenic dysfunction (sickle-cell disease)	Pneumococcus, *H influenzae*
COPD	Pneumococcus, *H influenzae*, *M catarrhalis*
Recent influenza infection	Pneumococcus, *S aureus* (including MRSA), *H influenzae*, enteric gram-negatives
High-risk aspiration	Anaerobes, enteric gram-negative bacilli (in nursing home patients)
Neutropenia (including neutrophil dysfunction from chronic corticosteroid therapy)	Gram-negative bacilli (especially *P aeruginosa*), *Aspergillus*
HIV infection	Pneumococcus, *H influenzae*, *Pneumocystis jiroveci*
Travel to Asia	Melioidosis, epidemic viral infection
Rabbit exposure	*Francisella tularensis*
Exposure to farm animals, parturient cats	*C burnetii* (Q fever)
Exposure to mouse droppings	Hantavirus
Nursing home-acquired (no prior antibiotics and good functional status)	Pneumococcus (including drug-resistant organisms) and other organisms of CAP
Nursing home-acquired (prior antibiotics or poor functional status)	Gram-negative bacilli (including *P aeruginosa*, *Acinetobacter* spp, ESBL-producing *Enterobacteriaceae*), *S aureus* (including MRSA)
Hospital-acquired and VAP	Gram-negative bacilli (including *P aeruginosa*, *Acinetobacter* spp, ESBL-producing *Enterobacteriaceae*), *S aureus* (including MRSA) Consider local microbiology

ESBL = extended-spectrum β-lactamase.

Nosocomial pneumonia often presents with less definitive clinical findings, particularly in those who are mechanically ventilated, where the clinical diagnosis is made in patients with a new or progressive radiographic infiltrate, along with some indication that infection is present (fever, purulent sputum, or leukocytosis). The Clinical Pulmonary Infection Score (CPIS) has been applied to patients with VAP, and 6 criteria are scored on a scale from 0 to 2 for each, and pneumonia is diagnosed with a total score of at least 6 (out of a maximum of 12).[45] These six criteria are fever, purulence of sputum, white blood cell count, oxygenation, degree of radiographic abnormality, and the presence of pathogens in the sputum. Of all these criteria, progressive hypoxemia is probably the most important for recognizing the onset of pneumonia and the response to therapy. Although the clinical diagnosis of VAP is more frequent than a bacteriologically confirmed diagnosis, it is often difficult to separate airway colonization from infection, making the finding of potential pathogens in the sputum of limited diagnostic value. In addition, some patients can have purulent sputum and fever without a new infiltrate and be diagnosed as having ventilator-associated tracheobronchitis (VAT), an infectious complication of mechanical ventilation that may also require antibiotic therapy, but is not pneumonia.[2] Whether VAT precedes VAP or whether it is an independent event is still uncertain, but if the former, then recognition and therapy could help to prevent pneumonia.

In the patient with nosocomial pneumonia, the history should focus on risk factors for drug resistant organisms which include prolonged ICU stay ($\geq$5 days), recent antibiotic therapy, and the presence of health-care-associated pneumonia.[2,46] In CAP patients, risk factors for drug-resistant pneumococcus include recent β-lactam therapy, exposure to a child in day care, alcoholism, immune suppression, and multiple medical comorbidities.[1,47] Malnutrition, corticosteroid therapy, bronchiectasis, and recent antibiotic therapy are also risk factors for enteric gram-negatives in patients with CAP.[1]

Physical Examination

Elevation of the respiratory rate is a finding present early in CAP, and its presence may have

prognostic significance.[1,20,48] In the elderly, an elevation of respiratory rate can precede other clinical findings by as much as 1 to 2 days, and tachypnea is present in over 60% of all patients, being present more often in the elderly than in younger patients with pneumonia.[48] Other vital sign abnormalities are important to document and, as discussed above, are important in prognostic scoring systems for CAP.

Etiologic Pathogens

CAP

The most common cause of CAP is pneumococcus (*S pneumoniae*), an organism that is frequently (at least 40% of the time) resistant to penicillin or other antibiotics, leading to the term drug-resistant *S pneumoniae* (DRSP). Fortunately, most penicillin resistance in the United States is still more commonly of the "intermediate" type (penicillin minimum inhibitory concentration [MIC] of 0.1 to 1.0 mg/L) and not of the high-level type (penicillin MIC of $\geq$2.0) and does not have an impact on patient outcome.[49] Pneumococcal resistance to other antibiotics is also common, including macrolides and trimethoprim-sulfamethoxizole. In clinical practice, only organisms with a penicillin MIC of $\geq$4 mg/L lead to an increased risk of death, and these organisms are uncommonly present.[49] Recently, the US definitions of resistance have changed for nonmeningeal infection, with sensitive being defined by a penicillin MIC of $\leq$2 mg/L, intermediate as an MIC of 4 mg/L, and resistant as an MIC $\geq$8 mg/L. With these new definitions of resistance, very few pathogens will be defined as resistant, but those that are may affect outcome.

All patients with severe CAP are at risk for DRSP, and, in addition, those admitted to the ICU can have infection with atypical pathogens that account for up to 20% of infections either as primary infection or as copathogens. The identity of these organisms varies over time and geography. In some areas, *Legionella* is a common cause of severe CAP, while in others, *C pneumoniae* or *M pneumoniae* predominate.[1] Other important causes of severe CAP include *Haemophilus influenzae*, *S aureus* (which includes MRSA, especially after influenza) and enteric gram-negatives (including *P aeruginosa*) in patients with appropriate risk factors (particularly bronchiectasis and steroid-treated COPD). In soldiers returning from the Middle East, CAP due to *Acinetobacter* spp has been reported.

While MRSA can be a nosocomial pathogen, a community strain can cause pneumonia after influenza or other viral infections, and the pneumonia may be severe due to the presence of toxin production by the bacteria. This community-acquired MRSA is biologically and genetically distinct from nosocomial MRSA, being more virulent and necrotizing and associated with the production of the Panton-Valentine Leukocidin.[50] Viruses can be a cause of severe CAP, including influenza virus, as well as parainfluenza virus and epidemic viruses such as coronavirus (which caused severe acute respiratory syndrome [SARS]) and avian influenza and the recently reported H1N1 influenza strain.[51] Viral pneumonia can lead to respiratory failure, and occasionally infections due to TB or endemic fungi can result in severe pneumonia.

Epidemiologic risk factors for specific pathogens may be present that increase the likelihood of CAP caused by certain pathogens.[1] Risk factors for DRSP include β-lactam therapy in the past 3 months, alcoholism, age >65 years, immune suppression, multiple medical comorbidities, and contact with a child in day care.[1,47] Risk factors for gram-negatives include residence in a nursing home (now leading to the patient being considered as HCAP), underlying cardiopulmonary disease, multiple medical comorbidities, probable aspiration, recent hospitalization (also an HCAP risk factor), and recent antibiotic therapy. Many of these patients who are at risk for gram-negatives have now been reclassified as having HCAP.[2,12] Some ICU patients are at risk for pseudomonal infection, while others are not, and the risk factors for *P aeruginosa* infection are structural lung disease (bronchiectasis), corticosteroid therapy (>10 mg prednisone per day), broad-spectrum antibiotic therapy for >7 days in the past month, previous hospitalization, and malnutrition.[2] Although aspiration has often been considered a risk factor for anaerobic infection, a study of severe CAP in elderly patients with aspiration risk factors found that this population is much more likely to have

gram-negative infection and that, even using sensitive microbiologic methods, anaerobes were uncommon.[52] Aspiration is also common in patients with HCAP.

Unusual CAP Pathogens

Several rickettsia can cause CAP, including Q fever (*C brunetti*), which occurs worldwide; Rocky Mountain spotted fever (RMSF); and scrub typhus (*Rickettsia tsutsugamushi*) in Asia and Australia. Transmission generally involves an intermediate vector, often ticks (Q fever, RMSF) or mites (scrub typhus) but also sheep, cows, and contaminated milk (Q fever). These infections have a variable incubation period ranging from days to a few weeks and are characterized by a febrile syndrome that may have a pneumonic component and a maculopapular rash (Q fever and RMSF).

SARS: An Example of Epidemic Viral Infection: In late 2003, SARS, a respiratory viral infection caused by a coronavirus, emerged in parts of Asia. The illness was also seen in North America when an outbreak occurred in Toronto, Canada. The virus spread from person to person, and as many as 20% of affected patients were health-care workers, particularly those caring for patients admitted to the ICU. Transmission risk was greatest during emergent intubation and was also possible during noninvasive ventilation, making this latter modality of therapy contraindicated if SARS was suspected. Infection control was essential, including the careful handling of respiratory secretions, ventilator circuits, and the use of N-95 respirator masks and careful gowning and gloving.[44] Clinically, SARS presented after a 2- to 11-day incubation period with fever, rigors, chills, dry cough, dyspnea, malaise, headache, and frequently pneumonia and ARDS. Laboratory data showed not only hypoxemia but also elevated liver function tests. In the Toronto experience, about 20% of hospitalized patients were admitted to the ICU, and 15% were supported on mechanical ventilation. Respiratory involvement typically began on day 3 of the hospital stay, but respiratory failure was not until day 8. The mortality rate for ICU-admitted SARS patients was over 30%, and when patients died, it was generally from multiple system organ failure and sepsis. There is no specific therapy, but anecdotal reports have suggested a benefit to the use of pulse doses of steroids and ribavirin.

Bioterrorism Considerations: Certain airborne pathogens can cause pneumonia as the result of deliberate dissemination by the aerosol route in the form of a biological weapon and present a clinical syndrome of CAP.[53] The pathogens that are most likely to be used in this fashion and that can lead to severe pulmonary infection are *Bacillus anthracis* (anthrax), *Yersinia pestis* (plague), and *F tularensis* (tularemia)

To date in the United States, anthrax is the only airborne respiratory agent that was used in a bioterrorism attack in the fall of 2001, with 11 confirmed cases of inhalational illness. Anthrax is an aerobic gram-positive, spore-forming bacillus that had rarely led to disease prior to 2001. Particle size determines the infectiousness of the spores, and a size of 1 to 5 microns is required for inhalation into the alveolar space, but generally infection requires an inoculum size of 8,000 to 40,000 spores. The organisms initially enter alveolar macrophages and are transported to mediastinal lymph nodes, where they can persist and germinate and produce two toxins (lethal toxin and edema toxin), and illness follows rapidly after germination. Anthrax is not a typical pneumonic illness but rather a disease characterized by hemorrhagic thoracic lymphadenitis, hemorrhagic mediastinitis, and pleural effusion. While the incubation period of anthrax has varied from 2 to 43 days in prior outbreaks, in the October 2001 series, the incubation period was from 4 to 6 days. In the US experience, all patients had chills, fever, and sweats, and most had nonproductive cough, dyspnea, nausea, vomiting, and chest pain. Chest radiographs were abnormal in all of the first 10 patients, and 7 had mediastinal widening, 8 had pleural effusions (generally bloody), and 7 had pulmonary infiltrates. Blood cultures were positive in all 8 patients in whom they were obtained prior to therapy, but sputum culture and Gram stain are unlikely to be positive. In the US attacks, 5 of 11 patients died.

Therapy for anthrax includes supportive management and antibiotics, with possibly some role for corticosteroids if meningeal involvement or mediastinal edema are present. Recommended therapy is ciprofloxacin, 400 mg IV twice a day, or doxycycline, 100 mg IV twice a day. Until the

patient is clinically stable, one or two additional agents should be added, including clindamycin, vancomycin, imipenem, meropenem, chloramphenicol, penicillin, ampicillin, rifampin, and clarithromycin. Therapy should be continued after an initial response with either ciprofloxacin or doxycycline for at least 60 days. Postexposure prophylaxis can be done with ciprofloxacin or alternatively doxycycline or amoxicillin for a total of 60 days.

Nosocomial Pneumonia, Including VAP and HCAP

All patients with nosocomial pneumonia are at risk for infection with a group of "core organisms, including pneumococcus, *H influenzae*, methicillin-sensitive *S aureus*, and non-resistant gram-negatives (*E coli*, *Klebsiella* spp, *Enterobacter* spp, *Proteus* spp, and *Serratia marcescens*).[2] In addition, some patients are also at risk for infection with other organisms, depending on the presence of risk factors such as prolonged hospitalization ($\geq$5 days), prior antibiotic therapy, recent hospitalization (within 90 days), recent antibiotic therapy, residence in a nursing home, or need for chronic care outside the hospital.[2,30] Patients with these risk factors can possibly be infected with MDR gram-positive and gram-negative organisms, including MRSA, *P aeruginosa*, and *Acinetobacter* spp. Up to 40% of patients with VAP have polymicrobial infection involving multiple pathogens.[30]

In patients with VAP, infection with enteric gram-negatives is more common than infection with gram-positives, although the frequency of MRSA infection is increasing in this population, as is infection with *Acinetobacter* spp.[54] HCAP patients have been included in the nosocomial pneumonia guidelines as being a group at risk for infection with MDR gram-positives and gram-negatives. Recent studies have made it clear that not all HCAP patients are at risk for MDR pathogen infection and that many can be treated effectively with a CAP regimen.[12] There are subsets of HCAP patients who are at risk for infection with MDR pathogens, and they include patients with multiple risk factors from the following list: severe illness, recent hospitalization, recent antibiotic therapy, poor functional status, and immune suppression.[12,46]

Each hospital and each ICU within a given hospital can have its own unique flora and antibiotic susceptibility patterns, and thus therapy needs to be adapted to the organisms in a given institution, which can change over time.[55] In addition, it is especially important to know this information since antibiotic resistance is a common factor contributing to initially inappropriate empiric antibiotic therapy. Choosing the wrong empiric therapy has been a particular problem for organisms such as *P aeruginosa*, *Acinetobacter* spp, and MRSA. These highly resistant organisms can be present in as many as 60% of patients who develop VAP after at least 7 days of ventilation and who have also received prior antibiotic therapy.[2,30]

Diagnostic Issues

Diagnostic testing is performed for two purposes: to define the presence of pneumonia and to identify the responsible pathogen. A chest radiograph can identify the presence of a lung infiltrate, but in some clinical settings, especially in suspected VAP, there can be noninfectious causes for the radiographic abnormality, or the radiograph may be difficult to interpret. Chest radiographic patterns are generally not useful for identifying the etiology of CAP, although findings such as pleural effusion (*Pneumococcus*, *H influenzae*, *M pneumoniae*, pyogenic streptococci) and cavitation (*P aeruginosa*, *S aureus*, anaerobes, MRSA, TB) can suggest certain groups of organisms. In those with VAP, bacteria are commonly present in samples of lower respiratory tract secretions, but the presence of a positive culture cannot reliably distinguish infection from colonization. With the recognition of VAT, there are patients who may have a respiratory tract infection that needs therapy but in whom the patient has a negative radiograph but with fever, leukocytosis, and purulent sputum.

CAP

For patients with CAP, a chest radiograph not only confirms the presence of pneumonia but also can be used to identify complicated and severe illness if the patient has findings such as multilobar infiltrates, cavitation, or a loculated pleural

effusion (suggesting an empyema). CAP patients admitted to the ICU should have a chest radiograph, blood and lower respiratory tract (sputum, endotracheal aspirate, bronchoalveolar lavage, or bronchoscopic specimen) cultures, an arterial blood gas, and routine hematologic and blood chemistry testing. If the patient has a moderate-sized pleural effusion, this should be tapped and the fluid sent for culture and biochemical analysis.[1] Blood cultures are positive in 10% to 15% of CAP patients, most often with pneumococcus, and severely ill patients should have two sets of blood cultures, which are most likely to be positive if the patient has not received antibiotics at the time of sampling or if there are signs of systolic hypotension, tachycardia, dehydration, or an elevated white blood cell count.[56] The presence of bacteremia may not worsen prognosis but does allow identification of drug-resistant organisms.

Sputum culture should be accompanied by a Gram stain to guide interpretation of the culture results but not to focus initial antibiotic therapy. In some situations, Gram stain can be used to broaden initial empiric therapy by enhancing the suspicion for organisms that are not covered in routine empiric therapy (such as *S aureus* being suggested by the presence of clusters of gram-positive cocci, especially during a time of epidemic influenza). Routine serologic testing is not recommended. However, in patients with severe illness, the diagnosis of Legionella can be made by urinary antigen testing, which is the test that is most likely to be positive at the time of admission but a test that is specific only for serogroup I infection.[1,57] Examination of concentrated urine for pneumococcal antigen may also be valuable. Bronchoscopy is not indicated as a routine diagnostic test but may be used to focus the initially broad-spectrum empiric therapy to a simpler regimen and is often used if the patient is not responding to initial empiric therapy.[58]

Nosocomial Pneumonia

Nosocomial pneumonia is diagnosed when a patient develops a new or progressive infiltrate on chest radiograph, accompanied by at least two of the following three: fever, leukocytosis, and purulent sputum after being in the hospital for at least 48 to 72 h. The clinical findings are sensitive but not specific for infection, and efforts to improve the clinical diagnosis of pneumonia have involved the previously mentioned CPIS.[59] Many patients with suspected nosocomial pneumonia can have other diagnoses that can be suggested by the rapidity of the clinical response and by the nature of the clinical findings. These diagnoses include atelectasis and congestive heart failure (very rapid clinical resolution) or, in the case of a lack of response to therapy, inflammatory lung diseases, extrapulmonary infection (sinusitis, central line infection, intra-abdominal infection), or the presence of an unusual or drug-resistant pathogen. In an effort to make the diagnosis more secure and to avoid the overutilization of antibiotics, some investigators have used quantitative sampling of lower respiratory secretions collected either bronchoscopically (bronchoalveolar lavage, protected specimen brush) or nonbronchoscopically (endotracheal aspirate, nonbronchoscopic catheter lavage) in patients with suspected VAP and defined the presence of pneumonia by the growth of bacteria at a concentration above a predefined threshold concentration.[4,5] Recent studies have not shown a benefit of quantitative cultures for improving mortality or enhancing the use of targeted antibiotic therapy.[4,5]

All patients with suspected nosocomial pneumonia should have a lower respiratory tract culture collected prior to the start of antibiotic therapy. If this is not a bronchoscopic quantitative sample, then a sputum or tracheal aspirate should be obtained and the findings reported "semiquantitatively" as light, moderate, or heavy growth of bacteria.[2,4] A negative culture is difficult to interpret if the patient has had initiation or change in antibiotic therapy in the preceding 72 h. If, however, either a quantitative or a semiquantitative culture is negative or does not show a highly resistant pathogen and antibiotics have not been changed in the past 72 h, then the therapy can often be stopped or focused to a more narrow spectrum.[2,4]

Therapy

Initial antibiotic therapy is decided on the basis of the most likely expected pathogen for a given patient in each clinical setting. In most

cases, this is empiric, but if diagnostic testing reveals a specific etiologic pathogen, then therapy can be focused. In addition, as mentioned above, if an anticipated drug-resistant pathogen is not present in a diagnostic sample, it may be possible to deescalate the empiric coverage of that organism.

General Considerations

Most patients with severe pneumonia require initial combination therapy. This can provide for a wide range of organisms and may lead to more rapid killing of organisms than a single agent, particularly in the setting of pneumonia with sepsis.[22] In patients with severe CAP, combination therapy should cover for bacterial and atypical pathogens, and for those with pneumococcal bacteremia, dual effective therapy has been shown to reduce mortality compared to single effective therapy.[23] Monotherapy with any agent, including a quinolone, has never been shown to be as effective as combination therapy for patients with severe CAP, and when combination therapy is used, the addition of a macrolide to a β-lactam is particularly effective, possibly because of the antiinflammatory effect of the macrolide.

In patients with nosocomial pneumonia at risk for infection with MDR pathogens, combination therapy should be used and is beneficial since it provides a broader spectrum than any single agent can and is more likely to lead to appropriate therapy than if a single agent is used.[60] While synergy between a β-lactam and an aminoglycoside against *P aeruginosa* may not be necessary for most patients, for those with bacteremic *P aeruginosa*, pneumonia this type of combination therapy been shown to be superior to monotherapy.[61,62] If aminoglycosides are used, it is important to recognize their narrow therapeutic-to-toxic ratio and their potential for nephrotoxicity, particularly in elderly patients. In the past, this meant monitoring peak and trough levels to ensure efficacy and minimize toxicity, respectively. Now it is standard to administer aminoglycosides by combining the total 24-h dose into a single dose rather than in divided doses to maximize peak levels (efficacy) while minimizing toxicity (tough), and while this has not been proven to always be effective, once-daily dosing is recommended because it is simpler and requires less intensive monitoring (measuring only trough levels).[63] Aminoglycosides penetrate poorly into bronchial secretions, achieving only 40% of the serum concentrations at this site, and some recent studies have explored the addition of adjunctive aerosolized aminoglycosides.[64] The antimicrobial activity of aminoglycosides is reduced at the low pH levels that are common in the bronchial secretions of patients with pneumonia. In spite of these limitations, aminoglycosides are a good second drug to be added to a β-lactam since they add to the antimicrobial coverage and do so more than if a quinolone is added to a β-lactam.[65] They are suitable to combine with a β-lactam, while the use of dual β-lactam therapy is not recommended. In patients with nosocomial pneumonia, the aminoglycoside may need to be continued for only 3 to 5 days since most of the benefit comes with early coverage of suspected pathogens, along with rapid killing, and this short duration can minimize the nephrotoxic potential of the aminoglycosides.

Once culture data become available, it is often possible to deescalate to monotherapy and to agents with a narrow spectrum of coverage. For patients with VAP, in the absence of certain high-risk organisms (*P aeruginosa*, *Acinetobacter* spp, and MRSA), monotherapy has been effective with the following agents: imipenem, meropenem, doripenem, cefepime, ciprofloxacin, high-dose levofloxacin (750 mg daily), and piperacillin/tazobactam.[2,29] In the treatment of nosocomial pneumonia, monotherapy should never be attempted with a third-generation cephalosporin if MDR pathogens are suspected because of the possibility of emergence of resistance during therapy as a result of production of chromosomal β-lactamases by the Enterobacteriaceae group of organisms.[2]

If *P aeruginosa* is a target organism of therapy, then the anti-pseudomonal β-lactam antibiotics include the penicillins, such as piperacillin, azlocillin, mezlocillin, ticarcillin, and carbenicillin; the third-generation cephalosporins, such as ceftazidime and cefoperazone; the fourth-generation cephalosporin cefepime; the carbapenems, such as doripenem, imipenem, and meropenem; the

monobactam aztreonam (which can be used in the penicillin allergic patient); and the β-lactam/β-lactamase inhibitor combinations ticarcillin/clavulanate and piperacillin/tazobactam. Other antipseudomonal agents include the quinolone ciprofloxacin, high-dose levofloxacin, and the aminoglycosides (amikacin, gentamicin, tobramycin).

CAP

For ICU-admitted CAP patients, initial therapy should be directed at DRSP, *Legionella,* and other atypical pathogens, enteric gram-negatives, and other selected organisms based on an epidemiologic risk assessment. Patients should be divided into those who are at risk for *P aeruginosa* ("modifying" risk factors listed above) and those who are not. In all the treatment algorithms, no ICU-admitted CAP patient should receive empiric monotherapy, even with one of the new quinolones.[1] In one study comparing levofloxacin with a β-lactam/quinolone combination, the single-agent regimen was not shown to be effective for patients in septic shock and for those treated with mechanical ventilation.[66] There are no data showing the efficacy of moxifloxacin as monotherapy for severe CAP. The use of a β-lactam/macrolide combination has also been shown to be more effective than quinolone monotherapy in seriously ill patients with CAP.[67]

For patients without pseudomonal risk factors, therapy should be with a selected IV β-lactam (cefotaxime, ceftriaxone, a β-lactam/β-lactamase inhibitor combination), combined with either an IV macrolide or an IV antipneumococcal quinolone (levofloxacin or moxifloxacin). While the macrolide has shown advantages in many clinical settings, if *Legionella* is present, the quinolone may be the preferred therapy. For patients with pseudomonal risk factors, therapy can be with a two-drug regimen, using an anti-pseudomonal β-lactam (doripenem, imipenem, meropenem, piperacillin/tazobactam, cefepime) plus ciprofloxacin (the most active anti-pseudomonal quinolone) or levofloxacin (750 mg daily), or, alternatively, with a three-drug regimen, using an anti-pseudomonal β-lactam plus an aminoglycoside plus either an IV antipneumococcal quinolone (levofloxacin or moxifloxacin) or a macrolide.[1,66] Penicillin-allergic patients should get aztreonam with levofloxacin or aztreonam with an aminoglycoside plus an antipneumococcal quinolone or macrolide.

As mentioned, all patients should have coverage for atypical pathogens using either a macrolide or a quinolone in the regimen, based on data that such an approach reduces mortality.[1,23,68] In addition, certain adjunctive therapies should be considered, including oxygen, chest physiotherapy (if at least 30 mL of sputum daily and a poor cough response), aerosolized bronchodilators, and corticosteroids (if hypotension and possible relative adrenal insufficiency is present). In addition to their value in patients with relative adrenal insufficiency, corticosteroids have been studied in severe CAP because of their immunomodulating effect. One early randomized controlled trial of 48 patients compared hydrocortisone infusion (240 mg/day) with placebo and found that steroid therapy reduced mortality, length of stay, and duration of mechanical ventilation.[69] These findings have not been confirmed in more recent studies, and routine therapy with corticosteroids is not recommended for severe CAP. They may have benefit for patients with pneumococcal meningitis if administered prior to the first dose of antibiotic therapy, where their use improves long-term neurologic function.[70]

The presence of extrapulmonary infection (such as meningitis) and the identification of certain pathogens (such as bacteremic *S aureus* and *P aeruginosa*) may require longer durations of therapy than the usual 5 to 7 days. Identification of *L pneumophila* pneumonia may require quinolone therapy, and durations as short as 5 days with levofloxacin, 750 mg, may be effective.[71] Patients with severe CAP should be evaluated for possible community-acquired MRSA infection, but routine coverage of this pathogen is not necessary. However, if the patient has pneumonia after influenza or a viral infection, particularly if it is severe, bilateral, and necrotizing, empiric MRSA therapy may be needed. This can be done with agents that are both antibacterial and stop bacterial toxin production and can be achieved using the combination of vancomycin and clindamycin or by using linezolid alone.[50]

Nosocomial Pneumonia, Including HCAP

Antibiotic therapy should be given promptly at the first clinical suspicion of pneumonia, and empiric therapy should be dictated by considering whether the patient is at risk for infection with MDR pathogens. Risk factors for MDR pathogens in patients with nosocomial pneumonia and HCAP include recent antibiotic therapy, prolonged hospital stay, poor functional status, and immune suppression. As discussed, not all HCAP patients are at risk for MDR pathogens, but those with at least one risk factor and severe pneumonia should be treated empirically for these organisms. Patients without risks for MDR pathogens can be treated for the "core pathogens" listed above, generally with a monotherapy regimen of a second-generation or non-pseudomonal third-generation cephalosporin, a β-lactam/β-lactamase inhibitor combination, ertapenem, or a quinolone (levofloxacin or moxifloxacin).[2] If the patient is penicillin allergic, therapy can be with a quinolone or a combination of clindamycin and aztreonam.

In the selection of an empiric therapy regimen, it is necessary to choose an agent that is in a different class of antibiotics than the patient has received in the past 14 days since repeated use of the same class of antibiotic may drive resistance to that class, especially if the pathogen is *P aeruginosa*.[72] Similar findings have been made for patients with bacteremic pneumococcal pneumonia and CAP, and repeated use of an agent within 3 months may mean that the patient is being treated with an agent to which pneumococcus is more likely to be resistant.[73] In addition, the recent use of quinolones may present a particular problem since in the ICU, recent quinolone therapy may predispose to not only quinolone-resistant organisms but also infection with MDR pathogens, extended-spectrum β-lactamase-producing gram-negatives, and MRSA.[74]

The concept of "antibiotic rotation" has been studied in VAP patients and involves using an empiric regimen that is intentionally varied over time to expose bacteria to different antibiotics and thus minimize the selection pressure for resistance.[75] Formal use of this approach is generally not done, but the introduction of antibiotic heterogeneity so that not all patients are receiving the same therapies all the time may be advantageous.

Patients at risk for MDR pathogens generally require combination therapy rather than monotherapy. The empiric therapy for patients at risk for MDR pathogens should include dual Pseudomonal coverage using an aminoglycoside or quinolone (ciprofloxacin or high-dose levofloxacin) plus an anti-pseudomonal β-lactam (doripenem, imipenem, meropenem, piperacillin/tazobactam, aztreonam, or cefepime). If the patient is at risk for a second ICU-acquired infection (and most are), it may be prudent to use an aminoglycoside for the first episode of infection, reserving the quinolone for any subsequent infection because of concern about quinolone induction of multidrug resistance, which could limit subsequent therapy options.[76] If the patient is suspected of having MRSA because of a tracheal aspirate, Gram stain showing gram-positive organisms or because of other risk factors, then a third drug should be added. This could be either linezolid or vancomycin, and recent data have suggested an advantage for clinical cure using linezolid in patients who have been documented to have MRSA VAP.[77]

If the patient has received a broad-spectrum regimen and the cultures do not show MDR organisms, then it is possible to deescalate, and even if *P aeruginosa* is present, combination therapy with a β-lactam and aminoglycoside should continue for 5 days, after which the patient can be switched to monotherapy with a β-lactam or quinolone agent to which the organism is sensitive.[2] When deescalation has been used, meaning a switch to either a more narrow-spectrum regimen, the use of fewer drugs, or both, mortality in VAP has been reduced compared with patients not having deescalation.[29]

If the lower respiratory tract cultures are negative, it may be possible to stop therapy (especially if an alternative diagnosis is suspected) or to shorten the duration of therapy. In addition, if cultures show that the initial empiric regimen was appropriate and if the patient has a good clinical response (reflected by a drop in the CPIS), then it may be possible to reduce the duration of therapy to as little as 7 to 8 days, although this may not be possible if the etiologic

pathogen is *P aeruginosa* or MRSA.[78] The use of serial measurements of procalcitonin has been helpful in guiding a reduction in duration of therapy, especially if a fall in procalcitonin is accompanied by a good clinical response.[79]

Adjunctive therapeutic measures are needed in some patients, including chest physiotherapy, aerosolized bronchodilators, and mucolytic agents. For selected patients who are infected with highly resistant organisms not responding to systemic antibiotics, it may be valuable to add aerosolized antibiotics (such as gentamicin, tobramycin, colistin, and ceftazidime).[80]

Evaluation of Nonresponding Patients

Nonresponding patients with either CAP or VAP should be evaluated for alternative diagnoses (inflammatory lung disease, atelectasis, heart failure, malignancy, pulmonary hemorrhage, pulmonary embolus, nonpneumonic infection), a resistant or unusual pathogen (including tuberculosis and fungal infection), a pneumonia complication (empyema, lung abscess, drug fever, antibiotic-induced colitis), or a secondary site of infection (central line infection, intra-abdominal infection). The evaluation of a nonresponding patient should be individualized but may include CT scanning of the chest, pulmonary angiography, bronchoscopy with culture, and possibly transbronchial biopsy and occasionally open lung biopsy.

Fungal infection is not considered in most patients with pneumonia but does become a consideration in the nonresponding patient. In patients with CAP, endemic fungi, such as coccidioidomycosis, histoplasmosis, and blastomycosis, should be considered in the appropriate endemic area, especially in patients with immune compromise (such as HIV infection) and after exposure to large concentrations of fungi (such as histoplasmosis in bat caves). Community-acquired *Aspergillus* infection can occur in patients on chronic systemic corticosteroid therapy for COPD. In addition, nosocomial *Aspergillus* should be considered in a patient with nonresponding nosocomial pneumonia, especially after prolonged courses of antibiotics and corticosteroids. Isolation of *Aspergillus* from a sputum sample in this setting should be aggressively evaluated and often treated empirically. On the other hand, *Candida* pneumonia is rare, and isolation of this fungus in a respiratory culture generally represents colonization, and invasive pneumonia should be considered only with isolation of *Candida* from multiple other sites, including the blood.

Prevention

Prevention of CAP includes vaccination with both pneumococcal and influenza vaccines and cigarette smoking cessation in all at-risk patients. Even for the patient who is recovering from CAP, hospital-based immunization is valuable to prevent future episodes of infection. If there is uncertainty about whether the patient has recently been vaccinated, it is probably best to give a pneumococcal vaccination since repeat administration, even more often than recommended, is not generally associated with an adverse reaction.[81]

Although no single method is able to reliably prevent nosocomial pneumonia, multiple small interventions may have benefit, especially those focused on modifiable risk factors for infection. Recently, these interventions have been combined into "ventilator bundles," which have been demonstrated to reduce the incidence of VAP if applied carefully.[6,82] Most of these bundles include multiple interventions, so it is difficult to know the importance of each component. Successful bundles have included interventions such as elevation of the head of the bed to 30 degrees (to avoid the risk of aspiration present with the supine position), daily interruption of sedation to attempt weaning, peptic ulcer disease prophylaxis, endotracheal tube suctioning (possibly with a closed suction system), hand washing, careful oral care, and chlorhexadine mouth rinses.[83] Other potentially valuable interventions are use of subglottic secretion drainage endotracheal tubes, maintenance of endotracheal tube cuff pressure >20 to 25 cm of water, use of polyurethane (rather than polyvinylchloride) high-volume low-pressure endotracheal tube cuffs, and use of antibiotics for 24 h after emergent intubation.[37] Early tracheostomy has not proven to prevent VAP, but aggressive weaning with noninvasive ventilation may be useful.

Other widely used measures in mechanically ventilated patients are avoidance of large inocula

of bacteria into the lung (careful handling of ventilator circuit tubing), mobilization of respiratory secretions (frequent suctioning, use of rotational bed therapy in selected individuals), nutritional support (enteral preferred over parenteral), placing of feeding tubes into the small bowel (to avoid aspiration, which is more likely with stomach tubes), and avoidance of large gastric residuals when giving enteral feeding.[84] In addition, any tube inserted into the stomach or trachea should be inserted through the mouth and not the nose whenever possible to avoid obstructing the nasal sinuses and to prevent nosocomial sinusitis, which can lead to nosocomial pneumonia. Recently, a silver-coated endotracheal tube has been studied and reported to reduce the risk of VAP.[85] Since endotracheal intubation is a risk for pneumonia, noninvasive positive pressure ventilation should be used whenever possible, and this approach is associated with a lower pneumonia risk than traditional mechanical ventilation. Selective digestive decontamination has also been studied, but recent data indicate that oral decontamination alone may be effective in preventing VAP and that the entire regimen may not be necessary.[86]

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Chapter 33. ICU Guidelines, Best Practices, and Standardization

Arthur P. Wheeler, MD, FCCP

Objectives:

- Appreciate the role of the intensivist in ICU organization.
- Learn basics of ICU organizational structure.
- Learn important common practices that benefit from protocolization.
- Understand the importance of multi-disciplinary rounds.

Key words: best practice; ICU; intensivist; protocolization

Synopsis:

A successful ICU balances three inextricably linked factors: quality of care, efficiency, and cost control. Although increasing resource utilization often does not lead to improved quality, inefficiency almost always hurts quality. Along the same lines, in most cases improving quality reduces resource utilization *and* costs while improving efficiency. Typically such savings are achieved by reducing length of stay, preventing complications and readmissions, limiting ineffective or excessive care, reducing staff turnover, and reducing complaints and litigation.

ICU Organization

Leadership

Although most ICUs always have a designated nursing director, surprisingly less than half of US ICUs have a dedicated medical director. The director must be accessible and play a central role in establishing policies and procedures; in smoothing the admission, discharge, and transfer processes; and in assembling a competent and efficient staff. To improve quality and control costs the ICU leaders must be provided with accurate performance data, remain open to new solutions, and have the authority to change practice. Ideally, the medical and nursing directors of a hospital's ICU should meet regularly to implement best practices.

The Intensivist

Ideally physicians working in ICUs should be critical care trained and readily available, yet less than 5% of ICUs has a senior physician present around the clock, and less than one-third of all ICUs have even continuous trainee coverage. Perhaps more striking is that <20% of hospitals have a critical care-trained physician on-site continuously during even daylight hours. This is unfortunate because the ICU poses a wide range of rapidly evolving, potentially deadly problems and uses sophisticated technology to which typically the generalist has limited exposure. Numerous studies indicate that establishing a "closed unit," where patients are cared for by a critical care physician, reduces ICU and hospital length of stay, mortality, and cost despite a higher severity of illness. Data from these same studies regarding resource utilization indicate flat or slightly increased use of technology. There are several possible reasons for improved outcomes with intensivist staffing. ICU physicians are more likely to be on-site and do not have competing office or operating room responsibilities. Expectedly, the benefits are eroded when intensivists are not physically present, as for example, when required to provide care in geographically separated units, or perhaps even in more than one hospital. Benefits may also result because intensivists have a body of experience that allows them to anticipate and preempt serious problems. A dedicated intensivist also increases consistency of care and compliance with recommended practices. For example, when no standards exist, deep venous thrombosis prophylaxis, fluid resuscitation for septic shock, glucose control, transfusion practice, nutrition, ventilation and weaning are often inconsistent in method and application. When a different plan is used for every patient, it is likely that the therapy will be overlooked for some patients, inappropriately applied to others, and suboptimally carried out in yet others. Despite fierce arguments for "autonomy" and "customization" of care, there usually is a best way to *begin* treating

the typical patient and reducing unnecessary variation contributes to improved quality. Furthermore, knowing which treatments have previously succeeded or failed in a given patient minimizes inefficiency and costs. In an era in which patient turnover is rapid, and staff changes frequent, well-crafted policies, protocols, checklists, and handoffs are essential to maintain consistent care. Another potential advantage of the on-site critical care physician is that he or she may be less likely to call on multiple consultants. Care is inefficient, costly, and potentially dangerous when a physician, especially one off-site, practices by consultation. In such a model each specialist responds at a pace dictated by his or her schedule, and communication between consultants, the primary physician, and the family is often suboptimal. The intensivist best fits the role of adjudicating and coordinating consultant recommendations, and communicating with the family and physicians who will provide care after discharge. Without effective coordination often redundant, diagnostic tests are ordered. An even worse situation occurs when the therapeutic goals of consultants are at odds or when one consultant is oblivious to the recommendations of another. In this situation, competing or potentially harmful combinations of therapy are prescribed.

Perhaps the intensivist is best qualified to identify patients who cannot benefit from ICU care because they either are not sufficiently ill or are not salvageable. Low risk patients tie-up needed resources and are more likely to experience an adverse event as a result of ICU admission than they are to experience benefit and this should be avoided. Likewise, moribund patients are not well served by the ICU, where they occupy beds that could be used for salvageable patients, suffer relative isolation from family and friends, are exposed to nosocomial hazards, and pay a high financial price. Despite difficulty in defining futile care, the intensivist is the best person to help the patient and family develop reasonable limits by having honest, open, and recurring discussions. Regular, preferably daily, consultation with the patient and family is important to maintain common goals. Such meetings often require 30 to 60 minutes per patient each day, a time commitment that few physicians with responsibilities outside of the ICU can manage. Beginning routine discussions early in the ICU stay makes later meetings when weighty decisions must be made much less daunting. This plan of communication has other benefits: patient and family satisfaction is enhanced by communication with fewer physicians delivering a consistent message.

Undoubtedly, an experienced on-site critical care-trained physician is the best person to care for critically ill patients with the input of necessary consultants. Unfortunately, this ideal model is currently impractical because even in large tertiary care centers there are rarely sufficient critical care physicians to provide in-house 24-hour-a-day coverage.

Nurse Practitioners and Physicians Assistants

The shortage of trained critical care physicians will persist for the foreseeable future, and over time physician trainees are becoming more observers than providers of care. Therefore alternative staffing models are essential and there is a growing body of evidence that well-supervised nurse practitioners (NPs) and physician assistants (PAs) can bridge the critical care physician shortage. Although there has long been a well-described role for NPs in pediatrics, a growing number of publications now indicate that with proper selection, training, and oversight, NPs can care for a wide range of critically ill adults. Recently published cohort studies suggest that for patients of comparable severity of illness, care provided by NPs and PAs results in equivalent ICU and hospital lengths of stay and mortality. To achieve these outcomes, however, extensive training and oversight are necessary, and at present it is unclear whether NP or PA services offer any financial advantage over physician staffing. Current literature does indicate that time allocation differs between physician trainees and NPs with the latter spending much more of each day involved in communication and coordination of patient care. These factors may be the reason that numerous publications have reported a high level of patient and family satisfaction with NPs and PAs.

ICU Nurses

Nurses are being asked to do more highly technical, labor-intensive tasks with greater independence than ever before. To assure good outcomes and making sure that they are not overburdened is as important as making sure that they are well trained. Given the intensity of activity, anytime an ICU nurse is asked to care for more than two (sometimes even one) critically ill patient(s), it is likely that less than ideal care is being delivered. Published data make it clear that reducing the nurse-to-patient ratio results in worse outcomes in almost every setting in which it has been tried. When task saturation occurs, it is common for nurses to keep performing essential patient-centered work but care of the family and documentation suffer. Although an unconventional idea, lapses in documentation are usually unimportant, unless a critical event or adverse occurrence is unnoted leading to its repetition. Bedside nurses, ICU leaders, and administrators must work together to assure adequate staffing and that the process of care is efficient. New programs and initiatives should be vetted before implementation to determine whether additional work or documentation requirements do not detract from care of the patient or family.

ICU nurses are not easily interchanged among ICUs. They develop specialized skills to deal with the common problems they see and become familiar with the policies and procedures of the unit in which they most often work. Simply not knowing where supplies or equipment are stored in an unfamiliar unit causes inefficiency and possibly danger. In addition, the teamwork and camaraderie among nurses who consistently work together provides the physical and emotional support to complete the difficult tasks they are called upon to do. For these reasons the use of temporary nurses or rotating nurses between ICUs of different disciplines should be discouraged.

Excellence requires much more than a caring attitude, technical knowledge, and meticulous documentation. Experience brings priceless insight. Every savvy critical care physician knows the folly of not promptly responding to an experienced nurse's intuition. Not only cannot one buy experience, it is very expensive to retrain or orient a new nurse to an ICU; some have estimated tens of thousands of dollars. Hence, it makes sense to do everything reasonably possible to retain quality nurses. Although salary, benefits, and work hours matter, satisfaction at work is a much more important factor for staff stability. There are numerous ways to improve staff satisfaction, probably most important of which is to treat all staff as the essential elements of a team providing care. Although it is clear one person (the attending physician) must make the strategic decisions, there is no room in the ICU for paternalism, patronization, or dismissiveness. For satisfaction, but more important safety, everyone caring for patients should understand care plans and must feel free to speak up when a course of action appears to not be working. Another method to promote satisfaction is to develop an environment where learning and teaching are valued and inquiry welcomed. By conducting formal clinical trials and quality control projects, an environment is established where questions are valued and a culture of discovery exists. Conducting regular educational programs designed to answer the questions that arise during patient care is also valuable. By having all members of the health care team present at educational sessions, the knowledge of the group is boosted, the stature of the presenter is enhanced, and as a result care improves.

Pharmacists, Nutritionists, and Physical and Occupational Therapists

Given the number of medications and complexity of the pharmacologic treatment of the modern critically ill patient, the ICU pharmacist is pivotal for optimal patient outcomes and cost control. Numerous studies now indicate that having a pharmacist on daily rounds results in multiple recommendations for changes in medications (Table 1).

The most common recommendations are discontinuation of nonindicated or redundant compounds and dose adjustments (usually for changing renal function); occasionally changes in route of administration are recommended. Contrary to cynical first reactions, pharmacists' recommendations are not merely for cost control;

Table 1—*Pharmacist-Driven Improvement Strategies*

Elimination of unnecessary and duplicative medications
Dose adjustment-optimization
Avoidance of drug interactions
Substitution of a less toxic regimen of equal efficacy
Substitution of less costly regimens of equal efficacy
Converting parenteral medications to an oral route as soon as feasible
Reducing the frequency of administration
Avoidance of drugs requiring monitoring

roughly half of all recommendations decrease costs, with about 40% of recommendations being cost neutral, and 10% increasing costs. Beneficial effects of pharmacist involvement have been shown on drug and laboratory costs, ICU length of stay, and ICU mortality. In addition, the recommendations made usually are sufficient to offset the cost of the pharmacist's salary devoted to rounding.

Similarly, the ICU dietitian provides valuable guidance for nutritional requirements and is essential to help navigate the vast array of nutritional products available. Nutrition experts are helpful in developing hospital-wide protocols to simplify nutritional support. Although clearly an oversimplification, just having someone on rounds each day to prompt the team to begin or transition to enteral feeding, to avoid costly unproven products, and to discourage irrational interruptions in support is probably valuable. With time there is evidence suggesting that parenteral nutrition should be avoided unless absolutely necessary and the dietitian can reinforce this idea.

Attention to immediate life-threatening concerns often lowers the perceived importance of problems that can affect long-term quality of life. Perhaps no better example exists than lack of attention to mobility. Saving the life of a critically ill patient is much less rewarding if the survivor is left with long-term or chronic physical disabilities from immobilization. In addition, it has recently been recognized that early mobilization for some critically ill patients may accelerate ventilator weaning, ICU and hospital discharge. Therefore, it is important to assure involvement of physical and occupational therapists as soon as feasible during the ICU stay.

Teamwork

A high intensity physician staffing model, in which a doctor is in the ICU many hours each day, reduces the risk of death compared with a low intensity model (irrespective of team design). The best outcomes are enjoyed by patients in an ICU with a high intensity physician staffing model and a multidisciplinary rounding structure. This observation is not surprising. Any journey would prove long, expensive, and dangerous if there were no clear destination, defined route, or even a map, and numerous travelers took turns navigating. In the same way, negotiating the ICU becomes perilous and expensive if the "driver" does not understand the route or destination. If the plan and priorities are not clear, bedside nurses "drive" for most of the day and a circuitous route is likely. For the ICU patient, this confusion is manifest as redundant or irrelevant diagnostic testing, inappropriate therapeutic interventions, missed opportunities, and miscommunication.

The most practical solution to such problems is to have a senior physician, leading the ICU team, to execute a carefully developed plan. To accomplish this goal it is essential to have at least daily multidisciplinary bedside rounds where participation of all team members is required. At a minimum, this group should include the physician, nurse, pharmacist, dietician, and respiratory therapist. Attendance of consultants is a bonus, but often not feasible. Whenever possible, occupational/physical therapists, social workers, case managers, palliative care specialists, and clergy should be included when circumstances suggest they would be beneficial. Each day, the success or failure to achieve goals set the previous day should be evaluated. New problems and major organ system function should be reviewed. Diagnostic information gained since the previous day and its implications should be discussed. The need for all medications, tubes, and catheters should be questioned. Changes in therapy should be agreed on, along with contingency plans for unexpected events. The information to be communicated to the patient, family, and referring physicians should be discussed, and plans for transfer or discharge should be finalized. Following these

steps guarantees that members of the team move efficiently in the same direction. This cooperative process offers the physician in charge the most current and accurate information, and yields a staff that is more cohesive, educated, happy, and respectful of one another.

In most hospitals nursing and respiratory therapy personnel change shifts two or three times daily, whereas physicians typically handoff responsibilities less often. Personnel changes have advantages and disadvantages. Although a new caregiver provides a rested body and mind, the oncoming provider lacks key information and recent experience with the patient. The process of "handing off" a patient may occur much more frequently, not just once or twice daily as personnel may differ during transport and patients are received from or taken to the CT scanner, operating room, recovery room, or general care floor. It is important that transfers be done in an orderly and systemized way to prevent misunderstandings, or ignorance by the oncoming staff of the patient's background, life support technology, recent events and problems, and future plans. These processes are often accomplished at several levels when bedside nurses exchange information, review medications, indwelling lines, and pertinent examination features. Charge nurses also review critical elements of illness and plan which nurses might need help or which patients are likely to require higher or lower levels of staffing. Respiratory therapists, likewise, review ventilator settings, treatment requirements, and recent problems. For physicians, the process of care transfer often involves making formal bedside rounds once daily.

Rapid Response, Transport, and Airway Teams

For many patients who transfer to the ICU from a general care floor, looking back on the day of admission is often like watching an accident in slow motion. Frequently, modest complaints and marginally vital sign abnormalities are responded to in a leisurely manner, often ordered by telephone without physician examination. When there is an in-person examination, it is often conducted by a house physician or an on-call doctor unfamiliar with the patient. The magnitude of physiologic abnormalities increases as does the intensity of treatment, but often nurses know that the prescribed treatment is ineffective. The sense of the patient's downhill trajectory is lost as personnel change shifts. Eventually, a crisis manifests and the patient suffers a cardiac or respiratory arrest, or is rushed to the ICU in extremis. One way to reduce this scenario is by developing independent in-house teams to respond to deteriorating patients. These groups known as medical emergency teams (METs) or rapid response teams (RRTs) have garnered wide endorsement. Although most calls do not end in movement of the patient to the ICU, surprisingly as many as 10% of MET/RRT calls end with a decision not to move the patient but rather establish comfort care with a "do not attempt resuscitation" designation. In some studies dramatic (~50%) reductions in unexpected cardiac arrest rates have been seen and for patients transferred to the ICU, shorter ICU stays with better outcomes are the rule. Delaying transfer until a patient experiences a cardiopulmonary arrest on the floor is bad medicine that ends up costing more. Admittedly, in some studies benefits of RRTs have not been observed. The reason for heterogeneous results is not certain; however, one explanation may stem from the pattern of use of such services. Surprisingly, in some hospitals MET/RRT groups exist but they are called late or not at all. Reason for suboptimal use of such teams is speculative but could be the result of inadequate education, inability of staff to recognize early signs of critical illness, inertia, or fear of retaliation of primary care team.

Best Practices

Roughly a dozen practices have been reasonably proven to be safe, cost effective methods of improving ICU patient outcomes (Table 2).

Because few people can reliably remember all of these interventions, it makes sense to construct a "checklist" or standardized order set to prevent inadvertent omissions and to assure appropriate application. Many physicians oppose the concept of treatment protocols largely based on two objections: (1) patients are too variable to have a set protocol, and (2) use of a plan or protocol diminishes the value of the expert clinician.

Table 2—*Best Practices*

Anemia prevention and transfusion protocols
Radiograph ordering schedule
Venous thromboembolism prevention
GI bleeding prophylaxis for ventilated patients
Objectively targeted sedation protocol
Spontaneous breathing trial protocol
Central line insertion protocol
Turning-repositioning decubitus ulcer prophylaxis
Pain control protocol
Daily reassessment of need for lines and tubes
Elevation of the head of the bed for ventilated patients
Oral hygiene
Influenza, pneumococcal vaccine immunization
Handwashing
Standardized enteral feeding protocol
Preprocedural "timeouts"
Severe sepsis treatment protocols

Often this debate is polarized, suggesting that treatment plans or protocols are always evil or good. The truth almost certainly lies in between. Protocols have immense value when the treatment plan is complex and has steps that are likely to be overlooked or misapplied and are probably most important in low intensity physician staffing models. Perhaps the best example is the one for severe sepsis, in which, at present, more than a dozen published studies have shown improved patient outcomes after establishing a severe sepsis treatment protocol.

Blood sampling eventually causes anemia, requiring transfusion with its attendant risks and costs. "Unnecessary" tests will yield some false-positive results, which then prompt more, increasingly expensive, and potentially dangerous tests. Legitimate concern over physiologic and chemical abnormalities is a major factor driving laboratory use. Unfortunately, the range and frequency of laboratory use is determined in large part by habit and a physician's comfort and experience in the care of critically ill patients. For example, less-experienced physicians often order chemistry and hematology profiles and blood gases daily. In addition, standing orders for blood, sputum, and urine cultures are often written to evaluate temperature elevations. There is little justification for such rigid practices; more flexibility and thought are required. In addition, numerous studies demonstrate that developing testing guidelines decreases laboratory use without compromising outcomes.

Another unappreciated problem is that of inadequate or improper sampling. Up to 25% of samples delivered to the clinical laboratory are improperly collected or labeled. The majority of these "preanalytical" errors are underfilled tubes, blood collected in the wrong tube, mislabeled, or inadequately labeled samples. In most cases this results in the sample being discarded. The impact in terms of wasted time and blood is enormous, and it logically follows that at some point wasted blood will be replaced by transfusion. The problem of mislabeled samples is particularly keen if the sample is unique or difficult to obtain (eg, spinal or BAL fluid). Clearly, measures such as point of care testing and dedicated phlebotomy teams should be taken to prevent this wasteful practice.

Laboratory evaluation of fever in the ICU is most fruitful when performed for new-onset fever in the absence of antibiotic therapy. A temperature threshold for obtaining cultures of $<96°F$ or $>101°F$ is rational in the absence of other alarming indicators. For patients with continuous or near continuous fever, it is reasonable to repeat cultures every 3 days, an interval sufficient for full evaluation of previously obtained cultures and for empiric antibiotics to work. Exceptions include patients with suspected endocarditis or septic thrombophlebitis in whom bacteremia may be continuous and for patients who have dramatic physiologic deteriorations associated with worsening of fever. Up to 50% of all "positive" blood cultures grow organisms ultimately deemed to be "contaminants." These false-positive cultures prove costly as they prompt additional diagnostic studies (cultures and imaging studies) and antibiotic therapy, as well as prolonging hospital stay. Meticulous technique in obtaining blood cultures, perhaps even using dedicated phlebotomists, will minimize contamination. It has been estimated that a contaminated culture can result in $10,000 to $15,000 of additional hospital charges.

Evaluation of electrolytes is often prudent several times a day during a period of instability, especially early in the hospitalization. Provision or removal of large amounts of fluid often leads to dramatic changes in electrolyte levels. Likewise, acid–base disorders alter bicarbonate and

potassium levels in these unstable patients. However, after 2 to 3 days in the ICU, daily chemistry evaluations are needed only for the occasional patient. Patients with acute renal failure, especially those receiving renal replacement therapy, and patients with severe hypokalemia or hyperkalemia warrant more frequent monitoring. Although very reasonable on admission, extensive automated blood chemistry profiles are rarely needed more than once or twice weekly. If specific components of the profile are necessary (eg, liver function tests, albumin), it is often more cost effective to order the individual components. It is also wasteful to repeatedly monitor values without instituting a reasonable corrective action. An example is potassium replacement in patients with severe hypokalemia. When potassium values decrease below 3 mEq/dL administering 20 or 40 mEq of potassium and rechecking the value is near useless—the ion deficit is close to 10 times as great.

Perhaps two of the most overused chemistry tests are those for calcium and magnesium levels. As largely intracellular cations, both are highly susceptible to plasma protein concentration, and acid–base status changes. In addition, changes in plasma values have little biological effect on broad ranges. Unless obtained to evaluate a specific clinical problem (eg, neuromuscular weakness or irritability), neither test is likely to be helpful. Because the therapeutic margin of magnesium is broad unless a patient has significant renal insufficiency, a reasonable strategy is to simply administer magnesium in situations where depletion is likely and potentially related to clinical findings. Magnesium depletion is common in the same clinical situation in which hypokalemia is observed (eg, diuretic use, alcoholism).

Like chemistry measurements, with some exceptions, daily or more frequent monitoring of hemoglobin, platelet count, and white blood cell count is probably not necessary after the initial period of instability. Patients undergoing therapeutic anticoagulation are prone to declines in hematocrit and possibly the thrombocytopenic effects of heparin, suggesting that monitoring should be more frequent. Thus, once-daily monitoring of each parameter is not unreasonable. Similarly, patients with active hemorrhage (especially trauma victims, patients with active GI bleeding, and patients receiving transfusion) probably should be monitored on at least a daily basis. But even for these patients, there is potential for cost reduction: white blood cell, particularly differential, counts are not necessary for patients in whom the purpose is to track hemorrhage. Furthermore, differential counts are seldom helpful after admission, except for patients with neutropenia from sepsis or chemotherapy.

In vitro tests of coagulation are overused. At the time of admission, it is reasonable to assay the prothrombin time (PT). Measuring the activated partial thromboplastin time (aPTT) is unlikely to yield useful information unless heparin therapy or hereditary coagulopathy is suspected. The combination of a normal PT and aPTT excludes hereditary coagulopathy, consumptive coagulopathy, and profound nutritional deficiency. After admission, the PT is subject to change by consumption, dilution, or decreased production of vitamin K-dependent clotting factors. Hence, disseminated intravascular coagulation (DIC), dilutional coagulopathy, progressive liver disease, or warfarin anticoagulation would be clear indications for monitoring the PT over time. The PT will not respond quickly to warfarin therapy and is essentially useless as a measure of heparin effect. Hence, it is wasteful to obtain repeated PT determinations from patients receiving heparin alone. The aPTT is increased by dilution, consumption, heparin therapy, or congenital coagulopathy. Therefore, it is reasonable to obtain aPTT measurements for patients being treated for DIC or dilutional coagulopathy, and it is essential for patients being treated with continuous infusion of unfractionated heparin. There is no indication for repeated aPTT determinations in patients being treated with low-molecular-weight heparin or those receiving warfarin alone. Another coagulation test that is vastly overused in the ICU patient population is the D-dimer test. Although a low result from an ultrasensitive D-dimer test is very useful in the outpatient setting to truncate the evaluation of venous thromboembolism, among inpatient testing it is usually wasteful. Essentially every condition that provokes ICU admission (eg, surgery, trauma, severe sepsis, hepatic failure,

DIC) also raises the D-dimer negating its usefulness for exclusion of thromboembolism.

Before wide application of pulse oximetry and realization that the arterial CO_2 concentration does not need to be normalized, arterial blood gases (ABGs) were recommended after every ventilator change and were frequently performed routinely on a daily basis for ventilated patients. Even daily ABGs are not necessary in the absence of a change in clinical status or noteworthy ventilator parameter change. Furthermore, changes in administered oxygen concentrations do not routinely require ABGs when saturation is monitored. In several centers, the application of simple clinical guidelines as to when ABGs should be obtained has been associated with dramatic declines (>50%) in use without detectable harm. ABG analysis remains quite valuable in the diagnosis of acid–base abnormalities. ABGs prove most useful in the initial period of hemodynamic and ventilatory instability or when metabolic acid–base disorders are suspected.

Typical ICU patients undergo phlebotomy to a degree that exceeds their ability to produce RBCs, especially if blood is easy to obtain (arterial line) and there are "standing orders" for daily broad-ranging testing. Sending more blood to the laboratory than a patient can make will result in anemia and eventual transfusion. Therefore, it should not be a surprise that more than 85% of all patients in an ICU for a week receive a transfusion. In addition to minimizing phlebotomy, numerous studies have now shown that in hemodynamically stable patients, accepting lower than traditional hemoglobin values (ie, 7 g/dL) is not only safe but results in better outcomes in some subsets of patients.

Like laboratory studies, doing more radiographic studies exposes patients to more radiation and contrast, often requires travel from the ICU, and spends money. Administration of contrast presents a risk to patients with volume depletion, diabetes, or underlying renal insufficiency (eg, acute kidney injury, nephrogenic fibrosing dermopathy). Furthermore, at present, many of the imaging studies require costly transport to the radiology department, during which time complications can occur. Strategies to sensibly limit procedures include eliminating low yield portable studies (eg, abdominal flat plate, sinus studies, bone films). For stable patients, reducing the frequency of "routine" studies, especially the daily portable chest radiograph, is a must. When two options of comparable quality and cost exist, using the one that can be performed in the ICU to avoid transport costs and risks; optimizing scheduling to minimize the number of trips to the radiology department; using the absolutely necessary visits to the radiology department as an opportunity to substitute higher quality images for less-optimal portable studies. When a series of procedures are done in rapid succession, wait until all are completed then obtain just one radiograph to evaluate placement and look for compilations. Also, when a diagnostic study is performed in the radiology department, it should be interpreted immediately so that additional views, complementary studies, or therapeutic intervention can be performed without a second trip. (This mandates the ready availability of an intensivist physician decision maker.)

Although some studies are almost always ordered they are of low yield or only partially informative. One example is the abdominal flat plate. It rarely finds free air or intraabdominal calcifications. Its sensitivity is very low and even if positive, almost certainly a more detailed study will be required before definitive intervention. Therefore, if viscous perforation or obstructive uropathy is suspected, it probably makes most sense to proceed directly, respectively, to an abdominal CT scan or ultrasound.

The portable chest radiograph (CXR) is the most common radiographic procedure that ICU patients undergo. Without guidelines most ICU patients undergo one to two portable CXRs each day at a charge of several hundred dollars. Although the CXR usually is abnormal in ICU occupants, in stable patients, abnormalities are often insignificant or equally evident by other less costly means (ie, physical examination). When hemodynamic and respiratory status is stable (typically 2–3 days after admission), the practice of ordering "routine" daily CXRs should be reconsidered. A justification commonly given for daily films is the necessity to evaluate endotracheal tube and vascular catheter position. However, because the CXR captures much less than 1 s of each day, that argument rings hollow

and loses validity for patients with the much more stable tracheostomy tube in place. Paradoxically, the very act of obtaining the CXR may displace tubes as the patient is repositioned. Several studies have now shown that foregoing "routine" daily CXRs for stable patients (even those on mechanical ventilators) is safe and can significantly reduce imaging costs. A significant change in cardiopulmonary status should prompt consideration of a CXR, as should insertion or manipulation of tubes or catheters. Practically, even when "routine" films are not obtained, patients are likely to have at least one CXR each day because of changing physiology or insertion of monitoring devices. Data also suggest that a CXR done at the time of ICU admission, even if one has been done relatively recently is of relatively high yield for new abnormalities. Financial savings can be had by performing only one CXR after a series of procedures (eg, thoracentesis, central catheter insertion) instead of a film after each intervention. Imaging should not be delayed if a life-threatening complication is suspected.

Substantial expense and risk are associated with transporting patients from the ICU—one report suggests costs of $300 to $500 for transport alone. Regardless of the true cost, it makes sense to travel as little as possible and only when necessary. When a diagnostic study can be performed in the ICU with comparable quality to that performed in the radiology department, opting for the portable examination avoids transport cost, risk, and inconvenience. One example would be the search for gallstones or biliary obstruction, in which portable ultrasound and department-based CT scan are viable options, but the portable study offers substantial cost advantage. Another example of when ICU imaging could avert a trip to the radiology department is with regard to thromboembolism diagnosis. A patient with a suspected pulmonary embolism could have the diagnosis of thromboembolism confirmed by a portable ultrasound of the legs instead of traveling for a chest CT or ventilation-perfusion scan. In most patients the treatment will be identical for the diagnosis of deep venous thrombosis and pulmonary embolism and such a strategy avoids contrast and ionizing radiation exposure.

Arranging for several imaging studies to be performed in the radiology department during the same visit is also a strategy to maximize safety and minimize cost. For example, if there are plans to perform an elective chest CT scan today and a head CT scan tomorrow, it is reasonable to consider rescheduling to accomplish both in a single trip. Finally, it makes sense to anticipate the need for therapeutic intervention when ordering diagnostic studies. For example, a patient with pancreatitis experiencing high fever and clinical deterioration is likely to have an area of the pancreatic bed needing to aspirated or drained. Thus it makes sense to plan the aspiration at the time of initial imaging, then abandon the intervention if not necessary.

Similarly, more medications increase the risk of an adverse drug reaction, often prompting additional diagnostic or therapeutic interventions. Imprudent use of antibiotics increases the risk of antibiotic-resistant infections, not only for the treated patient but for subsequent patients admitted to the ICU. The common past practice of deep sedation for all mechanically ventilated patients has also now been shown to be associated with worse outcomes. Standardized sedation protocols using regular objective nurse assessments of a patient's level of sedation and dosing their sedation to a desired target have been shown to reduce drug use, time on ventilation in the ICU and in the hospital. A recent enhancement on the practice of protocolized sedation is the daily awakening trial that has even been shown in one study to improve long-term survival.

Another factor leading to worse outcomes and increased cost of care is physicians' shortsightedness to exploit inexpensive or even free measures to prevent catastrophic consequences. Examples include failure to use maximal barrier precautions when inserting vascular catheters, omission of deep venous thrombosis or gastrointestinal bleeding prophylaxis in the right circumstances, and failure to elevate the head of the bed of mechanically ventilated patients. Finally, mortality, resource utilization, and costs may increase when physicians fail to adopt simple proven treatment strategies, such as lower tidal volume ventilation for acute lung injury. Another simple, effective best practice involves

the process of weaning and extubation. For most patients, "weaning" is neither complex nor prolonged. Because many physicians do not consider withdrawal of mechanical ventilation until certain targets are met for F_{IO_2} and positive end-expiratory pressure, it makes sense to empower the respiratory therapist to automatically reduce levels of support using predetermined unit-based guidelines. Doing so can reduce the time required for a patient to "qualify" for a spontaneous breathing trial (SBT). The majority of patients who are not paralyzed or in shock and who are receiving $\leq$10 cm H_2O of positive end-expiratory pressure and an F_{IO_2} $\leq$0.5 can safely undergo an SBT conducted by nurses or respiratory therapists using an established protocol. When spontaneous breathing is tolerated for 30 to 120 min (with careful observation) the physician can be consulted for a decision regarding extubation. Having the process of testing avoids inherent delays in physicians "ordering" an SBT, or even worse overlooking the possibility altogether. Numerous studies now confirm the value of the SBT, which reduces average time on ventilator by 2 to 3 days. An added benefit of liberating patients from the ventilator is that once extubated they cannot be classified as having "ventilator-associated pneumonia" for purposes of quality reporting.

Other simple measures can safely decrease costs of the weaning process. One is to avoid "T-piece" weaning unless absolutely necessary. Charges for the equipment and labor for setup are often substantial. Use the CPAP mode of the ventilator. When necessary, CPAP can be combined with a low level of pressure support ($<$5 cm H_2O) to overcome resistance of the ventilator circuit. For most patients, no significant increase in work of ventilation is realized in breathing through a well-adjusted ventilator circuitry, and the machine provides the advantage of an "apnea alarm." Another example is to immediately place patients on nasal cannula oxygen rather than mask or face tent. In common practice, the mask is discarded within minutes or hours in favor of a nasal cannula. Patients extubated from high F_{IO_2} and those with conditions that would impede nasal oxygen flow are poor candidates for such a strategy.

Summary

Dedicated and experienced leadership; a team approach to care; a defined procedure for admission, discharge, and transfer; restriction of attending privileges; and comprehensive guidelines for the use of drugs, imaging studies, ventilators, and laboratory tests can produce substantial cost savings while improving the quality of care.

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Notes

Chapter 34. Status Epilepticus, Stroke, and Increased Intracranial Pressure

Arthur P. Wheeler, MD, FCCP

Objectives:

- Learn the clinical presentations of seizures.
- Understand the principles of seizure control.
- Learn the key elements of ischemic and hemorrhagic stroke treatment.
- Understand techniques to manage elevated intracranial pressure.

Key words: intracranial hypertension; seizure; stroke

Synopsis:

This chapter reviews the basics of diagnosing and treating seizures, the differential diagnosis of stroke and its treatment, and key elements of managing elevated intracranial pressure.

Status Epilepticus

Pathophysiology

Seizures result from aberrant neuronal discharges causing generalized or focal neurologic signs. (Most seizures begin focally.) Knowledge of the cell biology of seizures has advanced considerably; seizures are associated with excessive activity of excitatory n-methyl-d-aspartate (NMDA) receptors and inadequate stimulation of suppressive γ-aminobutyric acid (GABA) receptors. Moreover, activation of the NMDA receptor is probably required for seizure propagation and neuron damage. Understanding the role these receptors helps explain the effectiveness of GABA stimulants (benzodiazepines, propofol, barbiturates, and ethanol) as anticonvulsants.

Although seizures have been classified in many ways, it is probably most useful to think of them in terms of their duration (brief and self-limited vs continuous) and scope (generalized vs focal). Duration is important because prolonged seizures become more refractory to treatment, irreversibly injure neuronal tissue, and cause systemic metabolic problems (eg, acidosis, hypoxia, hyperkalemia, hyperthermia, and rhabdomyolysis). There is no standard definition of the commonly used term "status epilepticus," but it is generally agreed that seizures lasting >10 min (some say as little 5 min) or a series of recurring seizures without an intervening period of consciousness qualifies. Similarly, although not standardized, the term "refractory status epilepticus" has been applied to seizures lasting >2 h or uncontrolled with two or more anticonvulsants. Focality is also noteworthy because it suggests a discrete structural abnormality. Although seizures usually present as localized or generalized phasic muscle contractions, in the ICU seizures occasionally masquerade as unexplained coma or puzzling sensory or psychiatric disturbances.

Etiology

One of five basic mechanisms is responsible for convulsions: intrinsic electrical instability (epilepsy); toxic or metabolic disturbances (eg, electrolyte imbalances, alcohol, drug effect); structural lesions (eg, trauma or tumor); infections (eg, meningitis, encephalitis, brain abscess); or abnormalities of brain perfusion. In general, these etiologic factors segregate into two prognostic groups. Patients with idiopathic epilepsy, anticonvulsant noncompliance, and alcohol-related seizures tend to have an excellent prognosis whereas victims of stroke, trauma, tumor, encephalitis, hypoxia, or CNS toxin tend to have a poor prognosis.

Seizures are more common at the extremes of age with etiology also varying by age. Children most commonly have seizures as the result of fever, infection, or a change in anticonvulsant medications. Young adults are much more likely to seize from subarachnoid hemorrhage, trauma, anticonvulsant noncompliance, or drug use or withdrawal (eg, tricyclic antidepressants, co-

caine, and alcohol). In the older adult, stroke, subdural hematoma, and tumor are more common. Hypoglycemia and CNS infections (eg, meningitis, encephalitis) affect all ages.

High fever (especially in children), drug withdrawal (particularly anticonvulsants, ethanol, barbiturates, benzodiazepines, baclofen), and overdoses of isoniazid, penicillin, imipenem, tricyclic antidepressants, theophylline, or lidocaine are common metabolic causes. Electrolyte disturbances may also induce seizures, especially when such changes occur abruptly (eg, acute hyponatremia, disequilibrium following dialysis).

Although most seizures in outpatients are idiopathic, this is true less often in the ICU, where such treatable conditions as drug or alcohol withdrawal, metabolic imbalances, drug toxicity, and acute structural lesions are more common. Most important among the metabolic precipitants are uremia, hypoglycemia, hypocalcemia, hypomagnesemia, and hyponatremia. CNS infections are frequent causes of ictus; about one-third of adults with bacterial meningitis will experience a seizure. HIV infection represents a particular hazard for infection, including toxoplasmosis and viral encephalitis.

Diagnosis

A seizure is usually diagnosed by history and observation of an attack in an appropriate clinical setting. Occasionally, historical features or the clinical appearance is so atypical as to require confirmation by EEG. In such cases, an intra-ictal EEG is diagnostic and the pattern of discharge may help determine etiology. For example, EEG localization of seizure discharge to the temporal lobes (especially with appropriate MRI findings) suggests herpes encephalitis. EEG recording may also reveal unsuspected seizure activity in a patient with unexplained coma. In fact, up to 37% of unresponsive ICU patients may have occult seizures, and an even higher percentage (50%) of patients who remain unresponsive after having a convulsion have been found to have ongoing nonconvulsive seizures. A head CT scan or MRI is indicated for new onset seizures, those accompanied by a preceding or persistent focal neurologic deficit, and in those refractory to simple medical therapy. In such patients, a CT scan often reveals a structural cause (eg, vascular malformation, primary or metastatic tumor, or subdural subarachnoid or parenchymal hemorrhage). In patients with a known seizure disorder, imaging is not necessary with each recurrence, especially if there is a clear history of anticonvulsant noncompliance; however, even patients with epilepsy develop strokes, tumors, and CNS infections. Hence, recurrent seizures should not be reflexly ascribed to a singular cause in perpetuity.

Effects of Seizures

Brief ictal episodes are of little consequence provided they do not occur while the patient is involved in a dangerous activity, and the airway, oxygenation, and ventilation are preserved. However, prolonged seizures deplete cellular reserves of oxygen and energy and allow intracellular accumulation of calcium, processes that culminate in neuronal death. By damaging the cortex, recurrent or prolonged seizures are associated with cognitive impairment. In humans, seizures >2 h in duration reliably cause permanent brain injury, but lasting injury may begin within 30 min and does not require loss of consciousness nor muscular contractions.

Catecholamine release during convulsions may induce arterial and intracranial hypertension and cause pulmonary edema. Adrenergic stimulation initially produces hyperglycemia, but during prolonged seizures glucose consumption can cause hypoglycemia. Fever from thermostatic reset and/or sustained muscular activity may rise to concerning levels (>105°F) and tends to respond poorly to antipyretics. Furthermore, thermoregulation may be disturbed for days after seizures. Because fever and leukemoid reactions (peripheral leukocyte counts often exceed 20,000 cells/μL) are common, infection is often suspected. Differentiating infectious from convulsive fever is further confounded by the common occurrence of cerebral fluid pleocytosis, with total leukocyte counts up to 80 cells/μL and a predominance of neutrophils.

Profound and rapid onset acidosis often accompanies seizures, with half of postictal acidemic patients exhibiting a metabolic (lactic)

acidosis alone whereas the other half has a mixed respiratory and metabolic acidosis. Although the seizure-associated acidosis may be severe (pH $<$ 6.5), no evidence links pH with outcome, and most patients resolve the acidosis within 1 h. The same vigorous muscular contractions causing acidosis can result in rhabdomyolysis, hyperkalemia, and, rarely, renal failure. Increased water losses from sweating and hyperventilation may increase serum osmolarity and Na^+ concentration. The combination of direct neuronal damage and metabolic pandemonium of status epilepticus results in mortality rates of 30% to 35%.

Treatment

The most important factors determining the outcome of status epilepticus are the etiology of the episode and the time to terminate the seizure. The longer that time, the more difficult is control and the worse the outcome. Airway protection, oxygenation, and maintenance of perfusion are primary considerations. Aspiration risk may be reduced by lateral decubitus positioning and endotracheal intubation when clinical judgment dictates. If paralysis is necessary for intubation, EEG monitoring assumes greater importance since muscular activity will be halted, but the seizure can continue unrecognized. If paralysis is necessary, a short-acting and nondepolarizing drug such as rocuronium is probably preferred over a depolarizing drug such as succinylcholine. As with all causes of altered consciousness, electrolytes and glucose should be tested and normalized. Testing for drugs of abuse should be used selectively. Thiamine (100 mg) should be administered in most cases to prevent Wernicke's encephalopathy.

For patients who experience a solitary seizure or several brief seizures with known precipitant, long-term anticonvulsants are usually not necessary; however, there is agreement that status epilepticus should be pharmacologically ended as rapidly as possible. Drugs that bind GABA receptors are the most effective seizure-quashing drugs. One strategy for acute anticonvulsant administration is suggested in Table 1.

There is no single ideal drug regimen for terminating seizures; however, benzodiazepines, specifically lorazepam, represent excellent initial choices because of their effectiveness, rapid action, and wide therapeutic margin. Benzodiazepines cannot be expected to provide long-term seizure control by themselves, but can "break" seizures long enough to accomplish intubation if necessary and to initiate therapy with a longer acting drug.

Initial IV doses of lorazepam (0.1 mg/kg) are very effective (60%–90%) in terminating seizure activity within minutes. Lorazepam's 2- to 3-h half-life and avid GABA receptor binding provide seizure protection for up to 24 h. In a randomized trial comparing lorazepam with phenytoin, diazepam plus phenytoin, or phenobarbital, lorazepam alone was the most effective initial therapy. The theoretical issue of slower onset of lorazepam compared with midazolam or diazepam does not appear to be clinically important. Diazepam (0.15 mg/kg) is an acceptable alternative and is also available as a rectal gel useful when IV dosing is not possible. The major disadvantages of diazepam are its shorter duration of action, lesser initial success rate (40%–70%), and potent sclerosant effect on peripheral veins. Midazolam (0.2 mg/kg bolus) can also be used in place of lorazepam, but because it has the shortest duration of action of all the benzodiazepines, a continuous infusion (0.2–1 μg/kg/min) is often required. Hypotension and hypopnea are complications of all benzodiazepines but occur rarely ($<$5%) unless other anticonvulsants (especially phenobarbital) have been administered.

After benzodiazepine administration, phenytoin is the preferred second-line drug for long-term control. Although phenytoin has a reputation to cause infusion site pain and adverse cardiovascular effects (eg, arrhythmias, hypotension, conduction disturbances) when administered rapidly, it is a safe and effective drug when given slowly. Because of its long half-life, seizure recurrence is rare. Initial loading doses (20 mg/kg), should be given at a maximum infusion rate of 50 mg/min. (Additional carefully titrated doses, up to 30 mg/kg, may be necessary in refractory cases.) Thus, an adult loading dose usually requires 30 to 45 min to administer. Phenytoin must be administered only in saline; it is not compatible with glucose-containing solutions. Although the adult daily

Table 1—*Therapy for Status Epilepticus*

Step 1 Stabilize vital signs
- Establish an airway, administer oxygen
- Ensure circulation with adequate BP
- Establish IV access
- Collect blood for values for electrolytes, glucose, hemoglobin, creatinine, and liver function tests; acid-base status; and possibly toxicologic analysis
- Administer D50W (1 mg/kg) and thiamine (1 mg/kg) unless patient is known to be normoglycemic or hyperglycemic

Step 2 Rapidly achieve seizure control
- Lorazepam (0.1 mg/kg) IV or
- Diazepam (0.15) mg/kg mg IV (initial doses of either may be repeated if necessary)
- Less desirable alternative: midazolam (0.2 mg/kg) bolus then 0.2 to 1.0 mg/kg/min infusion

Step 3 Achieve/maintain seizure control
- Phenytoin (20 mg/kg unfused at <50 mg/min) or
- Fosphenytoin (20 mg/kg phenytoin equivalents infused at 100 to 150 mg/min)

Step 4 Salvage therapy for resistant status epilepticus
- Propofol (2-10 mg/kg/h) or
- Phenobarbital (20 mg/kg) given by slow (30–50 mg/min) infusion

Step 5 Advanced treatment for refractory disease
- Pentobarbital (10 mg/kg load at 0.2 to 2.0 mg/kg/h, followed by 1 to 4 mg/kg/h) or
- Thiopental (3 to 7 mg/kg load, followed by 50 to 100 mg/min IV) or
- Midazolam infusion (0.2 mg/kg bolus followed by 0.05-0.5 mg/kg/h) or
- General anesthesia (eg, isoflurane)

Step 6 Diagnostic evaluation
- Consider CT scan, MRI, lumbar puncture, and toxicologic evaluation

maintenance dose averages 300 mg IV or orally, therapy should be guided by serum drug levels and clinical response. Phenytoin toxicity may produce diplopia, horizontal and vertical nystagmus, slurred speech, ataxia, and somnolence. Hemodynamic effects may be pronounced among severely hypoalbumenemic patients, even with slow infusion rates.

In an attempt to reduce infusion site reactions and cardiovascular effects, the water-soluble compound fosphenytoin was developed. Water solubility also permits intramuscular injection when IV access is problematic. Although it can be infused much more rapidly (100–150 mg/min) than phenytoin, fosphenytoin is a prodrug that must be hydrolyzed to the active compound (phenytoin) after administration. The infusion and conversion process requires just about as much time as does the safe infusion of phenytoin and in comparative trials the incidence of adverse effects is comparable. Because of differing molecular weights of phenytoin and fosphenytoin, doses differ, with the later typically ordered as "phenytoin equivalents." Failure to account for this difference can result in significant underdosing. Because of the substantially higher costs and lack of proven benefit with regard to speed or safety, routine use of fosphenytoin is not recommended.

Phenobarbital and propofol represent third-line treatments for status epilepticus. Phenobarbital, (20 mg/kg) infused at rates <100 mg/min, is moderately effective (~60%) in terminating seizures. Potent cardiorespiratory depressant effects and interaction with other drugs often makes its use problematic. Because it is a weak acid, brain levels of phenobarbital may be just half of those in plasma of acidemic patients. Phenobarbital has a very long half-life (~90 h) leading to prolonged sedation, which often complicates subsequent neurologic evaluation. As a GABA agonist and NMDA antagonist, propofol has strong theoretical advantages but published efficacy data are limited. If seizures are controlled by a loading dose of 1 to 2 mg/kg, the infusion is continued at rates between 2 and 10 mg/kg/h, for 12 to 24 h before beginning a slow taper. One potential advantage of propofol over benzodiazepines or barbiturates is its substantially shorter duration of action facilitating repeated neurologic examination. A significant disadvantage is the possibility of metabolic acidosis when high doses are infused for long periods of time (propofol infusion syndrome).

Status epilepticus is occasionally resistant to the methods outlined above. Reasons for failure can include inadequate drug dosing, prolonged seizures before initiating treatment, cerebral mass lesion (eg, tumor or hemorrhage), or profound metabolic abnormality (eg, hypoxemia, hyponatremia, or hypocalcemia). Refractory seizures may require more intense anticonvulsant therapy including valproate, levetiracetam, topiramate, tiagabine, high-dose benzodiazepine infusions, pentobarbital, or "general anesthesia" using a volatile anesthetic. With the exception of valproate, regardless of which "salvage" regimen is chosen, mechanical ventilation and hemodynamic support are nearly always required.

Although there is no consensus on the treatment of such refractory seizures, a continuous infusion of a short-acting barbiturate (pentobarbital 10 mg/kg load followed by 1–4 mg/kg/h or thiopental 3–7 mg/kg load followed by 50-100 mg/min IV) has been used traditionally. Such a regimen is usually effective but may be required for 12 to 36 h or longer to prevent seizure recurrence. Emergence from the protracted barbiturate-induced coma may require weeks. Another alternative is a midazolam infusion (0.2 mg/kg bolus followed by 0.05 to 0.5 mg/kg/h).

If salvage therapy is required, availably of EEG monitoring and expert neurologic consultation are essential. Unfortunately, there is no consensus for EEG endpoints of therapy; trained electroencephalographers are never continuously available, and for most ICU physicians EEG interpretation is enigmatic. With regard to goals, seizure control certainly does not require achieving an "isoelectric" EEG; the value of achieving a "burst suppression" pattern is even questioned. Outcomes of patients to burst suppression or a flat EEG are worse. Probably simply preventing organized seizure activity is an adequate endpoint in most cases. Although hardly a substitute for formal training, a couple of simple guidelines are useful to help the critical care physician differentiate normal from ictal EEGs. A normal EEG demonstrates asymmetric, high-frequency, low-amplitude waveforms in multiple channels—to a critical care physician best described as "ventricular fibrillation." Any time symmetric, large magnitude discharges, or for that matter any recognizable pattern (tachyarrhythmia), can be identified on EEG, seizure activity should be suspected. Once convulsions are controlled, the critical care physician should consider the possibility of continued nonconvulsive status and the need for brain imaging, lumbar puncture, and therapy for rhabdomyolysis.

Stroke

Stroke is a common cause of death and a frequent reason for ICU admission. The unifying factor in all stroke syndromes is neuronal ischemia from interruption of blood flow. The term *stroke*, from a biblical reference to being "struck down," implies an acute dramatic event; however, in the ICU, the presentation is often more subtle and atypical. Common occurrences such as altered mental status, delayed awakening from sedation, slurred speech, a decreased level of consciousness, agitation, or the new onset of seizures may be the only manifestations. Not only are the presenting signs in ICU patients different, so is the etiology: whereas the vast majority of strokes occurring in the community are caused by vascular occlusive disease, in hospitalized patients, more strokes are the result of cerebral emboli, intracranial bleeding, and diffuse hypoxia.

Pathophysiology

Two pathophysiologic mechanisms account for almost all strokes: ischemia from occlusive thrombosis, embolism, or systemic hypoperfusion (>90%); or hemorrhage into brain tissue or the subarachnoid space (10%). Although blocked venous drainage can cause ischemia, outside of very specific situations (eg, paranasal sinus infection, thrombophilia, sickle cell disease, L-asparaginase use), the syndrome is rare. Each of the four common stroke syndromes has its own predisposing factors, typical clinical presentation, and specific treatment summarized in Table 2.

Initial Evaluation

Time to definitive treatment is the largest controllable determinant of outcome. Because the treatment of ischemic and hemorrhage strokes and other common disorders that mimic stroke (Table 3) are drastically different, it is essential to promptly make the correct diagnosis.

Efficiency of care and outcomes are improved by establishing teams to evaluate patients with suspected stroke in a stereotypical fashion that includes a directed history and physical, concise laboratory evaluation and urgently obtained brain image. Essential historical elements are as follows: (1) the time the patient was last known to be normal, (2) recent trauma or surgery, and (3) medications, especially anticoagulants, anticonvulsants, antihypertensives, antiarrhythmics, and diabetic agents. Initial examination should evaluate the heart and great vessels and search for signs of liver disease, bleeding, and coagulopathy.

Table 2—*Characteristics of Stroke Syndromes*

	Embolic	Thrombotic	Hemorrhagic
Time course	Abrupt, maximal deficit at onset Occasional dramatic improvement	Abrupt, maximal deficit at onset Occasional brief improvement	Prodromal headache Abrupt, rapid progression Sudden loss of consciousness
Common deficits	Cortical infarcts	Cortical infarcts	Internal capsule, basal ganglia
Predisposing factors	Older Caucasian Atrial fibrillation Arterial catheter flushing Mitral stenosis Atrial septal defect Cardiac catheterization Central venous catheterization Endocarditis (esp. fungal) Left ventricular dilation	Older Caucasian Heart failure Hypercholes terolemia Diabetes Hypertension Smoking	Younger Black and Asian Hypertension Vascular malformation Amphetamine, cocaine, phenylpropanolamine Anticoagulant use
Antecedent history	Recent MI DVT-pulmonary embolism	TIA common *Amaurosis fugax* Central retinal artery occlusion	Recent thrombolytic therapy "Herald bleed"
Therapy	Antithrombotic	Thrombolytic (early) Elective endarterectomy	Correction of coagulopathy Surgical evacuation of selected lesions

The neurologic evaluation should be performed using a standardized tool like the National Institute of Health Stroke Scale (www.ninds.nih.gov/doctors/NIH_Stroke_Scale_Booklet.pdf). Although the history and examination are performed electrolytes, glucose, creatinine, hemoglobin, platelet count, and prothrombin time should be obtained to search for important nonstroke mimics and coagulopathy, and evaluate the safety of thrombolytic therapy. An ECG to evaluate cardiac rhythm and the possibility of ischemia is also prudent. Even though the yield of a chest radiograph is low, it is a rapid, inexpensive, safe test to screen for abnormalities of the aorta and to look for intrathoracic neoplasm as a potential source of metastases.

After initial stabilization immediate head imaging is indicated. There is some debate about the best initial imaging study; however, a noncontrasted CT scan is almost always adequate. If, for logistical reasons, MRI scanning can be accomplished faster, then it is an acceptable alternative. (In suspected brainstem stroke, MRI may add information to CT scan data.)

General Care of the Stroke Patient

The therapy for each specific stroke syndrome depends on its etiology and structural manifestations; however, the therapy of most strokes remains supportive. Because of the frequency of serious complications, simple prophylactic measures to prevent skin breakdown, gastric ulceration, and deep venous thrombosis make good sense. One to two weeks of anticonvulsant therapy may be useful for large hemorrhagic strokes. Regardless of etiology, all stroke patients should have oxygenation and perfusion evaluated on arrival. If saturations are below normal, supplemental oxygen should be administered; however, there is no evidence supplemental oxygen aids patients with normal Pa_{O_2} values. Symptomatic arrhythmias, particularly those causing hypotension, should be immediately corrected. Although there is little high-quality data to support the practice, anemia is usually corrected to a hemoglobin level $\geq$10 g/dL.

The appropriate target for BP in stroke victims is controversial because worse outcomes

Table 3—*Stroke Mimics*

Aortic dissection
Brain tumor or metastases
Hyponatremia
Hypoglycemia
Intoxication
Migraine
Seizures and postictal period

Table 4—*Unproven or Harmful Stroke Therapies*

Aminophylline
Antioxidant compounds
Calcium channel blockers
Corticosteroids
Glycerol
Hemodilution
Heparin (except for cardioembolic stroke)
Hyperbaric oxygen
Hypothermia
Mannitol
N-methyl-d-aspartate (NMDA) antagonists
Pit viper venom
Streptokinase

are associated both with hypotension and hypertension. Transient, moderate hypertension (systolic BP > 160 mm Hg) is nearly universal in all forms of stroke, as is a spontaneous decline in pressure over the first day of illness. Because self-correction is common, caution should be used to avoid overtreatment. Two points are clear: rapidly lowering BP or "normalizing" BP in the chronically hypertensive stroke victim is likely to do more harm than good. As a general rule, unless the patient is treated with thrombolytic therapy or has pulmonary edema, myocardial infarction, or aortic dissection, BPs <220/120 mm Hg should not be treated. (If thrombolytic therapy is used, a goal of <185/110 mm Hg is recommended.) Unless causing immediate harm, gradual reduction in BP over several hours to days using oral antihypertensive therapy is probably the best course of action. If pharmacotherapy is chosen, drugs without CNS depressant effects are preferred. Within a few days of the stroke, a reasonable low-end target for mean arterial pressure is 110 to 120 mm Hg.

The importance of glucose control is also debated. Older studies show an association of hyperglycemia with poor neurologic outcome; however, it is very possible that hyperglycemia is only a marker of severity of brain injury rather than a cause of damage. Even though no cause-and-effect relationship between hyperglycemia and brain injury is proven, it is hard to posit a benefit of uncontrolled hyperglycemia. As a general principle, even transient hypoglycemia is likely to be more harmful than sustained mild hyperglycemia. Use of a standardized protocol that frequently monitors glucose values, uses short-acting insulin, and aims for near levels (140–180 mg/dL) is advocated. An overview of stroke therapy is provided in Table 4 and discussed in detail below. Numerous other ineffective or harmful therapies have been used in stroke treatment and are presented in Table 4. A general overview of the treatment for stroke is presented in Table 5.

Ischemic Stroke

Ischemic strokes, the most common and important variety, typically result from the progressive occlusion of larger arteries (usually branches of the carotid). Hence, the risk of ischemic stroke is related to increasing age as the chronic risk factors of diabetes, hypertension, smoking, and hypercholesterolemia take their toll on vessel patency. (Thrombophilia, migraine, arterial dissection, and fibromuscular dysplasia

Table 5—*Pharmacologic Therapy of Acute Stroke Syndromes*

Transient ischemic attacks
Aspirin, 325 mg/day (ticlopidine or clopidogrel are alternatives in aspirin-sensitive patients)
Complete ischemic stroke
Aspirin, 325 mg/day to prevent recurrence
Progressive ischemic stroke
Tissue plasminogen activator (0.9 mg/kg) (if low bleeding risk and presentation within 4.5 h) or
aspirin, 325 mg/day to prevent recurrence if not TPA candidate
Cardioembolic stroke
If hemorrhage absent on CT scan at 48 h, begin low-molecular-weight or unfractionated heparin to aPTT of 1.5 to 2.0 baseline, then:
warfarin targeted to INR of 2.0 to 3.0
Exceptions: CVA involving >30% of a hemisphere (high risk for hemorrhagic extension)
Warfarin can be started without heparin for prophylaxis in atrial fibrillation

aPTT = activated partial thromboplastin time; CVA = cerebrovascular accident; INR = international normalized ratio; TPA = tissue plasminogen activator.

are much less common causes of thrombosis.) Although large vessels are usually the target, ischemic strokes can occur in small perforating vessels, resulting in a specific pattern known as a "lacune." Stroke may also occur in patients with less-than-critical vascular narrowing when hypotension, hypoxemia, or coagulopathy tips the balance of cerebral oxygen supply and demand unfavorably. When brain perfusion is impaired globally (eg, shock, cardiopulmonary arrest), regions at the border between two vascular distributions suffer the greatest. Ischemia of these so-called watershed zones results in three major clinical syndromes, including (1) bilateral upper extremity paralysis, (2) cortical blindness, and (3) memory impairment.

Slow progressive vessel narrowing can result in premonitory ischemic episodes known as transient ischemic attacks (TIAs). Although technically the neurologic deficits of a TIA can last up to 24 h, most (like angina) resolve in <10 min. TIAs serve as markers of a transition period during which stroke is likely. The risk of stroke correlates with the severity of the TIA—when temporary monocular vision loss (amaurosis fugax) is the only symptom, the risk of stroke is substantially lower than when large hemispheric defects occur. A TIA is a powerful warning sign that must not be ignored because at this stage, antithrombotic therapy or radiologic or surgical intervention can abort a fatal or disabling stroke in many patients. Other than TIAs, a diminished carotid pulse or a carotid bruit are perhaps the best indicators of large vessel occlusive disease.

Because ischemic strokes usually infarct the cerebral cortex, where sensory and motor functions are juxtaposed, equal losses of sensation and motor function to a given region occur. This is in contrast to small vessel strokes (lacunes), occurring deeper in the brain, where by virtue of the neuronal pathway arrangement, widespread deficits of isolated sensory or motor function are possible. For ischemic strokes, the distribution of the occluded vessel determines the neurologic deficit, which differs for the anterior, middle, and posterior cerebral artery circulations. Typically, ischemic strokes present with a near immediate maximal deficit, often noted upon awakening. When middle cerebral artery (MCA) flow is interrupted, the resulting sensory and motor deficits are greatest in the contralateral side of the face, with lesser deficits in the arm and leg. MCA occlusions of the dominant cortex may also produce an expressive or receptive aphasia when damage occurs to the anterior or posterior speech centers, respectively. A corresponding lesion of the nondominant hemisphere may produce an acute agitated or confused state with contralateral motor and sensory deficits. Homonymous hemianopsia and conjugate eye deviation toward the side of the lesion are less common but characteristic features of MCA occlusion.

Occlusion of the anterior cerebral artery produces the greatest neurologic deficit in the contralateral leg, followed in severity by the arm then face. A homonymous hemianopsia or loss of vision ipsilateral to the stroke is also possible. Frontal lobe signs of incontinence, grasp and suck reflexes, and perseveration are also common. Posterior cerebral artery ischemic does not usually impact the major centers for speech or motion; deficits are limited to homonymous hemianopsia, impaired recent memory, and prominent sensory loss.

The only effective treatment for ischemic stroke is rapidly delivered thrombolysis. Hence, when a clinical diagnosis is made, promptly obtaining a CT scan to distinguish patients with hemorrhage from those with ischemia is essential. Obviously thrombolytic treatment is contraindicated if hemorrhage is seen, but the CT scan can also help predict the safety of thrombolysis in patients with ischemic stroke. For patients with normal CT scans and those with subtle findings involving less than one-third of a hemisphere, thrombolysis is of low risk. When the CT scan shows subtle changes involving greater than one-third of a hemisphere, or mass effect or hypodensity of less than one-third of a hemisphere, thrombolytis should be carefully considered because of the higher risk of bleeding. There is general agreement that when a hypodense area is greater than one-third of a hemisphere, thrombolytic therapy should be withheld. Even without thrombolytic therapy, approximately 25% of ischemic strokes undergo spontaneous hemorrhagic transformation within 48 h. This conversion is often associated with worsening neurologic deficit and can be confirmed by repeating a CT scan. Large strokes, especially

those occurring in the elderly or in diabetics, are most prone to this complication, hence the reluctance to treat extensive strokes with thrombolytic therapy.

Clinical trials of thrombolytic agents have shown neurologic and survival benefits only when tissue plasminogen activator (TPA) (0.9 mg/kg) is administered rapidly after the onset of symptoms. Treatment delays of as little as 90 min, but certainly 180 min reduce benefits. Latest guidelines suggest a maximal interval from symptom onset to treatment of 4.5 h. Because patients must be free of systemic bleeding, present promptly after onset of symptoms, and undergo nearly immediate uncontrasted CT scanning that shows a favorable pattern, very few patients receive thrombolytic therapy. Even when carefully screened, a substantial number of patients develop significant intracranial (6%) and systemic bleeding after receiving TPA. When exclusionary criteria are ignored, bleeding rates of 40% have been reported. To minimize bleeding risks after thrombolytic therapy, control of BP (<185/110 mm Hg) and avoidance of invasive procedures and antiplatelet therapy should be routine. Because candidates for thrombolysis may have noteworthy bleeding complications, it should be used only by experienced physicians in a hospital with neurosurgical backup. If neurologic function deteriorates after administration of thrombolytic therapy, the lytic agent should be stopped, and coagulation status should be corrected using cryoprecipitate and platelet transfusions while a repeat CT scan is arranged. If intracranial hemorrhage is confirmed, neurosurgical consultation is prudent.

Aspirin reduces the incidence of thrombotic strokes when given prophylactically, (particularly to patients with premonitory transient ischemia), and decreases the incidence of recurrent stroke. Unfortunately, aspirin does not abort stroke in progress or reverse established neurologic deficits. Among patients with ischemic stroke who are not candidates for thrombolytic treatment, aspirin should be started within 48 h.

The outcome of ischemic stroke is not improved by hyperbaric oxygen therapy, therapeutic hypothermia, heparin anticoagulation, or surgery. Carotid endarterectomy or stenting is not indicated for treatment of acute ischemic stroke, but in patients with chronic or recurrent symptoms of cerebral ischemia, both may be beneficial. Endarterectomy is of proven benefit if performed by an experienced surgeon in symptomatic patients with >70% carotid stenosis and low operative risk. When the stenosis is in the 50% to 70% range, benefit is unproven, but endarterectomy is still probably acceptable provided the combined operative risk remains low. The surgeon's morbidity and mortality rate must, however, be very low (<3%) to favor surgical intervention in the asymptomatic patient.

Because of the rapid evolution of diagnostic techniques, an enduring discussion of the merits of diagnostic tests to evaluate the cerebral circulation is not possible. Currently, color flow Doppler ultrasound is usually the first diagnostic test to evaluate the extracranial circulation. If results of ultrasound are equivocal or if imaging the intracranial circulation is desired, CT angiogram or magnetic resonance angiogram is usually performed. Conventional carotid arteriography is now done less often.

Embolic Strokes

Embolic strokes result from the sudden impaction of a plug in a small cerebral artery branch, usually giving rise to isolated ischemic cortical defects. Because complete occlusion occurs nearly instantaneously, maximal deficits are typically immediate, but it is common for deficits to partially, even sometimes dramatically, improve within 1 to 2 days. Because of the embolic mechanism, multiple discrete areas of brain may be injured simultaneously. Although embolic strokes are considered to be second in frequency to thrombosis in the general population, patients in the ICU are at substantially higher risk of emboli because they are commonly subjected to procedures that predispose to arterial injury or thrombosis and cholesterol or air embolism (eg, central venous catheterization complications, left heart catheterization, aortic balloon pump insertion, and invasive BP monitoring). During such procedures, air, clot, or atherogenic material can be released or dislodged.

Cerebral embolism can result from foreign bodies, infected material, bland clot, air, or

cholesterol fragments. Bland clot formed either in a sluggishly flowing carotid system or in the heart of patients with mural thrombi, myocardial infarction, mitral valve disease, or atrial fibrillation are most common. Rarely, venous thromboemboli cause stroke as they cross a right to left intracardiac shunt entering the cerebral circulation (ie, paradoxical embolism). In most cases, the intracardiac defect is a patent foramen ovale or atrial septal defect. Left-sided endocarditis is another potential source of embolism. Bacteria, fungi, and amorphous material sloughed by structurally abnormal or infected heart valves can all cause cerebral vascular plugging. It is not widely appreciated that arterial pressure generated when "flushing" a peripheral arterial line can exceed systolic BP. A sustained flush can propel catheter tip clot or air retrograde into the cerebral circulation. Foreign materials, either illicitly injected or resulting from fracture of arterial monitoring catheters, also rarely result in cerebral embolism. Cerebral air emboli can result from disruption of the pulmonary veins by trauma, high ventilator inflation pressures, misadventures during cardiac catheterization, rapid ascent from underwater diving, or from atrial injury from radiofrequency ablation.

The diagnosis of embolic stroke is usually not difficult to make. History most often reveals one or more predisposing conditions, and the deficit is unexpected, immediate, and maximal in severity at onset. Because the heart is the most common embolic source, clinical examination often provides evidence of cardiac disease (eg, atrial fibrillation, murmur, or cardiomegaly). Neurologic evaluation typically reveals a cortically based deficit(s) with both sensory and motor loss to the same body region.

Because the volume of tissue infarcted may be small, the initial CT scan is often unremarkable. In patients with a history suggestive of embolic stroke without an obvious source, the combination of blood cultures to exclude endocarditis, cardiac monitoring to exclude arrhythmias, and a transthoracic echocardiogram (TTE) to diagnose aortic atheromatous disease, mural thrombi, valvular lesions, and to evaluate myocardial performance constitutes a good initial diagnostic battery. Because of the superior sensitivity of transesophageal echocardiography (TEE) in finding subtle valvular lesions and small clots in the left atrial appendage, it should be considered in patients with a history suggestive of embolism that have a nondiagnostic TTE. If symptoms localize to the carotid circulation and a cardiac source cannot be found, evaluation of the carotid branches should be undertaken using duplex ultrasound of the neck and transcranial Doppler. If symptoms are in the posterior circulation, imaging the origins of the vertebrobasilar and posterior cerebral arteries should be performed.

The therapy of embolic stoke should be dictated by the embolic material and stoke size. Obviously antimicrobial therapy is indicated in patients with emboli secondary to infective endocarditis. Valve replacement should be considered when large vegetations are present or when recurrent embolism occurs, despite appropriate therapy. In patients with nonhemorrhagic embolic stroke from a cardiac source, heparin or low-molecular-weight heparin followed by warfarin with a target International Normalized Ratio of 2 to 3 is indicated. Commonly, anticoagulation is delayed for 48 h after the event to document absence of hemorrhage. (Waiting 1–2 weeks to begin anticoagulation is prudent in those patients at high risk for hemorrhagic transformation.) For patients with atrial fibrillation, long-term anticoagulation has been demonstrated to reduce the risk of stroke by as much as 65% in patients aged 65 or older. There is no evidence that thrombolytic therapy or anticoagulation is effective for "stroke in evolution" or completed embolic stroke.

Lacunar Strokes

Lacunes are ischemic events of tiny vessels deep within the brain, usually occurring in hypertensive individuals. Lacunar syndromes can result from bland infarction or hemorrhage. Most often these events occur in the region of the internal capsule, producing a large functional deficit even though only a tiny area of brain is injured. Because neurons controlling distant regions are closely grouped, deficits of the face, arm, and leg are typically equal in severity. Similarly, because of the anatomic arrangement of neurons in this region, selective deficits of

sensory or motor function can occur. This pattern of deficits is in distinct contrast to cortical infarcts, where sensory and motor loses tend to occur in parallel and the limbs and face are usually affected to varying degrees.

The CT scan may be normal or show only a small lucency or density in patients with lacunes because of the typically small size of the infarct. MRI may be more informative. With the exception of appropriate supportive care and BP control, there is no specific therapy for a lacunar infarct.

Hemorrhagic Stroke

Hemorrhagic strokes can be divided into two broad categories: bleeding associated with rupture of an intraparenychmal artery or that from rupture of an artery on the surface of the brain. Intraparymemychal bleeding most commonly occurs in the putamen, internal capsule, thalamus, caudate nucleus, pons, and cerebellum when small vessels rupture as the result of chronic hypertension or vessel wall defects. Bleeding into the hemispheric parenchyma is less frequent and more commonly the result of excessive therapeutic anticoagulation, arteriovenous malformation, or venous hemangioma. Nonvascular risk factors may also contribute to the development of hemorrhagic stroke, including drug use (prescription or illicit) and systemic vasculitis. Anticoagulants account for about 10% of all cases of intracranial bleeding, and a 1% to 2% risk of intracranial hemorrhage is associated with the use of thrombolytic therapy for acute myocardial infarction. (Bleeding risk is about five times higher when thrombolytic therapy is given for ischemic stroke.) Cocaine, amphetamines, and phenylpropanolamine all can cause hemorrhage by boosting BP or by inducing vasculitis.

The site, relative frequency, and clinical characteristics of hemorrhagic stroke are presented in Table 6.

The deficits created by intracerebral hemorrhage are usually rapidly progressive, but late deterioration can be seen days after the initial bleed as the osmotic effects of extravasated blood recruit additional fluid and worsen localized swelling. Approximately 40% of hemorrhagic stroke victims have demonstrable hematoma enlargement over just 2 to 3 h, a finding associated with a much higher risk of death. If hemorrhage ruptures into the ventricular system, obstructive hydrocephalus can occur with a slow progressive downhill course. There are three classical clinical presentations of hemorrhagic stroke: (1) hemiplegia, sometimes with hemisensory impairment, when the thalamus or basal ganglia are involved; (2) sudden-onset quadraparesis, pinpoint pupils, midposition eyes, and coma occur when the pons is the site of the bleed; and (3) headache, ataxia, nausea, and vomiting when bleeding occurs in the cerebellum. Seizures are more common with hemorrhagic than ischemic strokes, hence the recommendation by some experts for 1 to 2 weeks of prophylactic anticonvulsant therapy. Virtually all hemorrhagic strokes are easily recognized on CT scan by the presence of "bright white" extravasated blood. MRI is an equally capable diagnostic tool.

Treatment of intracranial hemorrhage includes reversal of anticoagulation, correction of endogenous coagulopathy, and BP control. Excessive heparin effect can be reversed with protamine. Excessive warfarin treatment can be reversed with a combination of fresh frozen plasma and vitamin K. Without good evidence, if thrombocytopenia is present, it has traditionally been recommended that platelet counts be raised to at least $100{,}000/mm^3$. Two large trials testing recombinant human factor VII (rhVIIa) for intracranial hemorrhage have shown reduced hematoma volume growth but more extra-cranial thromboses. Outcome benefits suggested by the first smaller trial could not be confirmed in the larger second study. Hence, rhVIIa should not be used to treat intracranial hemorrhage.

Numerous studies have suggested a relationship between various severities of hypertension and hematoma growth; however, there are not yet good data to inform practice. An ongoing study is comparing control of systolic BP of $<$140 mm Hg to 140 to 180 mm Hg. While awaiting definitive data, it is reasonable and safe to produce 15% reductions in BP in patients with hemorrhage if the baseline systolic pressure is $>$180 mm Hg.

As one of the few surgically amenable neurologic problems, cerebellar hemorrhage should be quickly recognized, radiographically confirmed, and corrected by evacuation. CT scan

Table 6—*Sites and Characteristics of Intracerebral Hemorrhage*

Site	Frequency	Clinical Characteristics
Putamen	35%	Contralateral hemiparesis, hemisensory loss, dysphagia, or neglect
Thalamus	10%	Similar to putamen bleed, plus forced downward gaze, upgaze palsy, unreactive pupils
Caudate nucleus	5%	Confusion, memory loss, hemiparesis, gaze paresis, intraventricular blood, and hydrocephalus common
Lobar bleed	30%	Variable findings depending on location
Cerebellum	15%	Headache, vomiting, gait ataxia, nystagmus, cranial nerve palsies
Pons	5%	Quadriplegia, pinpoint pupils, gaze palsies, ataxia, sensorimotor loss

is the best technique to select candidates for surgery, which is generally reserved for patients with posterior fossa hemorrhages >3 cm in diameter and those with brainstem compression, rupture of blood into the third ventricle, or hydrocephalus. In contrast to cerebellar hemorrhage, a large randomized trial of decompressive surgery for supratentorial hemorrhage did not demonstrate improved outcomes. Investigations of mannitol, glycerol, corticosteroids, and hemodilution have all failed to show benefit.

Hydrocephalus is an uncommon complication for most forms of stroke but is far from rare in patients sustaining hemorrhagic infarction of the caudate or posterior fossa. Bleeds into the caudate nucleus rupture into the ventricular system with considerable frequency, often resulting in a waning level of consciousness and hydrocephalus on CT scanning.

Subarachnoid Hemorrhage

Subarachnoid hemorrhage (SAH) is a stroke syndrome in which headache, nausea, vomiting, confusion, or coma are typical, but paralysis is rarely seen. Although the headache very well may not be described as "the worst of my life," patients often identify the headache of SAH as unique. Rupture of an aneurysm or arteriovenous malformation allows escape of blood directly into the cerebral spinal fluid, where CT scanning and lumbar puncture offer rapid and reliable confirmation of the diagnosis. Early mortality rates from SAH approach 50%, with 20% to 30% of patients experiencing recurrent bleeding before definitive vascular repair. Thus, the trend has been to move to earlier diagnosis and repair of amenable lesions. The traditional approach using delayed open "clipping" has evolved to earlier placement of coils or other embolic material in the aneurysm using an endovascular approach. Both endovascular and extravascular approaches appear to be equally effective for most aneurysms, but some wide-mouthed aneurysms are not amenable to an endovascular approach. In addition, aneurysms of the posterior cerebral and basilar arteries are difficult to access by open craniotomy.

A second major problem occurring in about 20% of SAH patients is vasospasm, which usually manifests as a global decline in neurologic function 3 to 5 days after the bleed, with peak effect at 7 to 14 days. Although the pathophysiology of vasospasm continues to be debated, two lines of therapy appear beneficial: use of the calcium channel blocker, nimodipine, and use of induced hypertension, hemodilution, and hypervolemia, or the so-called "triple H" therapy. Nimodipine, 60 mg every 6 h, has been shown to decrease the risk of vasospasm after subarachnoid hemorrhage but can lead to detrimental hypotension. Induced hypertension, hemodilution, and hypervolemia have few high-quality studies to support its use; however, existing data consistently show modest benefit, and it appears to be of low risk and cost. In theory the therapy lowers blood viscosity while maintaining perfusion pressure. Likewise, although anticonvulsants are commonly administered after subarachnoid hemorrhage, there are limited data to support the practice.

Stroke Complications

DVT, decubitus ulcer formation, and gastric ulceration are all very common in stroke victims. Perhaps the largest overall gains in survival of stroke patients can be achieved by preventing death from thromboembolism. By one estimate, more than one-third of stroke victims develop DVT

in the absence of effective prophylaxis. Hence, early institution of pharmacologic prophylaxis (in patients at low risk for anticoagulation-related complications) or venous compression devices may be one of the most efficacious treatments for stroke victims. (In patients with ischemic strokes low molecular weight heparin has been shown to be superior to twice daily unfractionated heparin and is of comparable bleeding risk.) Similarly, because gastric stress ulceration is common, early enteral feeding, or proton pump inhibitor or histamine blocker treatment is prudent. Careful use of positioning, padding, turning, and therapeutic beds can prevent the devastating complication of skin breakdown and joint contractures.

Respiratory complications of stroke, including aspiration pneumonitis and bacterial pneumonia, are extremely common and are responsible for most episodes of poststroke fever. The risk of aspiration is particularly common for patients fed using a "bolus" rather than continuous infusion technique. Feeding patients maintained in a less than 30° head-up position also appears to be a risk factor for aspiration and pneumonia. Stroke may be one of the few situations in which near routine evaluation of the adequacy of swallowing makes sense.

Increased Intracranial Pressure

Mechanisms

Three tissues occupy the skull: brain substance, cerebrospinal fluid, and blood. None are readily compressible. Therefore, swelling of the brain substance, intracranial hematoma, or blockage of the normal venous or CSF outflow leads to increased intracranial pressure (ICP). Elevated ICP is mitigated by the movement of one of the "liquid" components (blood or CSF) out of the cranium. Increased ICP is itself deleterious when it compromises tissue perfusion or precipitates brain herniation.

Swelling of the brain matter happens by three common mechanisms. Vasogenic edema occurs when the blood-brain barrier is disrupted by trauma or high intravascular pressures (eg, malignant hypertension). Subsequent leak of serum proteins and water around neurons leads to interstitial edema. Cytotoxic brain edema results from impairment of cellular sodium potassium pumping mechanisms by glial cell injury. Disrupted ion pumping allows intracellular water accumulation, causing edema. The most common causes are hypoxia and toxin exposure (eg, carbon monoxide). Osmotic edema occurs when intracellular osmolality exceeds that of plasma and CSF, and water passively moves into brain cells. The gradient for water movement can be created by raising intracellular osmolarity or reducing plasma tonicity. For example, rapid IV, or even intrarectal, administration of large volumes of hypotonic fluid (eg, acute water intoxication) can cause brain swelling in a previously healthy person. Another example occurs when neurons have increased intracellular tonicity because of accumulated glucose (DKA), uremic toxins (renal failure), or idiogenic osmoles (hepatic failure). In each case, treatments that rapidly reduce plasma osmolality (eg, insulin, high-flow dialysis) can cause cerebral edema.

Bleeding into the cranial vault is especially problematic for intracranial hemodynamics. Not only does the bleeding increase ICP by mass effect, but it also clogs CSF absorption at the subarachnoid villi and increase CSF osmotic pressure when red cell lyse. The swelling of injured tissue typically peaks within 72 h. ICP, however, can remain elevated for weeks if there has been significant intracerebral or intraventricular bleeding.

Cerebral Hemodynamics

The pressure perfusing the brain (CPP) is the difference between mean arterial pressure (MAP) and either the ICP or the pressure within the cerebral veins (whichever is greater). ICP is normally quite low (<5 mm Hg) but often reaches critically high levels (20 to 40 mm Hg) in the head-injured patient. CPP normally exceeds 60 mm Hg; the lowest acceptable level is about 40 mm Hg where neural dysfunction occurs. Neuronal death occurs at CPPs <20 mm Hg. ICP should be kept low enough to maintain cerebral perfusion and prevent cerebral herniation. Thus, the goal should be to optimize the CPP gradient by lowering ICP and raising MAP if necessary. Although an absolute target for MAP cannot be declared, maintaining MAP above 90 mm Hg will ensure

an adequate CPP even as ICP approaches the critical 20 mm Hg value.

In health, cerebral autoregulatory mechanisms sensitive to arterial oxygen tension (Pa_{O_2}), arterial carbon dioxide tension (Pa_{CO_2}), and BP continuously adjust cerebral vascular resistance to maintain perfusion in proportion to metabolic need and changing perfusion pressure. Arterial blood gases, cerebral metabolism, and the components of perfusion pressure (BP, ICP) must be watched cautiously in brain-injured patients because the autoregulatory mechanisms of injured tissue are impaired. In this setting, tissue perfusion directly parallels CPP, and perfusion adequacy is directly influenced by cerebral metabolism.

Intracranial Pressure Monitoring

There are three reasons to insert an ICP monitor: (1) to detect intracranial hypertension; (2) to assess the effects of therapy aimed at reducing ICP; and (3) for therapeutic drainage of spinal fluid. Mean ICP of a supine patient is normally <10 mm Hg, and the ICP waveform normally undulates gently in time with the cardiac cycle. Extreme fluctuations of the ICP waveform (>10 mm Hg) suggest a position near the critical inflexion point of the cranial pressure volume curve, particularly when the contour shows a high "second peak" corresponding to the arterial pulse. Elevations of ICP to 15 to 20 mm Hg compress capillary beds and compromise the microcirculation. At levels of 30 to 35 mm Hg, venous drainage is impeded, and edema develops in even uninjured tissue. This level of intracranial hypertension produces a vicious cycle in which impeded venous drainage leads to accumulating edema and further ICP elevations. Even when autoregulatory mechanisms are intact, cerebral perfusion cannot be maintained if ICP rises to within 40 to 50 mm Hg of the mean arterial pressure. When ICP reaches mean arterial pressure, perfusion stops and the brain dies.

Of the three fluid components contained within the fixed cranial volume, only the volumes of CSF and blood may be changed (unless the skull opened, or brain is removed or made less edematous). Starting from normal levels, ICP shows little response to volume increases until a critical inflexion point is reached. Thereafter, small increments in volume dramatically boost ICP, risking sudden deterioration. Direct ICP monitoring is important because changes in other clinical indices—reflexes, BP, and heart rate—usually occur too late to avert disaster. Bradycardia, a preterminal sign, is the least reliable of all clinical indicators of increased ICP. (Tachycardia is seen more frequently.)

Specific Indications for ICP Monitoring

Closed Head Injury: Although the benefits of ICP monitoring are unproved by rigorous clinical trials, it remains a common practice in the head-injured patient. It is not practical or necessary to monitor ICP in all these patients, but three groups of trauma patients appear to derive benefit: (1) those with an abnormal CT scan at admission, (2) patients with normal CT scans at admission but who present with hypotension or posturing, and (3) patients >40 years. A normal CT scan of the head accurately predicts normal ICP in more than 80% of cases whereas ICP is elevated in about 50% of patients when any lesion is observed on head CT scan. Midline shift of more than 7 mm or blood in the lateral ventricles is especially worrisome. Head trauma patients with Glasgow Coma Scale scores <7 frequently have an increased ICP as do patients with decorticate/decerebrate posturing or abnormal evoked potential testing. Abnormal eye or pupil movements are unreliable guides to increased ICP. Repeat head CT scan is advocated approximately 24 h after injury to reassess wounds and edema.

Fulminant Hepatic Failure: The pathogenesis of increased ICP in fulminant hepatic failure is not certain but is probably a combination of cytotoxic and idiogenic osmolar mechanisms. ICP elevations are common among patients with fulminant hepatic failure but rare among patients with chronic end-stage cirrhosis. Even though ICP monitoring is commonly performed in fulminant hepatic failure, at present there is little evidence to suggest it reduces mortality.

Brain Tumors: ICP monitoring is rarely necessary in patients with chronic supratentorial lesions. However, ventriculostomy may be useful preoperatively to allow reduction in the CSF volume of

patients with large infratentorial lesions. In patients with large brain tumors or extensive edema on CT scanning, monitoring may help guide therapy.

Contraindications to Monitoring

Coagulopathy (platelet count <50–100,000/mm^3 or prothrombin time or activated partial thromboplastin time values >2 times control) are generally regarded as contraindications to ICP monitor placement. Among patients with fulminant hepatic failure, coagulation disorders are often corrected with fresh frozen plasma, vitamin K, and/or platelet transfusions before ICP placement. Isolated elevations of fibrin degradation products should not contraindicate catheter placement; fibrin degradation products levels may be increased by brain trauma alone. Immunosuppressive therapy (particularly steroids) is a relative contraindication to ICP monitoring.

Hardware and Devices

Intraventricular Catheters: Ventricular catheters may be inserted under local anesthesia at the bedside, typically through a burr hole in the skull on the "nondominant" side just anterior to the sagittal suture. Because intraventricular catheters provide continuous, reliable data and allow therapeutic removal of CSF, they are the preferred method of ICP monitoring by many clinicians. Unfortunately, ventriculostomy presents several problems. Perhaps foremost, because bleeding commonly accompanies insertion, uncorrected coagulopathy contraindicates placement. There may also be technical difficulty encountered placing the catheter into a lateral ventricle compressed by extensive edema or mass. After insertion, the CSF invariably shows evidence of catheter irritation (mild elevations of protein and leukocyte count), making laboratory evaluation of the fluid difficult. In addition, infection is frequent (~15%) after ventriculostomy and relates to duration of monitoring and to sterility of catheter placement and maintenance. Prophylactic antibiotics have shown no benefit in reducing infection rates, but tunneling the catheter through the skin may be helpful.

Epidural Transducers: Although epidural transducers present a lower risk of infection than ventricular catheters, they are technically more difficult to insert. Epidural catheters use fiberoptic or mechanical transducer membranes precisely juxtaposed to the dura. Past problems with calibration drift plaguing these devices have now largely been surmounted. The major drawback to the use of epidural transducers is the inability to remove CSF.

Subarachnoid Screws/Bolts: The subarachnoid screw is a hollow bolt inserted into the subarachnoid space through a burr hole (usually bored in the frontoparietal suture). During placement, the dura is opened and the device is inserted onto the brain surface. Problems with the subarachnoid screw include infection and the potential for seriously underestimating ICP if not placed on the side of an existing mass lesion. Brain herniation into the device is the most common cause for technical failure. Problems with damping and clotting are sufficiently frequent that regular flushing is mandatory. Such flushing, however, exposes patients to an increased risk of herniation and infection. Finally, these devices are frequently dislodged, even with meticulous care.

Problems With ICP Monitoring

Metallic monitoring devices preclude MRI scans and produce artifacts on CT scans that can obscure important information. Infection occurs in 2% to 5% of patients who undergo ICP monitoring. Infection risk increases with the "depth of insertion" (ventricular catheters are highest); duration of monitoring, and use of an open drainage systems. Flushing of devices adds to infection risk. *Staphylococcus epidermidis* is the most common infecting organism. Prophylactic antibiotics have not been demonstrated effective. As with any monitoring technique, poor-quality data may lead to inappropriate therapy. The intraventricular catheter gives the most consistent data whereas the subarachnoid screw is less reliable but carries the lowest infection risk.

Reducing Intracranial Pressure

Lowering Jugular Venous Pressure

The goal of reducing ICP is to maintain cerebral blood flow by keeping CPP >60 mm Hg.

Because the ICP cannot be lower than the downstream venous pressure (jugular/CVP), patient positioning is important. Neck flexion, head turning, and tracheostomy ties impeding venous drainage should be avoided. Raising the head to at least 30° virtually assures CVP will be less than ICP. Increases in CVP related to supine or prone positioning, straining, retching, and coughing should be minimized, and seizures should be prevented. Special caution should be taken during ventilation; by raising intrathoracic pressure and decreasing venous return, high levels of positive end expiratory pressure (PEEP) can simultaneously reduce MAP and raise ICP. However, judicious use of PEEP is not contraindicated, especially because the ICP of trauma patients often exceeds the PEEP-affected pressure within the superior sagittal sinus.

Sedation and Analgesia

A struggling agitated patient may acutely raise CVP thereby raising intracranial pressure. Even comatose patients can experience increased ICP in response to noxious stimuli; therefore, appropriate sedation and analgesia are indicated. Narcotics represent a good analgesic choice because they have some sedative effect, reduce pain, and their antitussive action can be used to avoid transient detrimental increases in ICP. Propofol is the sedative of choice for most patients because it has a rapid onset and offset of action, is readily titrated, lowers ICP, and has anticonvulsant properties. Benzodiazepine sedatives also provide the anticonvulsant benefit. Regardless of the sedative or analgesics chosen, it is important to avoid hypotension. In extreme cases, neuromuscular blocking drugs must be added to deep sedation and analgesia to avoid intracranial hypertension.

Diuretics

Loop diuretics (eg, furosemide) have twin therapeutic actions—decreasing CSF production and producing a diuresis that reduces intravascular volume. Caution must be exercised when using diuretics to avoid hypotension resulting from excessive preload reduction.

Osmotic Agents

Mannitol and hypertonic saline work by establishing an osmotic gradient between the CSF and blood, thereby promoting fluid transfer from brain cells and CSF to the circulation. Increasing the blood osmolality by 10 mOsm/L has a net effect of acutely removing about 100 mL of intracellular water from brain. The use of osmotic agents is not standardized because the optimal choice of agent, dose, and frequency of administration have not been determined in clinical trials. Mannitol given in boluses of 0.25 to 1 gm/kg every 4 to 6 h is a traditional choice, but hypertonic saline is now perhaps more popular. In doses that produce a serum osmolarity greater than 320 mOsm/dL, all osmotic agents eventually penetrate the blood-brain barrier, gradually counterbalancing their therapeutic effect. Even when serum osmolarity is maintained below this threshold, osmotic agents have a tendency to leak into the most severely damaged areas of the brain. Furthermore, when given rapidly, large doses of osmotic agents may expand the circulating volume, elevate ICP, and produce hemodilution. Simultaneous administration of loop diuretics can offset this unwanted intravascular volume expanding effect. By dehydrating red blood cells, osmotic agents can also result in a decrease in hematocrit value with a preserved or elevated hemoglobin concentration (pseudo-anemia). If used for long periods, excessive diuresis depletes intravascular and/or intracellular volume, delaying return to normal consciousness. Rebound intracranial hypertension is a significant problem that may be seen after discontinuation of any osmotic agent. Doses of mannitol that produce high osmolarity (>340 mOsm/dL) should be avoided because it may impair renal tubular function.

Hyperventilation

Hyperventilation is a method to temporarily lower ICP. Acute reduction of Pa_{CO_2} raises tissue pH, causing cerebral vasoconstriction in normally responsive cerebral vessels. Within wide limits, reduced flow through normal brain is well tolerated. As flow and intracranial vascular volume fall, ICP declines, thereby boosting CPP.

In contrast, flow to the injured, poorly autoregulated brain actually improves because flow through injured areas is CPP dependent. Although brief moderate hyperventilation tends to reduce ICP, improve CPP, and improve flow to damaged tissue, extreme ($Paco_2 < 25$ mm Hg) or prolonged hyperventilation offsets this beneficial action by causing excessive vasoconstriction and global reduction of perfusion. (Reducing $Paco_2$ is effective for 48 h at most, after which renal compensation restores acid-base status and eventually negates its effects.) For years, it has been known that prolonged hyperventilation is associated with worse neurologic outcomes than normocapnia. Thus, hyperventilation is best viewed as a stopgap measure to lower ICP for minutes to hours as other measures (ie, osmotic diuretics, ventricular drainage, or craniotomy) are undertaken to definitively lower ICP. Although therapeutic benefits of hyperventilation are debated, it is clear that hypoventilation should be avoided; increased blood flow and vascular volume can drive ICP quickly to life-threatening levels. Associated hypoxemia accentuates the risk because, like hypercapnia, hypoxemia is a cerebral vasodilator of brain tissue. If used within the first 72 h of brain injury, special caution should be exercised not to interrupt hyperventilation for more than brief periods. (For example, early prolonged ventilator disconnections to see whether the patient has spontaneous respirations are ill advised.) In salvageable patients, hyperventilation should be terminated in stages (over 24–48 h) to avoid causing rebound increases in ICP.

Corticosteroids

Corticosteroids reduce cerebral edema associated with tumors, but there is no evidence that they benefit patients with cerebral edema from head trauma or metabolic encephalopathy. Corticosteroids do, however, increase the risk of nosocomial infection and hyperglycemia.

Ventriculostomy Drainage

The removal of CSF may acutely lower ICP, especially when the system is poised on the steep portion of the intracranial pressure-volume curve. Because CSF production is a continuous process, the effects of intermittent CSF removal are transient (<2 h). Equipment for continuously venting the CSF to maintain ICP at or below a given hydrostatic level are effective in reducing ICP but increase the risk of infection. Nonetheless, CSF drainage makes consummate sense in the setting of aqueductal blockage (by clotted blood in the fourth ventricle, for example). Here, venting CSF output until clot lysis occurs (~5–7 days) may prove lifesaving. In contrast, withdrawal of spinal fluid from the lumbar region may precipitate brain herniation by increasing the pressure gradient across the tentorium.

Surgery

A direct attack on the cause of increased ICP may be indicated in such conditions as obstructive hydrocephalus (improved by shunting), tumor, or large but focal hemorrhage (particularly into the cerebellum). Similarly, prompt evacuation of a large subdural hematoma may be lifesaving and, if necessary, can be performed at the bedside. Removal of a cranial flap may be an effective maneuver to allow edematous brain room to expand outside the skull.

Therapy to Minimize Cerebral Oxygen Requirements

Fever and agitation greatly increase cerebral metabolic requirements and should be prevented. Nonsteroidal antiinflammatory agents such as ibuprofen are much more effective than acetaminophen for fever reduction. It is a mistake to use methods of temperature control (eg, cooling blankets) that induce shivering, a maneuver that dramatically increases oxygen consumption. Even if not shivering, conscious patients are made much more uncomfortable, thereby increasing cerebral metabolism and raising intrathoracic and intracerebral pressure. Although neuromuscular blocking drugs will effectively prevent shivering, they obliterate physical examination findings and predispose to a host of other complications, including skin breakdown and myopathy. Neither corticoste-

roids nor meperidine are effective antishivering agents.

High-dose barbiturates decrease cerebral metabolism and blood flow and therefore have been hypothesized to have a neuroprotective effect, but their role in intracranial hypertension is controversial, given conflicting data suggesting benefit and harm. Thus, barbiturate therapy for head injury is typically a last-ditch effort that mandates ICP monitoring. Pentobarbital is the drug most commonly used in loading doses of 10 mg/kg over 30 to 60 min followed by infusions of 1 mg/kg/h. Tachyphylaxis occurs quickly, making rapidly escalating doses necessary. Barbiturates induce hypotension with such frequency that volume expansion and vasopressor use are almost always necessary. These drugs also obliterate both the EEG signals and the clinical parameters used for neurologic assessment. As an alternative to barbiturates, benzodiazepines and propofol can be used to reduce cerebral oxygen consumption. When sedative drugs are used to control intracranial hypertension, they are typically continued for 24 to 48 h after ICP has normalized and are then slowly tapered.

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Chapter 35. Derangements of Serum Potassium, Sodium, Calcium, Phosphate, and Magnesium

Stephen P. Kantrow, MD

Objectives:

- Review basic physiology leading to clinically important increases or decreases in serum levels of major electrolytes.
- Recognize major disease associations and mechanisms leading to electrolyte derangements in critically ill patients.
- Understand key principles underlying short-term treatment of electrolyte abnormalities.

Key words: hypercalcemia; hyperkalemia; hypermagnesemia; hypernatremia; hyperphosphatemia; hypocalcemia; hypokalemia; hypomagnesemia; hyponatremia; hypophosphatemia

Synopsis:

Electrolyte abnormalities are common in critically ill patients, and treatment requires a strong foundation of physiologic principles and knowledge of clinical presentations. This chapter provides a review of derangements of serum potassium, sodium, calcium, phosphate, and magnesium, with an emphasis on clinical application of basic physiologic principles. We present important disease associations and clinical manifestations for each major derangement, and describe treatment approaches and challenges.

Hypokalemia

Fundamentals

More than 98% of total body potassium is intracellular, and most is in muscle. Na-K-ATPase pumps maintain the normal distribution between compartments. Normal potassium intake is 40–120 mEq/d, and the kidney can decrease normal excretion in the collecting tubules to less than 25 mEq to conserve potassium when its intake is low. Increased mineralocorticoid activity and/or increased delivery of sodium to the collecting tubule increases potassium loss in the kidney. When sodium arrives in the collecting tubule with endogenous or exogenous anions that cannot be reabsorbed (eg, bicarbonate or β-hydroxybutyrate), potassium loss is enhanced.

Clinical Applications

Any diuretic acting proximal to the potassium secretory site can cause hypokalemia through urinary losses, including (from proximal to distal sites) carbonic anhydrase inhibitors, loop diuretics, and thiazide diuretics (Table 1). These medications increase sodium delivery to the collecting tubule, which is reabsorbed in exchange for potassium, and also cause volume depletion that leads to activation of the renin-aldosterone system. Patients with aldosterone-producing adrenal adenoma or chronic licorice ingestion[1] have increased urinary potassium losses. Potassium loss is promoted by increased delivery of nonreabsorbable anions to the collecting tubule as a result of metabolic alkalosis and diabetic ketoacidosis, and hypokalemia is a striking feature of toluene sniffing-induced metabolic acidosis (due to nonreabsorbable hippurate).[2] In psychogenic polydipsia, chronic high urine output increases obligatory potassium losses even with maximal conservation of potassium in the collecting tubules. Hypomagnesemia is commonly present with hypokalemia and leads to increased potassium losses through uncertain mechanisms; correction of magnesium is often required to accomplish potassium repletion.

GI losses through vomiting, diarrhea, laxatives, or nasogastric suction will cause potassium loss and hypokalemia. Upper GI losses are modest because of the relatively low potassium concentration and lead to significant renal losses of potassium through metabolic alkalosis and increased sodium and bicarbonate delivery to the collecting tubule. Lower GI losses lead directly to potassium depletion. Other clinical scenarios that may lead to severe hypokalemia include bowel preparations for colonoscopy (including polyethylene-glycol formulations),[3,4] chronic ingestion of clay (a natural

Table 1—*Causes of Abnormal Potassium Level*

Hypokalemia
Diuretics
Adrenal adenoma
Licorice ingestion
Metabolic alkalosis
Diabetic ketoacidosis after insulin replacement
Gastric losses
Intestinal losses
Hypokalemic periodic paralysis (familial and thyrotoxic)
β_2 agonist medications
Dextrose solutions
Toluene, barium, cesium
Spurious
Hyperkalemia
Renal failure
Rhabdomyolysis
Tumor cell lysis
Exercise to exhaustion
Metabolic acidosis
Diabetic ketoacidosis
Adrenal insufficiency
Hyporeninemic hypoaldosteronism (type-4 renal tubular acidosis)
Hyperkalemic periodic paralysis
Ureterojejunostomy
Succinylcholine
Digitalis intoxication
Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers
Spironolactone
Calcineurin inhibitors

potassium binder),[5] and acute colonic pseudoobstruction with secretory diarrhea.[6]

Rapid decreases in serum potassium can occur through transport into the cell. Administration of exogenous insulin for diabetic ketoacidosis or for severe hyperglycemia promotes potassium movement into skeletal muscle and liver via Na-K-ATPase pumps. Dextrose-containing solutions stimulate endogenous insulin and lead to hypokalemia by promoting movement of potassium into cells. Endogenous catacholamines during stress, β-adrenergic agonists (albuterol for asthma, terbutaline in preterm labor, clenbuterol in contaminated heroin[7]), and decongestants can cause rapid onset of hypokalemia via β_2-adrenergic receptors. When renal function is replaced acutely by hemodialysis, rapid correction of acidosis may lead to marked hypokalemia as potassium enters the cells in exchange for exiting protons.

Hypokalemic periodic paralysis is an instructive example of symptomatic hypokalemia resulting from transcellular shifts and will be addressed later in this section. Hypothermia acutely increases transport of potassium into the cell and can lead to severe hypokalemia.[8] Hypothermic patients with hyperkalemia may be preterminal, with ongoing cell death and potassium release.[9] Barium intoxication does not occur with barium sulfate used in radiographic procedure but has been reported after ingesting fireworks[10] or depilatory treatment.[11] Barium blocks potassium movement out of the cell and is treated with potassium replacement to compete with barium binding, or hemodialysis. Cesium intoxication may occur in patients seeking alternative (ie, high pH) therapies for cancer and can cause hypokalemia, hypomagnesemia, and a prolonged QT interval with polymorphic ventricular tachycardia. Rapid increases in production of hematologic cells (eg, after vitamin B12 replacement or granulocyte colony-stimulating factor treatment) can consume potassium and lower serum levels. Spurious hypokalemia has been reported in blood samples with high numbers of metabolically active (white) cells.[12]

Clinical manifestations of hypokalemia include muscle weakness, rhabdomyolysis, cardiac arrhythmias, and renal dysfunction (chronic). Weakness typically begins in the lower extremities and ascends to include the trunk and upper extremities. Respiratory muscle weakness can lead to ventilatory failure, and ileus can progress to colonic pseudoobstruction. Cramps, rhabdomyolysis, and myoglobinuria can also occur. Electrocardiographic findings include ST segment depression, T wave flattening, and prominent U waves. Arrhythmia risk is increased particularly in the presence of ischemia, digitalis, β-adrenergic activity, and magnesium depletion; arrhythmias include ectopy, bradycardia, nodal blockade, and ventricular tachycardia and fibrillation.

Treatment of hypokalemia requires estimation of the potassium deficit. With chronic depletion, total body deficits may be 200–400 mEq for each mEq/L below 4 in serum. This estimate should not be used for diabetic ketoacidosis, nonketotic hyperglycemia, and other etiologies with important transcellular shift,

Table 2—*Causes of Abnormal Sodium Level*

Hyponatremia
Volume depletion
Cirrhosis
Congestive heart failure
Syndrome of inappropriate antidiuretic hormone (SIADH)
Adrenal insufficiency
Cerebral salt wasting
Psychogenic polydipsia
Low solute intake
Salt loss with hypotonic fluid resuscitation (exercise, surgery with SIADH)
Ecstasy (MDMA)
Irrigation solutions (glycine, sorbitol)
Hyperglycemia
End stage renal disease
Spurious (hyperlipidemia or paraproteinemia with measurement on diluted samples via indirect polarography)
Hypernatremia
Loss of fluids containing a sodium plus potassium concentration less than plasma
Diarrhea (osmotic, nonsecretory)
Sweat
Urine
Replacement of low sodium plus potassium concentration fluid losses with normal saline solution
Diabetes insipidus
Central (brain death, brain injury, granulomatous disease)
Nephrogenic (lithium, demeclocyline)
Abnormal thirst responses to ADH
Brain injury, granulomatous disease
Barriers to access to water
Altered mental status
Critical illness
Salt poisoning

including hypokalemic periodic paralysis. In patients with uncontrolled diabetes and hypokalemia, insulin therapy should be delayed until serum potassium has been replaced in order to avoid an additional decrease in potassium level. Severe (<2.5–3.0 mEq/L) or symptomatic (marked muscle weakness, arrhythmia, or rhabdomyolysis) hypokalemia should be replaced intravenously with potassium in saline solution. Dextrose-containing solution will stimulate insulin release and lower potassium levels further. Aggressive potassium replacement (>10 mEq/h) requires continuous cardiac monitoring, and maximum rates of 10–20 mEq/h are used in most cases. If the replacement is more rapid than 20 mEq/h, central venous access avoids painful irritation of the peripheral veins.

Thyrotoxic periodic paralysis is a sporadic form of hypokalemic periodic paralysis that causes painless muscle weakness, often precipitated by intense exercise, fasting, or carbohydrate loading. This condition occurs in approximately 10% of thyrotoxic Asian men, typically between the ages of 20 to 40 and is commonly the initial presentation of thyroid disease. The acute weakness must be distinguished from acute quadraparesis resulting from myasthenia gravis, Guillain-Barre syndrome, transverse myelitis, West Nile infection, tick paralysis, and botulism. Hypokalemia may be profound in periodic paralysis (<1.5 mEq/L) but does not reflect total body depletion. Cautious potassium repletion shortens recovery time; however, rebound hyperkalemia is common and requires continuous cardiac monitoring during treatment.[13] For thyrotoxic periodic paralysis refractory to potassium supplementation, propranolol can be effective, likely by blocking excessive Na-K-ATPase pump activity. Recurrence is completely prevented by euthyroid status. Carbonic anhydrase inhibitors have a role in familial hypokalemic periodic paralysis but not the thyrotoxic form.

Pearls

- Potassium loss is observed with metabolic alkalosis, diabetic ketoacidosis, and toluene sniffing, due in part to the delivery of nonreabsorbable anions to the collecting tubule (bicarbonate, hydroxybutyrate, and hippurate, respectively).
- Bowel preparations for colonoscopy, ingestion of clay, and acute colonic pseudoobstruction with diarrhea cause hypokalemia through GI losses.
- β-Agonists (albuterol, terbutaline, clenbuterol) and decongestants can cause acute hypokalemia.
- Hypothermia causes hypokalemia via transcellular shift, and the finding of hyperkalemia in a hypothermic patient suggests perimortem tissue injury.
- Acute, severe hypokalemia presents with muscle weakness and arrhythmias, and muscle involvement can progress to ventilatory failure and colonic pseudoobstruction.

Table 3—*Causes of Abnormal Calcium Level*

Hypocalcemia
Parathyroidectomy (also thyroidectomy, anterior neck dissection)
Hyperphosphatemia
Hypomagnesemia
Hypermagnesemia
Sepsis
Pancreatitis
Citrate binding (massive blood transfusions, leukopheresis)
Foscarnet, bisphosphonates, fluoride
Spurious (hypoalbumemia)
Hypercalcemia
Hyperparathyroidism
Malignancy
Milk-alkali syndrome
Thyrotoxicosis
Sarcoidosis
Paget disease of bone
Hypervitaminosis A and D
Lithium
Thiazide diuretics
Spurious (rarely monoclonal gammopathy)

- Potassium replacement should precede insulin administration when uncontrolled diabetes presents with significant hypokalemia.
- IV potassium replacement requires continuous electrocardiographic monitoring and should not utilize dextrose-containing solutions when hypokalemia is severe.
- Hypokalemic periodic paralysis due to transcellular shifts is common among young thyrotoxic men of Asian descent (10%), and rebound hyperkalemia occurs with aggressive potassium repletion.

Hyperkalemia

Fundamentals

More than 98% of total body potassium is intracellular. Na-K-ATPase pumps maintain the normal compartmentalization in muscle, and they are subject to regulation by insulin and β_2 receptor activity. Normal potassium intake is 40–120 mEq/d and normal kidneys can adapt excretion in the collecting tubules to more than 400 mEq/d. Decreased mineralocorticoid activity, hypoperfusion due to volume depletion, and most renal diseases will decrease renal potassium clearance.

Clinical Applications

Acute metabolic acidosis requires intracellular buffering, and potassium exits the cell in exchange for the entering proton to maintain electroneutrality (Table 1). In uncontrolled diabetes, the insulin deficiency and hyperosmolality of hyperglycemia combine to cause hyperkalemia despite total body depletion. In end-stage renal disease patients, decreased potassium clearance, decreased muscle uptake of exogenous potassium, and metabolic acidosis contribute to the development of hyperkalemia. Dialysis patients may develop acute hyperkalemia after fasting or somatostatin treatment as a result of decreased insulin levels.[14] Treatment with β-adrenergic blockade (labetalol) has also led to severe hyperkalemia in dialysis patients.[15] Tissue breakdown due to trauma, rhabdomyolysis, or tumor cell lysis can cause rapidly progressive and life-threatening hyperkalemia, and should result in prompt aggressive, preemptive therapy. Exercise to exhaustion may lead to acute potassium elevations of up to 2 mEq/L.

Succinylcholine can cause acute life-threatening hyperkalemia and is contraindicated in patients with a personal or family history of malignant hyperthermia, denervating neuromuscular disease (amyotrophic lateral sclerosis, Guillain-Barre syndrome, multiple sclerosis, spinal cord injury, stroke between 72 h and 6 months prior, muscular dystrophy), burns after 72 h, rhabdomyolysis, or significant hyperkalemia. Myasthenia gravis patients are not at increased risk for hyperkalemia and are relatively resistant to the depolarizing effects of succinylcholine.[16] Renal failure patients can receive succinylcholine unless there is known or clinically suspected hyperkalemia (ie, missed dialysis or electrocardiogram findings). Digitalis overdose causes hyperkalemia as a result of direct inhibition of Na-K-ATPase pump activity, and the degree of hyperkalemia correlates with mortality. Other medications that can cause hyperkalemia over time include angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, spironolactone, and calcineurin inhibitors.

Hyporeninemic hypoaldosteronism (type-4 renal tubular acidosis) is a common cause of chronic hyperkalemia among diabetics. Hyper-

Table 4—*Causes of Abnormal Phosphate Level*

Hypophosphatemia
Alcoholism
Anorexia nervosa
Morbid obesity with massive weight loss
Dextrose solutions
Respiratory alkalosis
Hyperparathyroidism
Refeeding after malnutrition
Hungry bone syndrome after parathyroidectomy
Phosphate binders (magnesium, aluminum)
Hyperphosphatemia
Renal failure
Rhabdomyolysis
Tumor cell lysis
Exogenous phosphate load (phosphate bowel regimen)
Spurious (analytical interference by monoclonal gammopathy)

kalemic periodic paralysis is an autosomal dominant disorder precipitated by rest after exercise, fasting, or potassium ingestion, and is unrelated to thyroid disease. Hyperkalemia can also be the consequence of ureterojejunostomy, in which excreted potassium is delivered from the kidney to the jejunum and reabsorbed.[17]

The most severe clinical manifestations of hyperkalemia include muscle weakness (usually without respiratory muscle involvement), cardiac conduction abnormalities, and arrhythmias. These typically are observed at a chronic serum potassium concentration higher than 7 mEq/L or at lower levels when the increase in potassium level is acute. Electrocardiogram changes are sensitive for symptomatic hyperkalemia (weakness and conduction abnormalities) but are not well correlated with absolute serum potassium levels. Peaked T waves and shortened QT interval precede PR and QRS interval widening. Conduction abnormalities include fascicular, bundle branch, and atrioventricular blocks; P wave disappearance and sine wave morphology are more advanced changes and can be followed by asystole. Hyperkalemic QRS widening with tachycardia may be confused with ventricular tachycardia.

Therapy for hyperkalemia must be tailored to the severity and anticipated trajectory of this electrolyte abnormality. Continuous cardiac monitoring is required for patients who need acute interventions. Rapid onset treatments include calcium, insulin with glucose, β_2-adrenergic agents, and sodium bicarbonate. Hyperkalemia with electrocardiographic changes or hyperkalemia expected to rapidly worsen (trauma, rhabdomyolysis, tumor cell lysis) should prompt immediate therapy. Calcium directly antagonizes the effects of hyperkalemia on cardiac conduction and works within minutes. Calcium gluconate has less elemental calcium than calcium chloride but is less likely to cause tissue necrosis if extravasated from a peripheral vein. Because the duration of action for calcium is less than 1 h, therapies that shift potassium into the cell are administered promptly. Insulin and glucose (10 units insulin plus 50 mL of 50% dextrose) begins to move potassium into skeletal muscle within 10 to 20 min, with a peak effect between 30 and 60 min and a duration of 4–6 h. Hypoglycemia is common 1 h after this treatment and is usually asymptomatic.

β_2-agonists are increasingly used as an adjunct to insulin and glucose,[18] and when administered by inhalation at a dose four to eight times higher than that used for bronchodilation, the peak effect is observed at 90 min. Epinephrine is not recommended because alpha-mediated effects can oppose the desired potassium movement into the cells. Sodium bicarbonate appears to have limited efficacy in the acute setting, especially in end-stage renal disease patients.[19] Hypertonic sodium bicarbonate solutions transiently promote the movement of potassium out of the cell and limit the effectiveness of this therapy.

After blockade of membrane effects with calcium and transcellular shift, definitive removal should be undertaken. Loop or thiazide diuretics increase potassium excretion in patients with adequate renal function but are not an effective therapy in the acute setting. Cation exchange resins (sodium polystyrene sulfonate) are frequently used to remove potassium. However, when sodium polystyrene sulfonate is administered in sorbitol, intestinal necrosis affecting the colon and ileum has been reported, and avoidance of sorbitol is recommended by the US Food and Drug Administration (lactulose or polyethylene glycol may be substituted). Single doses are relatively ineffective[20] and should be given as repeated doses of 15 to 30 g. Postoperative patients and renal transplant recipients appear to be at higher risk for intestinal necrosis after sodium

Table 5—*Causes of Abnormal Magnesium Level*

Hypomagnesemia
Alcoholism
Diuretics (loop and thiazide)
Diarrhea
Cisplatin, foscarnet
Citrate binding
Chronic proton pump inhibitor therapy
Hungry bone syndrome after parathyroidectomy
Hypermagnesemia
Therapeutic administration of magnesium sulfate
Magnesium-containing antacids, cathartics, enemas with renal insufficiency
Intestinal disease with increased absorption of therapeutic magnesium

polystyrene sulfonate, even without sorbitol.[21] Hemodialysis can remove 25–50 mEq/h of potassium and is much more efficient than peritoneal dialysis. Acute successful transcellular shift therapy for hyperkalemia may diminish the efficiency of hemodialysis and lead to rebound hyperkalemia within several hours, leading to repeated or prolonged dialysis. Patients with tissue injury (trauma, rhabdomyolysis, tumor cell lysis) are also at increased risk for rebound hyperkalemia.

Pearls

- Succinylcholine causes acute hyperkalemia in denervating neuromuscular disease (including recent stroke) but can be used in myasthenia gravis and in renal failure with normal potassium level.
- Severe hyperkalemia causes muscle weakness, peaked T waves, and shortened QT progressing to PR and QRS widening, and then asystole.
- Hyperkalemia with electrocardiographic changes or hyperkalemia as a result of trauma, rhabdomyolysis, or tumor lysis should be treated with calcium (immediate effect) and then dextrose and insulin with consideration of high-dose inhaled β-agonist therapy.
- Sodium bicarbonate is not effective for hyperkalemia in dialysis patients.
- Potassium removal can be accomplished with multiple doses of polystyrene sulfonate (without sorbitol), but this therapy increases the risk of intestinal necrosis in high-risk patients.
- Hemodialysis is required to remove potassium released from ongoing tissue injury.

Hyponatremia

Fundamentals

Intake of free water with inadequate water excretion is the underlying mechanism for hyponatremia for the vast majority of cases. As the serum sodium level decreases and antidiuretic hormone (ADH) is suppressed, normal kidneys can excrete more than 10 L/d of dilute urine. In hyponatremia caused by volume depletion, decreased tissue perfusion (low effective blood volume), and syndrome of inappropriate ADH secretion (SIADH), ADH is not suppressed and urine is not maximally dilute. Appropriate ADH suppression will accompany hyponatremia resulting from primary polydipsia, low solute intake, and renal dysfunction. Normal or suppressed ADH responses are determined by assessment of urine osmolality, urine sodium, and the clinical setting; direct measurement of ADH is not part of the evaluation of hyponatremia. Measurement of serum osmolality establishes whether hyponatremia is associated with low, normal, or high osmolality. Serum osmolality (mmol/L) is calculated by measuring the major serum solutes: (2 × serum [Na]) + (serum [glucose]/18) + (blood urea nitrogen/2.8). The correction factors for glucose and blood urea nitrogen convert mg/dL into mmol/L.

Clinical Applications

Volume depletion stimulates sodium retention to maintain the intravascular volume (Table 2). As volume depletion progresses, ADH secretion leads to retention of excess free water despite the very modest effect of free water on the intravascular volume (<10%). Hyponatremia in the setting of hypovolemia is accompanied by increased urine osmolality (not maximally dilute) and decreased urine sodium concentration (<25 mEq/L). However, increased urine sodium in the setting of volume depletion may be seen with diuretic therapy, adrenal insufficiency, and cerebral salt wasting. Replacement of electrolyte and volume losses with hypotonic solutions can lead to acute, severe hyponatremia. Thiazide diuretic use can lead to hyponatremia soon after initia-

Table 6—*Typical Findings in SIADH*

Low serum osmolality
Urine osmolality that is not maximally dilute (often above 400 mOsm/kg)
Urine sodium concentration greater than 40 mEq/L
Normal volume status
Normal adrenal and thyroid function
Normal acid-base, potassium, renal function
Low blood urea nitrogen and uric acid levels

tion, while loop diuretics are uncommonly the primary cause.

Heart failure and cirrhosis lead to low effective blood volume and decreased perfusion by decreasing cardiac output and increasing arterial vasodilation, respectively. Hyponatremia in these conditions is accompanied by evidence of total body sodium overload (edema) and correlates with severity of the underlying disease. Urine sodium concentration is low as a result of high sodium avidity in the kidney in these causes of decreased renal perfusion (as in true volume depletion). Another edematous state, nephrotic syndrome, is not a cause of hyponatremia in the absence of significant renal dysfunction.

SIADH should be suspected in an euvolemic patient with hyponatremia, decreased serum osmolality, urine osmolality that is not maximally dilute (usually >400 mOsm), and elevated urine sodium level (>40 mEq/L) (Table 6). SIADH is most commonly caused by diseases of the central nervous system (tumor, infection, hemorrhage, trauma, psychosis), malignancy (small cell lung cancer), or medications (antiepileptics, selective serotonin reuptake inhibitors, chemotherapeutic agents, antipsychotics). In patients with subarachnoid hemorrhage, SIADH is more common than cerebral salt wasting, which should be suspected if hypovolemia is also present. Adrenal insufficiency and hypothyroidism should be excluded. A reset osmostat, in which stable hyponatremia is maintained, can be differentiated from SIADH by a free water challenge.

Polydipsia is typically seen in psychiatric disease and should be suspected when hyponatremia and maximally dilute urine (<100 mOsm) are found. Intake of more than 10 L/d of water may overwhelm the maximum water excretion capacity of the kidneys. When limited solute is available, maximum dilute urine output may be less than 4 L/d. Low dietary solute intake is a feature of beer potomania and malnutrition, settings in which hyponatremia can develop with more modest free water intake. MDMA (3,4-methylenedioxymethamphetamine), also known as ecstasy, intoxication causes ADH release and a marked increase in thirst and water intake, leading to acute hyponatremia,[22] which is a major causes of death due to MDMA.

Hyperglycemia and mannitol administration lower sodium concentration by drawing water out of the cells, and hyponatremia in this setting is accompanied by a high measured serum osmolality. Serum sodium after correction of hyperglycemia can be estimated to increase by 1.6 mEq/100 mg glucose/dL, although very severe hyperglycemia (>400 mg/dL) has even greater effects on sodium concentration.[23] Renal failure is another cause of hyponatremia with increased serum osmolality.

Hyponatremia with normal serum osmolality can be seen with irrigation solutions (glycine, sorbitol) used for surgical procedures on the prostate, bladder, and uterus, and for laparoscopic procedures. Severe hyponatremia and neurologic symptoms may occur and appear to be mediated by hyponatremia and glycine as well as its metabolic products. Pseudohyponatremia is a measurement artifact resulting from increases in lipid or protein fractions (normally 7%) in serum, and the effect is important when a large dilution of the sample is analyzed with ion selective electrodes utilizing indirect (rather than direct) potentiometry.[24]

Treatment of hyponatremia associated with volume depletion is usually easily accomplished with isotonic saline solution infusion, initially leading to a slight increase in serum sodium as the modestly higher sodium concentration in the administered fluid equilibrates with the plasma. As the volume status improves, the stimulus for ADH release is removed, leading to a brisk mobilization of free water in dilute urine. This second phase is often accompanied by increased urine output and a rapid rise in serum sodium. Treatment of hyponatremia in the low effective blood volume states of congestive heart failure and cirrhosis usually includes free water restriction and consideration of vasopressin receptor

(ADH) antagonists (conivaptin, tolvaptin). Administration of sodium-containing solutions is likely to worsen the underlying sodium overload and edema in these patients.

Treatment of hyponatremia in the setting of SIADH depends upon the severity.[25] Chronic, mild hyponatremia with a sodium concentration >120 mEq/L is often asymptomatic, although subtle neurologic abnormalities can be found. These patients can be treated with free water restriction and salt tablet administration if necessary. For patients with symptomatic hyponatremia (altered mental status, seizures) or serum sodium <110–115 mEq/L, more aggressive treatment with hypertonic saline solution (3%) should be initiated. Normal saline solution will transiently improve and then worsen hyponatremia caused by SIADH. The 308 mOsm solute/L of 0.9% sodium chloride infused will be excreted at a higher concentration (400–600 mOsm/L is typical in SIADH), with free water retained in the body. The administered solute concentration must exceed that of the urine to raise the serum sodium level; therefore, hypertonic saline solution is indicated.

For moderately symptomatic patients (confusion, lethargy) with hyponatremia due to SIADH, hypertonic saline solution is infused to increase the serum sodium concentration by up to 1 mEq/h for the first few hours, with an increase of no more than 10 mEq/h over the first 24 h and 18 mEq/L over the first 48 h.[25,26] It is very important to avoid more rapid correction with the accompanying risk of osmotic demyelination syndrome (ODS) (also called central pontine myelinolysis), a devastating neurologic complication. Calculation of the sodium deficit, which equals total body water $\times$ (target serum sodium $-$ current serum sodium), is used to guide the initial therapy. For example, for a 70-kg young man requiring sodium correction from 100 to 108 mEq/L, the calculation would be $0.60 \times 70\ (108 - 100) = 42 \times 8 = 336$ mEq of sodium over 24 h. Note that for a 200-kg obese man (5 ft, 8 in tall), the total body water is calculated from the ideal (lean) body weight ($\sim$68 kg).

Typical infusion rates range from 20 to 60 mL/h for hypertonic saline solution. It is imperative to adjust the treatment based upon measurements of serum sodium every 2 to 3 h because the rate of correction frequently does not proceed as expected. If the rate of correction exceeds the limits above, an intervention to slow or reverse the rise in serum sodium is indicated, which will be addressed later in this section. Note that sodium and potassium are exchangeable, osmotically active electrolytes throughout the total body water. Administration of potassium to correct hypokalemia will result in an increase in serum sodium, as most of the administered potassium enters the cell in exchange for sodium.

For chronic, minimally symptomatic hyponatremia due to SIADH, congestive heart failure, or cirrhosis, vasopressin antagonist therapy (oral tolvaptin) has been used.[27] A small percentage of patients have rates of correction that are excessive (>10 mEq/L in the first 24 h), and these therapies should be initiated with monitoring in the hospital. Patients with SIADH can usually be managed with free water restriction (typically <800 mL/d), oral salt tablets, and loop diuretics if necessary. Demeclocyline and lithium are now rarely used to oppose ADH effects in the kidney in this disorder.

Acute symptomatic hyponatremia is well described in marathon runners, psychotic patients, acute water intoxication, MDMA users, and postoperative patients with intracerebral pathology and SIADH. Cerebral edema leads to altered mental status, seizures, coma, and death. Premenopausal women are at markedly increased risk for irreversible neurologic injury,[28] and delayed therapy may lead to brain herniation. Minimal symptoms should be treated aggressively in this population. Hypertonic saline solution (3%) is the only established treatment for this condition, and a 100 mL IV bolus can be expected to raise the serum sodium concentration by 2 to 3 mEq/L and may be repeated after 10 min.[26]

Excessively rapid correction of hyponatremia can be anticipated after administration of saline solution to volume-depleted patients, administration of glucocorticoids in patients with adrenal insufficiency, and in resolving SIADH due to rapidly reversible causes (pain, discontinuation of medications). Discontinuation of thiazide diuretics and treatment with a vasopressin receptor antagonist may also lead to rapid

increase in serum sodium. An abrupt increase in free water clearance and serum sodium may be heralded by an increased urine output, which should be carefully monitored. Therapies that can stop or reverse the rise in serum sodium include desmopressin with or without dextrose in water.[29] Rapid spontaneous correction is also observed in marathon runners, psychotic patients, acute water intoxication, and ecstasy users. If the hyponatremia is known to be acute (<24 h), the risk of ODS is low.

ODS is caused by overly rapid correction of chronic (>24 h) severe (<120 mEq/L) hyponatremia.[30] Most cases have been described with a serum sodium value at presentation of <105 mEq/L. Be aware that the clinical manifestations of ODS (dysarthria, lethargy, spastic quadraparesis, uncommonly seizures) do not develop until 2–6 days after overcorrection and that they are often irreversible.[31] Case reports suggest a benefit for acute interventions to lower sodium when ODS is recognized using desmopressin and dextrose solution to reach a target sodium level 18 mEq/L above the presenting value. Findings of magnetic resonance images are consistent with diffuse demyelination in the pons, but the demyelination may be delayed for weeks.

Pearls

- Thiazide diuretics can cause severe hyponatremia soon after initiation.
- Patients with heart failure and cirrhosis (not nephrotic syndrome) have hyponatremia with decreased renal perfusion, decreased urine sodium, and relatively concentrated urine. Treatment with salt solutions should be avoided in favor of free water restriction and vasopressin antagonist therapy.
- SIADH is more common than cerebral salt wasting (suspected with hypovolemia) after subarachnoid hemorrhage.
- Low solute intake (beer potomania, malnutrition) can lead to hyponatremia with maximally dilute urine after modest water intake (<4 L/d).
- Hypertonic saline solution is used to increase by no more than 10 mEq over the first 24 h and 18 mEq over the first 48 h for moderately symptomatic patients (confusion, lethargy) with SIADH.
- Calculated sodium deficit guides the initial therapy, but changes in hypertonic saline solution treatment are frequently necessary and monitoring the serum sodium every 2 to 3 h is mandatory.
- Aggressive potassium replacement will increase serum sodium, an effect that should be accounted for when replacing sodium and potassium simultaneously.
- Acute (<24 h) symptomatic hyponatremia causes cerebral edema, altered mental status, seizures, and death; premenopausal women are at very high risk of death and should be treated for minimal symptoms with hypertonic saline solution bolus (100 mL).
- Excessively rapid correction of chronic hyponatremia can be anticipated after treatment of volume depletion, adrenal insufficiency, resolving SIADH, discontinuation of thiazides, and treatment with vasopressor antagonist therapy; patients are treated with desmopressin and dextrose in water if necessary.
- ODS with irreversible quadraparesis usually becomes apparent 2–6 days after overcorrection of chronic (>24 h) and severe (<120 mEq/L) hyponatremia.

Hypernatremia

Fundamentals

Hypernatremia is caused by water loss (dehydration) in most patients but uncommonly may be due to excess salt intake or hypertonic salt solutions. The serum sodium concentration is responsive to net loss of sodium- and potassium-containing fluids because both of these exchangeable cations are osmotically important throughout the body water. The sodium plus potassium content of a lost (or administered) fluid, not the osmolality, determines the effect on the serum sodium concentration.[32] Replacement of free water is under the powerful control of the hypothalamus, and so hypernatremia develops only with altered mental status, limited free water access, or hypothalamic disease. When thirst is normal and access to water is unrestricted, near

normal sodium concentration is maintained, even in diabetes insipidus.

Clinical Applications

Secretory diarrhea due to cholera or vipoma has sodium and potassium concentrations similar to plasma and should not lead to hypernatremia (Table 2). Osmotic, viral, or bacterial diarrheas typically have lower concentrations of sodium and potassium, and lead to hypernatremia even when diarrheal fluid loss is isoosmotic with the serum. Sweat and gastric secretions have low sodium and potassium concentrations relative to plasma, and osmotic diuresis (due to glucosuria or mannitol) is also accompanied by relatively low sodium and potassium concentrations in the urine. Resuscitation with isotonic saline solution for conditions in which losses have low sodium and potassium concentrations will cause hypernatremia.[33]

Diabetes insipidus (central or nephrogenic) may be unrecognized until the patient is unable to maintain free water intake in a perioperative or critical care setting. Hypernatremia caused by diabetes insipidus with acute water deprivation is usually acute (<24 h) and should be corrected rapidly with dextrose in water. Transient but marked hypernatremia can occur immediately after severe exercise or electroshock therapy but resolves within minutes. Aggressive hypertonic sodium bicarbonate treatment (50 mEq sodium/50 mL) can also cause acute hypernatremia. Salt poisoning occurs in pediatric populations, for example, with the custom of salting newborns in Turkey,[34] and can cause brain injury, including osmotic demyelination. Salt poisoning may be distinguished from dehydration by the finding of weight gain and increased sodium excretion in the urine, and is treated with acute dialysis.

Treatment of hypernatremia is based upon estimation of the free water deficit, which is equal to the current total body water $\times$ (serum sodium $\times$ 140)/140. The total body water estimate is based on lean body weight (adipose has little water) and is 60% of lean body weight in young men and 50% in young women. The current total body water in the setting of hypernatremia is decreased by an additional 10% as a result of expected water depletion. A simple estimate of the water deficit is 3 mL/kg of lean body weight/mEq excess sodium above the target.[35] For a 70-kg nonobese man with a sodium of 160 mEq/L, the calculation is 3 mL $\times$ 70 kg $\times$ 20 mEq = 4,200 mL. Note that this calculation does not account for modest differences in total body water that accompany age or gender. The correction rate should not exceed 10 mEq/d if hypernatremia has been present for 24 h or longer because encephalopathy and cerebral edema can develop. Ongoing water loss in sweat and stool (40 mL/h) and urine losses (variable) must be replaced. Inclusion of electrolyte replacement (eg, potassium) in resuscitation fluids decreases the effective free water administration and will decrease the rate of correction. Free water replacement for dehydration and normal saline solution replacement for volume depletion can be performed using a single IV solution or two independent solutions; however, needs should be determined separately. Intensive monitoring may be required (every 4 h) if rapid changes are anticipated, as in diabetes insipidus.

Pearls

- Osmotic, viral, and bacterial diarrhea can have a low concentration of sodium and potassium even while being isoosmotic with serum and will lead to hypernatremia if thirst is blunted or access to water is limited. Cholera is an exception and leads to hypovolemia without hypernatremia.
- Diabetes insipidus (central or nephrogenic) can cause acute hypernatremia when water access is limited (perioperative, critical illness) and should be corrected rapidly.
- Free water deficit is estimated as current total body water $\times$ (serum sodium $-$ 140)/140, or by using a simple calculation of 3 mL/kg lean body weight/mEq excess sodium above the target.
- Ongoing water losses in sweat, stool, and urine must also be replaced for correction of hypernatremia.

Hypocalcemia

Fundamentals

Nearly half of the calcium in the blood (40%) is ionized and freely available for metabolism.

The remainder is bound to proteins (mostly albumin) and anions (phosphate). Calcium homeostasis is regulated by parathyroid hormone and vitamin D. Total calcium level decreases by 0.8 mg/dL for each 1 g/dL decrease in albumin concentration, while the ionized calcium is unaffected by changes in albumin. Alkalemia increases albumin binding and decreases ionized calcium without affecting total calcium levels. Critically ill patients may have marked shifts in both pH and albumin concentration, making total calcium measurement with correction based upon albumin a less reliable assessment than ionized calcium measurement in this setting.[36]

Clinical Applications

Critical illness due to sepsis or pancreatitis is commonly accompanied by hypocalcemia (Table 3).[37] Proposed mechanisms include impaired parathyroid hormone secretion, increased binding of calcium to lactate or citrate (with massive blood product administration[38] or leukopheresis[39]), and deposition in fats (saponification). In renal failure patients with hyperphosphatemia, calcium is depleted by deposition with phosphate into bone and soft tissues. Life-threatening hypocalcemia can occur acutely after parathyroidectomy, thyroidectomy, or head and neck dissection, and can persist (with hypophosphatemia) in hungry bone syndrome. Hypoparathyroidism with symptomatic hypocalcemia can also be caused by autoimmune and infiltrative disorders. Magnesium depletion causes parathyroid hormone resistance and hypocalcemia that can only be corrected with magnesium replacement. Note that hypermagnesemia can also cause hypocalcemia, via parathyroid hormone suppression. Medications that cause hypocalcemia include foscarnet, bisphosphonates, and fluoride poisoning.

Hypocalcemia may be present without striking clinical signs, particularly in critically ill patients. Prolongation of the QT interval may be observed. Distinctive acute manifestations of hypocalcemia include tetany, seizures, hypotension, and papilledema. Tetany may be observed as carpopedal spasm with severe hypocalcemia (ionized calcium less than 4.4 mg/dL or 1.1 mmol/L) particularly in the setting of respiratory alkalosis; Trousseau's sign or Chvostek's sign may be present. Seizures can be grand mal, petit mal, or focal and may present without evidence of tetany.

IV calcium is recommended for acutely symptomatic patients with rapid decreases in calcium concentration (eg, after anterior neck operation) or severe hypocalcemia. Calcium gluconate contains less elemental calcium than calcium chloride but is less likely to cause tissue damage with extravasation from a peripheral IV administration. IV calcium should be infused over 10–20 min, and bolus infusions can cause asystole. One IV dose of calcium lasts only for a few hours and should be followed by a continuous infusion if necessary. Acute hypocalcemia and hyperphosphatemia as a result of tumor lysis or rhabdomyolysis should not be treated with IV calcium to avoid precipitation of calcium phosphate; symptomatic patients should undergo acute dialysis. IV calcium should not be administered to asymptomatic patients with chronic hypocalcemia caused by hyperphosphatemia (eg, renal failure).

Pearls

- Critically ill patients have rapid albumin and pH shifts, decreasing the accuracy of total compared with ionized calcium measurements.
- Life-threatening hypocalcemia can occur acutely after parathyroidectomy, thyroidectomy, or head and neck dissection.
- Hypomagnesemia causes parathyroid hormone resistance and hypocalcemia that is refractory to therapy other than magnesium replacement.
- Clinical manifestations of hypocalcemia include prolongation of the QT interval, tetany (carpopedal spasm), seizures, hypotension, and papilledema.
- Symptomatic hypocalcemia is treated with infusion of calcium chloride or calcium gluconate; bolus administration can cause asystole.
- IV calcium should be avoided if hyperphosphatemia is the cause (tumor lysis, rhabdomyolysis, renal failure); dialysis is preferred.

Hypercalcemia

Fundamentals

Hypercalcemia can result from one or more of the following: increased mobilization from

bone, increased GI absorption, and decreased renal excretion. Under normal circumstances, calcium homeostasis is regulated by parathyroid hormone and vitamin D availability. In disease, hyperparathyroidism, parathyroid-related peptide, osteolytic bone lesions, and increased vitamin D are common mechanisms of hypercalcemia. More than 90% of hypercalcemia presentations are attributable to hyperparathyroidism (typically mild) or malignancy.

Clinical Applications

In primary hyperparathyroidism, parathyroid hormone mediates increased bone resorption and intestinal absorption of calcium, leading to mild hypercalcemia (<12 mg/dL) (Table 3). Renal failure patients commonly have secondary hyperparathyroidism, with parathyroid hormone elevated in response to a low calcium level caused by hyperphosphatemia. These patients can develop hypercalcemia when parathyroid hyperplasia leads to autonomous parathyroid hormone production (tertiary hyperparathyroidism). Hypercalcemia has been described following renal transplantation resulting from persistent parathyroid hormone production.

Severe hypercalcemia (calcium level >14 mg/dL) is likely due to malignancy. Hypercalcemia in patients with solid tumors (eg, squamous cell carcinoma, breast cancer, genitourinary carcinomas) is usually mediated by parathyroid-related peptide.[40] Hypercalcemia due to lymphoma is most often caused by vitamin D production within the local granulomatous response, although mediation by parathyroid-related peptide is also reported. Direct bone resorption in osteolytic metastases from solid tumors can also lead to hypercalcemia, and in multiple myeloma, numerous osteoclast-activating factors have been identified. Very uncommonly, calcium-binding paraproteinemia in multiple myeloma will raise the total calcium level with normal ionized calcium measurements.

Milk alkali syndrome is a well-described cause of hypercalcemia in hospitalized patients.[41] In this condition, high intake of milk or calcium carbonate leads to hypercalcemia, metabolic alkalosis, and renal insufficiency. Other causes of hypercalcemia include thyrotoxicosis, sarcoidosis, Paget disease of bone, hypervitaminosis A, hypervitaminosis D, lithium, thiazide diuretics, and during recovery from rhabdomyolysis with mobilization of deposited calcium.

Symptoms and signs of hypercalcemia include constipation and fatigue (mild; calcium level <12 mg/dL); polyuria, hypovolemia, anorexia, and weakness (moderate; calcium level 12–14 mg/dL); and lethargy and coma (severe; calcium >14 mg/dL). A shortened QT interval, nephrolithiasis, nephrogenic diabetes insipidus, nephrocalcinosis, mild weakness, and rarely band keratopathy may be seen in hypercalcemic patients.

Patients with severe hypercalcemia or moderate hypercalcemia with altered mental status should be treated aggressively. Therapy includes administration of saline solution to restore volume (combined high volume saline solution and diuretic are no longer recommended), calcitonin to rapidly (maximum effect 12–24 h) but transiently (<48 h) lower calcium levels, and bisphosphonates to achieve longer term control with an onset of 2 to 4 days. Calcitonin is administered intravenously or subcutaneously, while nasal administration is not effective. Zoledronic acid and pamidronate are administered intravenously and may cause flu-like symptoms or nephrotoxicity acutely; osteonecrosis of the jaw has been reported with long-term use. Bisphosphonates can be used to treat or prevent hypercalcemia in metastatic malignancy. Dialysis is uncommonly required but can be used with a low calcium bath.

Pearls

- Mild hypercalcemia is usually caused by hyperparathyroidism.
- Severe hypercalcemia (calcium level >14 mg/dL) is usually due to malignancy (parathyroid-related peptide for solid tumors; vitamin D production by lymphoma-induced granulomas).
- Milk alkali syndrome is a common cause of hypercalcemia leading to hospitalization.
- Severe hypercalcemia and moderate hypercalcemia (12–14 mg/dL) with altered mental status are treated with saline solution to restore volume status, calcitonin for rapid, temporary lowering of calcium levels, and bisphosphonates for longer term control (onset over days).

Phosphate Derangements

Fundamentals

Phosphate levels can be altered by cellular metabolism, intestinal absorption, and urinary excretion. Acute increases in substrate availability or plasma pH can markedly increase cellular utilization of circulating phosphate. Glucose metabolism in the liver and skeletal muscle is an important cause of cellular phosphate uptake and plasma phosphate depletion. The normal kidney can halt renal phosphate losses when intake decreases, limiting total body phosphate depletion, and can increase excretion dramatically to adapt to excessive dietary intake.

Clinical Applications

In malnourished patients with total body phosphate depletion (eg, alcoholism,[42] anorexia nervosa, morbid obesity with massive weight loss), the most severe hypophosphatemia may follow administration of dextrose solutions during the first day of hospitalization (Table 4). Dextrose solutions should be avoided in patients with hypophosphatemia who do not have another indication for dextrose supplementation (alcoholic ketoacidosis). Acute respiratory alkalosis stimulates phosphate utilization and can exacerbate hypophosphatemia in alcoholics during withdrawal. Other causes of hypophosphatemia include hyperparathyroidism, aluminum- or magnesium-containing antacids (phosphate binders), parathyroidectomy with hungry bone syndrome, and refeeding after prolonged starvation. Diabetic ketoacidosis is frequently accompanied by hypophosphatemia caused by osmotic urinary losses and cellular phosphate uptake; however, clinical manifestations are uncommon as total body phosphate stores are not severely depleted.

Clinical manifestations of hypophosphatemia in critical illness can occur when the phosphate level is less than 1 mg/dL (0.32 mmol/L) and include respiratory muscle weakness, congestive heart failure, rhabdomyolysis, and encephalopathy.[43] IV phosphate replacement is indicated for severe symptomatic hypophosphatemia, with caution in renal insufficiency. In alcoholics, rhabdomyolysis can complicate hypophosphatemia and obscure the etiology resulting from phosphate release from injured muscle.

Severe hyperphosphatemia may be due to cell breakdown (tumor lysis,[44] rhabdomyolysis), massive exogenous phosphate load (phosphate-containing bowel regimens), or advanced renal failure. Coexistent hyperkalemia, hyperuricemia, and/or elevated creatine phosphate may provide clues to the etiology. Ingestion of phosphate bowel preparations can cause fatal hyperphosphatemia and hypocalcemia, particularly in dialysis patients.[45] In the presence of normal renal function, phosphate is rapidly excreted. Hemodialysis can treat the life-threatening hypocalcemia that accompanies severe hypophosphatemia. Calciphylaxis is a devastating, frequently fatal tissue necrosis that occurs in the setting of hyperphosphatemia and end-stage renal disease through uncertain mechanisms.[46,47] Spurious hyperphosphatemia as a result of interference with analytical methods is described with monoclonal gammopathy.

Pearls

- Total body phosphate depletion occurs in alcoholism and anorexia nervosa, and hypophosphatemia can be acutely worsened by dextrose administration, refeeding, or hyperventilation.
- Symptomatic hypophosphatemia occurs when the phosphate level is less than 1 mg/dL and presents with respiratory muscle weakness, congestive heart failure, rhabdomyolysis, which can obscure the etiology, and encephalopathy.
- IV phosphate replacement is indicated for symptomatic hypophosphatemia, cautiously with renal insufficiency.
- Severe hyperphosphatemia can develop with cell breakdown (tumor lysis, rhabdomyolysis), exogenous loads (phosphate bowel preparations), or renal failure.
- Hypocalcemia is the major symptomatic manifestation of severe hyperphosphatemia and can be treated with hemodialysis.

Magnesium Derangements

Fundamentals

Renal and GI magnesium losses may lead to acute decreases in serum magnesium level as a

result of the slow exchange between the extracellular and (large) intracellular magnesium compartments. Renal losses of magnesium are common, and in the GI tract, intestinal losses are greater than gastric losses. Much of an IV magnesium dose is rapidly excreted because of the limited exchange with the intracellular compartment and increased urinary magnesium clearance.

Clinical Applications

Severe hypomagnesemia (<1.0 mEq/L, <0.5 mmol/L, or <1.2 mg/dL) is frequently accompanied by hypokalemia due to urinary potassium wasting and hypocalcemia resulting from parathyroid hormone resistance (Table 5).[48] In some patients with hypocalcemia who are at risk for magnesium depletion (eg, alcoholics), magnesium supplementation has reversed the hypocalcemia despite normal serum magnesium levels. Common causes of hypomagnesemia include loop and thiazide diuretic use, alcoholism,[49] and diarrhea. Uncommon causes include chronic proton pump inhibitor use,[50] foscarnet, massive citrate exposure, and hungry bone syndrome after parathyroidectomy. Manifestations of hypomagnesemia may include weakness, tetany, and ventricular arrhythmias. In the management of torsades de pointes with prolonged QT interval, IV magnesium is indicated even with normal serum magnesium levels. IV replacement is indicated for symptomatic hypomagnesemia but should be administered slowly to maximize uptake into the cells and to minimize excretion in the urine. Careful monitoring is indicated in the presence of renal disease.

Hypermagnesemia is a therapy for preeclampsia and eclampsia because of its inhibitory effects on the neuromuscular junction, and magnesium concentrations of 4 to 6 mEq/L are associated with decreased muscle contraction (deep tendon reflexes), nausea, flushing, and lethargy. Higher concentrations cause hypotension, bradycardia, conduction abnormalities (prolonged PR, QRS, QT intervals), and hypocalcemia. Levels above 10 mEq/L cause paralysis, respiratory failure, and complete heart block. Community-acquired causes of life-threatening hypermagnesemia include ingestion of magnesium-containing antacids, cathartics, or enemas in patients with renal disease.[51] Elderly adults with GI disease may absorb more magnesium and are at increased risk for symptomatic hypermagnesemia.[52] Ingestion of magnesium sulfate (epsom salts) has been reported to cause fatal hypermagnesemia in healthy individuals. Hypermagnesemia resolves rapidly with normal renal function or may require hemodialysis. When symptoms attributable to hypermagnesemia are severe, calcium is administered acutely to oppose the effects of magnesium on neuromuscular junctions and cardiac conduction (analogous to calcium use in hyperkalemia).

Pearls

- Severe hypomagnesemia is frequently accompanied by hypokalemia (due to increased renal potassium losses) and hypocalcemia (due to parathyroid hormone resistance), and these can be reversed with magnesium replacement.
- Clinical manifestations of hypomagnesemia include weakness, tetany, and polymorphic ventricular tachycardia with prolonged QT interval.
- IV replacement is most effective with slow administration because of rapid excretion of magnesium in the urine.
- Hypermagnesemia causes muscle weakness, decreased deep tendon reflexes, nausea, and flushing at 4 to 6 mEq/L; bradycardia, conduction abnormalities, and hypocalcemia at 6 to 10 mEq/L; and heart block and paralysis at levels >10 mEq/L.
- Patients with renal failure and elderly adults with GI disease taking magnesium-containing remedies and patients with accidental overdoses with magnesium sulfate can present with symptomatic hypermagnesemia.
- Treatment of hypermagnesemia can include IV calcium for neuromuscular or cardiac manifestations and dialysis if renal impairment limits the normally rapid excretion of the magnesium.

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Chapter 36. Antibiotic Therapy in Critical Illness

Michael S. Niederman, MD, FCCP

Objectives:

- Review the mechanism of action of commonly used antibiotics.
- Review principles of pharmacokinetics and pharmacodynamics of antibiotic use to define how to optimize antibiotic dosing.
- Define strategies for antibiotic stewardship in the critically ill that could minimize the development of antibiotic resistance.
- Illustrate the principles of antibiotic use by examining the treatment of pneumonia.
- Review mechanisms of antibiotic resistance.

Key words: antibiotic resistance; antimicrobial stewardship; bactericidal; de-escalation therapy; drug penetration; minimum inhibitory concentration; pharmacodynamics; pharmacokinetics

Synopsis:

Antibiotic therapy must be optimized in critically ill patients to lead to the greatest likelihood of success to treat severe infection. To effectively treat patients, it is necessary to give appropriate therapy (matching the pathogen to the drug), but also adequate therapy, which requires proper dosing. Some critically ill patients with sepsis have hyperdynamic circulation and require higher than normal doses of antibiotics to achieve effective serum levels. When dosing antibiotics, especially if infection with a potentially drug resistant pathogen is present, it is necessary to optimize bacterial killing by being aware of antimicrobial bactericidal mechanisms. Drugs such as aminoglycosides and quinolones kill in a concentration-dependent fashion, and maximizing the peak serum concentrations by once daily dosing may be most effective. Other agents, such as the β-lactams, kill in a time-dependent fashion and therapy can be optimized by prolonged or continuous infusion. Some older antimicrobials are not as effective as in the past, including third generation cephalosporins which can induce bacterial β-lactamase production, and quinolones which are not as effective against resistant gram-negatives as in the past. To preserve antibiotics for the future, it is necessary to understand mechanisms of antibiotic resistance and to practice antimicrobial stewardship by focusing on proper antibiotic dosing, de-escalation therapy, the development of local protocols for antibiotic choice, but not by restricting access to potentially effective broad-spectrum agents.

In the treatment of infection in critically ill patients, antibiotics form the backbone of management, but the choice of agents varies according to the type of infection present (community-acquired pneumonia [CAP], intraabdominal infection, systemic sepsis, healthcare-related or nosocomial pneumonia). Dosing also varies depending on the renal and liver function of the patient, the site of infection, the age of the affected patient, the presence of various comorbid illnesses, and the presence of risk factors for infection by specific pathogens. For most patients, initial therapy is empiric and is targeted at a broad spectrum of potential pathogens dictated by suspected site of infection and patient comorbidities. Therapy can be pathogen specific, once culture data become available, and often it is possible to "deescalate" from broad-spectrum therapy to fewer drugs, with a narrower antimicrobial spectrum.[1,2] In some cases, diagnostic testing is not revealing, and initial empiric therapy must be continued because no etiologic pathogen is identified. When a pathogen is defined, the term "appropriate" refers to the use of at least one antimicrobial agent to which the pathogen is sensitive in vitro.[1] The term "adequate" includes not only appropriate therapy, but also the use of that agent in the correct dose, via the right route, given in a timely fashion, and with penetration to the site of infection.

Timely and appropriate antibiotic therapy can improve survival in patients with CAP, hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), as well as with sepsis, and the benefits are most evident in patients who are not otherwise terminally ill.[3–5] In general, when patients have severe infection, the sooner appropriate therapy is started, the lower the mortality, with the risk of death rising for each hour of delay of therapy in patients with sepsis, during the first 6 h of hypotension.[6]

In the setting of CAP, effective initial antibiotic therapy is associated with a marked improvement in survival, compared to ineffective initial therapy, particularly in patients with severe illness.[2,7] In fact, in patients with severe CAP, the

Table 1—*Principles of Antibiotic Therapy for HAP*

- Provide prompt empiric therapy, especially in the setting of septic shock: initiate when there is clinical suspicion of infection.
- For patients with septic shock, start therapy with at least two potentially effective agents.
- Obtain a lower respiratory tract culture (sputum, tracheal aspirate, protected brush, bronchoalveolar lavage) prior to initiation of antibiotic therapy. Samples can be obtained bronchoscopically or nonbronchoscopically and cultured quantitatively or semiquantitatively.
- Most patients require broad-spectrum empiric therapy, but a narrow spectrum can be considered for patients at risk for infection with "core pathogens," early onset infection, and with no risk factors for multiple-drug resistant (MDR) pathogens.
  - Narrow spectrum therapy options: ceftriaxone, ampicillin/sulbactam, ertapenem, levofloxacin, or moxifloxacin. For penicillin allergy, use a quinolone or the combination of clindamycin and aztreonam.
- Use combination therapy with a broad-spectrum regimen for patients with risk factors for MDR pathogens. Use a regimen containing at least two antimicrobials directed at gram-negative organisms, plus an anti-methicillin-resistant *Staphylococcus aureus* (MRSA) agent (if at risk). Specific choices should be guided by a knowledge of local microbiology patterns.
  - Use an aminoglycoside (preferred) or an antipneumococcal quinolone (ciprofloxacin or high-dose levofloxacin) PLUS an antipseudomonal β-lactam such as: cefepime, ceftazidime, doripenem, imipenem, meropenem, or piperacillin-tazobactam. If there is concern about MRSA, add either linezolid or vancomycin.
- Use the correct therapy in recommended doses (see text and Table 3).
- Choose an empiric therapy that uses agents from a different class of antibiotics than the patient has received in the past 2 weeks.
- Try to de-escalate to monotherapy after initial combination therapy, after reviewing culture data and clinical response.
  - If *Pseudomonas aeruginosa*, consider stopping the aminoglycoside after 5 days and finish with a single agent to which the organism is sensitive.
  - If a nonpseudomonal infection, switch to a single agent that the organism is sensitive to, using either: imipenem, meropenem, cefepime, piperacillin/tazobactam, ciprofloxacin, or high-dose levofloxacin.
- The drug of choice for *Acinetobacter* is a carbapenem, but colistin should be considered if there is carbapenem resistance. Tigecycline monotherapy in this setting is not recommended for patients with VAP.
- Consider linezolid as an alternative to vancomycin in patients with proven MRSA VAP, in those with renal insufficiency, and in those receiving other nephrotoxic medications (such as an aminoglycoside).
- Consider adjunctive aerosolized aminoglycosides in patients at risk for infection with highly resistant gram-negative pathogens.

use of an effective and timely empiric therapy can reduce mortality, while identification of a specific pathogen has little impact, particularly if the data become available late in the course of illness. In patients with HAP and VAP, survival is improved with the use of antibiotics to which isolated pathogens are susceptible, compared to empiric, nonspecific therapy.[1,5] In serious infection, timely therapy is vital, and a delay of at least 24 h in starting therapy is an important mortality risk factor in VAP.[1,5] In the treatment of sepsis of any cause, each hour of delay in starting antibiotic therapy raises mortality by as much as 7% to 8%.[6]

However, the use of appropriate and adequate therapy does not permit all patients to recover, and the "attributable mortality" of infection has been measured in the presence of therapy. In studies of VAP, the use of appropriate therapy can reduce this attributable mortality, but not eliminate it, which is a reflection of host response limitations (which may in part have a genetic determination) and the fact that not all deaths are the direct result of infection.[8]

In this discussion, the principles underlying antibiotic use are examined, followed by a discussion of the commonly used antibiotics for critically ill patients, with a focus on respiratory tract infections. The treatment of severe pneumonia can be used as a paradigm to demonstrate the principles of antibiotic treatment of critically ill patients. While the focus of this discussion will be on empiric antibiotic therapy, the principles of antibiotic penetration and concentration in the lung are summarized in Table 1. The focus on optimizing pharmacokinetics and pharmacodynamics (PK/PD) is an important one, because there are few new antibiotics being developed, at a time when ICU pathogens are increasingly antibiotic resistant. PK/PD considerations are a theoretical way to optimize the delivery of antibiotics, but recent data indicate that the use of such "optimized therapy" may have clinical benefit.[9]

Principles of Antibiotic Use

Mechanisms of Action

Antibiotics interfere with the growth of bacteria by undermining the integrity of their cell wall or by interfering with bacterial protein synthesis or common metabolic pathways.[10] The terms bactericidal and bacteriostatic are general categories; they may not apply for a given agent against all organisms or at all sites of infection, with certain antimicrobials being bactericidal for one bacterial pathogen but bacteriostatic for another.[11] Bactericidal antibiotics kill bacteria, generally by inhibiting cell wall synthesis or by interrupting a key metabolic function of the organism. Agents of this type include: the penicillins, cephalosporins, aminoglycosides, fluoroquinolones, vancomycin, daptomycin, colistin/polymyxin, rifampin, and metronidazole. Bacteriostatic agents inhibit bacterial growth, do not interfere with cell wall synthesis, and rely on host defenses to eliminate bacteria. Agents of this type include: the macrolides, tetracyclines, tigecycline, sulfa drugs, chloramphenicol, linezolid, and clindamycin. While the distinction between bactericidal and bacteriostatic agents is usually not clinically relevant, when neutropenia is present, or if there is accompanying endocarditis or meningitis, the use of a bactericidal agent is preferred.

Antimicrobial activity and the susceptibility of a pathogen to therapy is often described by the minimum concentration of an antibiotic that inhibits the growth of 90% of a standard-sized inoculum (MIC), leading to no visible growth in a broth culture. At this concentration not all the bacteria have necessarily been killed. An organism is considered "susceptible" to therapy if the anticipated serum concentration exceeds the MIC. Antimicrobial activity and the susceptibility of a pathogen to therapy is also described by the minimum concentration needed to cause a 3-logarithmic decrease (99.9% killing) in the size of the standard inoculum, and generally all pathogenic bacteria are killed at this concentration. The term "sensitivity" must be interpreted cautiously in the treatment of specific infections, because the clinician must consider the MIC data in light of the penetration of an agent into the site of infection, with some agents achieving higher than serum levels at certain sites of infection, and others reaching lower levels.[12] Thus a pathogen that is sensitive to a specific agent when causing bacteremia may be less susceptible when causing pneumonia, if the agent penetrates into the lung less well than into the serum.

In recent years, most respiratory infections have been dominated by concerns of antimicrobial resistance, and a new term has emerged, the mutant prevention concentration (MPC).[13] The MPC is defined as the lowest concentration of an antimicrobial that prevents bacterial colony formation from a culture containing greater than 10^{10} bacteria. At lower than MPC concentrations, spontaneous mutants can persist and proliferate during therapy. The concept has been most carefully studied with pneumococcus and the fluoroquinolones. In general the MPC is higher than the MIC, implying that it is possible to use an antimicrobial to successfully treat an infection, but not to prevent the remaining organisms (which are not causing illness) from emerging as resistant, and persisting and spreading to other patients.

Penetration Into the Lung (A Relevant Consideration for the Treatment of Pneumonia)

Antibiotic penetration into the lung is vital to eliminate infection, but the site for measuring antibiotic concentration that is most relevant in pneumonia management is uncertain. Sputum and bronchial concentrations may be most relevant for bronchial infections, while concentrations in lung parenchyma, epithelial lining fluid, and cells such as macrophages and neutrophils are probably more important for pneumonia. The localization of the pathogen may also be important, and intracellular organisms such as *Legionella pneumophila* and *Chlamydophila pneumoniae* may be best eradicated by agents that achieve high concentrations in macrophages. The concentration of an antibiotic in the lung depends on the permeability of the capillary bed at the site of infection (the bronchial circulation), the degree of protein binding of the drug, and the presence or absence of an active transport site for the antibiotic in the lung.[10,12] Local concentrations of an antibiotic must be

Table 2—*Antibiotic Penetration Into Respiratory Secretions*

Good penetration: concentration is not inflammation-dependent
Quinolones
Macrolides: azithromycin, clarithromycin
Tetracyclines
Tigecycline penetrates epithelial lining fluid, but penetration is enhanced by infection
Clindamycin
Linezolid
Trimethoprim/sulfamethoxizole
Poor penetration: inflammation-dependent for concentration in the lung
Aminoglycosides
Colistin/polymixins
β-Lactams
Penicillins
Cephalosporins
Monobactams
Carbapenems

considered in relation to local conditions, with, for example, aminoglycosides having reduced activity at acidic pHs, which may be present in infected lung tissues. In addition, high local concentrations of antibiotic can mitigate against certain bacterial resistance mechanisms, such as production of destructive bacterial enzymes (such as β-lactamases), altered permeability of the outer bacterial cell wall, and pumping (efflux) of the antimicrobial from the interior of the bacterial cell. Thus, delivery by the aerosol route can achieve such high local concentrations that in vitro resistance might be overcome.

The concentration of an antibiotic in lung parenchyma depends on its penetration through the bronchial circulation capillaries. The bronchial circulation has a fenestrated endothelium, so antibiotics penetrate in proportion to their molecular size and protein binding, with small molecules that are not highly protein bound passing readily into the lung parenchyma. When inflammation is present, penetration is further improved. For an antibiotic to reach the epithelial lining fluid, it must pass through the pulmonary vascular bed (the other pulmonary circulation besides the bronchial circulation), which has a nonfenestrated endothelium. This presents an advantage for lipophilic agents, which are generally not inflammation dependent; they include chloramphenicol, the macrolides (including the azalides and ketolides), linezolid, clindamycin, the tetracyclines, the quinolones, and trimethoprim-sulfamethoxazole. Agents that are poorly lipid soluble are inflammation dependent and include the penicillins, cephalosporins, aminoglycosides, vancomycin, carbapenems, and monobactams.

Some general categories of antibiotic penetration have been established (Table 2). Drugs that penetrate well into the sputum or bronchial tissue include the quinolones, the newer macrolides and azalides (azithromycin and clarithromycin), the ketolides, the tetracyclines, clindamycin, and trimethoprim-sulfamethoxazole. However, tigecycline penetration is primarily intracellular and not in the epithelial lining fluid. On the other hand, the aminoglycosides, vancomycin, and, to some extent, the β-lactams penetrate less well into these sites. With the use of once-daily aminoglycoside dosing, high peak serum concentrations (Cmaxs) can be achieved; the alveolar lining fluid concentration in patients with pneumonia is only 32% of the serum level over the first 2 h, but the two sites have more similar concentrations later in the dosing interval.[14] Since aminoglycosides require high peak concentrations for optimal killing (below), their poor penetration with systemic administration often makes this impossible, suggesting a potential role for delivery by the aerosol route (discussed below).

Antibiotic PK/PD

Pharmacokinetics refers to the absorption, distribution, and elimination of a drug in the body, and the information can be used to describe the concentration of a drug in the serum. Pharmacokinetics also includes the study of the concentration at other sites of the body, including the site of infection, and the relationship between drug concentrations and their pharmacologic or toxic effect.[13] For antibiotics, this means the relationship of antibiotic concentrations at the site of infection, compared to the MIC of the target organism.

The way in which an antibiotic reaches the site of infection, considering the frequency of administration and dose administered, can affect its ability to kill bacteria, thus defining a close PK/PD relationship. There are three types of

bactericidal antibiotics: those that kill in relation to how long they stay above the MIC of the target organism (time-dependent killing), those that kill in relation to the peak concentration achieved, relative to the MIC (concentration-dependent killing), and those that are time-dependent, but have a prolonged persistent effect (similar to concentration-dependent killing agents).[13] To optimize time-dependent killing, dosing should be chosen to achieve the maximal time above the MIC of the target organism, and this can be done with continuous or prolonged (over 3–4 h) infusions. Antibiotics of this type include the β-lactams (penicillins and cephalosporins), carbapenems, aztreonam, macrolides, and linezolid. The rate of killing is saturated once the antibiotic concentration exceeds four times the MIC of the target organism. In spite of these considerations, for many organisms, the concentration of the antibiotic only needs to be above the MIC for 40% to 50% of the dosing interval, and possibly for as little as 20% to 30% of the interval in the case of carbapenems. For the time-dependent killing drugs listed above, the pharmacodynamic parameter that best predicts clinical efficacy is the time above the MIC.

When killing is concentration-dependent, activity is related to how high a concentration is achieved at the site of infection and how great the area under the curve (AUC) (of drug concentration plotted vs time) is in relation to the MIC of the target organism. Alternatively, the action of these agents can be described by how high the Cmax is in relation to the organism MIC. Classic agents of this type include the aminoglycosides and the fluoroquinolones, but the ketolides and daptomycin are also concentration-dependent antibiotics.[8] For these types of agents, the optimal killing of bacteria is defined by the ratio of AUC to MIC, often referred to as the area under the inhibition curve, or the AUIC. The target AUIC for gram-negative bacteria is 125 or greater, while for most antibiotics that treat pneumococcus, the target value is at least 30. For both the aminoglycosides and quinolones, some studies have shown that efficacy can also be defined by the ratio Cmax/MIC, aiming for a target of 12 for quinolones against *pneumococcus*. Optimal use of these agents would entail infrequent administration but with high doses—the underlying principle behind the once-daily administration of aminoglycosides. With once-daily aminoglycoside dosing regimens, the patient achieves a high peak concentration (maximal killing) and a low trough concentration (minimal nephrotoxicity), relying on the "post-antibiotic effect" (PAE) to maintain the efficacy of the antibiotic after the serum (or lung) concentrations fall below the MIC of the target organism. If an antibiotic has a PAE, it is capable of suppressing bacterial growth even after its concentration falls below the MIC of the target organism. While most agents exhibit a PAE against gram-positive organisms, a prolonged PAE against gram-negative bacilli is achieved by the aminoglycosides and fluoroquinolones.[13] The third category of agent is time-dependent in its killing but also has a prolonged persistent effect, and efficacy is optimized by maximizing exposure to the drug, as reflected by the AUC/MIC ratio for a 24-h period. Drugs of this type include azithromycin, clindamycin, the tetracyclines, and vancomycin. For vancomycin, optimal therapy can be achieved by prolonged infusion but also by maintenance of high trough concentrations, reflecting both time-dependent killing and persistent killing.

Another property of antibiotics is their ability to stimulate inflammation as a consequence of the host inflammatory system's exposure to killed bacterial products.[11] For example, certain antibiotics liberate bacterial cell wall products that can interact with cytokine-producing cells, stimulating the production of high levels of cytokines; this could lead to the development of, or worsening of, sepsis syndrome immediately after antibiotic administration, a phenomenon seen in the treatment of *Pneumocystis jiroveci* pneumonia and pneumococcal meningitis, leading to recommendations to use adjunctive corticosteroids with antibiotics when treating these infections. The phenomenon may apply to other antibiotics; if, for example, an antibiotic has a high affinity for certain bacterial penicillin-binding proteins, it may kill slowly and lead to filamentous cell wall products that are potent stimuli for cytokine release. On the other hand, agents that kill rapidly and do not interact with penicillin-binding protein 3 are associated with lower levels of in vitro stimulation of cytokine

production by host inflammatory cells. In addition to these considerations, some antibiotics (linezolid, clindamycin) can inhibit protein synthesis and may have an advantage in treating illnesses caused by bacteria that release exotoxins, such as in infections with community-acquired methicillin-resistant *S aureus* (ca-MRSA) and in toxic shock.[15]

Features of Specific Antimicrobials

Macrolides (Including Azalides)/Tetracyclines

Macrolides are bacteriostatic agents that bind to the 50S ribosomal subunit of the target bacteria and inhibit RNA-dependent protein synthesis. The macrolides have traditionally had good activity against pneumococci, as well as atypical pathogens (*C pneumoniae, Mycoplasma pneumoniae*, *Legionella*), but the older erythromycin-like agents are not active against *Haemophilus influenzae* and have poor intestinal tolerance, so that prolonged therapy is difficult. The new agents in this class include azithromycin (also referred to as an azalide) and clarithromycin and have better intestinal tolerance than erythromycin. These agents have enhanced activity against *H influenzae* (including β-lactamase–producing strains), although, on an MIC basis, azithromycin is more active. Erythromycin is active against *Moraxella catarrhalis*, although the new agents have enhanced activity against this pathogen.[10]

Azithromycin can be used in its IV form for patients with severe pneumonia; it should be dosed at 500 mg daily, with the duration defined by the clinical course of the patient, but usually for 7 to 10 days.[2] Because of its IV administration, the serum levels achieved have been adequate for the treatment of bacteremic pneumococcal pneumonia.[16] Clinical studies of CAP have consistently shown a mortality benefit of using macrolide therapy, usually in conjunction with a β-lactam, but the mechanism for this favorable effect is not known.[17,18] Efficacy may be related to the treatment of atypical pathogen coinfection, a possibility supported by studies that have found the benefit of the addition of macrolides to vary over the course of time.[18] Other explanations have been that macrolides have anti-inflammatory effects or that they interfere with "quorum sensing" between bacteria, which could inhibit the in vivo proliferation of *Pseudomonas aeruginosa* after colonization has occurred.[19]

Although macrolides remain an important therapeutic option for community respiratory tract infections, pneumococcal resistance is becoming increasingly common, being present in as many as 35% to 40% of all pneumococci, especially in patients who have received an agent of this class in the past 3 months.[20] In addition, macrolide resistance can also coexist with penicillin resistance, and as many as 30% to 40% of penicillin-resistant pneumococci are also erythromycin resistant. The clinical relevance of these in vitro findings remains to be defined. However, there are two forms of pneumococcal macrolide resistance, one involving efflux of the antibiotic from the bacterial cell, and the other involving altered ribosomal binding of the antibiotic. The former mechanism is associated with much lower levels of resistance than the latter and is present in two-thirds of the macrolide-resistant pneumococci in the United States. The latter form of resistance is fortunately less common, because, if present, it is unlikely that macrolide therapy for pneumococcal infection would be effective.[21]

The tetracyclines are also bacteriostatic agents that act by binding the 30S ribosomal subunit and interfering with protein synthesis. These agents can be used in CAP as an alternative to macrolides, because they are active against *H influenzae* and atypical pathogens; but, in the United States, pneumococcal resistance to tetracyclines may be approaching 20% and may exceed 50% among organisms with high-level penicillin resistance. A modification of tetracycline, tigecycline has become available for use in critically ill patients as IV therapy for skin and intraabdominal infections. It has in vitro activity against *Acinetobacter* spp, but, in clinical trials of VAP, it has not been as effective as the comparator agent imipenem, possibly because of the use of too low a dose.[22]

Trimethoprim-Sulfamethoxazole (TMP-SMX)

This combination antibiotic has been used as a mainstay for the treatment of *P jiroveci* pneumonia but has limited value in other severe

infections. It has bactericidal activity against *Pneumococcus*, *H influenza,* and *M catarrhalis*, but not against atypical pathogens. Recently, it has become less popular for the treatment of CAP because of the emergence of pneumococcal resistance, since 80% to 90% of organisms that are penicillin resistant are also resistant to TMP-SMX. The sulfa component of the drug inhibits the bacterial enzyme responsible for forming the immediate precursor of folic acid, dihydropteroic acid. Trimethoprim is synergistic with the sulfa component because it inhibits the activity of bacterial dihydrofolate reductase. TMP-SMX is available in a fixed combination of 1:5 (TMP:SMX) and is dosed as either 80/400 mg or 160/800 mg orally bid for 10 days, but the dosage should be adjusted in renal failure. An IV preparation is also available. Side effects generally result from the sulfa component and include rash, GI upset, and occasional renal failure (especially in elderly patients). Availability of this agent has recently become limited.

β-Lactam Antibiotics

All of these bactericidal antibiotics share the presence of a β-lactam ring, which is bound to a five-membered thiazolidine ring in the case of the penicillins and to a six-membered dihydrothiazine ring in the case of the cephalosporins. Modifications in the thiazolidine ring can lead to agents such as the penems (doripenem, imipenem, ertapenen, and meropenem), while absence of the second ring structure characterizes the monobactams (aztreonam). These agents can also be combined with β-lactamase inhibitors, such as sulbactam, tazobactam, or clavulanic acid, to create the β-lactam/β-lactamase inhibitor drugs. These agents extend the antimicrobial spectrum of the β-lactams by providing a substrate (sulbactam, clavulanic acid, tazobactam) for the bacterial β-lactamase enzymes, thereby preserving the antibacterial activity of the parent compound. β-Lactam antibiotics lead to cell wall lysis by interfering with the synthesis of bacterial cell wall peptidogylcans after binding to bacterial penicillin-binding proteins.

The penicillins include the natural penicillins (penicillin G and V), the aminopenicillins (ampicillin, amoxicillin), the antistaphylococcal agents (nafcillin, oxacillin), the antipseudomonal agents (piperacillin, azlocillin, mezlocillin, ticarcillin), and the β-lactam/β-lactamase inhibitor combinations (ampicillin/sulbactam, amoxicillin/clavulanate, piperacillin/tazobactam, and ticarcillin/clavulanate). Among the antipseudomonal penicillins, piperacillin is the most active agent.

The cephalosporins span from first to fourth generation, with some authors referring to certain newer agents as being fifth generation. The earlier agents were generally active against gram-positive organisms, but they did not extend activity to the more complex gram-negative organisms, or anaerobes and were susceptible to destruction by bacterial β-lactamases. The newer generation agents are generally more specialized, with broad-spectrum activity, and with more mechanisms to resist breakdown by bacterial enzymes. The second-generation and newer agents are resistant to bacterial β-lactamases, but recent data suggest that cefuroxime may not be an optimal pneumococcal agent if resistance is present in a patient with bacteremic CAP.[23] On the other hand, the third-generation agents such as ceftriaxone and cefotaxime are reliable and active against penicillin-resistant pneumococci, while ceftazidime is not reliable against pneumococcus but is active against *P aeruginosa*. The third-generation agents may induce β-lactamases among certain gram-negative organisms (especially the *Enterobacteriaceae* spp) and thus promote the emergence of resistance during monotherapy. In addition, the third-generation agents can promote the emergence of extended-spectrum β-lactamases in an ICU and thus be a risk factor for multiple-drug-resistant (MDR) pathogen emergence in the ICU. The fourth-generation agent, cefepime, is active against pneumococci and *P aeruginosa* but is also less likely to induce resistance among the Enterobacteriaceae than the third-generation agents. Ceftaroline is a modification of the fourth-generation agents; it has been referred to as a fifth-generation agent that is active against gram-positive pathogens, including MRSA, and is approved for the treatment of CAP.

Imipenem, doripenem, and meropenem are the broadest spectrum agents in this class, being active against gram-positive pathogens, anaerobes, and gram-negative pathogens, including *P*

aeruginosa and *Acinetobacter* spp. They have shown efficacy for patients with severe pneumonia, both CAP and nosocomial, as well as a variety of nonpulmonary (intraabdominal) infections. On an MIC basis, doripenem is the most active agent in this class against *P aeruginosa*, but it is not currently approved for the treatment of nosocomial pneumonia in the United States. Considering their PK/PD properties, the carbapenems have been administered to critically ill patients with potentially MDR pathogens by prolonged infusion, and in high doses.[24] Doses as high as 6 g per day of meropenem have been used in the ICU. A nonpseudomonal carbapenem, ertapenem, is also available and has been used effectively in the treatment of CAP and intraabdominal infection; it has activity against extended-spectrum β-lactamase–producing organisms but not *Pseudomonas* or *Acinetobacter* spp. Aztreonam is a monobactam that is so antigenically different from the rest of the β-lactams that it can be used in penicillin-allergic patients. It is only active against gram-negative organisms, having a spectrum very similar to the aminoglycosides. It is uncertain if it can completely replace aminoglycosides in combination with a β-lactam, since this would represent dual β-lactam therapy, which is a risk for both agents being inactivated in the presence of certain bacterial resistance mechanisms.

Because β-lactams kill bacteria in a time-dependent fashion, clinical trials have been conducted using either continuous or prolonged (over 3–4 h) infusions of these agents. To date, these trials have not shown superiority but have shown safety and efficacy, using continuous infusions of penicillins, cefepime, and piperacillin/tazobactam, and prolonged infusions of doripenem and meropenem.[25–27]

Fluoroquinolones

These bactericidal agents act by interfering with bacterial DNA gyrase and/or topoisomerase IV, leading to impaired DNA synthesis repair, transcription, and other cellular processes, resulting in bacterial cell lysis.[10] DNA gyrase is only one form of a bacterial topoisomerase enzyme that is inhibited by quinolones, and activity against other such enzymes is part of the effect of a variety of quinolones. The earlier quinolones (such as ciprofloxacin and ofloxacin) were active primarily against DNA gyrase, which accounts for their good activity against gram-negative organisms. The newer agents (levofloxacin and moxifloxacin) bind both DNA gyrase and topoisomerase IV and have extended their activity to gram-positive organisms, including drug-resistant *Streptococcus pneumoniae*. Resistance to quinolones can occur through mutations in the topoisomerase enzymes, by altered permeability of the bacterial cell wall, or by efflux of the antibiotic from the inside of the bacteria.[28] Because quinolones kill in a concentration-dependent fashion, optimal antibacterial activity can be achieved with infrequent dosing and with high peak concentrations and high ratios of either AUC/ MIC or Cmax/MIC. In addition, because quinolones have a PAE against both gram-positive and gram-negative organisms, they can continue to kill even after local concentrations fall below the MIC of the target organism. These properties make the quinolones well-suited to infrequent dosing, with the ideal being once-daily dosing, particularly given the relatively long half-life of the newer compounds. On the basis of the AUC/MIC ratio for pneumococcus, moxifloxacin is up to four times more active than levofloxacin. The only factor limiting a switch to once-daily dosing for all quinolones is the toxicity associated with high doses of some agents (such as ciprofloxacin), particularly concerns related to neurotoxicity and possible seizures. In clinical trials, optimizing the Cmax for levofloxacin or the AUC/MIC ratio for ciprofloxacin has been associated with improved clinical outcomes in CAP and nosocomial pneumonia, respectively.[29,30]

In the treatment of respiratory infections, quinolones have the advantage of excellent penetration into respiratory secretions and inflammatory cells within the lung, achieving local concentrations that often exceed serum levels. In addition, these agents are highly bioavailable with oral administration, and, thus, similar serum and tissue levels can be reached if administered orally or intravenously, promoting early transition from IV to oral therapy in responding patients.

The fluoroquinolones have excellent antimicrobial activity against β-lactamase–producing *H influenzae* and *M catarrhalis*, but the newer agents (levofloxacin and moxifloxacin) extend the activity of the quinolones by having enhanced gram-positive activity, as well as by being more active against *C pneumoniae* and *M pneumoniae*, compared to older agents. The new agents are also highly effective against *L pneumophila* and may be the drug of choice for this organism, with cure rates of over 90%, even in patients with severe CAP.[31] However, if *P aeruginosa* is the target organism (as it is in certain patients with CAP and HAP), then only ciprofloxacin (750 mg bid orally or 400 mg q8h IV) or levofloxacin (750 mg orally or IV daily) are active enough for clinical use.[1] When levofloxacin is used for patients with severe CAP, the recommended dose to ensure pneumococcal efficacy is also 750 mg daily.[3]

Although pneumococcal resistance to quinolones is uncommon, many organisms contain mutations that may lead to future resistance emergence, and the use of the most active agents (defined in vitro) may have an advantage to avoid future resistance.[3] One potent risk factor for pneumococcal resistance and failure of therapy is repeated therapy with a quinolone in a 3-month period. Other risk factors for quinolone resistance among pneumococci are recent hospitalization and residence in a nursing home.

One major concern among quinolones is their profile of toxic side effects. A number of agents have been removed from clinical use (temafloxacin) because of toxicities such as QT prolongation (grepafloxacin), phototoxicity (sparfloxacin), hypoglycemia (gatifloxacin), and liver necrosis (trovafloxacin). The side effects of available agents have generally been acceptable, but, as with any therapy, the risks of use should be weighed against the benefits. A recent study compared moxifloxacin with levofloxacin in elderly hospitalized patients with CAP and a high frequency of heart disease; it showed comparable safety, including, for both drugs, a low frequency of cardiac arrhythmias and *Clostridium difficile* diarrhea.[32]

Currently there are no good studies of severe CAP showing efficacy of any of the quinolones as monotherapy, and they are not recommended to be used in this fashion.[3] However, in nosocomial pneumonia, monotherapy has been tested and shown to be effective, provided that the organism is susceptible in vitro and, if *P aeruginosa*, that a concomitant aminoglycoside be used for the first 5 days.[1]

Aminoglycosides

These bactericidal agents act by binding to the 30S ribosomal subunit of bacteria, thus interfering with protein synthesis. Aminoglycosides have a gram-negative spectrum of activity and are usually not used alone, but rather in combination with other agents, targeting difficult organisms such as *P aeruginosa* or other resistant gram-negative organisms, where they may be more active as a second agent than quinolones.[33] When combined with certain β-lactam agents, they can achieve antibacterial synergy against *P aeruginosa*. Amikacin is the least susceptible to enzymatic inactivation by bacteria, while tobramycin is more active than gentamicin against *P aeruginosa*. Aminoglycosides penetrate poorly into lung tissue and can be inactivated by acid pHs, which are common in pneumonic lung tissue. The use of a combination regimen, including an aminoglycoside, has not been shown to be more effective in preventing the emergence of pseudomonal resistance during therapy than a monotherapy regimen with a β-lactam.[1,34] In the treatment of bacteremic pseudomonal pneumonia, aminoglycoside combination therapy may be more effective than monotherapy.

As discussed above, aminoglycosides kill in a concentration-dependent fashion and can be dosed once daily to optimize killing while minimizing toxicity (primarily renal insufficiency). In clinical practice, once-daily dosing is comparable in efficacy to multiple dose regimens and may have a reduced rate of nephrotoxicity, but it requires less serum level monitoring.[35] When aminoglycosides are used, it is necessary to monitor serum levels to minimize the occurrence of acute renal failure. Peak concentrations correlate with efficacy, with optimal efficacy occurring with a Cmax:MIC value $\geq$10. Trough concentrations are monitored to minimize toxicity and probably should be followed regardless of dosing regimen.

Because of poor penetration into tissues, some investigators have used nebulized aminoglycosides for the treatment of gram-negative pneumonia, as discussed below.

New Agents Active Against MRSA

In the past several years, MRSA has become an important pathogen in patients with a variety of severe infections, particularly VAP and skin and soft tissue infections, and recently has been described as a potential pathogen in patients with necrotizing postinfluenza CAP (ca-MRSA). Although, traditionally, vancomycin has been the agent used most commonly for this pathogen, therapy with this agent may not be optimal for organisms with MIC values $\geq$1 mg/L because vancomycin is characterized by poor penetration into respiratory secretions and has potential synergistic nephrotoxicity with aminoglycosides. In the treatment of ca-MRSA, vancomycin cannot inhibit bacterial exotoxin production and may need to be combined with clindamycin for this purpose. Alternative agents to vancomycin for MRSA therapy include quinupristin/dalfopristin, telavancin, and linezolid for the treatment of pneumonia, and daptomycin for the treatment of nonrespiratory infections.[36]

Linezolid is the first agent in a new antibiotic class, the oxazolidinones, and is active against MRSA; it may also block the production of antibacterial toxins, such as the Panton-Valentine leukocidin, which can be produced by ca-MRSA strains. The oxazolidinones act to inhibit bacterial protein synthesis, by binding to the 50S ribosomal subunit, preventing the binding of transfer RNA, and preventing the formation of the 70S initiation complex. Linezolid is not only active against MRSA but also against drug-resistant *Streptococcus pneumoniae* and vancomycin-resistant enterococci (both *Enterococcus faecium* and *Enterococcus faecalis*). It has high bioavailability, and thus serum levels are the same with oral or IV therapy. Renal and nonrenal clearance occur, and dosing adjustment is not needed for patients with renal failure. Efficacy has been shown for nosocomial pneumonia and CAP, but a recent prospective randomized trial has shown that linezolid may have better clinical efficacy than vancomycin for the treatment of VAP that is proven to be caused by MRSA.[37] Side effects are not common and include nausea, diarrhea, anemia, thrombocytopenia, and neuropathy (especially with prolonged use). It is also a weak monoamine oxidase inhibitor. Quinupristin/dalfopristin has been tested in patients with VAP and was not as effective against MRSA as vancomycin, in spite of good in vitro activity. Although daptomycin has excellent MRSA activity, it is not used to treat pneumonia because it has been shown to be inactivated by pulmonary surfactant. Daptomycin is an effective therapy for MRSA bacteremia, including endocarditis, possibly because of its bactericidal action. Tigecycline has activity against MRSA but is available only for nonrespiratory tract infections; it does have in vitro activity against MRSA, as well as many gram-negative organisms, including *Acinetobacter* spp, but not *P aeruginosa*. Telavancin is a glycopeptide with efficacy against MRSA and has been shown to be comparable to vancomycin in the treatment of MRSA pneumonia, although with better efficacy for organisms with a vancomycin MIC $>$1 mg/L.[36]

Aerosolized Antibiotics for Respiratory Tract Infections

Local administration of antimicrobials has been used in the treatment of bronchiectasis, especially in the setting of cystic fibrosis and in the treatment of VAP, in order to achieve high local antibiotic concentrations, especially for agents that penetrate the lung poorly with systemic administration.[38] Direct delivery of antibiotics is usually achieved by nebulization, and this approach not only achieves high intrapulmonary concentrations but may do so with low systemic absorption and, thus, a reduced risk of systemic toxicity. The use of this approach in mechanically ventilated patients has been proposed for patients with either infectious tracheobronchitis or VAP, since both infections can involve highly resistant gram-negative bacteria and the local delivery of antibiotics may effectively treat some pathogens that cannot be eradicated by systemic therapy. Early studies did not show enhanced efficacy for routine nosocomial pneumonia but did show a possible benefit as adjunctive therapy with highly resistant pathogens, when limited systemic therapies were available.[38] However, one recent trial has sug-

gested that adjunctive aerosol therapy may speed the rate of pneumonia resolution and minimize the need to escalate systemic antibiotic therapy, while enhancing the frequency of de-escalation.[39] Aerosol therapy may also be effective in treating ventilator-associated tracheobronchitis, leading to resolution and prevention of progression to VAP.[40]

In mechanically ventilated patients, local antibiotic administration, by instillation or nebulization, has been used to prevent pneumonia, but this is not a recommended approach; even when it has been successful, there has been concern about the emergence of MDR gram-negative pathogens in those who subsequently do develop infection, and these organisms may be difficult to treat. Most studies in VAP have involved nebulization of aminoglycosides, colistin, ceftazidime, or polymyxin B. The devices used for nebulization vary widely, and device design can impact the size of the particles generated, the site of particle deposition in the lung, and the percent of administered drug that is retained in the lung. One side effect of aerosolized antibiotics has been bronchospasm, which can be induced by the antibiotic or the associated diluents present in certain preparations. A specially formulated preparation of tobramycin for aerosol administration was designed to avoid this complication. When aerosol therapy is used in mechanically ventilated patients, it must be carefully synchronized with the ventilator cycle, and the optimal delivery device is not yet defined. To optimize delivery, inspiratory time may need to be as high as 50% of the ventilatory cycle, and routine humidification should be stopped during antibiotic administration. In ventilated patients, the ventilator may need to be set with a tidal volume of 8 to 10 mL/kg, with no humidification system in use during the use of the ultrasonic nebulizer, which should be set to deliver 8 L/min.

Additional Principles of Antibiotic Use

Pneumonia Therapy

Achieving Proper Dosing (Table 3): In the American Thoracic Society/Infectious Disease Society (ATS/IDSA) guideline for HAP, the terms "appropriate " and "adequate" therapy were defined. While "appropriate" refers to the use of an antibiotic that is active in vitro against the identified pathogen, the term "adequate" refers to not only using an antibiotic to which the organism is sensitive but also using that therapy without delay, using it in the right doses, having it penetrate to the site of infection, and using combination therapy, if needed. For example, for critically ill patients with normal renal function who were effectively treated for nosocomial pneumonia in clinical trials, the correct doses of common antibiotics include: cefepime, 1–2 g q8-12h; imipenem, 500 mg q6h or 1 g q8h; doripenem, 500 mg q8h (as a 1-h or 4-h infusion); meropenem, 1 g q8h, piperacillin-tazobactam 4.5 g q6h; levofloxacin 750 mg daily or ciprofloxacin, 400 mg q8h; vancomycin, 15 mg/kg q12h, leading to a trough level of 15–20 mg/L; linezolid, 600 mg q12h; and aminoglycosides of 7 mg/kg per day of gentamicin or tobramycin, and 20 mg/kg of amikacin.[1]

While there is often a tendency to dose cautiously and often conservatively in critically ill patients, some studies have shown that patients with severe sepsis have a hyperdynamic

Table 3—*Recommended Doses of Commonly Used Respiratory Antibiotics for Critically Ill Patients With Normal Renal Function*

β-Lactams
- Cefepime 1–2 g q8-12h
- Ceftazidime 2 g q8h
- Ceftriaxone 2 g qd
- Imipenem 1 g q8h or 500 mg q6h. Can give by prolonged infusion
- Meropenem 1 g q6-8h, but can use up to 2 g q6-8h by prolonged infusion
- Doripenem 500 mg q8h (1-h or 4-h infusion) (not approved for pneumonia)
- Piperacillin/tazobactam 4.5 g q6h

Aminoglycosides
- Gentamicin or tobramycin 7 mg/kg qd or amikacin 20 mg/kg qd

Antistaphylococcal agents (MRSA)
- Vancomycin 15 mg/kg q12h, aiming for a trough of 15–20 mg/L
- Linezolid 600 mg q12h

Quinolones
- Ciprofloxacin 400 mg q8h
- Levofloxacin 750 mg qd

Colistin (polymyxin E)
- 9 million units/d in 3 divided doses

Table 4—*Empiric Treatment of Common Sources of Sepsis (Not Pneumonia)*

Source unknown
Organisms: *S aureus* (especially if IV line), gram-negative organisms, fungi (steroids, prior antibiotics)
Therapy: dual pseudomonal (β-lactam + aminoglycoside) +/− oxacillin (if methicillin-sensitive is likely) or (if MRSA) vancomycin or alternatives (telavancin, daptomycin) + consider voriconazole (aspergillus) or echinocandin (candida)
Intraabdominal source: secondary peritonitis
Organisms: gram-negative organisms, anaerobes, enterococci (latter two more with secondary vs primary infection)
Therapy: piperacillin/tazobactam, ertapenem, ampicillin/sulbactam, moxifloxacin
OR ciprofloxacin, levofloxacin, or cefepime PLUS metronidazole
If *P aeruginosa* suspected:
Imipenem or meropenem
PLUS cipro or levo or antiseudomonal aminoglycoside
Meningitis
Adult < age 50
Organisms: *S pneumoniae, H influenzae*. Others unlikely if immune competent
Therapy: cefotaxime or ceftriaxone + vancomycin + dexamethasone (just prior to antibiotics)
Chloramphenicol and TMP/SMX if PCN allergic
Adult > age 50, alcoholic or immune-suppressed
Organisms: *S pneumoniae*, gram-negative pathogens, *Listeria*
Therapy: ampicillin, cefotaxime or ceftriaxone + vancomycin + dexamethaxone
OR meropenem + vancomycin + dexamethasone
Vancomycin + TMP/SMX if PCN allergic

cardiac output; as a result, many drugs can be cleared more rapidly than is normal, and, unless antibiotics are dosed aggressively, they may be in fact underdosed.

Deescalation Therapy: To use antibiotics appropriately and effectively, it is necessary to use them when needed, understanding that overuse can drive resistance and that resistance can lead to inappropriate empiric therapy choices. To minimize resistance, it is necessary to deescalate after an initial broad-spectrum therapy, which can involve using fewer drugs, drugs of a narrower spectrum, and short durations of therapy.[2] It is possible to effectively treat VAP with 6 to 8 days of therapy, provided that the initial therapy is appropriate.[1] The optimal duration of therapy for infections caused by *P aeruginosa* and MRSA is still uncertain, but prolonged therapy may be no better than short duration therapy, in the absence of bacteremia.

In clinical studies of VAP, the rate of deescalation has varied from 22% to 74%, with the highest rates being in those who are treated with a protocol, when initial therapy is appropriate, when initial cultures are positive (although it can be done with negative cultures), when the therapy involves broad-spectrum agents and multiple agents, and if the frequency of MDR pathogens is not high.[2] Deescalation does not appear to be dangerous and may be associated with reduced mortality, compared to no change in antibiotics.

Algorithms for Initial Empiric Therapy: Empiric treatment of any infection requires an assessment of risk factors for MDR pathogens, which include: recent antibiotic therapy within the past 90 days, immunosuppressive illness or therapy (corticosteroids or chemotherapy), admission to a unit with a high rate of MDR organisms, recent hospitalization for 2 or more days within the past 90 days, residence in a nursing home or long-term care facility, or regular visits to a hospital clinic or hemodialysis center. Representative empiric therapy regimens for nonrespiratory sepsis are listed in Table 4.

Antibiotic Resistance

There are four basic mechanisms of resistance: (1) Decreased permeability of microbial cell wall. This is an important mechanism for gram-negative resistance and is caused by alteration of porin channels. (2) Production of destructive enzymes, such as β-lactamases. This is the major mechanism for gram-negative resistance and can combine with altered permeability in specific organisms. In gram-negative organisms, these inactivating enzymes often localize to the periplasmic space between the inner and outer membrane. Since gram-positive organisms lack

an outer membrane, inactivating enzymes cannot be localized easily and are thus not a common cause of resistance for these pathogens. β-lactamases can be type I or extended spectrum and are commonly produced by organisms like *P aeruginosa* and the *Enterobacteriaceae*. Resistance to third-generation cephalosporins is often mediated by this mechanism. (3) Alteration of the target site of action, such as the penicillin-binding proteins, the DNA gyrase (quinolones), and RNA polymerase. This is an important mechanism for gram-positive resistance. For pneumococcus, resistance can occur to β-lactams by alteration of the penicillin-binding proteins and to macrolides by alteration of the ribosomal target of action. This type of macrolide resistance is coded by the erm gene and confers a high level of resistance, much higher than if resistance is caused by an efflux mechanism (below). (4) Active efflux of the antibiotic, which can occur in gram-positive and gram-negative organisms; it is an important mechanism of macrolide resistance in pneumococci, encoded for by the *mef* gene.

Antimicrobial Control Programs

Antimicrobial control or stewardship programs involve a number of interventions, which commonly include restricting access to specific antibiotics. Several studies have shown that restricting access has a limited ability to control resistance and that other interventions are more valuable.[41] Any antimicrobial control program should include a knowledge of local antibiotic usage and resistance patterns. The principles for antimicrobial stewardship have been compiled into a guideline, where the focus is on prospective audit and feedback of antibiotic use, de-escalation of broad-spectrum therapy, proper dosing, and the development of local guidelines for antibiotic use, based on a knowledge of local microbiology.[41] Antibiotic restriction was not a highly recommended strategy, nor was restricting access to specific antibiotics.

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Notes

Chapter 37. Transplant-Related Issues

Stephen P. Kantrow, MD

Objectives:

- Recognize basic immunosuppressive approaches to solid organ transplant recipients.
- Anticipate common infectious and malignant complications of solid organ transplantation.
- Be aware of indications for solid organ transplantation and critical care issues early and late after major types of transplantation.
- Know common challenges to donor management in the ICU.
- Identify major causes of critical illness after hematopoietic cell transplantation.

Key words: cardiac transplantation; hematopoietic cell transplantation; immunosuppression; liver transplantation; lung transplantation; organ donor; organ transplantation; renal transplantation

Synopsis:

Solid organ transplantation is frequently complicated by critical illness, and care of these patients requires a basic understanding of immunosuppressive therapy and the overwhelming infections and serious malignancies that can occur. An awareness of indications for transplantation in critically ill patients and complications of common transplant procedures improves medical decision making in the ICU. Deterioration in graft function that occurs over time contributes to critical illness in recognizable and unique ways for each kind of transplanted organ. Management of organ donors presents challenges that can be anticipated by the intensive care physician. Patients who receive hematopoietic cell transplantation are at risk to develop numerous early and late complications that require care in the ICU.

Immunosuppression in Solid Organ Transplantation

Immune reactivity to transplanted organs is most intense during the first 3 to 6 months after implantation. For this reason, immunosuppression is aggressive early after transplantation, with gradual tapering to lower doses during subsequent months. Many programs utilize intense perioperative "induction" immunosuppression at the time of transplantation to attempt to decrease the risk of early immune attack on the graft. All patients receive maintenance immunosuppression with multiple medications, including calcineurin inhibitors, cell cycle inhibitors, and corticosteroids. Immunosuppressive drugs can protect the allograft but increase the risk of infection and malignancy, and treatment strategies are designed to balance these risks.

Induction Immunosuppression

In centers that use induction immunosuppression, several antilymphocyte antibodies have been employed to interrupt or deplete key components of the adaptive immune response (Table 1). Modest nondepleting immunosuppression can be accomplished with an IL-2 antagonist (basilixumab), and this treatment has a relatively low risk of subsequent infection and malignancy. In contrast, monoclonal and polyclonal antibodies to T and B cells cause lymphocyte depletion and result in a more significant and durable immunosuppression. Polyclonal antithymocyte sera (ATGAM and Thymoglobulin) are generated by immunizing horses or rabbits with human thymocytes. Mild-moderate serum sickness with fever, chills, myalgia, and rash may occur, and severe leukopenia prompts dose adjustments. Despite their origin, horse and rabbit sera do not usually induce an immune response to the antilymphocyte antibodies and can be used repeatedly. Murine monoclonal antibody to the T cell receptor/CD3 complex (OKT3) causes T cell depletion that lasts 1 week, and anti-mouse antibody responses decrease the effectiveness of later doses. These lymphocyte-depleting therapies can cause a cytokine release syndrome, with fever, chills, GI symptoms, myalgias, hypotension, and wheezing. The most potent antilymphocyte therapy is alemtuzumab (Campath-1H), a humanized rat monoclonal antibody directed at the CD52 antigen on immune cells. The resulting immune suppression is profound and lasts from

Table 1—*Induction Immunosuppression for Solid Organ Transplantation*

	Origin	Mechanism	Adverse Effects
Basilixumab	Monoclonal antibody to IL-2 receptor	Blocks IL-2 signaling on activated T-lymphocytes	Moderate immunosuppression
ATGAM	Horse sera against human thymocytes	T- and B-lymphocyte depletion	Serum sickness, intense immunosuppression, cytokine release syndrome
Thymoglobulin	Rabbit sera against human thymocytes	T- and B-lymphocyte depletion	Serum sickness, intense immunosuppression, cytokine release syndrome
OKT3	Murine antibody to T-lymphocyte receptor CD3	T-lymphocyte depletion	Cytokine release syndrome, intense immunosuppression
Alemtuzumab	Humanized rat monoclonal antibody to CD52	T- and B-lymphocyte depletion	Very intense and long-lasting immunosuppression (6 mo to 3 y)

6 months to 3 years, with an increased risk of infectious and malignant complications.

Maintenance Immunosuppression

Maintenance immunosuppression is begun in the perioperative period but can be delayed for days to weeks if intense induction immunosuppression is used. Calcineurin inhibitors (cyclosporine, tacrolimus) are the foundation of the three-drug maintenance protocol that has made modern organ transplantation possible (Table 2). These drugs block the calcineurin-dependent transcription of IL-2 and other proinflammatory cytokines, with a net effect of inhibiting T-lymphocyte activation and proliferation in response to alloantigens in the graft. Major toxicities of both calcineurin inhibitors are renal insufficiency (acute and chronic) and neurotoxicity[1] (tremors, headaches, seizures, cortical blindness, cerebellar ataxia, leukoencephalopathy). Hypertension, diabetes mellitus, and hyperlipidemia are also common adverse effects. Cyclosporine, a xenobiotic derived from the fungus *Tolypocladium inflatum*, binds to cyclophilin to inhibit calcineurin. Neoral and Gengraf are microemulsion formulations of this lipid-soluble drug with improved absorption characteristics and can be given intravenously at one third of the oral dose. Toxicities unique to cyclosporine are gingival hyperplasia and hirsutism. Tacrolimus is a macrolide derived from the fungus *Streptomyces tsukubaensis*, and binds to FK-binding protein to inhibit calcineurin. Tacrolimus causes more new-onset diabetes mellitus, but less hypertension and hyperlipidemia, compared to cyclosporine. When IV dosing is required, one-third of the oral dose should be administered. Levels of cyclosporine and tacrolimus are monitored carefully, particularly with dose adjustments or when drug interactions are expected (eg, cytochrome P-450 3A4 inhibitors, including macrolide antibiotics, nondihydropyridine calcium channel blockers, amiodarone, and grapefruit juice or cytochrome P-450 3A4 inducers, including antiepileptic drugs, rifampin, and St. John's wort).

Cell cycle inhibitors are widely used as part of the three-drug maintenance regimen, with most programs using azathioprine or mycophenolate mofetil. Azathioprine (Imuran) is pro-drug for 6-mercaptopurine, which is further converted into a purine analogue and incorporated into the DNA of rapidly dividing cells, where it inhibits nucleotide synthesis. Polymorphisms in the enzyme thiopurine S-methyltransferase can decrease metabolism of 6-mercaptopurine and increase the risk for leukopenia. A decrease in the WBC count should prompt temporary discontinuation of this medication. Allopurinol increases 6-mercaptopurine levels and marrow toxicity and should be avoided with azathioprine. Many transplant centers use mycophenolate mofetil (Cellcept) as the cell cycle inhibitor of choice. Mycophenolate mofetil is converted to mycophenolic acid, which reversibly inhibits inosine monophosphate dehydrogenase. This enzyme is required for guanine synthesis in lymphocytes, and inhibition blocks rapid proliferation of T- and B-lymphocytes. Oral bioavailability is high, and IV dosing is the same as oral dosing when necessary. Common toxicities include leukopenia and GI manifestations (nausea, gastritis, and granulomatous enterocolitis).

Table 2—*Maintenance Immunosuppression After Solid Organ Transplantation*

Calcineurin inhibitors			
Cyclosporine	Xenobiotic	Binds cyclophilin and inhibits calcineurin-dependent IL-2 production	Nephrotoxicity, neurotoxicity, hypertension, hyperlipidemia, diabetes, gingival hyperplasia, hirsutism
Tacrolimus	Xenobiotic	Binds FK-binding protein and inhibits calcineurin-dependent IL-2 production	Nephrotoxicity, neurotoxicity, hypertension, hyperlipidemia, diabetes
Cell cycle inhibitors			
Azathioprine	Synthetic prodrug for 6-mercaptopurine	Inhibits DNA synthesis in rapidly dividing lymphocytes	Leukopenia
Mycophenolate mofetil	Xenobiotic prodrug for mycophenolic acid	Inhibits guanine synthesis in lymphocytes	Leukopenia, GI toxicity (nausea, diarrhea, granulomatous colitis)
Corticosteroids			
Prednisone			Osteoporosis, compression fractures, diabetes mellitus
Cell proliferation inhibitors			
Sirolimus, everolimus	Xenobiotic	Binds FK-binding protein and inhibits mTOR to block IL-2-dependent cell proliferation	Leukopenia, thrombocytopenia, hyperlipidemia, acute lung toxicity

Proliferation signal inhibitors, also known as mammalian target of rapamycin (mTOR) inhibitors, have been used in place of the cell cycle inhibitors. Sirolimus (Rapamune) is a macrolide isolated from *Streptomyces hygroscopicus*. Sirolimus and its metabolite everolimus bind the FK-binding protein targeted by tacrolimus but inhibit the protein kinase mTOR rather than calcineurin, blocking IL-2-dependent proliferation signals and decreasing T- and B-lymphocyte proliferation. Drug toxicities include leukopenia, thrombocytopenia, hyperlipidemia, and acute pulmonary infiltrates. A toxicity that limits the use of these drugs early after transplant is inhibition of wound healing, which can lead to dehiscence of graft anastomoses.

Glucocorticoids cause a dose-dependent inhibition of multiple aspects of immune activation, particularly NFKB-mediated pathways, through nuclear induction of the inhibitor IkBa. Steroids are used in modest doses as part of the three-drug maintenance regimen to prevent acute rejection, and are tapered over time.

Treatment of Acute Rejection

The presentation of acute rejection after solid organ transplantation is organ specific and will be discussed below. While treatment of acute rejection varies according to organ and transplant center, common approaches are outlined here. Initial therapy is typically high-dose corticosteroids (0.5 to 1 g of IV methylprednisolone daily for several days), and this may be repeated for subsequent episodes of acute rejection. Polyclonal antilymphocyte sera (ATGAM or thymoglobulin) or anti-CD52 monoclonal antibody (alemtuzumab) are used for refractory acute rejection and cause marked immunosuppression. OKT3 may be used; however, repeated administration diminishes efficacy as anti-mouse antibodies develop. In the face of recurrent acute rejection, maintenance immunosuppression is modified, including switching the calcineurin inhibitor, switching the cell cycle inhibitor, or substituting a proliferation (mTOR) inhibitor for a cell cycle inhibitor.

Acute rejection refractory to the aggressive measures above has been treated with photopheresis, in which leukocytes are separated from RBCs in an extracorporeal circuit and are then exposed to 8-methoxypsoralen and ultraviolet to damage rapidly proliferating lymphocytes. Total lymphoid irradiation may also have a role in treatment of acute rejection.

Pearls

- Immune attack on the donor organ is most intense during the first 3 to 6 months after transplantation.

- Induction immunosuppression with antilymphocyte therapy is used in many centers, and serum sickness (horse and rabbit sera) or cytokine release syndrome (depleting antilymphocyte therapy) may occur.
- Calcineurin inhibitors (cyclosporine, tacrolimus) are the foundation of a three-drug maintenance regimen (with cell cycle inhibitors and corticosteroids), and adverse effects include renal insufficiency and neurotoxicity (seizures, cortical blindness).
- Cell cycle inhibitors (azathioprine or mycophenolate mofetil) inhibit proliferation of T and B cells and can cause leukopenia; mycophenolate also causes GI symptoms.
- Proliferation signal (mTOR) inhibitors (sirolimus and everolimus) inhibit IL-2-dependent cell cycle signaling and can cause cytopenias and acute lung toxicity.
- Treatment for acute rejection is usually high-dose methylprednisolone and, for refractory cases, potent antilymphocyte therapy (ATGAM, Thymoglobulin, alemtuzumab); photopheresis or total body irradiation may also be used.

Infections After Solid Organ Transplantation

An aggressive approach to diagnosis and treatment of infections in solid organ transplant recipients is essential to achieving good clinical outcomes.[2,3] Pulmonary infections can rapidly progress to respiratory failure; and invasive, disseminated infections can cause hemodynamic compromise and multiorgan failure. Focal findings may be modest even as invasive infection progresses due to limited local inflammatory responses. Clinical samples for diagnostic testing (culture, stains, enzyme-linked immunosorbent assay, polymerase chain reaction) should be obtained early and evaluated for a broad spectrum of bacterial, mycobacterial, viral, and fungal pathogens. Biopsies are frequently indicated to establish invasive disease quickly. Microbial resistance to antibiotics is common in transplant recipients, and surgical drainage or debridement may be required to control space-occupying or invasive infection.

First Month After Transplantation

During the first month after transplantation, infection is frequently caused by microorganisms from the transplant recipient, the transplant donor, or the hospital environment. Lung recipients may have residual sinopulmonary colonization or infection after transplantation (eg, cystic fibrosis [CF], bronchiectasis), and antibiotic-resistant organisms are an important cause of transplant morbidity and mortality. Reactivation of hepatitis B and C, particularly in liver transplant recipients, can occur early in the course of immunosuppression. Hyperinfection with *Strongyloides* should be suspected in transplant patients with meningitis and gram-negative sepsis.[4]

Donor organs can carry numerous important pathogens to the recipient, including antibiotic-resistant enterococci, staphylococci, and *Candida* spp. Transmission of viral infections can be lethal, with rapidly progressive disease in the immunosuppressed patient early after transplant. Lymphocytic choriomeningitis virus from donors has been described to cause clusters of encephalopathy with very high mortality in organ recipients. Donor transmission of West Nile virus has resulted in clusters of neuroinvasive disease in transplant recipients. Other viral infections transmitted from donor to recipient include HIV, hepatitis C, herpes simplex virus, human herpes virus 8, and rabies. Rarely, transmission of parasites causes disease in recipients (toxoplasmosis, Chagas disease, amebic encephalitis due to *Balamuthia mandrillaris*).

Bacterial or fungal infections may complicate surgical anastomoses and fluid collections, with nosocomial pathogens and site-specific pathogens predominating. Invasive nosocomial infections can complicate central venous catheters, mechanical ventilation, biliary drainage, and bladder catheterization. Colitis due to *Clostridium difficile* is common early after transplantation.

1 to 6 Months After Transplantation

Opportunistic infections become important considerations during the first through sixth month after transplantation. *Pneumocystis jiroveci* pneumonia (PCP) develops in up to 15% of patients undergoing solid organ transplantation

without prophylaxis (up to 80% in lung recipients), with the highest risk during the first 6 months. The clinical presentation is acute onset of diffuse bilateral pulmonary infiltrates, with ground glass and occasionally cystic abnormalities seen on CT scans. The diagnostic yield for PCP stains on bronchoalveolar lavage samples is uncertain and may be lower than for HIV-infected patients. Polymerase chain reaction appears to increase the diagnostic yield of bronchoscopy for PCP but is not widely used. PCP prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX) is highly effective and universally used after organ transplantation. PCP prophylaxis failure is more common with alternatives, including dapsone.

Opportunistic fungal infection can be due to molds (*Aspergillus*, *Rhizopus*, *Scedosporium*, *Fusarium*) or endemic fungi with the appropriate exposure history (*Histoplasma*, *Coccidioides*, *Cryptococcus*, *Blastomyces*). Lung transplant recipients are at particularly high risk for fungal infection, and colonization with *Aspergillus* species is common in patients with CF. Tracheobronchial infection, pneumonia, and dissemination due to *Aspergillus* (most commonly *A fumigatus*) are well described after lung transplantation. Mucormycosis is a rapidly progressive necrotizing infection of the lung or sinuses due to *Rhizopus* or *Mucor* species, with angioinvasion and broad nonseptate hyphae branching at right angles noted on biopsy specimens. Voriconazole is the treatment of choice of invasive *Aspergillus* infection, but is ineffective against mucormycosis, for which amphotericin B and emergent debridement are indicated. Endemic fungal infections can present with localized or disseminated disease and may become symptomatic when immune suppression is decreased, similar to immune reconstitution in HIV-infected patients on highly active antiretroviral therapy.

Common viral infections after immunosuppression for solid organ transplants include herpes simplex, varicella zoster, and cytomegalovirus (CMV). CMV is an important cause of pneumonia, hepatitis, colitis, and disseminated disease, particularly in CMV-seronegative recipients of seropositive donor organs. Prophylaxis with ganciclovir or valganciclovir is effective for CMV prophylaxis, while acyclovir is not. Invasive CMV infection may be established by biopsy, CMV antigen detected on circulating WBCs, or CMV viremia quantified by polymerase chain reaction, and it should be treated with IV ganciclovir. Reactivation of hepatitis B or C may also occur during this time period. In kidney transplant recipients, BK polyomavirus is a cause of ureteral obstruction, graft dysfunction, and cystitis.

Mycobacterial infection (*Mycobacterium tuberculosis, Mycobacterium avium intracellulare* complex, *Mycobacterium abscessus*) and *Nocardia* sp may cause progressive nodular disease with dissemination in transplant patients. Toxoplasmosis is an uncommon but serious infection, particularly after cardiac transplantation, when it is carried within donor cardiac muscle and can cause myocarditis, cardiomyopathy, and dissemination to the brain and lung. Prophylaxis for PCP with TMP-SMX appears to be effective for toxoplasmosis. Other latent protozoal infections (eg, leishmaniasis and Chagas disease) can reactivate during prolonged immunosuppression.

More Than 6 Months After Transplantation

For patients with uncomplicated transplantation and good organ function, opportunistic infections are common. However, these patients remain at increased risk for severe infection due to community-acquired pathogens, including pneumococcus, legionella, and respiratory viruses (influenza, parainfluenza, respiratory syncytial virus, adenovirus, metapneumovirus). Patients with complicated courses, including acute rejection with repeated intensification of immunosuppression, graft dysfunction, or severe viral infection (eg, CMV), also remain at increased risk for the opportunistic infections described for the first 6 months.

Pearls

- During the first month after transplantation, pathogens from the donor, the recipient, and the hospital environment cause most infections.
- From 1 to 6 months after transplant, opportunistic infections become more important, including PCP, fungi, CMV, mycobacteria, *Nocardia*, and toxoplasmosis.
- After 6 months, uncomplicated transplant patients with modest immunosuppression remain vulnerable to serious infection with

community-acquired bacteria or viruses, while complicated patients continue to have a high risk of opportunistic infection.

Malignancy After Solid Organ Transplantation

All malignancies appear to have an increased incidence in solid organ transplant recipients, and this increase has been attributed to immune suppression and viral infection. Notably, skin cancer, non-Hodgkin lymphoma, and Kaposi's sarcoma are dramatically increased (20-fold). In renal transplant recipients, the risk of renal cell cancer in the native kidney is markedly increased (15-fold).

Posttransplant Lymphoproliferative Disease (PTLD)

Most PTLD occurs during the first year after transplantation, although cases can present several years later.[5,6] They are most often polyclonal or monoclonal B cell tumors (non-Hodgkin lymphoma), and a majority have evidence of Epstein-Barr virus (EBV) infection. The risk of PTLD is 1% to 5% in kidney, liver, and heart recipients, but higher in lung and multiorgan recipients. EBV-negative recipients of seropositive organs are at highest risk, particularly with intense immunosuppression. Most PTLD presents as one or more extranodal masses, and CNS or allograft involvement is common. Elevated lactate dehydrogenase or positron emission tomography may be useful when PTLD is suspected. Diagnosis of CNS lymphoma or cardiac lymphoma in heart transplant recipients is challenging. Reduction in immunosuppression, chemotherapy, and anti-B-lymphocyte therapy with rituximab are commonly attempted. A high tumor burden or a dramatic response to therapy can cause tumor lysis syndrome.[7]

Kaposi's Sarcoma

Transplant recipients chronically infected with human herpes virus 8 may develop angiomatous lesions affecting the legs and causing lymphedema and may less commonly develop visceral disease.[8] The more aggressive pulmonary and disseminated form seen with concomitant HIV and human herpes virus 8 infection is not usually observed after organ transplantation.

Pearls

- All malignancies are increased after organ transplant, with striking increases in nonmelanoma skin cancer, non-Hodgkin lymphoma, Kaposi's sarcoma, and renal cell cancer (in renal transplant patients).
- PTLD is most common during the first year after transplant in association with EBV infection and affects extranodal sites, including the graft and CNS; treatments include reduced immunosuppression, chemotherapy, and rituximab.

Organ Transplantation in HIV-Infected Individuals

In the setting of well-controlled HIV infection (undetectable HIV RNA), liver, kidney, and heart transplants have been performed.[9,10] Outcomes have been slightly worse than observed in HIV-negative populations, with higher rates of rejection and graft failure. HIV disease progression does not appear to be accelerated by the addition of immunosuppressive therapy. Drug interactions between components of highly active antiretroviral therapy and immunosuppressive therapies used after solid organ transplantation are common, frequently requiring much lower doses of calcineurin inhibitors. Increased risks of opportunistic infection and progression to AIDS have not been observed after aggressive treatment for acute rejection.

Liver Transplantation

The Model for End-Stage Liver Disease (MELD) score is a chronic liver disease severity scoring system originally developed to assess risk and survival for cirrhotic patients undergoing transjugular intrahepatic portosystemic shunt; it has been modified for use by the United Network for Organ Sharing (UNOS) for organ allocation by removing the contribution of liver

disease etiology.[11] The UNOS MELD = 3.8[Ln serum bilirubin (mg/dL)] + 11.2[Ln international normalized ratio] + 9.6[Ln serum creatinine (mg/dL)] + 6.4. Note that the natural logarithm (Ln) component requires a calculator. Addition of complications of portal hypertension (ascites, bleeding, encephalopathy, peritonitis) does not add to the predictive accuracy of the bilirubin, coagulation, and renal parameters. The international normalized ratio measurement can differ across laboratories based upon the thromboplastin source, and assays for creatinine may be confounded by markedly elevated bilirubin concentrations, which may alter prioritization scores. The MELD score assists in management of critically ill patients in whom transjugular intrahepatic portosystemic shunt is being considered, as best outcomes are seen with MELD less than 18 (including liver disease etiology in the formula) and should probably be avoided unless emergent in patients with a MELD greater than 24, in whom liver transplantation is a safer option.[12]

Prioritization for liver transplantation by UNOS criteria includes the MELD score (transplant survival is better than waiting list at MELD 20 or higher[13]) and blood type. Waiting time on the list is used to break ties. Patients with acute liver failure (eg, acetaminophen- and nonacetaminophen-induced, acute posttransplant graft failure) are exempt from MELD score prioritization and are UNOS status 1 (highest priority) due to the very high short-term mortality for these conditions without transplantation. MELD exceptions assign modifying points to chronic liver disease patients with hepatocellular carcinoma (single lesion <5 cm, 2 or 3 lesions <3 cm), hepatopulmonary syndrome with Pa_{O_2} <60 mm Hg, and portopulmonary hypertension (after it has been decreased to <35 mm Hg with therapy).

Perioperative issues include hemodynamic instability, capillary leak, volume overload with graft congestion, and acute hemorrhage requiring aggressive blood product support.[14] Coagulopathy is monitored intraoperatively by thromboelastogram. Hyperkalemia may be severe due to preservative solution washout from the graft, acute correction of hyponatremia may cause osmotic demyelination syndrome, and hypoglycemia may herald poor graft function.

Technical complications early after liver transplantation can lead to graft loss, retransplantation, or death.[15] Hepatic artery thrombosis is the most common, occurring in ~3% of transplants. Hepatic ischemic necrosis develops with hypotension, encephalopathy, and coagulopathy, and exploration with operative arterial reconstruction can save the graft. Portal vein thrombosis presents with ascites, intestinal edema, and GI bleeding, and may progress to acute liver failure. The diagnosis can be established by Doppler ultrasound, and mortality approaches 100% without treatment. Emergent operative thrombectomy is recommended over thrombolysis because of bleeding risk and frequent reocclusion. Hepatic vein thrombosis causes acute elevation in serum aminotransferases and bilirubin, abdominal pain, hepatomegaly, and ascites. Interventions may be percutaneous or operative, and retransplantation may be required.

After transplantation, persistent nonfunction of the graft is lethal without emergent retransplantation. Causes may include ischemia-reperfusion injury, prolonged warm ischemia time, and hyperacute rejection (usually ABO-incompatible grafts). One-year survival after liver transplantation exceeds 85%, and patients may present for acute care outside of dedicated transplant centers. Acute cellular rejection is common during the first month after transplant but has little impact on overall graft survival. The diagnosis is suspected by a rise in serum aminotransferases, alkaline phosphatase, and bilirubin levels. Liver biopsy reveals venulitis and cholangitis, which usually improve quickly with high-dose methylprednisolone.

Infectious complications within 1 month of transplantation include peritonitis and abdominal abscesses due to anastamotic leak (enteric pathogens), intrahepatic abscesses (often associated with hepatic artery thrombosis), cholangitis, and wound infections. *C difficile* is common after liver transplant, and one-half of cases occur within the first month. When bacteremia occurs, methicillin-resistant *Staphylococcus*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* predominate. Non-*albicans Candida* sp are common causes of fungemia and may be resistant to fluconazole. From months 1 to 6, CMV infection presents with fever, pancytopenia, and hepatitis,

or, less commonly, pneumonia, enteritis, or retinitis. *Aspergillus* infection usually involves the lung but is also the most common cause of brain abscess after liver transplantation. Cryptococcal meningitis may develop in patients profoundly immunosuppressed after acute rejection. Viral infection can lead to liver injury and hepatocellular carcinoma (hepatitis B and C) or posttransplant lymphoproliferative disorder (EBV). *Listeria* meningitis, hepatitis, and bacteremia have been described after ingestion of contaminated dairy products.

Pearls

- Priority for liver transplant is given to patients with acute hepatic failure, followed by ranking according to UNOS modified MELD score, ABO blood type matching, and length of time on the waiting list.
- Technical complications include hepatic artery thrombosis, portal vein thrombosis, hepatic vein thrombosis, intrahepatic abscess, and anastomotic leak with peritonitis.
- Hemodynamic instability, capillary leak, volume overload, and hemorrhage are common in the perioperative period.
- Hyperkalemia with graft reperfusion, correction of hyponatremia with osmotic demyelination syndrome, and hypoglycemia with graft dysfunction can occur in the perioperative period.

Lung Transplantation

The most common diagnoses leading to lung transplantation are COPD, idiopathic pulmonary fibrosis, CF, α_1-antitrypsin deficiency emphysema, and idiopathic pulmonary hypertension. Priority for transplantation is based upon a lung allocation score that combines a measure of transplant urgency (expected survival on waiting list for 1 year) and a measure of posttransplant benefit (expected survival during the first year posttransplant) to generate a score between 0 and 100, with higher scores representing higher priority. Patients with the very highest scores have higher posttransplant mortality. According to 2009 registry data, median survival is 4.6 years for single lung recipients and 6.6 years for bilateral lung recipients, a difference that may be explained by underlying disease and choice of operation. COPD patients have the best 1-year survival, but 10-year survival is highest in CF and α_1-antitrypsin deficiency emphysema.

In the immediate postoperative period, primary graft failure is the most common cause of morbidity and mortality.[16] Nearly all lung recipients have evidence of lung injury and edema, and patients with findings consistent with ARDS (Pa_{O_2}/F_{IO_2} ratio <200 and bilateral airspace disease) (primary graft dysfunction grade 3) at 48 h have a 33% 90-day mortality. Pulmonary infection is the leading cause of death during the first year and beyond, including infection due to bacteria, fungi, CMV, community-acquired respiratory viruses, and mycobacteria.[17]

Chronic allograft dysfunction is caused by obliteration of small airways (bronchiolitis obliterans) and occurs in half of lung recipients by 5 years. Diagnosis of bronchiolitis obliterans syndrome is made by spirometry, and patchy air trapping (mosaicism) on expiratory CT scan supports this diagnosis. Pathologically, the disease is focal and not reliably detected by transbronchial biopsies. Abnormal airways and increased immunosuppression lead to additional complications, including recurrent bronchitis (commonly *Pseudomonas*), pneumonia, and opportunistic infections. Ventilatory impairment can be striking, and metabolic acidosis or mild exertion can lead to respiratory distress in advanced cases.

Single lung transplantation is often performed for patients with emphysema or pulmonary fibrosis. The strongest indication for bilateral lung transplant is bilateral suppurative lung disease (CF, bronchiectasis). However, bilateral lung transplants are increasingly performed despite limited donor availability, with the hope of improved survival. Patients with pulmonary hypertension can undergo single or bilateral lung transplantation with acceptable outcomes.[18] During transplantation, cardiopulmonary bypass may be required when pulmonary vascular resistance is high and cardiac output falls, and it is commonly used in patients with idiopathic pulmonary hypertension or restrictive lung disease.

Postoperative liberation from the ventilator can usually be accomplished in the first 48 h with careful attention to volume status in the setting of expected lung injury. After single lung transplant for COPD, overinflation of the compliant native lung should be minimized by avoiding positive end expiratory pressure and maximizing expiratory time. When graft dysfunction is significant, independent lung ventilation may be required to allow differential application of positive end expiratory pressure. For lung transplant recipients with severe primary graft dysfunction, inhaled nitric oxide and extracorporeal membrane oxygenation have been used. Intraoperative air embolism (coronary, systemic) has been described. Atrial dysrhythmias are common in the postoperative period. Prolonged air leak (bronchopleural fistula), self-limited pleural effusions, and pulmonary embolism occur. Fatal hyperammonemia has been described in several case reports (mechanism unknown). Graft vs host disease is a rare but deadly complication later after solid organ transplantation, presenting with rash, diarrhea, cholestasis, and chimerism (persistence of donor leukocytes) in circulating blood.

Surveillance for acute rejection may be undertaken with serial spirometry followed by bronchoscopy (for a 10% decline in FEV_1 or FVC) or routine scheduled surveillance bronchoscopy over the first 1 to 2 years posttransplant. Evaluation for infection (purulence, positive BAL cultures) and rejection (biopsy) are performed together, as both are common causes of lung dysfunction after transplant and require very different approaches. Airway complications occur in 15% of transplant recipients, most commonly during the first year, with anastomotic infection and dehiscence (high mortality) observed early, and bronchomalacia, stenosis, and fistula formation (pleural or vascular) later. Balloon dilatation, stenting, or open repair may be required.

Nearly half of pneumonias in lung transplant patients occur during the first month, with host-derived bacteria and hospital-acquired pathogens most commonly isolated. CF patients are colonized in the sinuses and are at high risk for multidrug-resistant infection with *P aeruginosa*, *Burkholderia cepacia*, and methicillin-resistant *Staphylococcus aureus*. Chest infections include bronchitis, pneumonia, and empyema, with fungi commonly isolated from the pleural space. *Burkholderia cepacia* is a multidrug-resistant organism frequently cultured from the airways in CF patients and is not a contraindication to transplantation. However, *Burkholderia cenocepacia* (genomovar III) is associated with a 1-year survival of 29%, with progressive ARDS and sepsis (cepacia syndrome).[19] *Streptococcus pneumoniae* infection is frequently invasive, and it may be TMP-SMX- and penicillin-resistant in lung transplant recipients. *Nocardia* sp can cause pneumonia after lung transplant, despite thrice weekly TMP-SMX prophylaxis for PCP. *C difficile* infection is observed early after lung transplant and with prolonged hospitalization. CMV infection usually presents as pneumonia and may occur after discontinuation of CMV prophylaxis or with ganciclovir-resistant CMV strains.[20]

Primary disease may recur in the transplanted lung and can affect graft function in long-term survivors. Sarcoidosis commonly recurs histologically but infrequently is symptomatic, and other recurrent diagnoses include lymphangioleiomyomatosis, pulmonary alveolar proteinosis, bronchioloalveolar cell carcinoma (older nomenclature), α_1-antitrypsin deficiency, pulmonary Langerhans cell histiocytosis, and others.

Pearls

- Primary graft failure presenting as ARDS (P_{O_2}/F_{IO_2} ratio $<$200) at 48 h has a mortality of 33%.
- After single lung transplant for COPD, patients should be ventilated without positive end expiratory pressure, and acute allograft dysfunction may require an independent lung ventilation strategy.
- Bronchopleural fistula, pulmonary embolism, air embolism, and fatal hyperammonemia occur.
- Acute rejection that is not distinguishable from infection on clinical grounds should be investigated by bronchoscopy with bronchoalveolar lavage and transbronchial biopsies.
- Airway complications include anastomotic infection and dehiscence early, then bronchomalacia, stenosis, and, rarely, fistula formation later.
- Pneumonia is common during the first month, particularly in patients colonized with resistant bacteria (CF, bronchiectasis).

- *Burkholderia cenocepacia* (genomovar III), but not *B cepacia*, is an important cause of respiratory failure and sepsis, with a very high mortality after transplant.
- Bronchiolitis obliterans is the major cause of graft failure and death after lung transplantation and leads to severe ventilatory impairment, frequently complicated by infection with resistant bacteria and molds.

Cardiac Transplantation

Cardiac transplantation is performed for patients with symptoms refractory to aggressive medical management, and median patient survival after transplant is 11 years. Advances in medical therapy have improved 1-year survival without transplant for the highest priority (status 1) patients to nearly 70%. Absolute indications for cardiac transplantation include (1) refractory cardiogenic shock, (2) documented dependence on IV inotropic support, (3) severe ischemia not amenable to revascularization, and (4) refractory symptomatic ventricular arrhythmias. Low ejection fraction and class IV symptoms alone are not sufficient indications for transplantation. Exercise testing with $V_{O_2} \leq 10$ mL/kg/min appears to be a strong predictor of patients at high risk for death. High pulmonary vascular resistance that is unresponsive to vasodilator therapy (milrinone, dobutamine, prostaglandin E1, inhaled nitric oxide) is a contraindication to transplantation. Select patients above the age of 60 years have outcomes comparable to younger transplant recipients. Posttransplant survival in the first year is worse after left ventricular assist device use compared with other recipients.

Elevated serum troponin levels in cardiac donors are predictive of the development of early graft failure (odds ratio >40).[21] Other causes of early left ventricular dysfunction include hyperacute rejection (rare but seen with ABO mismatch, human leukocyte antigen sensitization by multiparity or transfusions) and reperfusion injury (cold ischemia time longer than 5 h). In addition to early graft failure, death after cardiac transplantation is due to acute allograft rejection, infection, allograft vasculopathy, and lymphoma or other malignancy. Acute rejection can cause ventricular dysfunction during the first months after transplantation and can be confirmed by endomyocardial biopsy. Biopsy procedures have been reported to cause traumatic tricuspid regurgitation (flail leaflet) in some patients, which may be severe.[22] Acute myocarditis due to CMV or toxoplasmosis is described, and lymphoma infiltrating the myocardium can compromise graft function and present a diagnostic challenge.

Allograft vasculopathy is an important cause of late ventricular dysfunction and mortality after transplantation and can manifest as silent myocardial infarction (due to denervation), sudden death, and congestive heart failure. Angiography is less accurate in these patients due to the diffuse distribution of disease but can predict the group with the highest mortality (left main, two primary vessels or three branch vessels >70% occluded). Noninvasive testing with dobutamine stress echocardiogram is abnormal in up to 85% of patients with high-risk disease on angiogram.

Conduction abnormalities are common (incomplete right bundle-branch block), and bradycardia may be symptomatic. Atropine is not effective due to cardiac denervation; however, the AV node remains sensitive to catecholamine therapies. Atrial dysrhythmias are common early after transplantation, and when adenosine is used for supraventricular tachycardia lower doses are recommended. Ventricular arrhythmias are observed with allograft rejection and graft vasculopathy.

Pearls

- Indications for cardiac transplantation are refractory cardiogenic shock, IV inotrope dependence, severe inoperable ischemia, and refractory symptomatic ventricular tachycardia.
- Elevated donor troponin level, prolonged cold ischemia time, and hyperacute rejection are associated with early graft dysfunction.
- Acute rejection causes ventricular dysfunction in the first several months after transplant.
- Tricuspid regurgitation is associated with multiple endomyocardial biopsy passes.
- Allograft vasculopathy causes silent myocardial infarction, sudden death, or congestive heart failure months to years after transplant.

- Atropine is ineffective for bradycardia after cardiac transplant, and sensitivity to adenosine for treatment of supraventricular tachycardia is increased.

Renal Transplantation

Renal transplantation improves the quality of life and decreases mortality for most patients compared with hemodialysis and can be beneficial over age 60. Patients with renal transplants are commonly encountered in practice, and renal transplant recipients have an increased risk of death compared with healthy control subjects. The most important cause of death is cardiovascular disease, followed by infectious complications and malignancy. Common contraindications to transplantation include heart disease, barriers to compliance, and cancer. The risk of recurrence of primary disease is not usually significant, but early transplantation is avoided for serologically active Goodpasture's disease and carefully considered for focal segmental glomerulosclerosis, which can recur quickly.

Acute graft dysfunction may be due to volume depletion, hypotension, thrombosis of renal vessels, antibody-mediated rejection (due to preexisting ABO or human leukocyte antigen antibodies; by definition hyperacute rejection occurs within first 24 h), postischemic acute tubular necrosis, atheroemboli, or ureteral/bladder obstruction. Calcineurin inhibitors are a cause of acute, reversible and chronic, irreversible renal dysfunction in all solid organ recipients, including renal allograft recipients. Infection with BK polyoma virus can affect the graft, ureters, and bladder. Late renal dysfunction may be due to chronic allograft nephropathy.

Critical care after renal transplant may be required for cardiovascular disease, acute infection, or uncontrolled hypertension. Stenosis of the renal artery supplying the allograft can cause hypertension and cardiac destabilization with flash pulmonary edema.[23] The renal artery supplying the graft may be evaluated with Doppler ultrasound, MRI, or computerized tomographic angiography, and balloon dilatation is effective in most cases.

Pearls

- Cardiovascular complications are the most common cause of death after renal transplantation, followed by infection and malignancy
- Recurrence of the primary nephropathy is unusual, with the exception of serologically active Goodpasture's disease and focal segmental glomerulosclerosis.
- Stenosis of the renal artery anastomosis may cause uncontrolled hypertension and flash pulmonary edema.

Critical Care Management of the Deceased Donor

When brain death occurs or when there is no meaningful chance of recovery in the ED, ICU, or operating room, the treating physician and an individual with specialized training in organ donation (usually the organ procurement coordinator) should address wishes for organ donation documented on the driver's license or known to the family.

Determination of brain death is based upon a comprehensive clinical assessment. A confirmatory test (eg, brain perfusion by CT angiography or nuclear imaging) is not required in the United States[24] but may be necessary if the clinical evaluation is confounded (hypothermia, overdose). The apnea test is occasionally interrupted due to hemodynamic instability or hypoxemia, and confirmatory imaging is useful in these cases.[25] Apnea testing may be complicated by pneumothorax when a high pressure oxygen catheter is placed in the airway.[26]

Brain death is accompanied by significant perturbations in hemodynamic status, endocrine function, and end organ function. Hypotension is observed in most cases and may be due to decreased sympathetic tone, volume losses due to bleeding or diabetes insipidus, adrenal insufficiency, or cerebral salt wasting. Volume resuscitation and use of vasopressors or inotropes may be required to achieve hemodynamic stability. When large losses of hypotonic urine become evident, diabetes insipidus should be suspected and treated rapidly if present. Adrenal insufficiency and thyroid dysfunction are not clinically obvious but are frequently detected biochemically, and some

centers treat organ donors with a protocol-driven approach that may include desmopressin, methylprednisolone, and levothyroxine.[27]

When a potentially suitable donor does not meet brain death criteria, but there is no hope of recovery, donation after circulatory death using cardiac criteria should be considered.[28] Critical care physicians may be requested to accompany their patients to the operating room, where discontinuation of life support measures (eg, mechanical ventilation, vasopressors, intra-aortic balloon pump, ventricular assist device) is expected to be followed by death within minutes.[29] Determination of death by a nontransplant physician (absence of circulation, respiration, responsiveness) is followed by entry of the transplant surgical team into the operating room to harvest organs, without a brief waiting period. Heparin is administered before circulatory collapse, and warm ischemia time (measured from onset of hypotension or hypoxemia to organ cooling) should not be longer than 45 min.

Pearls

- A confirmatory imaging study may be required to establish brain death if the clinical assessment cannot be completed or confounding factors are present (hypothermia, overdose).
- Brain death commonly causes hypotension and endocrine dysfunction (diabetes insipidus, adrenal insufficiency, hypothyroidism) that should be treated aggressively.
- Donation after cardiac death requires the participation of a nontransplant clinician to determine when death has occurred.

Hematopoietic Cell Transplantation (HCT)

Preparative regimens are major contributors to toxicity early after HCT using progenitor cells derived from bone marrow, peripheral blood, or umbilical cord blood. The most aggressive regimens are myeloablative and are intended to eradicate residual disease and to prevent rejection of transplanted cells. High-dose busulfan plus cyclophosphamide or cyclophosphamide plus total body irradiation have been used to achieve these goals. In patients treated with a myeloablative regimen, host hematopoietic cells are destroyed and early survival depends upon successful repopulation with progenitor cells. Transplanted cells can be derived from the patient (autologous) or a donor (allogeneic). Some HCT recipients receive a nonmyeloablative regimen (eg, fludarabine) to induce profound lymphopenia without destroying all hematopoietic cell lines. Progenitor cells from an allogeneic donor will engraft in these patients and eradicate host hematopoietic cells over time. Allogeneic HCT provides graft vs tumor effects that increase the chance of tumor eradication compared with autologous transplant.

The duration of leukopenia is shortened by routine administration of granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor after autologous HCT, but this appears to increase the risk of acute graft vs host disease and mortality after allogeneic HCT, where it is reserved for treatment of delayed engraftment. A platelet transfusion threshold of 10,000 platelets/μL in the absence of bleeding has been recommended to avoid alloimmunization against donor platelets. Packed RBCs should be irradiated to decrease the risk of transfusion-associated graft vs host and should be from CMV-seronegative donors for CMV-seronegative patients. Erythropoetin administration has not been beneficial in studies of HCT recipients.

Mucositis is a painful complication of myeloablative preparative regimens and increases the risk of aspiration and infection. Diarrhea occurs commonly after HCT and may be due to acute graft vs host disease (high volume, watery, then bloody), mucosal injury, *C difficile* or viral colitis, neutropenic enterocolitis, or cord colitis (after umbilical blood stem cell transplant). Neutropenic enterocolitis (typhlitis) should be considered in a neutropenic patient with fever and abdominal pain. Necrotizing infection usually involves the cecum, and abdominal CT scanning may demonstrate diffuse cecal wall thickening, intramural air, or evidence of perforation. Hepatic venoocclusive disease is multifactorial (graft vs host disease, preparative regimen), characterized by painful hepatomegaly, ascites, jaundice, and edema, and can progress to fulminant hepatic

failure. Encephalopathy is common during myeloablative HCT.

Infectious complications within the pre-engraftment period (first 3 to 4 weeks) include nosocomial bacteria, candidemia, molds, and viruses (herpes and respiratory).[30] Overall candidemia is decreased by triazole prophylaxis; however, resistant *Candida* species (*C krusei* and *C glabrata*) have become more common. *Aspergillus*, *Zygomycete*, and *Fusarium* spp cause invasive, nodular pulmonary disease, sinus infection, and CNS invasion. Persistent neutropenia due to delayed engraftment is an important risk factor for fungal infection. Herpes simplex virus-1 can cause severe mucositis in the absence of antiviral prophylaxis. Respiratory virus outbreaks (respiratory syncytial virus, parainfluenza, rhinovirus, influenza, metapneumovirus) in HCT centers can cause severe pulmonary disease.

In the immediate postengraftment period (3 to 4 weeks to 3 months), infection with intracellular bacteria (*Listeria*, *Legionella*), invasive molds, CMV, PCP, and toxoplasmosis should be considered. Infectious complications after the first 3 months are uncommon in autologous HCT recipients but remain an important cause of mortality, along with chronic graft vs host disease, in allogeneic recipients.

Pulmonary complications can lead to admission to the ICU after autologous or allogeneic HCT.[31,32] HCT recipients treated with myeloablative preparatory regimens can develop respiratory insufficiency due to infection, pulmonary edema (cardiogenic and noncardiogenic), diffuse alveolar damage, engraftment syndrome (fever, rash, pulmonary infiltrates), and drug toxicity from chemotherapy and irradiation. Fiberoptic bronchoscopy can be safely performed in patients with significant thrombocytopenia.[33] After autologous or allogeneic HCT, life-threatening diffuse alveolar hemorrhage is well described and presents with bilateral pulmonary infiltrates and hypoxemia, usually without hemoptysis.[34] The diagnosis is confirmed by progressively bloody lavage aliquots at bronchoscopy, and empiric treatment with corticosteroids is recommended.

After allogeneic HCT, CMV pneumonitis has a high mortality and occurs in patients with active CMV infection soon after re-engraftment. CMV infection is confirmed by direct detection of CMV antigens (blood or BAL specimens) and is treated with ganciclovir and IV immunoglobulin. Idiopathic pneumonia syndrome presents with acute onset of bilateral pulmonary infiltrates and hypoxemia within 4 months of autologous or allogeneic HCT, without evidence of infection at bronchoscopy, and has a high mortality. Chronic graft vs host disease after allogeneic transplant can lead to severe obstructive lung disease (obliterative bronchiolitis) with a high mortality.

Treatment-related mortality at 1 year is 10% after autologous HCT and approximately 50% after allogeneic HCT. Risk factors for death when admitted to the ICU after HCT are mechanical ventilation, shock, multiorgan failure, and elevated bilirubin. While mortality is high, mechanical ventilation during the engraftment period has a better outcome than mechanical ventilation in the setting of acute graft vs host disease.[35] Most patients who survive for 2 years after allogeneic HCT are alive at 10 years.

Pearls

- Acute graft vs host disease after HCT causes a high-volume, progressively bloody diarrhea and rash and is treated with immunosuppression, while neutropenic enterocolitis and *C difficile* infection may require surgical intervention.
- Hepatic venoocclusive disease presents with hepatomegaly, jaundice, and ascites after HCT and is a cause of fulminant hepatic failure.
- Serious pulmonary complications of HCT include acute pulmonary edema, CMV pneumonitis, diffuse alveolar hemorrhage, idiopathic pneumonia syndrome, and severe obstructive lung disease (late).
- Bronchoscopy with BAL can be performed safely in thrombocytopenic HCT patients with acute pulmonary disease.
- Respiratory failure after HCT has a very high mortality, and survival is unusual in the setting of acute graft vs host disease.
- Mortality at 1 year is 10% for autologous HCT and 50% for allogeneic HCT.

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Notes

Chapter 38. Acute Kidney Injury in the ICU

Harold M. Szerlip, MD, MS, FCCP

Objectives:

- Be able to define acute renal injury.
- Understand the epidemiology of renal injury in the ICU.
- Recognize the increase in mortality associated with acute renal injury.
- Identify the pathophysiology of acute kidney injury.
- Evaluate and treat a patient with acute kidney injury.

Key words: acute kidney injury; acute tubular necrosis; renal replacement; RIFLE

Synopsis:

Acute kidney injury in the ICU increases morbidity and mortality. There are now accepted criteria that define the level of injury based on either an increase in creatinine or a decrease in urine volume. The higher the stage of renal injury, the worse the outcome will be. More sensitive biomarkers are presently under investigation that will enable a diagnosis of acute kidney injury even before the creatinine begins to rise. When approaching a patient with an elevated creatinine, the clinician needs to determine whether the cause is the result of a reversible decrease in renal perfusion, injury to the kidney itself, or obstruction to urine flow. Prerenal and postrenal etiologies should be identified and promptly treated. The most common cause of kidney injury in critically ill patients is sepsis. It is now known that sepsis, by activating numerous inflammatory cytokines, causes blood flow obstruction at the microvascular level and tubular apoptosis. The treatment of patients with kidney injury is aimed at preventing complications. Renal replacement therapy should be considered early, especially in patients with oliguria. Many of the patients who suffer acute kidney injury never completely regain renal function. Because of the increased mortality associated with kidney injury, every effort should be made to identify patients at high risk and avoid insults to the kidney.

Defining Acute Kidney Injury

Renal failure in the ICU is a devastating event associated with a decrease in survival. Until recently, however, there have been no accepted criteria defining acute kidney injury (AKI). This made it difficult to compare studies related to treatment or prognosis. In 2004, an expert group put together a consensus definition of AKI known as the RIFLE (Risk, Injury, Failure, Loss, and ESRD) criteria (Table 1).[1] The first three categories describe decreases in renal function and can be defined by either an increase in creatinine or a decrease in urine output. The latter two categories represent outcomes. The RIFLE criteria were subsequently modified by the Acute Kidney Injury Network (AKIN) to include the caveat that patients had to be adequately fluid resuscitated and the acknowledgement that a change in creatinine level by as little as 0.3 mg/dL (as opposed to a 50% increase) over a 48-h period represents renal injury that prognosticates a worse outcome.[2–5] Along with the development of this specific staging came a name change: acute renal failure became AKI.

Although this staging is an important advance, the use of creatinine as the biomarker for kidney injury is problematic. A rise in creatinine may not represent true injury but merely renal insufficiency. Both hemodynamic factors and obstruction to urine flow may produce a rise in creatinine level without coexistent renal injury. In addition, medications that interfere with the tubular secretion of creatinine will elevate the serum creatinine value in the absence of renal injury. More importantly, a rise in the serum creatinine value may take 24 h or more after the initial injury before becoming significant. Such a delay prevents interventions that might be beneficial in ameliorating or actually reversing the tubular damage. Recently several biomarkers have been identified that allow for the recognition of renal injury within hours of the insult. These biomarkers include cystatin C, neutrophil gelatinase-associated lipocalin (NGAL), IL-18, kidney injury molecule 1 (KIM1), and microalbumin.[6–8] In the future, a panel of these biomarkers will enable clinicians to more precisely identify AKI and differentiate true renal injury from a more benign increase in creatinine. The biomarkers are already altering the way we think about kidney injury and what exactly is the gold standard for kidney injury. For example, these markers may be present in situations in which the creatinine does not rise or

Table 1—*Consensus Definition of AKI*

	Creatinine Value-Based	Urine Output-Based
Risk (stage 1)	Increase in creatinine × 150% Increase in creatinine by 0.3 mg/dL	Urine output < 0.5 mL/kg/h × 6 h
Injury (stage 2)	Increase in creatinine × 200%	Urine output < 0.5 mL/kg/h × 12 h
Failure (stage 3)	Increase in creatinine × 300% Or Creatinine ≥ 4.0 mg/dL with an increase by at least 0.5 mg/dL Any renal replacement	Urine output < 0.3 mL/kg/h × 24 h or anuria × 12 h
Loss	Complete loss of renal function >4 weeks	
End stage	Complete loss of renal function >3 months	

Underlined text indicates differences between AKIN criteria and RIFLE.

in which the etiology is not felt to be tubular injury but rather decreased renal blood flow.[6,9,10]

Epidemiology and Outcomes of AKI

Both the RIFLE and AKIN staging have been validated in numerous studies to predict mortality; as a patient develops worsening renal function, mortality increases.[11,12] The worse the level of injury, the longer the ICU stay will be. The relative risk of death increases from 2.4 for those classified as Risk to 4.15 for Injury and finally to 6.37 for those with Failure. Patients requiring renal replacement therapy have mortality between 44% and 53%.[13–15] It is important, however, to rule out reversible increases in creatinine that do not reflect the same poor prognosis. The relationship between a rise in the serum creatinine value and morbidity may be skewed, however, by the number of individuals in these studies who had tubular injury; whether acute glomerular disease or acute interstitial disease have the same guarded outcome as acute tubular injury remains to be determined.

Using the consensus criteria, AKI develops in 35% to 70% of patients admitted to the ICU depending on the specific patient population.[16,17] The incidence of AKI appears to be increasing either because of greater recognition of this disorder or because of the higher acuity of illness among hospitalized patients.[18] Because there are no standard criteria for the initiation of renal replacement therapy, the percentage of patients requiring dialysis is less well documented but ranges between 1% and 4% of critically ill patients. Morbidity and mortality significantly increase the higher the stage of kidney injury.

The reason for such a marked increase in mortality is not yet understood. It may be secondary to the uremic state although this would not adequately explain why minimal increases in creatinine levels worsen outcome. It is also possible that renal failure is a surrogate marker of underlying endothelial function or other inflammatory state. Patients who develop contrast-induced nephropathy not only have greater 30-day mortality but also a greater 1-year and 5-year mortality.[19] Finally, there is evidence that renal injury induces injury in other organ systems. Animal studies have shown that experimentally induced kidney injury is associated with damage in other organs such as the heart and lungs.[20,21] This suggests that there is cross-talk between the injured kidney and other organs. Death is frequently secondary to infections, respiratory failure, or GI bleeding.

Pathophysiology

Before assuming a rise in the creatinine value reflects underlying renal dysfunction, it is important to rule out spurious causes of hypercreatininemia. Drugs such as cimetidine and trimethoprim block the tubular secretion of creatinine and can give rise to elevated levels. A falsely elevated creatinine level can also be caused by substances that interfere with the chemical assay for creatinine (eg, ketones and hyperbilirubinemia). Interference occurs more commonly when measurements are made using

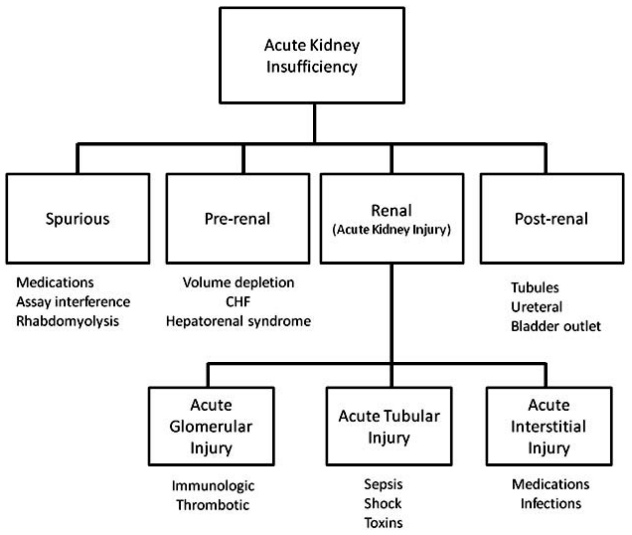

Figure 1. Schematic representation of the causes for elevation in serum creatinine levels.

the alkaline picrate method than with newer enzymatic assays. A rise in the creatinine level may also occur with rhabdomyolysis as muscle creatine is converted to creatinine.

Renal failure has classically been divided into three major categories: (1) prerenal, (2) intrinsic renal, and (3) postrenal (Fig 1). Although the development of specific biomarkers of tubular injury has raised questions concerning the relevance of this categorization, at the present time it remains a useful heuristic approach for the evaluation of azotemia. In the majority of cases of both prerenal and postrenal azotemia, prompt recognition and treatment can produce rapid reversal and prevent renal injury.

Prerenal Renal Failure

Prerenal azotemia is caused by an actual or effective decrease in intravascular volume. Intravascular volume depletion can be caused by acute blood loss, vomiting, diarrhea, the lack of adequate intake or though renal salt wasting as can occur in adrenal insufficiency. In some disease states, despite intravascular overload, the effective intravascular volume is often inadequate. This can be seen in congestive heart failure with inadequate cardiac output or in vasodilatory states such as sepsis or cirrhosis. Prerenal conditions represent the majority of cases of azotemia in the critical care setting. It is important to recognize them in order to provide appropriate therapy and prevent intrinsic renal injury.

Renal blood flow is tightly regulated throughout a wide range of perfusion pressures. As long as the mean arterial pressure remains above 70 mm Hg, renal perfusion is regulated by changes in the vascular tone of the afferent arteriole. Patients with hypertension, chronic kidney disease, diabetes mellitus, or who are taking nonsteroidal antiinflammatory drugs (NSAIDs) are less able to compensate for a decrease in perfusion pressure and require higher perfusion pressures. A decrease in intravascular volume activates a variety of baroreceptors that increase the secretion of catecholamines, angiotensin, aldosterone, and vasopressin. Glomerular filtration is maintained despite a decrease in renal perfusion by vasoconstriction of the efferent glomerular arteriole, which results in an increase in glomerular pressure and therefore the fraction of plasma filtered across the glomerular capillary (Fig 2). In addition, this hormonal cascade increases both salt and water reabsorption from the tubular lumen, thus expanding intravascular volume. The physiologic response to the decrease in renal perfusion produces the classic laboratory findings associated with prerenal renal failure (Table 2), including elevated BUN:creatinine ratio, concentrated urine, and low fractional excretion of sodium (FENa). Although such laboratory findings help support the diagnosis of a prerenal state, the astute clinician needs to recognize that these findings are not 100% sensitive or specific. Thus patients receiving diuretics may not have a low fractional excretion of sodium or concentrated urine despite intravascular volume depletion. In that case, a fractional excretion of urea less than 30% supports a prerenal state.[22] In addition, it should be recognized that a low fractional excretion of sodium can be seen in cases of intrinsic renal disease. This has been reported in AKI secondary to radiocontrast, rhabdomyolysis, and in patients who had been extremely sodium avid prior to the renal injury (eg, patients with decompensated cirrhosis or heart failure).

Hepatorenal Syndrome: A somewhat unique form of prerenal failure is hepatorenal syndrome (HRS). In patients with advanced cirrhosis or

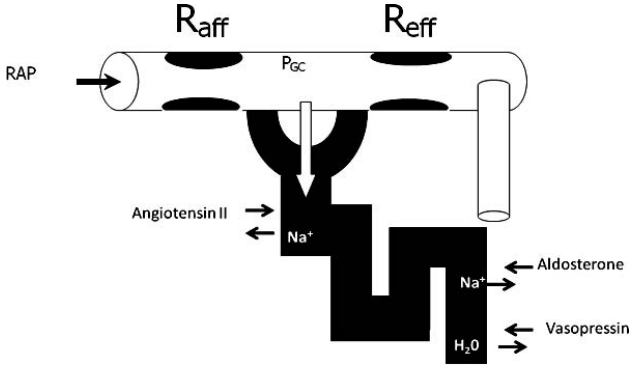

Figure 2. Hemodynamic control of renal blood flow and glomerular filtration rate. Despite variations in blood pressure, renal perfusion is maintained by altering the vascular tone of the afferent renal arteriole (Raff). Vasodilatation will increase flow to the glomerulus and vasoconstriction will decrease flow. When renal perfusion decreases, glomerular filtration is maintained by vasoconstriction of the efferent renal arteriole (Reff) with a resultant increase in glomerular pressure (Pgc).

fulminant hepatic failure dilatation of the splanchnic vascular bed with concurrent vasoconstriction of the renal vessels produces a severe prerenal state.[23] Kidneys from patients with HRS function normally when transplanted into a healthy host. HRS is usually precipitated by an acute insult such as a GI bleed or infection, in particular spontaneous bacterial peritonitis or possibly over diuresis. HRS is defined as a 50% decrease in glomerular filtration rate that occurs within a 2-week period and is unresponsive to volume expansion and discontinuation of diuretics. Oliguria is commonly present and urine sodium excretion is markedly decreased. These findings, although common, are not necessary for the diagnosis of HRS. Urinalysis is usually bland; however, marked hyperbilirubinemia can be associated with pigmented granular casts, as seen in acute tubular necrosis (ATN). The presence of greater than 50 RBCs or proteinuria greater than 500 mg/24 h points to other causes of AKI.

Abdominal Compartment Syndrome: There is growing recognition that increases in intra-abdominal pressure above 15 mm Hg can compromise renal function.[24] Abdominal pressure is easily measured using a urinary catheter connected to a manometer. Elevated intra-abdominal pressure can occur after abdominal surgery, with severe pancreatitis, mesenteric ischemia, or in patients with tense ascites. As intra-abdominal pressure rises, compression of the inferior vena cava decreases cardiac preload and therefore cardiac output. In addition an increase in the pressure in the renal veins compromises glomerular filtration. Urine output is reduced and the FENa is usually low.[25] Without appropriate treatment, renal injury will develop.

Intrinsic Renal Failure

Intrinsic renal failure is divided into the histologic area of the kidney most affected: the glomerulus, the tubule, or the interstitium. The vast majority of intrinsic renal failure in the ICU is secondary to what had been called acute tubular necrosis. Both acute glomerulonephritis and acute interstitial nephritis are far less common in the critical care setting.

Acute glomerulonephritis almost always develops prior to admission to the critical care unit. The causes are usually immunologic or thrombotic injury to the glomerulus or other small

Table 2—*Urinary Findings in AKI*

	Prerenal	Acute Tubular Necrosis	Acute Glomerulonephritis	Acute Interstitial Nephritis	Postrenal
BUN:creatinine	>20:1	10:1	>20:1	10:1	10:1
Urine sodium	<10 mEq/L	>20 mEq/L	<10 mEq/L	>20 mEq/L	>20 mEq/L
Fractional excretion of sodium (FENa)[a]	<1%	>1%	<1%	>1%	>1%
Urine osmolality	>500	~300	>500	~300	Variable
Urinalysis	Bland	Renal tubular cells; muddy brown granular casts	Dysmorphic red cells; proteinuria; red cell casts	WBCs; WBC casts; eosinophiluria	Bland

[a] (FENa) = (Serum creatinine × Urine sodium)/(Serum sodium × Urine creatinine).

blood vessels within the kidney. The obstruction of the capillary lumen from the inflammatory process or from thrombosis leads to a decline in glomerular filtration rate (GFR). The typical causes are poststreptococcal glomerulonephritis, lupus glomerulonephritis, antiglomerular basement membrane disease, antineutrophil cytoplasmic antibody-positive vasculitidies, and thrombotic microangiopathies (ie, hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, scleroderma, pre-eclampsia, malignant hypertension). The appropriate diagnosis is made by history, laboratory tests, and urinalysis. The hallmark of glomerular disease is a urinalysis showing proteinuria, dysmorphic red cells (having abnormal vesicle-shaped protrusions), and RBC casts. Acute glomerulonephritis is frequently associated with avid sodium retention and therefore a concentrated urine and low FENa.

Acute interstitial nephritis most usually occurs secondary to allergic or idiopathic reactions to medications. Although the list of drugs reported to cause interstitial nephritis is extremely long, the medications that have been most frequently implicated are antibiotics (penicillins, ciprofloxacin, trimethoprim/sulfamethoxazole, and rifampin), NSAIDs, omeprazole, lansaprozole, cimetidine, and allopurinol. The rise in creatinine level generally occurs within days of starting the medication but may happen only after months of exposure. Other causes of acute interstitial disease are infections such as legionella, cytomegalovirus, and leptospirosis. The classic triad associated with acute drug-induced interstitial nephritis is fever, rash, and eosinophilia/eosinophiluria. This triad, however, is seen in only about 10% of cases. NSAIDs, an increasingly recognized cause of interstitial nephritis, are rarely associated with these findings but more commonly cause proteinuria, which can be in the nephrotic range. Other common findings with acute interstitial are WBCs and WBC casts found on examination of the urine.

The overwhelming majority of AKI in the ICU is secondary to what has been called acute tubular necrosis. Although tubular injury is frequently associated with shock and tubular toxins, in the critical care unit approximately 60% of the cases are caused by sepsis.[14] Decreased blood flow to the nephron, either at the macrovascular or the microvascular level, compromises oxygen delivery. The straight segment of the proximal tubule and the medullary thick ascending limb of Henle are two metabolically active nephron segments that both function near hypoxic conditions and are most prone to ischemic insult. It is now recognized that in the early stages of sepsis, renal blood flow is actually increased and not decreased.[26,27] It is believed that the sepsis-induced inflammatory cascade activates both leukocytes, which attach to vascular endothelium and the coagulation pathway. These events cause reduced blood flow at the microvascular level. In addition, various cytokines induce apoptosis of tubular cells. The tight junctions between tubular cells become damaged and cell polarity is lost such that vectorial transport from the lumen to the renal interstitium no longer occurs. Furthermore, sloughing of tubular cells into the lumen causes luminal obstruction. The decrease in GFR is caused by blood flow obstruction by leukocytes, loss of tubule cell polarity, and tubular obstruction from the sloughed cells.

The serum creatinine value usually begins to rise within 24 h of the insult. Urine output can be decreased (oliguria) or normal. Anuric or oliguric renal failure is associated with worse outcome than nonoliguric renal failure, likely reflecting more extensive damage. Depending on the cause of injury, renal mesenchymal cells will begin tubular repair within 1 to 3 weeks. This leads to a polyuric phase wherein the kidney appropriately excretes excess solute and water. Rarely the kidney exhibits true salt wasting during this phase. It is important to recognize those rare patients with salt wasting and provide IV crystalloid to avoid intravascular volume depletion.

It is now known that many patients with AKI may never regain normal renal function.[28,29] Some remain dialysis dependant while others are left with chronic kidney disease that may progress to end-stage disease over time. AKI is becoming a common cause of chronic kidney disease.

In addition to sepsis, nephrotoxins are frequently implicated as causative agents producing renal injury. These toxins include radiocontrast dye, aminoglycosides, vancomycin, and myoglobin. The etiology of contrast nephropathy remains unclear but likely is caused by changes in renal hemodynamics, direct tubular toxicity, and the

production of reactive oxygen species.[30] The creatinine level rises within 24 to 72 h and usually peaks within 5 days, at which time recovery begins. Urine output may be normal or oliguria may be present. Aminoglycosides act as tubular toxins. They are reabsorbed by the proximal tubule and concentrated up to 90-fold. A rise in creatinine most commonly occurs after 5 days of therapy. In patients with chronic kidney disease, however, renal injury can be seen within several days. Because aminoglycosides are concentrated within the proximal tubule, the rise in creatinine may actually occur after discontinuation of the medication. Aminoglycoside nephrotoxicity is nonoliguric. Recovery of renal function is often prolonged and may take up to 3 to 4 weeks. Vancomycin is becoming increasingly recognized as a cause of renal injury.[31] Toxicity occurs when trough levels are elevated above 20 mg/mL.

Postrenal Failure

Obstruction anywhere within the urinary tract from the tubules to the urethra can cause renal failure. Unless there is only a solitary functioning kidney, both kidneys must be affected to produce a rise in the creatinine. Obstruction at the tubular level can be caused by uric acid crystals as can occur with tumor lysis, protein casts as seen in myeloma, or the precipitation of drugs such as acyclovir, methotrexate, sulfonamides, and indinavir. Malignancies involving the ureters or bladder trigone can obstruct both kidneys. In individuals with a single functioning kidney, renal stones or sloughed papilla can cause renal failure. Tumors, prostatic hypertrophy, anticholinergic medications, and neuropathic disease can prevent emptying of the bladder, producing renal failure. Anuria may be present, but the presence of urine output does not rule out obstructive nephropathy. It is important to review all medications. When the obstruction is at the level of the ureters or below, a pelvic ultrasound will frequently show dilation of the ureters or renal pelvis.

Prevention of AKI

Because of the morbidity and mortality associated with AKI, it is far better to prevent its occurrence than to treat it. Prevention requires recognition of those at greatest risk. Risks that increase the likelihood of AKI include older age, volume depletion, underlying chronic kidney disease, diabetes, and NSAID use. In those at risk, it is important to avoid or minimize the use renal toxins whenever possible. Intravascular volume depletion should be promptly treated. Particular attention needs to be paid to proper dosing of all medications to prevent toxicity. If aminoglycosides are indicated, once-daily dosing may produce less renal toxicity.[32] Consideration should be given to using alternate imaging modalities whenever possible to avoid intravenous radiocontrast. Volume expansion with 0.9% saline or an isotonic sodium bicarbonate solution is mandatory in at-risk individuals requiring an intravenous contrast study. These agents should be started prior to the procedure and continued after the procedure. Low osmolar or iso-osmolar contrast agents that are less nephrotoxic have routinely replaced high osmolar agents. There is no convincing evidence that n-acetylcysteine prevents contrast nephropathy, and its use is no longer routinely recommended. In patients who present with rhabdomyolysis, volume expansion with 0.9% saline or an isotonic sodium bicarbonate solution can often prevent renal injury.

Treatment of AKI

The first step in the treatment of AKI is to identify the cause. This requires a thorough history and physical, assessment of volume status, urinalysis, urine electrolytes, serologies, and a renal ultrasound (Table 3).

Prerenal Renal Failure

The treatment of prerenal renal failure depends on whether it is fluid responsive or fluid unresponsive. Fluid responsive prerenal azotemia is managed by expansion of the intravascular fluid space using isotonic crystalloid solution (0.9% saline or its equivalent). The routine use of colloids offers no benefit and should be discouraged. In cases of prerenal failure caused by hemorrhage, obviously the transfusion of RBCs is appropriate. Urine output and blood chemistries should be closely followed. It is essential to avoid

Table 3—*Evaluation of AKI*

1. History and physical to identify risk factors, renal insults, and volume status
2. Urinalysis
   a. Dysmorphic RBC, RBC casts, and proteinuria → glomerulonephritis
   b. Muddy brown casts → acute tubular necrosis
   c. WBCs, eosinophiluria, WBC casts → acute interstitial nephritis
   d. Bland urine → prerenal or postrenal failure
3. Labs
   a. Lactate → sepsis-induced acute tubular necrosis
   b. Eosinophils → acute interstitial nephritis
   c. Antinuclear antibodies → systemic lupus erythematosis
   d. Complement → low in postinfectious acute Glomerulonephritis
   e. Antiproteinase-3 antibodies (C-ANCA) → Wegeners
   f. Antimyeoperoxidase antibodies (P-ANCA) → microscopic polyarteritis
   g. Anti–glomerular basement membrane antibodies → Goodpastures
   h. Schistocytes → thrombotic microangiopathies
4. Renal ultrasound to rule out obstruction
5. Renal biopsy if etiology remains in doubt and recovery lagging

volume overload. When the cause of the decreased renal perfusion is secondary to heart failure, treatment is aimed at maximizing cardiac hemodynamics and improving cardiac output.

The treatment of hepatorenal syndrome is more problematic. Initial therapy includes intravenous albumin and the discontinuation of all diuretics. The use of the α-adrenergic agonist, midodrine, and octreatide, which inhibits the release endogenous vasodilators, has been shown to improve outcomes in small nonrandomized trials.[33] Terlipressin, a vasopressin analog, appears to improve renal function although long-term survival remains unchanged. Terlipressin, however, is not available in the United States. Dialysis is often used to treat the renal complications of HRS but does not improve outcome. Mortality in HRS is greater than 70%. The only treatment that has successfully improved survival is liver transplantation.

Patients at risk for increased abdominal pressures should have frequent measurements of urinary bladder pressure. If the pressure rises greater than 25 mm Hg, abdominal decompression either by surgical means or paracentesis is the treatment of choice.

Intrinsic Renal Failure

In patients with presumed intrinsic failure, it is important to distinguish between tubular, glomerular, and interstitial injury. The treatment of acute glomerulonephtis is beyond the scope of this chapter and should always be done in collaboration with nephrologic consultation. In cases of acute interstitial nephritis secondary to medications, discontinuation of the suspected drug is the treatment of choice. Steroids may hasten the time to recovery and are often used.[34] In cases of tubular injury, the goal is to avoid further insults and prevent complications. The use of a loop diuretic to increase urine flow is indicated only if there is clear evidence of volume overload. Inappropriate use of diuretics has been associated with worse outcomes.[35] Whenever possible, all nephrotoxins should be withdrawn. Medications should be dosed appropriately for the level of GFR. It is essential to remember that using mathematical formulas to calculate GFR require a steady state. If the creatinine is rising, GFR should be considered to be less than 15 mL/min. When available, therapeutic drug monitoring will help guide proper dosing. Azotemia decreases protein binding of certain drugs (eg, phenytoin), necessitating measurement of free levels. Avoid volume overload and hyperkalemia by limiting intravenous fluids and potassium supplementation. In patients with clear evidence of volume overload, loop diuretics may be useful in decreasing intravascular volume and possibly improving survival.[36] If the serum potassium increases above 5.5 mEq/L, therapy should be aimed at removing potassium from the body. If the patient

has adequate urine output and appears able to respond to diuretics, the administration of a loop diuretic may increase urinary potassium losses. Otherwise, attempts should be made to increase gastrointestinal losses of potassium. Sodium polystyrene sulfonate mixed with 33% sorbitol is the agent commonly employed; however, because of reported cases of GI ulcerations caused by sorbitol and the unclear efficacy of this resin when administered without sorbitol, its use has become somewhat controversial.[37,38]

One of the most difficult questions to answer is when to initiate renal replacement therapy. In the past, dialysis was not begun until there was clear evidence of complications. These complications included uremic symptoms, unresponsive volume overload, severe metabolic acidosis, or hyperkalemia. More recently there has been a paradigm shift toward beginning dialysis earlier. Retrospective analysis of existing data suggests that early dialysis is better than late dialysis.[39,40] Because there are no randomized controlled trials, exactly what constitutes early remains undetermined. It is clear that intravascular volume overload prognosticates a worse outcome in the critically ill.[41] Thus, dialysis is usually initiated earlier in oliguric patients than in patients with good urine output.

What mode of dialysis to use is presently based on center preference. Renal replacement therapy can be done using hemodialysis or peritoneal dialysis. The use of peritoneal dialysis in the United States has fallen out of favor because of cost, and lack of evidence supporting its efficacy in critically ill patients. Small studies comparing peritoneal dialysis to hemodialysis have shown conflicting results.[42,43] Blood side therapies have become the modality of choice. Hemodialysis requires placement of a large bore, double lumen catheter in a central vein. The right internal jugular is the vein of choice. In addition, to avoid clotting of the hemodialysis circuit, anticoagulation using heparin or citrate is often necessary.

In hemodynamically unstable patients, the tendency is to use continuous replacement over intermittent therapies. Several studies, however, have not shown a difference in outcomes between these two modalities.[44,45] In fact, there is a suggestion that continuous treatment may be associated with worse outcomes.[46] One of the reasons continuous therapy may be associated with a worse outcome is the difficulty in appropriately dosing antibiotics when using this modality. Without a large randomized trial, a definitive answer cannot be given. Continuous renal replacement can be performed using hemodialysis (CVVHD), hemofiltration (CVVHF), or a combination of the two, hemodiafiltration (CVVHDF). In dialysis, clearance is accomplished by diffusion of low-molecular-weight solutes across a semipermeable membrane. With hemofiltration, a pressure gradient is applied across a relatively porous membrane, producing an ultrafiltrate of plasma. The ultrafiltrate is replaced with an appropriate electrolyte solution. Which one of these techniques to use is again center-dependent.

Small studies had suggested that more intensive therapy improved survival when compared with less intense treatment.[47,48] Two recent well-done randomized trials have answered the question of how intense the renal replacement should be.[13,15] There appears to be a minimum solute clearance necessary above which further clearance does not improve survival and is associated with more adverse events. For continuous therapies, an effluent flow rate of 20 to 25 mL/kg/h had the same survival and less adverse events than an effluent flow rate of 35 to 40 mL/kg/h. For intermittent therapy dialysis three times a week, providing a urea clearance as measured by Kt/V of 1.3 had the same survival as intermittent therapy six times a week.

Postrenal Renal Failure

In patients with obstructive uropathy, the treatment depends on the level of obstruction. If the obstruction is reversed quickly, renal injury can be avoided. Simply placing a urinary catheter will alleviate obstruction at the bladder outlet. If the obstruction is within the ureters or at the ureteral-pelvic junction, retrograde or antegrade nephrostomy tubes will be necessary. Obstruction within the tubules is more difficult to treat. The goal is to try to wash out the crystals by volume expansion. The solubility of urate, methotrexate, and sulfonamide crystals is increased at alkaline pH. Therefore, alkalization of

the urine with sodium bicarbonate is often helpful. In patients receiving methotrexate who have worsening renal function and elevated methotrexate levels, glucarpidase will rapidly lower methotrexate levels.

Conclusion

In conclusion, kidney injury in the ICU is a catastrophic event associated with increased morbidity and mortality. It is important to identify those patients at risk and institute preventative strategies to avoid nephrotoxicity. Once renal failure develops, attention needs to be paid to appropriate drug dosing and avoidance of complications. Renal replacement therapy should be initiated early enough to avoid complications.

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Notes

Chapter 39. Nervous System Infections and Catheter Infections

George H. Karam, MD, FCCP

Objectives:

- Review clinical presentations of nervous system infections that may present as serious or life-threatening processes.
- Outline principles influencing diagnosis and management of nervous system infections.
- Present an approach to infections related to catheters placed in the vasculature, urinary bladder, or peritoneum.
- Summarize existing opinions and data about management of catheter-related infections.

Key words: botulism; brain abscess; catheter-related infections; cavernous sinus thrombosis; encephalitis; meningitis; rabies; spinal epidural abscess

Synopsis:

Infection affecting various parts of the nervous system has the potential to be life-threatening or to result in severe sequelae if the infection is not appropriately diagnosed and treated. Although infections such as meningitis, encephalitis, and brain abscess are the most frequently encountered, processes such as spinal epidural abscess, septic intracranial thrombophlebitis, rabies, and botulism may present as emergent problems that require a high level of clinical suspicion for prompt diagnoses to be made. Infections associated with catheters placed in the vasculature, urinary bladder, or peritoneum can also result in morbidity and create diagnostic or therapeutic dilemmas for the clinician. This review will attempt to summarize these infections as they relate to the critical care setting.

Nervous System Infections

Meningitis

From 1986 to 1995, the median age of persons with bacterial meningitis increased from 15 months to 25 years, making meningitis in the US predominantly a disease of adults rather than of infants and young children.[1]

The basic diagnostic tool in the diagnosis of meningitis is examination of cerebrospinal fluid (CSF). When such fluid is obtained, important clinical studies include (1) stains and cultures, (2) glucose, (3) protein, and (4) cell count with differential. Gram stain and culture of CSF are highly specific but may have a median sensitivity of about 75%. Helpful in understanding the pathogenesis of meningitis due to varied processes is the CSF glucose level. Glucose enters the CSF by facilitated transport across choroid plexuses and capillaries lining the CSF space.[2] Normally the CSF to blood glucose ratio is 0.6. Although consumption of glucose by white blood cells and organisms may contribute to low CSF glucose levels (which is referred to as hypoglycorrhachia), the major mechanism for low glucose levels is impaired transport into the CSF; this classically occurs because of acute inflammation or with infiltration of the meninges by granulomas or malignant cells. Protein is usually excluded from the CSF but levels rise after disruption of the blood-brain barrier. Levels are lower in cisternal and ventricular CSF than in lumbar CSF. Usual elevations in patients with meningitis are in the 100 to 500 mg/dL range. Extreme elevations (ie, >1,000 mg/dL) are often indicative of subarachnoid block. When protein levels exceed 150 mg/dL, the fluid may appear xanthochromic.

The diagnosis of meningitis is made by the finding of a CSF pleocytosis and may occur on the basis of both infectious and noninfectious processes. In the absence of a positive stain result for the CSF, the most helpful study in the initial approach to the patient with meningitis is a cell count with differential on the CSF. As summarized in Table 1, an approach for diagnosing the etiology of meningitis, based on the CSF analysis, would include three common categories: (1) polymorphonuclear meningitis, (2) lymphocytic meningitis with a normal glucose level, and (3) lymphocytic meningitis with a low glucose level. In addition, on rare occasions patients may have a predominance of eosinophils in the CSF, but eosinophilic meningitis is uncommon.

Table 1—*An Approach to CSF Pleocytosis*[a]

Polymorphonuclear	Lymphocytic With Normal Glucose Level	Lymphocytic With Low Glucose Level
Bacterial (see Table 2)	Viral meningitis	Fungal
Early meningitis	Enteroviruses, including poliovirus	Tuberculous
Tuberculosis	Herpes simplex virus (usually type 2)	Certain forms of meningoencephalitis (eg, herpes simplex) or viral meningitis
Fungal	HIV	Partially treated bacterial meningitis
Viral	Adenovirus	Carcinomatous meningitis
Drug induced	Tick-borne viruses	Subarachnoid hemorrhage
Parameningeal foci	Meningoencephalitis, including viral causes	Chemical meningitis
Brain abscess	Parameningeal foci	
Subdural empyema	Partially treated bacterial meningitis	
Epidural abscess	Listeria meningitis	
Sinusitis	Spirochetal infections	
Mastoiditis	Syphilis	
Osteomyelitis	Leptospirosis	
Persistent neutrophilic meningitis	Lyme disease	
	Rickettsial infections	
	Rocky Mountain spotted fever	
	Ehrlichiosis	
	Infective endocarditis	
	Immune-mediated diseases	
	Sarcoidosis	
	Drug-induced	

[a] Although not clinically common in the US, eosinophilic meningitis can occur, and the characteristic pathogens causing such a process are *Angiostrongylus cantonesis*, *Trichinella spiralis*, *Taenia solium*, *Toxocara canis*, *Gnathostoma spinigerum*, *Paragonimus westwermani*, and *Baylisascaris procyonis*.

Polymorphonuclear Meningitis: Because of the acute inflammation, this process is usually associated with a low CSF glucose level owing to impaired transport across the meninges. This is most notable with bacterial meningitis. In the differential diagnosis of polymorphonuclear meningitis, there are four major groups of disease: (1) bacterial infection, (2) the early meningeal response to any type of infection or inflammation, (3) parameningeal foci, and (4) persistent neutrophilic meningitis. Because of the sequelae that may be associated with a delay in therapy, the single most important cause of a polymorphonuclear meningitis is bacterial infection. Discussion in this syllabus will be limited to this topic.

Likely etiologic agents for bacterial meningitis are summarized in Table 2 from the perspectives of (1) the age of the patient, and (2) underlying predispositions to meningitis. Presented in a different manner, rates of meningitis per 100,000 population in 22 counties in four states revealed the following: *Streptococcus pneumoniae*, 1.1; *Neisseria meningitidis*, 0.6; group B streptococci, 0.3; *Listeria monocytogenes*, 0.2; and *Haemophilus influenzae*, 0.2.[1] The most notable change in etiologic agents during the past decade has been the dramatic decrease in the incidence of *H influenzae* meningitis, which has occurred as a result of vaccination against this pathogen.

Although pneumococci are the most common pathogens in bacterial meningitis, the problematic strains of *S pneumoniae* are those that are penicillin resistant. Strains with relative, or intermediate, resistance will have a penicillin minimal inhibitory concentration (MIC) of 0.12 to 1.0 μg/mL. High-level resistance to penicillin is defined as an MIC $\geq$2 μg/mL.[3] Compounding this problem is the inability of certain antibiotics to cross the blood-brain barrier effectively enough to yield CSF levels significantly above the MIC for the infecting organism. For pneumococcal meningitis caused by penicillin-susceptible strains, penicillin G and ampicillin are equally effective. Although high-dose penicillin (150,000 to 250,000 units/kg/d) has been useful in patients with pneumonia caused by strains of pneumococci with intermediate resistance, such high doses do not predictably lead to CSF levels of penicillin that exceed the MIC of intermediately resistant strains.[4]

Table 2—*Likely Pathogens in Bacterial Meningitis Based on Patient's Age or Underlying Conditions*

Neonates	Enterobacteriaceae, group B streptococci, *Listeria monocytogenes*
Age <6 y	*Neisseria meningitidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae*
Age 6 y to young adult	*N meningitidis*, *S pneumoniae*
Adults <50 y	*S pneumoniae*, *N meningitidis*
Alcoholic and elderly	*S pneumoniae*, *N meningitides*, Enterobacteriaceae, *L monocytogenes*
Closed skull fracture	*S pneumoniae*, *H influenzae*, *Staphylococcus aureus*, coagulase-negative staphylococci, Gram-negative bacilli
Open skull fracture	Gram-negative bacilli, including *Klebsiella pneumoniae* and *Acinetobacter calcoaceticus* (when meningitis develops from a contiguous postoperative traumatic wound infection), *S aureus*
Penetrating trauma; postneurosurgery	*S aureus*, coagulase-negative staphylococci, aerobic gram-negative bacilli (including *Pseudomonas aeruginosa*)
CSF leak	*S pneumoniae*, *H influenzae*, gram-negative bacilli staphylococci
CSF shunt associated	Coagulase-negative staphylococci, *S aureus*, aerobic gram-negative bacilli (including *P aeruginosa*), *Propionibacterium acnes*
Diabetes	*S pneumoniae*, gram-negative bacilli, *S aureus*
Defects in cell-mediated immunity	*L monocytogenes*
Concern of bioterrorism	*Bacillus anthracis*

In 2002, the National Committee for Clinical Laboratory Standards began offering differing cephalosporin breakpoints for pneumococcal susceptibility based on the site of infections.[5] For *S pneumoniae* from a meningeal source, the ceftriaxone and cefotaxime breakpoints were listed as follows: susceptible, 0.5 μg/mL; intermediate susceptibility, 1 μg/mL; and resistant, 2 μg/mL. This was in contrast to nonmeningeal breakpoints, which were stated as follows: susceptible, 1 μg/mL; intermediate susceptibility, 2 μg/mL; and resistant, 4 μg/mL.[5] These recommendations have been repeated in subsequent National Committee for Clinical Laboratory Standards reports.[3] To assess the effect of these new criteria on reporting of nonsusceptible *S pneumoniae* isolates, the Centers for Disease Control and Prevention (CDC) analyzed cefotaxime MIC data from the Active Bacterial Core Surveillance of the Emerging Infections Program Network from 1998 to 2001.[6] This analysis indicated that after the new criteria were applied, the number of isolates defined as nonsusceptible to cefotaxime decreased 52.1% to 61.2% each year. Even though cefotaxime or ceftriaxone has been recommended for pneumococci with intermediate susceptibility to penicillin, clinical failures have been reported when these agents have been used for such strains. For isolates with high-level resistance, vancomycin is the drug of choice. The less-than-optimal penetration of vancomycin into CSF has an impact on this therapeutic option. Steroids given concomitantly for meningitis may further decrease vancomycin's penetration.

In December 2004, the Infectious Diseases Society of America (IDSA) published recommendations for the management of bacterial meningitis[7] to update recommendations that have been available since 1997.[8] A summary of the empiric therapy recommendations from those guidelines is included in Table 3. Because of the importance of *S pneumoniae*, including those strains demonstrating antibiotic resistance, the guidelines provided an approach to therapy of proven pneumococcal meningitis based on in vitro susceptibility. For penicillin-susceptible isolates, penicillin or ampicillin was suggested. With intermediate susceptibility to penicillin (MIC, 0.1–1.0 μg/mL), a third-generation cephalosporin was recommended. It was suggested that the regimen of a broad-spectrum cephalosporin plus vancomycin be used if the *S pneumoniae* isolate is resistant to penicillin (MIC ≥2 μg/mL) and to ceftriaxone and cefotaxime (MIC ≥1 μg/mL). Clinical data on the efficacy of rifampin in patients with bacterial meningitis are lacking but some authorities would use this agent in combination with a third-generation cephalosporin, with or without vancomycin, in patients with pneumococcal meningitis caused by highly penicillin- or cephalosporin-resistant strains.[7] This statement was qualified in the IDSA guidelines for treatment of bacterial meningitis with the

Table 3—*CSF Recommendations for Empiric Therapy for Meningitis When Lumbar Puncture Is Delayed or for Patients With a Nondiagnostic CSF Gram Stain*

Patient Group	Recommended Drugs
Age 2 to 50 y	Vancomycin plus a third-generation cephalosporin
Age >50 y	Vancomycin plus ampicillin plus a third-generation cephalosporin
Penetrating head trauma, or post neurosurgery, or CSF shunt	Vancomycin plus ceftazidime or vancomycin plus cefepime,[a] or vancomycin plus meropenem[b]

Adapted from Tunkel and colleagues.[7]
[a] Not approved by the FDA for meningitis.
[b] FDA-approved for bacterial meningitis in pediatric patients aged ≥3 mo.

comment that rifampin should be added only if the organism is shown to be susceptible and there is a delay in the expected clinical or bacteriologic response. The usual duration of therapy for pneumococcal meningitis is generally stated to be 10 to 14 days.[7]

The role of steroids in adults with meningitis has not been definitively established. An early opinion by experts in the field suggested that adult patients who might be candidates for steroid therapy in meningitis are those with a high CSF concentration of bacteria (ie, demonstrable bacteria on Gram stain of CSF), especially if there is increased intracranial pressure.[9] A prospective, randomized, double-blind, multicenter trial[10] assessed the value of adjuvant treatment with dexamethasone compared with placebo in adults 17 years of age or older with suspected meningitis who had cloudy CSF, bacteria in CSF on Gram staining, or a CSF leukocyte count of >1,000/mL. Early treatment with dexamethasone was shown to improve the outcome and did not increase the risk of GI bleeding. The dose of dexamethasone used in this study was 10 mg IV q6h for 4 days. In the 2004 IDSA guidelines for the treatment of bacterial meningitis in adults, it was recommended that dexamethasone (0.15 mg/kg q6h for 2 to 4 days, with the first dose administered 10 to 20 min before, or at least concomitant with, the first dose of antimicrobial therapy) be given in adults with suspected or proven pneumococcal meningitis.[7] It was stated that adjunctive dexamethasone should not be given to adult patients who have already received antimicrobial therapy, because administration of dexamethasone in this circumstance is unlikely to improve patient outcome. Even though the data are inadequate to recommend adjunctive dexamethasone in adults with meningitis caused by bacterial pathogens other than *S pneumoniae*, it was acknowledged that some authorities would initiate dexamethasone in all adults because the etiology of meningitis is not always ascertained at initial evaluation.[7]

The infectious syndromes caused by *N meningitidis* are somewhat broad and include meningococcal meningitis, meningococcal bacteremia, meningococcemia (purpura fulminans and the Waterhouse-Friderichsen syndrome), respiratory tract infections (pneumonia, epiglottitis, otitis media), focal infection (conjunctivitis, septic arthritis, urethritis, purulent pericarditis), and chronic meningococcemia.[11] Important in the pathogenesis of the clinical illnesses caused by the meningococcus is the organism's natural reservoir in the nasopharynx. It is this site from which disease may develop. The epidemiology of meningococcal meningitis is evolving. The traditional groups of patients at risk have included children and young adults, especially college students or military recruits who live in relatively confined quarters. A report from Argentina[12] described epidemic meningococcal disease in the northeastern part of that country associated with disco patronage, supporting the pathogenetic point that close confinement allows aerosolization and spread of the organism from the nasopharynx. An additional observation from this study, which has been raised in previous studies, is the association with passive or active cigarette smoking. This report, which was titled "Disco Fever," expanded the closed settings in which meningococcal meningitis originates to include dance clubs and discos. Air travel-associated meningococcal disease has also been

described and is defined for a patient who meets the case definition of meningococcal disease within 14 days of travel on a flight of at least 8-h duration.[13] Pneumonia, sinusitis, and tracheobronchitis are important sources of bacteremic meningococcal disease. Although meningitis is the characteristic infection caused by *N meningitidis*, a report from Atlanta noted that only 14 of the 44 adult patients (32%) with meningococcal infection had meningitis.[14] When it occurs, meningococcal meningitis is usually acute and often associated with purpuric skin lesions (although the Atlanta report noted that only 10 of the 14 adults with meningitis [71%] had a generalized rash). During the very early stages of infection, the CSF analysis may be relatively normal even though the clinical course is hyperacute with fever, nuchal rigidity, and coma. Although variably reported through the years, the potential for *N meningitidis* to cause purulent pericarditis should be noted. The illness may progress to acidosis, tissue hypoxia, shock, disseminated intravascular coagulopathy, and hemorrhagic adrenal infarction. The potential for β-lactamase-producing strains remains a concern as does the existence of relatively resistant strains, presumably caused by alterations in the penicillin-binding proteins; however, active surveillance among a large, diverse population in the US has failed to identify any such strains.[15] Penicillin or ampicillin, therefore, remains a drug of choice for treating meningitis caused by this pathogen. The usual duration of therapy is generally 7 days.[7]

With meningococcemia, a fulminant complication is acute, massive adrenal hemorrhage with the resultant clinical entity of the Waterhouse-Friderichsen syndrome. However, not all patients who die of meningococcemia have evidence of adrenal hemorrhage at autopsy, and many steroid-treated patients succumb despite therapy, implying that adrenal insufficiency may not be the primary cause of circulatory collapse. Because of the implications of such a complication, it would be helpful to have definitive recommendations about the role, if any, of steroids in management of patients with meningococcal meningitis. There are anecdotal reports in the literature of improved outcome in such patients treated with corticosteroids. In some patients with meningococcal infection, cortisol levels may be elevated. In contrast, other reports have noted that not all patients with severe meningococcal infection who have been given adrenocorticotropic hormone have responded to adrenocorticotropic hormone stimulation of cortisol production, and this raises the issues of whether adrenal reserves may be decreased in certain patients and whether steroids may have a role. In 1992, IDSA published a review of the role of steroids in patients with infectious diseases.[16] There were 10 infections for which steroids were strongly supported or suggested as having a role, and meningococcemia was not one of those listed. At the present time, the role of steroids in meningococcemia is unresolved. Because fulminant meningococcal septicemia represents an extreme form of endotoxin-induced sepsis and coagulopathy, with clinical consequences that include amputations and organ failure, investigators have addressed other potential therapeutic modalities that may be beneficial in patients with overwhelming meningococcal infection. The dual function of protein C as an anticoagulant and as a modulator of the inflammatory response was recently reviewed in the context of experimental data showing that activated protein C replacement therapy reduces the mortality rate for fulminant meningococcemia.[17] Such data become especially noteworthy given the efficacy and safety data about recombinant human activated protein C in patients with severe sepsis.[18]

In patients treated with penicillin for meningococcal meningitis, posttreatment with rifampin, ciprofloxacin, or ceftriaxone has been recommended to eradicate the nasal carrier state, as penicillin will not eliminate organisms at this site.[19] These recommendations are similar to those for chemoprophylaxis for individuals exposed to a person with known meningococcal disease. Those recommendations are summarized in Table 4. Prophylaxis is recommended for close contacts, which include household members, day-care center contacts, and anyone directly exposed to the patient's oral secretions (eg, kissing, mouth-to-mouth resuscitation, endotracheal intubation, endotracheal tube management). Because the rate of secondary disease for close contacts is highest during the first few

Table 4—*Schedule for Administering Chemoprophylaxis Against Meningococcal Disease*

Drug	Age Group	Dosage	Duration/Route of Administration[a]
Rifampin[b]	Children <1 mo	5 mg/kg q12h	2 Days
	Children >1 mo	10 mg/kg q12h	2 Days
	Adults	600 mg q12h	2 Days
Ciprofloxacin[c]	Adults	500 mg	Single dose
Ceftriaxone	Children <15 y	125 mg	Single IM dose
	Adults	250 mg	Single IM dose

Reprinted from the Centers for Disease Control and Prevention.[19]

[a] Oral administration unless indicated otherwise.

[b] Rifampin is not recommended for pregnant women because the drug is teratogenic in laboratory animals. Because the reliability of oral contraceptives may be affected by rifampin therapy, consideration should be given to using alternative contraceptive measures while rifampin is being administered.

[c] Ciprofloxacin generally is not recommended for persons aged <18 years or for pregnant and lactating women, because the drug causes cartilage damage in immature laboratory animals. However, ciprofloxacin can be used for chemoprophylaxis in children when no acceptable alternative is available.

days after the onset of disease in the primary patient, antimicrobial chemoprophylaxis should be administered as soon as possible (ideally within 24 h after the case is identified). Chemoprophylaxis administered >14 days has been stated to be of limited or no value.[13]

Since 1991, there have been increased numbers of outbreaks of serogroup C meningococcal disease in the US. Meningococcal polysaccharide vaccine has been shown to be effective against serogroup C meningococcal disease in a community outbreak, with a vaccine efficacy among 2- to 29-year-old persons of 85%.[20] Based on this observation, it has been recommended that emphasis be placed on achieving high vaccination coverage in future outbreaks, with special efforts to vaccinate young adults. The Advisory Committee on Immunization Practices and the American Academy of Pediatrics have recommended that health-care providers and colleges educate freshmen college students—especially those who live in dormitories—and their parents about the increased risk of meningococcal diseases and the potential benefits of immunization so that informed decisions about vaccination can be made.[21] A predisposing factor for neisserial infections is deficiency in the late complement components (ie, C5 to C8). Because previous studies have demonstrated an incidence as high as 39% in populations of patients with meningococcal infections, at a minimum a screening test for complement function (CH_{50}) has been suggested for all patients who have invasive meningococcal infections[22]; it was also noted that direct assessment of complement (C5, C6, C7, C8, and C9) and properdin proteins should be considered.

Like the meningococcus, *H influenzae* may be isolated from the nasopharynx, and this may be the immediate source of invading pathogens. Rates of infection caused by this pathogen have decreased because of vaccination against *H influenzae*. In patients with meningitis due to this organism, a contiguous focus of infection such as sinusitis or otitis media should be investigated. In adults without these underlying processes, a search for a CSF leak, which may be the basis for the meningitis, is necessary. Because about one-third of *H influenzae* isolates are β-lactamase producers, agents that are stable in the presence of these enzymes and that cross the blood-brain barrier should be used. The third-generation cephalosporins cefotaxime and ceftriaxone have had the most successful record of use in this regard. Even though the second-generation cephalosporin cefuroxime is active against *H influenzae*, it has been shown to result in delayed sterilization of the CSF when compared with ceftriaxone.[23] A lower incidence of sensorineural hearing loss was demonstrated in children who adjunctively received dexamethasone (3.3%) vs those who did not receive steroids (15.5%). Similar findings have not been corroborated in adults. The usual duration of therapy for *H influenzae* meningitis is generally 7 days.[7]

Meningitis due to gram-negative bacilli occurs most characteristically after neurosurgical procedures, with head trauma being a less likely

predisposition. Medical conditions, including urosepsis, account for about 20% of episodes of this infection. In certain patient populations in which gram-negative meningitis develops in the setting of impaired cell-mediated immunity, one should exclude *Strongyloides stercoralis* infection as the underlying predisposing cause. Of note, hyperinfection with the resultant predisposition to gram-negative meningitis is uncommon in two groups of patients with defects in cell-mediated immunity: (1) transplant recipients who receive cyclosporine, because of the anthelminthic properties of this rejection agent; and (2) HIV-infected patients, unless the $CD4^+$ cell count is $\leq$200 cells/mL and the patient is concomitantly receiving corticosteroids.[24] Parenterally administered aminoglycosides do not cross the blood-brain barrier after the 28th day of life. For these antibiotics to be useful beyond the neonatal period, they need to be administered intrathecally or intraventricularly. Chloramphenicol has activity against some gram-negative bacilli, and it crosses the blood-brain barrier. Concern about toxicity issues such as aplastic anemia has decreased the use of this agent over the years, although it still plays an important role in persons with meningitis and type I (IgE-mediated) hypersensitivity to penicillins. Third-generation cephalosporins have become the mainstay of therapy for gram-negative meningitis because of their spectrum and their penetration into the CSF. All of the presently available third-generation agents except for cefoperazone have an indication for meningitis due to susceptible pathogens. For meningitis due to *Pseudomonas aeruginosa*, ceftazidime is an efficacious agent. It is usually administered with a parenteral aminoglycoside, recognizing that this latter agent will not cross the blood-brain barrier in adults but that it might help to eradicate the site of infection outside the CNS that served as the focus for the meningitis. According to the recent IDSA guidelines for the management of bacterial meningitis, cefepime has greater in vitro activity than the third-generation cephalosporins against Enterobacter spp and *P aeruginosa* and it has been used successfully in some patients with meningitis caused by these bacteria.[7] The guidelines summarized these observations by stating that they support cefepime as a useful agent in the treatment of patients with bacterial meningitis. This should be taken within the context that as of 2005, cefepime does not have an Food and Drug Administration (FDA)-approved indication for the treatment of bacterial meningitis.[25] For meningitis due to gram-negative pathogens, the IDSA guidelines list 21 days as the duration of therapy.[7]

Pharmacologic and microbiologic issues are important for two important pathogens that cause meningitis. *L monocytogenes* is an intracellular gram-positive rod that characteristically infects persons with defects in cell-mediated immunity. It may also cause disease in diabetics and elderly persons, and about 30% of infected adults have no apparent risk. Acquisition has been associated with consumption of contaminated coleslaw, milk, and cheese. Although the CSF cellular response is usually polymorphonuclear, some patients present either with lymphocytes or with a normal glucose level. Like fungal and tuberculous meningitis, Listeria meningitis has a predilection for involving the meninges at the base of the brain. This may lead to hydrocephalus. Ampicillin or penicillin is the drug of choice and there is no significant activity by third-generation cephalosporins against this pathogen.[26] Some experts suggest the addition of an aminoglycoside given parenterally because of in vitro synergy. For those patients who are allergic to penicillin, trimethoprim-sulfamethoxazole is the agent of choice. Because of the intracellular location of this pathogen, 21 days of therapy have been recommended.[7] A review of *Staphylococcus aureus* meningitis divided this disease entity into two categories: (1) hospital acquired and (2) community acquired.[27] It was noted that hospital-acquired infection occurred as an occasional complication of neurosurgical procedures, with the presence of medical devices, or with certain skin infections; it generally had a favorable prognosis and a relatively low mortality rate. In contrast, community-acquired *S aureus* meningitis was associated with valvular heart disease, diabetes mellitus, or drug or alcohol abuse, and the mortality rate was significantly higher than for nosocomial infection. In this review of 28 patients with community-acquired *S aureus* meningitis, 8 had negative or no CSF culture findings. Of these eight patients, four had received antibiotics before lumbar puncture. This finding is

consistent with the observation that an important presentation of *S aureus* is in patients with addict-associated infective endocarditis. For *S aureus*, nafcillin or oxacillin has better activity against methicillin-sensitive strains than does vancomycin. In addition, the penetration of vancomycin into CSF may be variable, even in the setting of meningeal inflammation.

Beginning with the September 11, 2001, episode of terrorism in the United States, anthrax is an important consideration in the differential diagnosis of patients with a life-threatening illness that includes a meningeal component. Inhalational anthrax is a biphasic clinical syndrome with initial nonspecific flulike symptoms (fatigue, malaise, myalgia, headache, nonproductive cough, and nausea/vomiting), followed by a second phase with hemodynamic collapse, septic shock/multiorgan dysfunction syndrome, and rapid death with overwhelming bacterial spread. It is during the stage of bacteremia that there is a strong likelihood of meningitis, which some sources cite as occurring in 50% of cases. The index case of bioterrorism anthrax in Florida presented with hemorrhagic meningitis,[28] which is characteristic of disseminated anthrax; however, meningitis without hemorrhage can occur with anthrax. In patients in whom infection with *Bacillus anthracis* is suspected to be the cause of meningitis, some have suggested adding either penicillin or chloramphenicol to the multidrug regimen that would be given for inhalational anthrax.[29]

Empiric therapy for meningitis has changed in recent years. In previously healthy, nonallergic individuals with acute pyogenic community-acquired meningitis for whom little information is available, ampicillin was suggested in a 1993 review as a reasonable empiric agent.[30] For patients with a type I (IgE-mediated) penicillin allergy, chloramphenicol was offered in that review as appropriate therapy. In 1997, recommendations suggested a broad-spectrum cephalosporin (eg, cefotaxime or ceftriaxone) as empiric therapy for individuals aged 18 to 50 years who have a nondiagnostic Gram stain.[8] As summarized in Table 3, the 2004 IDSA guidelines suggested vancomycin plus a third-generation cephalosporin as empiric therapy of meningitis when lumbar puncture is delayed or in patients with a nondiagnostic CSF Gram stain.[7] This evolution from 1993 to 2004 in the recommendations for empiric therapy of meningitis is influenced by penicillin resistance in pneumococci. The addition of ampicillin to a broad-spectrum cephalosporin plus vancomycin is reasonable empiric therapy for polymorphonuclear meningitis undiagnosed by Gram stain in patient populations with the following underlying conditions: (1) advanced age; (2) alcoholism; and (3) immunocompromised states. The activity by ampicillin against *Listeria* is an important component of the coverage in this regimen.

Certain epidemiologic situations may exist that influence the acquisition of specific pathogens, which may then cause meningitis. Those conditions (including skull fractures and shunt-associated infections) and the pathogens likely to occur in their setting are summarized in Table 2.

Lymphocytic Meningitis With Normal Glucose Level: The meningeal response to infection or inflammation may be less marked in certain conditions, and the response may therefore be less associated with the inability to transport glucose across the meninges. Those conditions associated with the findings of lymphocytes and normal glucose levels in the CSF are listed in Table 1. The classic consideration in this differential has been viral meningitis. Enteroviruses, which are recognized causes of pleurodynia and pericarditis, are the most common cause of aseptic meningitis and characteristically cause a self-limited form of meningitis that presents with fever, headache, and lymphocytic pleocytosis, most often in the late summer or early fall. Recently, however, two other viruses have gained importance in the differential diagnosis of viral meningitis. With initial episodes or flares of genital herpes simplex virus (HSV) infection, patients may develop meningitis as a systemic manifestation of their herpes infection. This process is distinctly different from the life-threatening entity of herpes encephalitis in that it is self-limited and does not require therapy. Because of the propensity for herpes genitalis to recur, this form of meningitis may similarly present as a recurrent form of lymphocytic meningitis. HIV has a predilection for neural tissue, and patients, including those with the acute retroviral syndrome, may present with

viral meningitis that may resolve spontaneously. In those individuals who have risk factors for HIV and present with an illness consistent with viral meningitis, HIV infection is an important consideration.

Encephalitis may occur on the basis of both infectious and noninfectious causes. When these conditions are associated with WBCs in the CSF, the diagnosis of meningoencephalitis may be made. The traditional teaching has been that meningoencephalitis, like viral encephalitis, will give a normal glucose level in association with lymphocytes. As outlined in Table 1, herpes encephalitis may result in a low glucose level.

Spirochetal infections are an important cause of lymphocytic meningitis with normal glucose level. *Treponema pallidum*, the etiologic agent of syphilis, is a recognized cause of asymptomatic infection of the CNS in nonimmunocompromised hosts. Meningovascular syphilis has been increasingly diagnosed in the era of HIV infection; it may take the form of syphilitic meningitis or a stroke syndrome. In December 2004 new guidelines were published for the management of infections in HIV-infected persons.[31] Several important points were made regarding neurosyphilis. Because CNS disease can occur during any stage of syphilis, a patient who has clinical evidence of neurologic involvement with syphilis (eg, cognitive dysfunction, motor or sensory deficits, ophthalmic or auditory symptoms, cranial nerve palsies, and symptoms or signs of meningitis) should undergo a CSF examination. Because it is highly specific (although insensitive), the Venereal Disease Research Laboratory (VDRL) test in CSF (VDRL-CSF) is the standard serologic test for CSF. When reactive in the absence of substantial contamination of CSF with blood, it is considered diagnostic of neurosyphilis. However, with syphilitic meningitis, patients may present without symptoms of nervous system disease and analysis of their CSF may reveal only a few lymphocytes and a negative VDRL-CSF test result. The fluorescent treponemal antibody absorption test on CSF is less specific for neurosyphilis than the VDRL-CSF test, but the high sensitivity of the study has led some experts to believe that a negative CSF fluorescent treponemal antibody absorption test result excludes neurosyphilis.[31] The guidelines now state that a reactive CSF-VDRL test and a CSF WBC count $\geq$10 cells/μL support the diagnosis of neurosyphilis. An analysis of laboratory measures after treatment for neurosyphilis revealed that HIV-infected patients were less likely than non-HIV-infected patients to normalize their CSF-VDRL reactivity with higher baseline titers, even though the CSF WBC count and serum rapid plasma reagin reactivity in both populations were likely to normalize.[32] Neurosyphilis can present as cerebrovascular insufficiency, often in young patients with a stroke syndrome caused by an endarteritis, which most characteristically involves the middle cerebral artery.

According to guidelines,[31] the recommended regimen for patients with neurosyphilis is 18 to 24 million units/d of aqueous crystalline penicillin G, administered as 3 to 4 million units IV q4h or continuous infusion, for 10 to 14 days. If compliance with therapy can be ensured, patients may be treated with procaine penicillin (2.4 million units IM once daily) plus probenecid (500 mg orally four times a day), both for 10 to 14 days. Because these durations are shorter than those of the regimen used for late syphilis in the absence of neurosyphilis, some specialists administer benzathine penicillin (2.4 million units IM once per week for up to 3 weeks after completion of these neurosyphilis treatment regimens) to provide a comparable total duration of therapy. The CSF leukocyte count has been stated to be a sensitive measure of the effectiveness of therapy.

The classic presentation of neurologic Lyme disease, which is caused by *Borrelia burgdorferi*, is seventh nerve palsy (which may be bilateral) in association with a lymphocytic meningitis.

Leptospirosis, caused by *Leptospira interrogans*, is epidemiologically linked to such factors as infected rat urine or exposure to infected dogs. It presents as two distinct clinical syndromes.[33] Anicteric leptospirosis is a self-limiting illness, which progresses through two well-defined stages: a septicemic stage and an immune stage. The septicemic stage occurs after a 7- to 12-day incubation period and is primarily manifested as fever, chills, nausea, vomiting, and headache. The most characteristic physical finding during this stage is conjunctival suffusion. The causative organism can be isolated from blood or CSF at

this point. After a 1- to 3-day asymptomatic period, the immune stage develops; it is characterized by aseptic meningitis. Leptospira are present in the urine during this stage and may persist for up to 3 weeks. Icteric leptospirosis, or Weil syndrome, is a less common but potentially fatal syndrome that occurs in 5% to 10% of cases. Jaundice, renal involvement, hypotension, and hemorrhage are the hallmarks of this form of leptospirosis; however, the severity of these manifestations can vary greatly and renal involvement is not universal. In icteric leptospirosis, the biphasic nature of the disease is somewhat obscured by the persistence of jaundice and azotemia throughout the illness, but septicemic and immune stages do occur. Leptospires can be isolated from blood or CSF during the first week and from the urine during the second week of illness. Additionally, the diagnosis can be made by demonstrating rising antibody titers. Treatment of leptospirosis involves intense supportive care as well as antibiotic coverage. The use of IV penicillin (1.5 million units every 6 h) has been shown to shorten the duration of fever, renal dysfunction, and hospital stay. In a prospective, open-label, randomized trial, ceftriaxone and penicillin G were shown to be equally effective for the treatment of severe leptospirosis.[34]

Over the years, Rocky Mountain spotted fever (RMSF), which is caused by *Rickettsia rickettsii*, has been considered the classic rickettsial infection in the United States. Results of CSF analysis are usually normal unless patients have stupor or coma, in which case there may be a lymphocytic pleocytosis with normal glucose and elevated protein levels. An important emerging infection in the US is ehrlichiosis. The clinical illness attributable to this infection is discussed in this syllabus in the section on encephalitis. The characteristic CSF abnormalities in patients with ehrlichiosis have been a lymphocytic pleocytosis with elevated protein. In a recent review of the subject, the CSF glucose level was normal in most patients, with 24% of the patients having borderline low CSF glucose concentrations.[35] In this review, morulae were seen in CSF white cells in only a small minority of the patients. Clinical features supporting the diagnosis of ehrlichiosis are leukopenia (because of the intracellular location of the organism), thrombocytopenia, and elevated liver enzymes. From the limited clinical data available, it appears that chloramphenicol or tetracycline is the agent most frequently used for this infection.

Certain infectious diseases, such as infective endocarditis, may cause a lymphocytic pleocytosis with normal glucose level that is the result of a vasculitis, which the infectious process causes in the CNS. A review[36] of a 12-year experience at the Cleveland Clinic included the results of lumbar punctures done on 23 of 175 patients with endocarditis. There was a CSF pleocytosis in 14 and no CSF WBCs in 9. Of the 14 patients who had a pleocytosis, the etiology was attributed to a stroke in 8 and to encephalopathy in 5; the remaining patient only had isolated headaches. No positive CSF culture results were reported in any of these 14 patients. Such information underscores a dilemma for the clinician managing a patient with endocarditis who has a CSF pleocytosis: Is the pleocytosis due to secondary bacterial seeding of the meninges, or is it due to other events associated with endocarditis that lead to a CNS response that is associated with a secondary cellular response?

A group of noninfectious causes of lymphocytic meningitis with a normal glucose level is described in Table 1.

Lymphocytic Meningitis With Low Glucose Level: With chronic processes, it is not surprising that the cellular CSF response would be lymphocytes. Low CSF glucose level has been described in this syllabus as occurring owing to impaired transport from acute inflammation of the meninges. In certain conditions, glucose transport may be associated with infiltration of the meninges by either granulomatous processes or malignant cells. Such is the situation for several of the conditions summarized in Table 1 that cause lymphocytic meningitis with a low glucose level.

Viral meningitis due to mumps and lymphocytic choriomeningitis have characteristically been associated with a low CSF glucose level. As previously discussed, certain forms of meningoencephalitis, including that due to HSV, may present in this manner. Partially treated bacterial meningitis and certain chemical-induced meningitides may have similar findings. Four other groups of conditions that are important in this

setting are tuberculous meningitis, fungal meningitis, carcinomatous meningitis, and subarachnoid hemorrhage.

A review of 48 adult patients with tuberculous meningitis who were admitted to an ICU demonstrates the potential for this infectious process to cause serious disease.[37] It also emphasizes the difficulty often encountered in establishing the diagnosis. Repeated large volumes (10 to 20 mL) of CSF have a higher yield for acid-fast bacilli.[38] When four CSF smears for acid-fast bacilli are obtained, positive findings may occur for up to 90% of patients with tuberculous meningitis. Some studies have shown that elevated CSF titers of adenosine deaminase,[39] or CSF chloride levels <110 mEq/L in the absence of bacterial infection, support the diagnosis of tuberculous meningitis. Enzyme-linked immunosorbent assays (ELISAs) are felt by some to be helpful with this diagnosis. Polymerase chain reaction (PCR) for *Mycobacterium tuberculosis* may be helpful when performed on CSF, but false-negative results have been reported. Because of a predilection for tuberculous meningitis to involve the base of the brain, imaging studies of the CNS may reveal an obstructing hydrocephalus. In addition to antituberculous therapy with agents such as isoniazid, rifampin, pyrazinamide, and ethambutol, corticosteroids may play a role, especially in situations of increased intracranial pressure or obstruction resulting from the infection. The most recent guidelines[40] of the American Thoracic Society give steroids in the treatment of tuberculous meningitis an A-1 recommendation. A randomized, double-blind, placebo-controlled trial.[41] in Vietnam in patients older than 14 years of age with tuberculous meningitis showed that adjunctive treatment with dexamethasone improved survival but probably did not prevent severe disability. From the series of patients with tuberculous meningitis admitted to an ICU, several important clinical points can be extracted[37]: (1) Ischemic lesions with signs of localization may be present. (2) Extrameningeal tuberculous infection may support the diagnosis. (Overall, the rate has been stated to be 40% to 45%, but in this review it was 66%.) (3) Clinical features and CSF profiles did not appear to be modified in the HIV-infected patients. (4) Delay to onset of treatment and the neurologic status at admission were identified as the main clinical prognostic factors. In low-incidence geographic areas, clinicians should suspect tuberculous meningitis in members of immigrant groups from high-incidence areas, as well as in patients who abuse alcohol or drugs and those with immunosuppression from any cause.[42]

Although fungal meningitis may be due to several etiologic agents, the two most common ones are *Cryptococcus neoformans* and *Coccidioides immitis*. Although both of these pathogens have been increasingly diagnosed as a cause of meningitis because of HIV infection, both caused meningitis in normal hosts before the AIDS era. Both organisms gain access to the body via the lungs. In HIV-infected persons with cryptococcal meningitis, there may be a lack of inflammation in the CSF, and therefore findings may include <20 CSF WBCs/mL and a normal glucose level. The India ink stain, latex agglutination test, and fungal culture of the CSF are, therefore, important in the diagnosis. Potentially helpful in establishing the diagnosis are other sites of involvement including lung, skin, and blood. Based on data from the Mycoses Study Group of the National Institutes of Health (NIH), it appears that therapy for cryptococcal meningitis in HIV-infected patients should begin with amphotericin B (0.7 mg/kg/d) in combination with flucytosine (100 mg/kg/d in persons with normal renal function) for the initial 2 weeks of therapy, followed by fluconazole (400 mg/d orally) for an additional 8 to 10 weeks.[43] In the 381 patients with cryptococcal meningitis treated in this double-blind, multicenter trial, 13 of 14 early deaths and 40% of deaths during weeks 3 through 10 were associated with elevated intracranial pressure. Based on the association of elevated intracranial pressure and mortality in patients with cryptococcal meningitis, it was suggested that measurement of intracranial pressure be included in the management of such patients. Included in the recommendations were daily lumbar punctures, use of acetazolamide, and ventriculoperitoneal shunts for asymptomatic patients with intracranial CSF pressure >320 mm H_2O and for symptomatic patients with pressure >180 mm H_2O. More recently, it was recommended that in the absence of focal lesions,

opening pressures ≥250 mm H_2O should be treated with large-volume CSF drainage (defined in this report as allowing CSF to drain until a satisfactory closing pressure had been achieved, commonly <200 mm H_2O).[44] The IDSA guidelines for the management of cryptococcal meningitis in HIV-infected persons with opening CSF pressure of >250 mm H_2O recommended lumbar drainage sufficient to achieve a closing pressure ≤200 mm H_2O or 50% of initial opening pressure.[45] Maintenance therapy is required after completion of primary therapy and studies have defined fluconazole (200 mg/d orally) as the agent of choice.

Meningitis due to *C immitis* commonly presents with headache, vomiting, and altered mental status. Although the CSF formula is usually one of lymphocytes with a low glucose level, eosinophils are occasionally present. In addition to direct examination and culture of CSF, complement-fixing antibodies in the CSF may be an especially important aid to the diagnosis of coccidioidal meningitis. As with cryptococcal meningitis, the epidemiologic history and the other body sites of involvement (including lung, skin, joints, and bone) are important in making the diagnosis. In contrast to cryptococcal meningitis, management strategies for coccidioidal meningitis may vary from patient to patient. Recent IDSA guidelines noted that oral fluconazole is currently the preferred therapy, with itraconazole being listed as having comparable efficacy.[46] It was acknowledged that some physicians initiate therapy with intrathecal amphotericin B in addition to an azole on the basis of their belief that responses may be more prompt with this approach. Because Coccidioides has a predilection for the basilar meninges, hydrocephalus may occur. Regardless of the regimen being used, this potential complication nearly always requires a shunt for decompression.

Other fungi have the capability of causing meningitis but they are less likely to do so. Because CNS involvement may be clinically recognized in 5% to 10% of cases of progressive disseminated histoplasmosis, the diagnosis and management of CNS histoplasmosis has been recently reviewed.[47] As a general rule, fungal meningitis, like tuberculous meningitis, may involve the base of the brain and cause obstruction of CSF flow with resulting hydrocephalus.

Eosinophilic Meningitis: The subject of eosinophilic meningitis has been recently reviewed.[48]

Angiostrongylus cantonensis is a nematode that can infect humans who ingest poorly cooked or raw intermediate mollusk hosts, such as snails, slugs, and prawns. Infection can also occur when fresh vegetables contaminated with infective larvae are eaten. Once ingested, the infective larvae penetrate the gut wall and migrate to the small vessels of the meninges to cause a clinical picture of fever, meningismus, and headache. CSF analysis reveals an eosinophilic pleocytosis; larvae are usually not found. Such a process has been most characteristically described in Asia and the South Pacific. A recent report described an outbreak of meningitis due to *A cantonensis* that developed in 12 travelers who traveled to the Caribbean and whose clinical illness was strongly associated with the consumption of a Caesar salad at a meal.[49] From this outbreak, it was suggested that *A cantonensis* infection should be suspected among travelers at risk who present with headache, elevated intracranial pressure, and pleocytosis, with or without eosinophilia, particularly in association with paresthesias or hyperesthesias.

Less classic infectious causes of eosinophilic meningitis include *Trichinella spiralis*, *Taenia solium*, *Toxocara canis*, *Gnathostoma spinigerum*, *Paragonimus westermani*, and *Baylisascaris procyonis*. Important noninfectious causes include malignancy (eg, Hodgkin's disease, non-Hodgkin's lymphoma, and eosinophilic leukemia), medications (eg, ciprofloxacin, ibuprofen), and intraventricular medications or shunts.

Meningitis Caused by Protozoa or Helminth: Of the causes, five deserve special comment. The most common is due to *Toxoplasma gondii* and presents most often as multiple ring-enhancing lesions in HIV-infected patients. These lesions may be associated with a CSF pleocytosis, but meningitis is not the most likely presentation of CNS toxoplasmosis. Because this infection usually represents reactivation disease, the IgG antibody to Toxoplasma is positive in about 95% of these individuals. Therapy is with sulfadiazine and pyrimethamine.

Naegleria fowleri is a free-living ameba that enters the CNS by invading the nasal mucosa at the level of the cribriform plate. The classic

presentation is of an acute pyogenic meningitis in a person who recently swam in fresh water.[50] The CSF analysis shows a polymorphonuclear pleocytosis, many RBCs, and hypoglycorrhachia. The diagnosis is confirmed by identifying the organism on CSF wet mount as motile ameba or it can be made by biopsy of brain tissue. Amphotericin B administered systemically and intraventricularly is the drug of choice. Another amebic pathogen infecting the nervous system is Acanthamoeba, which may infect individuals with defects in cell-mediated immunity (including patients with AIDS or after organ transplant) and results in a granulomatous amebic encephalitis. Clinical manifestations include mental status abnormalities, seizures, fever, headache, focal neurologic deficits, meningismus, visual disturbances, and ataxia. An important clinical clue may be preexisting skin lesions that have been present for months before CNS disease and may take the form of ulcerative, nodular, or subcutaneous abscesses. Pneumonitis may also be a part of the clinical presentation.

Neurocysticercosis, which is caused by the pork tapeworm *T solium,* is the most common cause of acquired epilepsy in the world and is highly endemic in all parts of the developing world where pigs are raised, especially Latin America, most of Asia, sub-Saharan Africa, and parts of Oceania.[24] Even though seizures are the most common manifestation of neurocysticercosis, other symptoms include headache, hemiparesis, and ataxia. Symptoms typically begin years after the initial infection, when a host inflammatory response develops against *T solium* antigens released after the death of the parasite. Although not the most classic presentation of neurocysticercosis, eosinophilic meningitis may be part of the clinical presentation. Brain imaging studies may reveal intracranial lesions, which may be cystic or calcified; because of chronic inflammation at the base of the brain, hydrocephalus may be present. The epidemiologic history, combined with brain imaging studies and serology tests (serum enzyme-linked immunoelectrotransfer blot or CSF ELISA), helps make the diagnosis. The drug treatment of choice for neurocysticercosis includes albendazole or praziquantel; steroids should be given concomitantly to reduce edema produced by medical treatment, especially for meningeal infection.[24] Most experts agree that the inflammatory response produced by the death of the cyst produces symptomatic neurocysticercosis and that inactive infection (ie, presence of calcified or ring-enhancing lesions) does not require anthelminthics.[24]

As previously noted, *A cantonensis* may be a cause of eosinophilic meningitis.

Miscellaneous Issues in the Diagnosis and Management of Meningitis: The timing of diagnostic studies in patients with meningitis is of critical importance. An important issue is focality. During the last several decades, many have limited the designation of focality to such processes as hemiparesis, isolated abnormalities on an imaging study of the brain, or an abnormal focus on an EEG. More recently, it has been stated that altered mental status indicates bilateral hemispheric or brainstem dysfunction and severely compromises the ability to determine whether the patient's neurologic assessment is nonfocal.

Because of the potential for severe neurologic sequelae in individuals with bacterial meningitis who are treated in a suboptimal manner, attention has been focused in recent years on the appropriate sequencing of diagnostic studies. A prospective study[51] of 301 adults with suspected meningitis was conducted to determine whether clinical characteristics present before CT imaging of the head was performed could be used to identify patients who were unlikely to have abnormalities on CT scan. Thirteen baseline clinical characteristics were used to predict abnormal findings on head CT scan: age $\geq$60 years; immunocompromised state; history of CNS disease; seizure within 1 week before presentation; abnormal level of consciousness; inability to answer two questions correctly; inability to follow two commands correctly; gaze palsy; abnormal visual fields; facial palsy; arm drift; leg drift; and abnormal language (ie, aphasia, dysarthria, and extinction). From the results of the study, the authors concluded that adults with suspected meningitis who have none of the noted baseline features are good candidates for immediate lumbar puncture, since they have a low risk of brain herniation as a result of lumbar puncture. It was acknowledged that such an approach would have resulted in a 41% decrease in the frequency of CT scans performed

in the study cohort. When imaging is indicated, the following sequence of evaluation and management has been suggested: (1) obtain blood cultures; (2) institute empiric antibiotic therapy; and (3) perform lumbar puncture immediately after the imaging study if no intracranial mass lesion is present.[8]

Supporting the importance of the timing of antibiotics in patients with meningitis are the findings of a retrospective, observational cohort study[52] of patients with community-acquired bacterial meningitis. In this study, patients with microbiologically proven, community-acquired bacterial meningitis were stratified into three groups by the clinical findings of hypotension, altered mental status, and seizures. Patients with none of these three predictor variables were in stage I; those with one predictor variable, stage II; and those with two or more predictor variables, stage III. Delay in therapy after arrival in the ED was associated with adverse clinical outcome when the patient's condition advanced from stage I or II to stage III before the initial antibiotic dose was given, a finding that underscores the need for prompt administration of antibiotics in patients with bacterial meningitis. This study was further interpreted as suggesting that the risk for adverse outcome is influenced more by the severity of illness than the timing of initial antibiotic therapy for patients who arrive in the emergency department at stage III.

A recent analysis[53] of the causes of death in adults hospitalized with community-acquired bacterial meningitis provides some important insights. Although 50% of the 74 patients had meningitis as the underlying and immediate cause of death, 18% of patients had meningitis as the underlying but not immediate cause of death, and 23% had meningitis as neither the underlying nor immediate cause of death. A 14-day survival end point discriminated between deaths attributable to meningitis and those with another cause. It was concluded that such an end point will facilitate greater accuracy of epidemiologic statistics and will assist investigations of the impact of new therapeutic interventions.

For many years, clinicians have relied on a CSF pleocytosis for diagnosing meningitis. Because of implications in both therapy and prophylaxis of meningitis, rapid and accurate diagnostic tests for bacterial meningitis are important. A recent report[54] describes the potential role for broad-range bacterial PCR in excluding the diagnosis of meningitis and in influencing the decision to initiate or discontinue antimicrobial therapy.

In the *Medical Knowledge Self-Assessment Program IX* of the American College of Physicians,[55] it was acknowledged that there are at least four clinical entities in which patients may have fever, coma, and nuchal ridigity but a normal CSF analysis: (1) early bacterial meningitis; (2) cryptococcal meningitis with concomitant HIV infection; (3) parameningeal foci; and (4) herpes simplex encephalitis.

Encephalitis

Characteristic of processes involving cortical brain matter are alterations of consciousness and/or cognitive dysfunction. A representative clinical entity with such findings is acute viral encephalitis, which occurs on the basis of direct infection of neural cells with associated perivascular inflammation, neuronal destruction, and tissue necrosis.[56] Pathologically, the involvement in acute viral encephalitis is in the gray matter. This may be associated with evidence of meningeal irritation and CSF mononuclear pleocytosis, in which the process is referred to as meningoencephalitis. In addition to infectious agents, which may cause direct brain injury, there are indirect mechanisms including induction of autoimmune diseases. This process is referred to as postinfectious encephalomyelitis and is characterized by widespread perivenular inflammation with demyelination localized to the white matter of the brain. The list of infectious and noninfectious processes causing encephalitis is lengthy and is partially summarized in Table 5. An additional process, which represents the sequelae of an infection, is production of neurotoxins as occurs with shigellosis, melioidosis, and cat-scratch disease.

Of all the mechanisms by which an infectious process leads to involvement of the brain, direct viral invasion of neural cells is the most classic. Although the most common cause of acute viral meningitis is enteroviral infection (notably coxsackie A and B viruses and echoviruses), it has

Table 5—*Encephalitis*

Infectious	Postinfectious Encephalomyelitis	Noninfectious Diseases Simulating Viral Encephalitis
Viral	Vaccinia virus	Systemic lupus erythematosus
Rabies	Measles virus	Granulomatous angiitis
Herpes viruses: HSV 1 and 2, varicella-zoster, herpes B (simian herpes), Epstein-Barr, CMV, human herpes 6	Varicella-zoster virus	Behçet disease
Arthropod-borne (Table 6)	Rubella virus	Neoplastic diseases, including carcinomatous meningitis
Mumps	Epstein-Barr virus	Sarcoid
Lymphocytic choriomeningitis	Mumps virus	Reye syndrome
Enteroviruses: coxsackievirus, echovirus, hepatitis A	Influenza virus	Adrenal leukodystrophy
HIV	Nonspecific respiratory disease	Metabolic encephalopathies
Bacterial (including *Brucella*, *Listeria*, *Nocardia*, *Actinomyces*, relapsing fever, cat-scratch disease, Whipple disease, infective endocarditis, parameningeal foci)	...	Cerebrovascular disease
M tuberculosis	...	Subdural hematoma
Mycoplasma pneumoniae	...	Subarachnoid hemorrhage
Spirochetes: syphilis, Lyme disease, leptospirosis		Acute multiple sclerosis
Fungal: including *Cryptococcus*, *Coccidioides*, *Histoplasma*, *Blastomyces*, *Candida*	...	Toxic encephalopathy, including cocaine-induced
Rickettsial: RMSF, typhus, *Ehrlichia*, Q fever	...	Drug reactions
Parasites: *Toxoplasma*, *Naegleria*, *Acanthamoeba*, *Plasmodium falciparum, Trichinella*, *Echinococcus*, *Cysticercus*, *Trypanosoma cruzii*	...	

CMV = cytomegalovirus.

been stated that <3% of the CNS complications from such infections would be classified as encephalitis. Diagnostic studies should include viral pharyngeal, rectal, and urine cultures, but confirmation using acute- and convalescent-phase serology is important because viral shedding from the sites of culture may occur without clinical disease. No specific therapy is available for enteroviral encephalitis.

From the clinical perspective, the most emergent encephalitis to diagnose is that due to HSV.[57] This infection is characteristically caused by HSV type 1 and results in inflammation or necrosis localized to the medial-temporal and orbital-frontal lobes. Although it may have an insidious onset, in its most classic form HSV encephalitis presents as an acute, febrile, focal illness. Because of the temporal lobe localization, personality change may be prominent for a few days to as long as a week before other manifestations. Headache is also a prominent early symptom. Patients may progress rapidly from a nonspecific prodrome of fever and malaise, to findings such as behavioral abnormalities and seizures, to coma. A hallmark of the diagnosis is focality, which may be demonstrated with history (eg, changes in personality or in olfaction), physical examination, imaging studies of the brain, or EEG. These findings most characteristically involve the temporal lobes. Subtle clues to focality may include abnormalities, such as changes in olfaction, which may be influenced by the fact that HSV might access the brain via the olfactory tract. CSF analysis may initially be unrevealing even in some acutely ill patients who have fever, nuchal rigidity, and coma. Characteristic features with lumbar puncture include increased intracranial pressure, CSF lymphocytosis, and the presence of RBCs in the CSF. Although CSF glucose level is characteristically normal, patients may have hypoglycorrhachia. For many years, brain biopsy with viral culture was considered the gold-standard diagnostic study. In suspected cases, such pathologic examination of brain tissue often yielded another treatable diagnosis. Because of the invasiveness

Table 6—*Arthropod-Borne Encephalitis*

Encephalitis	Mortality, %	Neurologic Sequelae, %
Eastern equine encephalitis	30–70	80
St. Louis encephalitis	2–20	20
California encephalitis[a]		
West Nile encephalitis	11[b]	
Western equine encephalitis	5-15	30
Venezuelan equine encephalitis	1	Rare
Powassan encephalitis	15	. . .

[a] Uneventful recovery in most patients; abnormal EEG findings in 75%, with seizures in 6% to 10%.
[b] The limited data available suggest that many patients have substantial morbidity.[60]

of the procedure and because neurosurgic services are not available at all hospitals, there has been attention to noninvasive diagnostic procedures. PCR analysis of CSF (when performed with optimal techniques in an experienced laboratory) has been reported to be 100% specific and 75% to 98% sensitive. In a decision model comparing a PCR-based approach with empiric therapy, the PCR-based approach yielded better outcomes with reduced acyclovir use.[58] Prompt initiation of IV therapy with acyclovir is critical in management of patients in whom this infection is suspected because prognosis is influenced by the level of consciousness at the time therapy is begun. It has been stated that one cannot anticipate an accuracy of >50% in the diagnosis of HSV encephalitis in the early course of the infection, even when one uses physical examination, spinal fluid analysis without PCR, and neuroimaging studies. Relapse of HSV encephalitis has been stated to occur in some patients 1 week to 3 months after initial improvement and completion of a full course of acyclovir therapy. Retreatment may be indicated in these patients.

The arthropod-borne encephalitides are a group of CNS infections in which the viral pathogen is transmitted to humans via a mosquito or tick vector. Of those described in Table 6, all are mosquito-borne except for Powassan encephalitis, which is transmitted by the tick *Ixodes cookei*. The distinguishing features of these illnesses are summarized in this table. Of these, Eastern equine encephalitis is associated with the highest mortality rate (30% to 70%), and this fulminant process results in neurologic sequelae in >80% of survivors. St. Louis encephalitis is caused by a flavivirus, which induces clinical disease in about 1% of those infected. Following a nonspecific prodrome, patients may experience the abrupt onset of headache, nausea, vomiting, disorientation, and stupor. Common laboratory findings include inappropriate secretion of antidiuretic hormone and pyuria. In contrast to Eastern equine encephalitis, the overall mortality related to SLE is about 2%, with the highest mortality rate occurring in elderly persons. Emotional disturbances are the most common sequelae.

The outbreak of arboviral encephalitis described in metropolitan New York City in the late summer and fall of 1999 was caused by West Nile virus (WNV), a flavivirus that is serologically closely related to St. Louis encephalitis virus and that was responsible for 61 human cases, including 7 deaths.[59] In 2002, the virus became much more widespread in its prevalence across the US, making WNV an important diagnostic consideration in patients with an acute viral illness. In the summary of pertinent information on this virus,[60] several important points were made. It was noted that 1 in 5 infected persons had developed a mild febrile illness, with 1 in 150 developing meningitis, encephalitis, or both. Advanced age was the greatest risk factor for severe neurologic disease, long-term morbidity, and death. The most efficient diagnostic method noted in that review was IgM antibody-capture ELISA for IgM antibody to WNV in serum or CSF. Important bases for using this diagnostic study are that IgM antibody does not cross the blood-brain barrier and that 90% of serum samples obtained within 8 days of symptom onset had been positive for IgM antibody. A feature clinicians need to be familiar with is that related flaviviruses—such as those causing St. Louis encephalitis or dengue—may produce a false-positive assay result for WNV. The cited review presents a concise summary of the criteria for making possible, probable, and confirmed diagnoses of WNV, based on the US national case definitions for WNV encephalitis. Recently reported is the experience with WNV infection in 28 patients, 54% of whom had a focal neurologic deficit at presentation.[61] In 47% of these patients with focal deficits, a meningitis or encephalitis

syndrome was absent. During the outbreak of WNV in the summer of 2002, several patients were described who presented with acute flaccid paralysis syndrome.[62] Noteworthy features in these patients included an asymmetrical weakness without pain or sensory loss in association with a CSF pleocytosis. Although some of these patients were initially thought to have Guillain-Barré syndrome, they did not have the symmetric pattern with sensory changes, paresthesias, and CSF protein elevation in the absence of CSF pleocytosis, which are typical of Guillain-Barré syndrome. Preliminary interpretation of the findings of acute flaccid paralysis in WNV-infected patients is that the pattern is a poliolike syndrome with involvement of the anterior horn cells of the spinal cord and motor axons. Treatment for WNV encephalitis is supportive. Several approaches, including interferon-α2b and immunoglobulin with high titer against WNV, offer promise based on animal models and limited clinical experience.[63] Like St. Louis encephalitis virus, WNV is transmitted principally by Culex mosquitoes.

Health-care providers should consider arboviruses in the differential diagnosis of aseptic meningitis and encephalitis cases during the summer months. According to recommendations by the CDC, serum (acute and convalescent) and CSF samples should be obtained for serologic testing and cases should be reported promptly to state health departments.[64] Diagnosis of arbovirus encephalitis may be rapidly facilitated by testing acute serum or spinal fluid for virus-specific IgM antibody. Unfortunately, no effective specific therapy is available for any of these infections. Supportive measures should focus on cerebral edema, seizures, or ventilation if problems related to any of these occur.

HIV has tropism for neural tissue and a significant number of patients will develop involvement of the CNS. As a part of the acute retroviral syndrome that follows initial infection with HIV, patients may develop an acute encephalitis that can include seizures and delirium and from which patients may spontaneously recover with few, if any, neurologic sequelae. On a chronic basis and occurring later in the course of HIV infection, patients may develop an encephalopathy associated with cerebral atrophy and widened sulci on CT imaging studies of the brain. Clinical features may initially include forgetfulness and impaired cognitive function; these may progress to include weakness, ataxia, spasticity, and myoclonus.

The DNA polyoma virus JC is the etiologic agent in progressive multifocal leukoencephalopathy (PML). In this primary demyelinating process involving white matter of the cerebral hemispheres, patients present subacutely with confusion, disorientation, and visual disturbances, which may progress to cortical blindness or ataxia. CSF is characteristically acellular. A feature on neuroradiology imaging studies is lack of mass effect. No definitive therapy is presently available for this infection and clinical efforts have recently focused on the role of immune reconstitution in modifying the clinical course of the illness. In a multicenter analysis[65] of 57 consecutive HIV-positive patients with PML, neurologic improvement or stability at 2 months after therapy was demonstrated in 26% of patients who received highly active antiretroviral therapy, in contrast to improvement in only 4% of patients who did not receive this therapy ($P = .03$). In this study, decreases in JC virus DNA to undetectable levels predicted a longer survival. In the context that untreated PML may be fatal within 3 to 6 months, the potential for preventing neurologic progression and improving survival by controlling JC virus replication becomes clinically relevant.

In recent months, there have been increasing reports of human rabies in the US. Although this infection does not occur very often, it raises some important points about epidemiology, transmission, clinical presentation, and prevention. Rabies is probably best considered to be an encephalomyelopathy. After inoculation, the virus replicates in myocytes and then enters the nervous system via unmyelinated sensory and motor nerves. It spreads until the spinal cord is reached; it is at this point in the clinical course that paresthesias may begin at the wound site. The virus then moves from the CNS along peripheral nerves to skin and intestine, as well as into salivary glands, where it is released into saliva.[66] Knowledge of these factors allows an understanding of both clinical presentation and prevention. A review of the topic by the CDC stated

Table 7—*Clinical Presentation of Rabies*

	Clinical Feature					
	Encephalitis Symptoms	Pain and Weakness	Findings of CI	Myoclonus	Paralysis	Autonomic Instability
Case 1[67]	Hallucinations	Left arm	Yes	Yes	Total body	No
Case 2[67]	Hypersalivation	Left arm	Yes	Yes	No	Yes
Case 3[69]	Confusion	Left face, ear	Yes	Yes	Vocal cord, ocular	No
Case 4[70]	Hallucinations	Right shoulder	Yes	No	No	Yes
Case 5[71]	Confusion	Right wrist	No	Yes	No	Yes
Case 6[71]	Confusion, hypersalivation	Right arm	No	Yes	Dysphagia	Yes
Case 7[71]	Disorientation, hypersalivation	No	No	No	No	Yes
Case 8[71]	No	Right arm	Yes	No	Flaccid paralysis	No
Case 9[71]	Delirium	Left arm	Yes	Yes	Dysphagia	Yes
Case 10[72]	Agitation	Both legs	Yes	No	No	Yes
Case 11[73]	Agitation, hypersalivation	Right arm	Yes	No	Dysphagia	Yes
Case 12[74]	Hallucinations, intractable seizures	Abdominal	No	No	Respiratory dysfunction	No
Case 13[75]	Ataxia, confusion	No	Yes	Yes	No	No
Case 14[76]	Confusion	Right arm	Yes	No	No	No
Case 15[77]	Hypersalivation	Left arm	Yes	Yes	Sixth nerve palsy	Yes

CI = cerebrovascular insufficiency.

that "... this infection should be considered in the differential diagnosis of persons presenting with unexplained rapidly progressive encephalitis."[67] A recent report[68] acknowledges the potential for rabies to be spread through organ transplant and provides further support for the contention that rabies should be considered in any patient with unexplained encephalitis. It is the CNS involvement that leads to the cognitive dysfunction characteristic in encephalitis. Because the rabies virus may in the early stages localize to limbic structures, changes in behavior may result. Although an ascending paralysis simulating the Guillain-Barré syndrome has been described, the most classic presentation is of encephalitis associated with hypertonicity and hypersalivation. Noteworthy in Table 7 is that 13 of the 15 patients had pain and/or weakness, explainable since rabies is a myelopathic infection.[67–77]

Of the cases of bat-related rabies reported in the US since 1980, the minority is definitively related to an animal bite. Only 3 of the 15 cases reported in the recent *Morbidity and Mortality Weekly Reports* cited in Table 7 were bite related.

When the management of rabies in humans was reviewed in 2003,[78] it was acknowledged that the only survivors of the disease had received rabies vaccine before the onset of illness. In 2004, a previously healthy 15-year-old girl developed rabies after being bitten by a bat approximately 1 month before symptom onset. Her case represented the sixth known occurrence of human recovery after rabies infection; however, the case was unique because the patient received no rabies prophylaxis either before or after illness onset.[77] Despite this very rare occurrence, there is still a strong impetus for postexposure prophylaxis, which is discussed in the following paragraph. The cited review notes that the normal management of patients with rabies should be palliative. In those individuals who might be candidates for aggressive management, a combination of specific therapies was listed for consideration, including rabies vaccine, rabies immunoglobulin, monoclonal antibodies, ribavirin, interferon-α, and ketamine. A summary of the potential role of each of these agents was included. Because severe brain edema with herniation has been rare in patients with rabies and because corticosteroids have been associated with increased mortality and shortened incubation period in mouse models of rabies, the review stated that corticosteroids should not be used.

Rabies prophylaxis has been recently reviewed.[79] In individuals who were not previously vaccinated against rabies but have an indication for rabies postexposure prophylaxis, the treatment regimen includes local wound cleansing, human rabies immune globulin, and vaccine. The doses of human rabies immune

globulin and vaccine have been summarized.[79] The administration of rabies immune globulin has been modified and recommendations now are that as much as anatomically feasible of the 20 IU/kg body weight dose should be infiltrated into and around the wound(s), with the remainder administered IM in the deltoid or quadriceps at a location other than that used for vaccine inoculation to minimize potential interference. An important consideration is the prevention of rabies infection after exposure of family members or health-care providers to an index case. Possible percutaneous or mucous membrane exposure to a patient's saliva or CSF is an indication for postexposure prophylaxis. In the reports of the 15 patients summarized in Table 7, the following numbers of persons received postexposure prophylaxis: case 1, 46; case 2, 50; case 3, 60; case 4, 53; case 5, 48; case 6, 37; case 7, 71; case 8, 20; case 9, 27; case 10, 23; case 11, 46; case 12, 53; case 13, 8; case 14, 6; and case 15, 5. For persons in whom preexposure prophylaxis is indicated, only vaccine is recommended.[79]

A group of viruses including dengue virus, enteroviruses, adenoviruses, and cytomegalovirus may cause direct infection that results in encephalitis. In addition to viruses producing direct infection of the brain, certain viruses may cause a postinfectious encephalomyelitis. At one time, this form of CNS pathology accounted for about one-third of fatal cases of encephalitis (with acute viral encephalitis being the major cause of infectious mortality in this category). With the elimination of vaccinia virus by vaccination for smallpox, the mortality attributable to postinfectious encephalomyelitis is now estimated to be 10% to 15% of cases of acute encephalitis in the US. The pathogenesis of this process has not been definitively elucidated. The pathologic changes have been compared with those occurring in persons in whom acute encephalomyelitis developed after rabies immunization with vaccine prepared in CNS tissue. It has been suggested that certain viral infections may cause a disruption of normal immune regulation, with resultant release of autoimmune responses. The viruses that have been associated with postinfectious encephalomyelitis are summarized in Table 4. Treatment of patients with such problems is limited to supportive care.

Two common infections that usually have benign courses in adolescents and young adults may progress to serious disease, which may include involvement of the CNS. Mononucleosis due to Epstein-Barr virus may, on rare occasions, cause direct infection of the brain and an encephalitic process, which is the most common cause of death resulting from this infection. CNS infection is the most significant extrarespiratory manifestation of infection caused by *Mycoplasma pneumoniae*. Even though this organism has been isolated from the CSF, the mechanism by which it causes encephalitis is thought to be an autoimmune one.

Rickettsiae have the ability to produce infection of the CNS. Of these, the most characteristic is RMSF, caused by *R rickettsii*. After being transmitted to humans via a tick bite, this intracellular pathogen can produce a constellation of symptoms and signs that includes fever, petechial skin lesions (involving the palms, soles, wrists, and ankles), and a meningoencephalitis. Because of the skin lesions and neurologic involvement, acute forms of this infection may mimic disease caused by *N meningitidis*. Chloramphenicol is effective against both of these pathogens, but tetracycline is considered the usual first-line drug when only RMSF is suspected. In contrast to the distal skin lesions that progress centrally in RMSF, epidemic typhus caused by *Rickettsia prowazekii* is characterized by central lesions that move distally. This infection is more likely to occur during the winter months than is RMSF, which usually occurs during the late summer and early fall. The emerging rickettsial pathogen identified as a cause of nervous system involvement is *Ehrlichia*. Pathogens within the genus *Ehrlichia* have the propensity to parasitize either mononuclear or granulocytic leukocytes, with the resultant infections referred to as human monocytic ehrlichiosis or human granulocytic ehrlichiosis, respectively. The epidemiology of ehrlichiosis, including outdoor activity and exposure to ticks, is similar to that of RMSF but in contrast to RMSF, ehrlichiosis is associated with rash in only about 20% of cases. In addition to causing the characteristic findings of fever, leukopenia, thrombocytopenia, and abnormal liver enzymes, nervous system involvement in ehrlichiosis may include

severe headache, confusion, lethargy, broad-based gait, hyperreflexia, clonus, photophobia, cranial nerve palsy, seizures, blurred vision, nuchal rigidity, and ataxia. The characteristic CSF abnormalities have been a lymphocytic pleocytosis with an elevated protein level. In a recent review of the subject, the CSF glucose level was normal in most patients, with 24% of the patients having borderline low CSF glucose concentrations. In this review, morulae were seen in CSF white cells in only a small minority of the patients. Radiographic and encephalographic studies did not reveal any lesions that supported a specific diagnosis. Although the definitive agent for treating this infection has not been established by clinical trials, it appears that chloramphenicol or tetracycline is the agent most frequently used. The clinical experience with this process has been limited and the outcome in patients with nervous system involvement is not well established.

As summarized in Table 5, certain noninfectious diseases may mimic viral encephalitis.

Brain Abscess

Among bacterial infections of the CNS, brain abscess is the second most common. On a pathogenetic basis, this infection may develop after hematogenous dissemination of organisms during systemic infection (which often occurs in the context of such conditions as infective endocarditis, cyanotic congenital heart disease, and lung abscess), with extension from infected cranial structures (eg, sinuses or middle ear) along emissary veins, or as a consequence of trauma or neurosurgery. The classic presentation may include recent onset of severe headache, new focal or generalized seizures, and clinical evidence of an intracranial mass. In the non-immunocompromised host, brain abscess represents a deviation from the classic tenet that *Bacteroides fragilis* is not a significant pathogen above the diaphragm. In the patient without predisposing factors, streptococci (including the *Streptococcus intermedius [milleri]* group) along with anaerobes (including *B fragilis*) are the predominant pathogens.[80] Excision or stereotactic aspiration of the abscess is used to identify the etiologic agents and has been recommended for lesions >2.5 cm.[81] Some experts have advocated using empiric antimicrobial therapy without aspiration of the abscess in patients who are neurologically stable and have an abscess <3 cm in diameter that is not encroaching on the ventricular system; however, if such a decision is made, they have advised that the patient must be followed up meticulously with a brain imaging study such as CT scan or MRI, and enlargement of the abscess during therapy mandates surgery. Because of the lack of consistent efficacy of metronidazole against streptococci and upper airway anaerobic cocci, penicillin or a third-generation cephalosporin (eg, cefotaxime or ceftriaxone) is usually combined with this agent. An alternative to metronidazole in this regimen would be chloramphenicol. In the settings of penetrating head trauma, following neurosurgical procedures, or with acute bacterial endocarditis, therapy for *S aureus* should be included. Those patients with a presumed otic or sinus origin for their abscess should have coverage against enterobacteriaceae and *H influenzae* with a third-generation cephalosporin.

In HIV-infected persons, *T gondii* classically presents as fever, headache, altered mental status, and focal neurologic deficits, especially in individuals whose $CD4^+$ count falls below 100 cells/mL. Because the disease is due to reactivation of latent infection in about 95% of cases, IgG antibody to Toxoplasma is generally present. A review[82] of neuroimaging studies in patients with AIDS is summarized in Table 8, with a key point being whether or not mass effect is present. Imaging studies of the brain in AIDS patients with Toxoplasma brain abscess show multiple (usually ≥3) nodular, contrast-enhancing lesions with mass effect found most commonly in the basal ganglia and at the gray-white matter junction. In the classic setting described above, empiric therapy with sulfadiazine and pyrimethamine is recommended. Clindamycin-containing regimens may be considered in sulfa-allergic patients. Brain biopsy is reserved for atypical presentations and for patients who do not respond to initial therapy. After acute therapy for toxoplasmic encephalitis, prophylaxis to prevent recurrence has been recommended with a regimen such as sulfadiazine plus pyrimethamine plus leucovorin, but may be discontinued

Table 8—*Approach to Mass Lesions in HIV-Infected Persons*

Focal Lesions With Mass Effect in HIV-Infected Persons	Focal Lesion Without Mass Effect in HIV-Infected Persons
Toxoplasmosis Primary lymphoma of the CNS Cerebral cryptococcosis[a] Neurotuberculosis[a] Syphilitic gumma[b]	Progressive multifocal leukoencephalopathy

Adapted from Walot and colleagues.[82]
[a] Rarely present as abscesses.
[b] Rare presentation of neurosyphilis.

once $CD4^+$ cells are $>200/\mu L$ for ≥ 6 months.[83] The lesions of toxoplasmosis may be confused with primary CNS lymphoma, which also causes a mass effect owing to surrounding edema and which may undergo central necrosis and present as ring-enhancing masses.

Spinal Epidural Abscess and Subdural Empyema

A review[84] of spinal epidural abscess provides the basis for understanding two common threads included in literature published about this infection: reports of poor prognosis and appeals for rapid treatment. Spinal epidural abscess represents a neurosurgical emergency because neurologic deficits may become irreversible when there is a delay in evacuating the purulent material. Although the basis for this irreversibility has not been definitively established, mechanisms for the associated spinal cord necrosis include a decrease in arterial blood flow, venous thrombosis, or direct compression of the spinal cord. The triad of findings that supports the diagnosis is fever, point tenderness over the spine, and focal neurologic deficits. The predisposing factors to this infection shed light on the likely pathogens. Skin and soft tissue are the most probable source of infection and provide an understanding of why *S aureus* is the most common pathogen in this infection. Spinal epidural abscess has been reported to follow surgery, trauma, urinary tract infections, and respiratory diseases. Of increasing importance are the reports of this infection occurring as a complication of lumbar puncture and epidural anesthesia. In 16% of cases, the source of infection may be unknown. Usual pathogens include *S aureus,* streptococci (both aerobic and anaerobic), and gram-negative bacilli.

Gadolinium-enhanced MRI has replaced myelography as the diagnostic study of choice because it identifies not only mass lesions, but also signal abnormalities that are consistent with acute transverse myelopathy and spinal cord ischemia.[85]

Subdural empyema is an infection that occurs between the dura and arachnoid and that results as organisms are spread via emissary veins or by extension of osteomyelitis of the skull. The paranasal sinuses are the source in over half the cases, with otitis another likely predisposing condition. In young children, it is usually a complication of meningitis. The clinical features include fever, headache, vomiting, signs of meningeal irritation, alteration in mental status, and focal neurologic deficits that progress to focal seizures. The usual pathogens are aerobic streptococci (including *S pneumoniae*), staphylococci, *H influenzae*, gram-negative bacilli, and anaerobes (including *B fragilis*). The diagnosis is often made with MRI, but CT scan with contrast enhancement may offer the advantage of imaging bone. Antibiotics directed against the likely pathogens and surgical interventions are mainstays of therapy.

Septic Intracranial Thrombophlebitis

Thrombosis of the cortical vein may occur as a complication of meningitis and is associated with progressive neurologic deficits including hemiparesis, bilateral weakness, or aphasia. Thrombosis of the intracranial venous sinuses classically follows infections of the paranasal sinuses, middle ear, mastoid, face, or oropharynx although the process may be metastatic from

lungs or other sites. The most frequent pathogens are *S aureus,* coagulase-negative staphylococci, streptococci, gram-negative bacilli, and anaerobes. Five anatomic sites may be involved with varying clinical presentations.[86] Superior sagittal sinus thrombosis results in bilateral leg weakness or in communicating hydrocephalus. Lateral sinus thrombosis produces pain over the ear and mastoid, with possible edema over the mastoid. Superior petrosal sinus thrombosis causes ipsilateral pain, sensory deficit, or temporal lobe seizures. Inferior petrosal sinus thrombosis may produce the syndrome of ipsilateral facial pain and lateral rectus weakness referred to as *Gradenigo syndrome*.

Of the forms of venous sinus thrombosis, cavernous sinus thrombosis is the most frequently discussed. Within this sinus lie the internal carotid artery with its sympathetic plexus and the sixth cranial nerve. In the lateral wall of the sinus are the third and fourth cranial nerves, along with the ophthalmic and sometimes maxillary divisions of the trigeminal nerve. The clinical presentation is influenced by these anatomic considerations. The process, which is considered life-threatening, begins unilaterally but usually becomes bilateral within hours. High fever, headaches, malaise, nausea, and vomiting are the predominant findings. Patients progress to develop proptosis, chemosis, periorbital edema, and cyanosis of the ipsilateral forehead, eyelids, and root of the nose. Ophthalmoplegia may develop, with the sixth cranial nerve usually involved first. Trigeminal nerve involvement may manifest itself as decreased sensation about the eye. Ophthalmic nerve involvement may present as photophobia and persistent eye pain. Papilledema, diminished pupillary reactivity, and diminished corneal reflexes may also develop. The disease may be relentless in its progression to alteration in level of consciousness, meningitis, and seizures. The mainstays of therapy include broad-spectrum antibiotics and surgical drainage with removal of infected bone or abscess. The issue of anticoagulation in patients with suppurative intracranial thrombophlebitis is controversial. It is the opinion of some experts in the field that heparin followed by warfarin may be beneficial,[87] but heparin-induced thrombocytopenia has been noted as a potential complication. Steroids may be necessary if involvement of the pituitary gland leads to adrenal insufficiency and circulatory collapse.

Neuritis

Infection of nervous tissue outside of the CNS can take place on the basis of several pathogenetic mechanisms. Certain pathogens, such as *Borrelia burgdorferi* (the etiologic agent of Lyme disease), HIV, cytomegalovirus, HSV type 2, and varicella-zoster virus, can produce peripheral neuropathy. Direct infection of nerves may occur with *Mycobacterium leprae* and Trypanosoma spp. *Corynebacterium diphtheriae*, *Clostridium tetani*, and *Clostridium botulinum* can produce toxins that can injure peripheral nerves.

C diphtheriae produces a toxin that directly involves nerves to cause a noninflammatory demyelination. Clinical sequelae of such a process initially include local paralysis of the soft palate and posterior pharyngeal wall, followed by cranial nerve involvement, and culminating in involvement of peripheral nerves. Myocarditis occurs in as many as two-thirds of patients, but <25% develop clinical evidence of cardiac dysfunction. Antitoxin is indicated in infected patients, along with antibacterial therapy. Both penicillin and erythromycin have been recommended as treatment of diphtheria by the World Health Organization. In a study in Vietnamese children with diphtheria that compared IM benzylpenicillin with erythromycin, both antibiotics were efficacious, but slower fever clearance and a higher incidence of GI side effects were associated with erythromycin.[88] Erythromycin resistance was noted in some of the isolates tested, but all were susceptible to penicillin. Both *C tetani* and *C botulinum* cause indirect nerve involvement on the basis of toxin production. The epidemiology of tetanus has changed somewhat in recent years. Joining elderly patients as a patient population at risk for tetanus are injection drug users who inject drugs subcutaneously (ie, "skin pop"). The toxin of *C tetani* is transported up axons and binds to presynaptic endings on motor neurons in anterior horn cells of the spinal cord. This blocks inhibitory input and results in uncontrolled motor input to skeletal muscle and tetanic spasm. Antitoxin is not available for this

disorder, but tetanus immune globulin and tetanus toxoid are given for clinical disease. Prevention plays a pivotal role in controlling the number of cases of tetanus. A population-based serologic survey[89] of immunity to tetanus in the US revealed protective levels of tetanus antibodies ranging from 87.7% among persons 6 to 11 years of age to 27.8% among those 70 years of age or older. Although there is an excellent correlation between vaccination rates (96%) and immunity (96%) among 6-year-old children, antibody levels decline over time such that one-fifth of older children (10 to 16 years of age) do not have protective antibody levels. Such data argue strongly for ongoing tetanus immunization throughout a person's life in an attempt to prevent this potentially fatal disease.

The toxin of *C botulinum* binds to the presynaptic axon terminal of the neuromuscular junction, with inhibition of acetylcholine release. This results in a symmetric, descending, flaccid paralysis of motor and autonomic nerves, usually beginning with the cranial nerves. Recent reports of botulism have noted not only foodborne outbreaks associated with consumption of contaminated fish, commercial cheese sauce, and baked potatoes held in aluminum foil for several days at room temperature, but also wound botulism in injection drug users who injected Mexican black tar heroin subcutaneously. The classic presentation includes neurologic and GI findings. Nausea and vomiting may be followed by diminished salivation and extreme dryness of the mouth and by difficulty in focusing the eyes, which occurs owing to interruption of cholinergic autonomic transmission. Patients progress to cranial nerve palsies (with common presentations being diplopia, dysarthria, or dysphagia) and then to a symmetrical descending flaccid voluntary muscle weakness that may progress to respiratory compromise. Normal body temperature and normal sensory nerve examination findings are typical, as is an intact mental status despite a groggy appearance. A large outbreak occurred in 1994 in El Paso, Texas, and was traced to a dip prepared in a restaurant from potatoes that had been baked in aluminum foil and then left at room temperature for several days.[90] In that report, the following criteria were used for making the diagnosis of botulism: (1) an electromyographic (EMG) study showing an increase of >50% in the evoked train of compound muscle action potentials with rapid repetitive stimulation (20 to 50 Hz); (2) stool culture positive for *C botulinum*; and (3) blurred vision, dysphagia, or dysarthria in a person who did not have EMG findings indicating botulism and who did not have *C botulinum* detected in stool (findings consistent with the diagnosis of "suspected case"). In addition, the mouse inoculation test result for toxin, using serum, stool, or food, may be positive. In a recent review of laboratory findings in foodborne botulism, the following were listed: normal CSF values; specific EMG findings (normal motor conduction velocities; normal sensory nerve amplitudes and latencies; decreased evoked muscle action potential; facilitation following rapid repetitive nerve stimulation); and standard mouse bioassay finding positive for toxin from clinical specimens and/or suspect food.[91] Researchers from the CDC and the Republic of Georgia's National Center for Disease Control studied 706 cases of botulism in Georgia, which has the highest reported rate of foodborne botulism of any country.[92] They discovered that the patients at highest risk of dying were those who reported to the hospital with shortness of breath and impaired gag reflex but no diarrhea. This constellation of symptoms, if validated in the US and other countries as predictors of death, would allow doctors to give first consideration to patients who are at highest risk of dying in a botulism outbreak.[92]

Intestinal botulism, which occurs most commonly in infants and is rare in children and adults, is the most common form of human botulism in the US.[93] Along with the traditional forms of botulism, there are two additional forms of importance. Since 1978, the CDC has recorded cases of botulism in which extensive investigation failed to implicate a specific food as the cause. These have been referred to as cases of undetermined origin. Investigation has shown that some of these cases were caused by colonization of the GI tract by *C botulinum* or *Clostridium baratii* with in vivo production of toxin, analogous to the pathogenesis of infant botulism. In some cases of botulism strongly suspected to represent intestinal colonization, the

Table 9—*Toxin-Mediated Peripheral Neuritis*

Direct toxin injury
C diphtheriae[a]
Indirect toxin injury
C tetani
C botulinum
Traditional categories
Adult botulism[a]
Infant (intestinal) botulism[b]
Wound botulism[a]
Intestinal colonization botulism[c]
New category
Inhalational botulism[c]

[a] Antitoxin indicated.
[b] Role for botulism immune globulin IV (human).
[c] See text.

patients had a history of GI surgery or illnesses such as inflammatory bowel disease, which might have predisposed them to enteric colonization. This form of botulism has been referred to as intestinal colonization botulism (also termed by some as adult-type infant botulism). Of more recent interest is inhalational botulism, which could occur as a component of bioterrorism with intentional release of aerosolized botulinum toxin.

As summarized in Table 9, antitoxin is indicated for adult botulism, which occurs on the basis of ingestion of preformed toxin, and for wound botulism, in which toxin is produced locally at the infected wound. A review of botulism has noted that antitoxin is released from the CDC for cases of intestinal colonization botulism.[94] With inhalational botulism, it has been suggested that antitoxin be given as early as possible based on clinical suspicion and should not be delayed while awaiting microbiologic testing.[95] It has been noted with this form of botulism that antitoxin might only prevent progression of disease but not reverse paralysis once it has occurred. It is important to be aware that skin testing should be performed to assess for sensitivity to serum or antitoxin before administration of antitoxin. In contrast, infant botulism, which occurs when the ingested organism produces toxin within the GI tract, does not respond to antitoxin. A human-derived human botulism immune globulin has been administered to infants with botulism and has been shown to reduce length of stay with this pattern of disease. Although this product is not yet commercially available, it may be obtained for the treatment of infant botulism under a Treatment Investigational New Drug protocol by contacting the California Department of Health Services [telephone: (510) 540-2646]. The acute, simultaneous onset of neurologic symptoms in multiple individuals should suggest a common source for the problem and increase the suspicion of botulism.

Certain toxins produced by fish and shellfish have been associated with neurologic involvement. Ciguatera fish poisoning follows consumption of marine fish (most characteristically grouper, red snapper, and barracuda) that have been contaminated with toxins produced by microalgae known as dinoflagellates. The classic constellation of findings involves GI, cardiovascular, and neurologic systems. The characteristic neurologic findings include paresthesias (which may be chronic) periorally and in distal extremities, often associated with a debilitating hot-to-cold reversal dysesthesia. Taste sensation is often altered. Implicated toxins include ciguatoxin (which induces membrane depolarization by opening voltage-dependent sodium channels), maitotoxin (which opens calcium channels), and palytoxin (which causes muscle injury). Therapy is primarily symptomatic and supportive. Paralytic shellfish poisoning is caused by consumption of shellfish (most characteristically butter clams, mussels, cockles, steamer clams, sea snails, or razor clams) or broth from cooked shellfish that contain either concentrated saxitoxin (a heat-stable alkaloid neurotoxin) or related compounds, with resultant sensory, cerebellar, and motor dysfunction. Characteristic neurologic findings include paresthesias of the mouth and extremities, ataxia, dysphagia, muscle paralysis, coma, and total muscular paralysis. Treatment is supportive.

The ascending paralysis that comprises the Guillain-Barré syndrome characteristically follows respiratory infection, GI infection (notably, Campylobacter infection), or immunization. The pathology is segmental inflammation with perivascular mononuclear cells and demyelination. An exact etiology for this process has not been elucidated.

Catheter-Related Infections

Urinary Bladder Catheters

A clinical situation frequently associated with injudicious use of antibiotics in the critical care setting is asymptomatic bacteriuria. In March 2005, the IDSA published guidelines[96] for the diagnosis and treatment of asymptomatic bacteriuria in adults. In that document, the diagnosis of asymptomatic bacteriuria was based on results of a culture of a urine specimen collected in a manner that minimizes contamination. For asymptomatic women, bacteriuria was defined as two consecutive voided urine specimens with isolation of the same bacterial strain in quantitative counts $\geq 10^5$ cfu/mL. Asymptomatic bacteriuria was defined as (1) a single, clean-catch voided urine specimen with one bacterial species isolated in a quantitative count $\geq 10^5$ cfu/mL in men, or (2) a single catheterized urine specimen with one bacterial species isolated in a quantitative count $\geq 10^2$ cfu/mL in women or men. Of note is that pyuria accompanying asymptomatic bacteriuria was not considered to be an indication for antimicrobial therapy. In adults, two A-1 recommendations were made regarding treatment of asymptomatic bacteriuria in adults: (1) pregnant women and (2) men scheduled to undergo transurethral resection of the prostate. An A-III recommendation was given for treatment of asymptomatic bacteriuria before urologic procedures (other than transurethral resection of the prostate) for which mucosal bleeding is anticipated. The guidelines stated that antimicrobial treatment of asymptomatic women with catheter-acquired bacteriuria that persists 48 h after indwelling catheter removal may be considered for treatment. Table 10 summarizes those situations where therapy for asymptomatic bacteriuria was not recommended and reviews situations for which the data are evolving but not conclusive.[96–107]

A clinically important area, but one in which there are no definitive data, relates to renal transplant recipients. It has been acknowledged that urine culture surveillance and periodic renal scan or ultrasound examinations are recommended by some authors, at least during the first months after transplant. Based on cited references that treatment of asymptomatic urinary tract infections in renal transplant recipients are largely unsuccessful and that such therapy may not have an observable effect on graft function, it was noted that asymptomatic urinary tract infections in this immunocompromised patient population may be left untreated.[101] Frequent or inappropriate use of antibiotics exerts selective pressures that are responsible for the increasing prevalence of bacterial resistance. Because of this, it is important to use antibiotics in situations for which the clinical benefits exceed risks such as adverse effects and the selection of resistant organisms. A recent report of the NIH-sponsored Mycoses Study Group[108] evaluated the issue of treatment for candiduria that was asymptomatic or minimally symptomatic. Patients were randomly assigned to receive fluconazole (200 mg/d) or placebo for 14 days. In 50% of cases, the isolate was *Candida albicans*. At the end of treatment, urine was cleared in 50% of patients given fluconazole vs 29% of those given placebo. However, the cure rate was about 70% in both groups at 2 weeks posttreatment. Although these data represented

Table 10—*Treatment of Asymptomatic Bacteriuria in Adults*

Adults for whom therapy is recommended
Pregnant women.[97]
Men about to undergo transurethral resection of the prostate or other urologic procedures for which mucosal bleeding is anticipated.[96,100]
Adults for whom therapy may be considered
Women with catheter-acquired bacteriuria that persists 48 h after indwelling catheter removal.
Persons for whom definitive recommendations are not available but for whom some provide therapy
Certain immunocompromised patients, especially those who are neutropenic or who have undergone renal transplant (see comments in text about renal transplant patients[101]).
Elderly persons with obstructive uropathy.[102–105]
Patients with diabetes mellitus.[106]
Persons with positive urine culture results both at the time of catheter removal and then again 1 to 2 wk after catheter removal.[107]
Those undergoing certain types of surgery, particularly when prostheses or foreign bodies (notably vascular grafts) may be left in place. Some patients with struvite stones. Persons with spinal cord injury.[96]
Catheterized patients while the catheter remains in situ.[96]

short-term eradication of candiduria (especially following catheter removal), the long-term eradication rates were not associated with clinical benefit. Notable in this study were the observations in the placebo group that candiduria resolved in about 20% of chronically catheterized patients when their catheter was only changed and in 41% of untreated patients when the catheter was removed.

Peritoneal Dialysis Catheters

Abdominal pain and/or fever and/or cloudy peritoneal fluid are the clinical features usually found in patients who are undergoing either continuous ambulatory peritoneal dialysis or automated peritoneal dialysis and who develop peritonitis. The organisms most frequently isolated in such processes have been coagulase-negative staphylococci (eg, *Staphylococcus epidermidis*) or *S aureus,* but the incidence of Gram-negative pathogens has increased in patients using disconnect systems. When caused by *S aureus,* a toxic shock-like syndrome has been occasionally noted. The finding of >100 WBCs/μL, of which at least 50% are polymorphonuclear neutrophils, is supportive of the diagnosis of peritonitis. Recent trends in the management of this infection have been affected by the emergence of vancomycin resistance, both in enterococci as well as in *S aureus*. Vancomycin use has influenced this resistance. In a review[109] of vancomycin-intermediate *S aureus,* it was noted that of the first 6 patients reported in the US with this pathogen, all but 1 had had exposure to dialysis for renal insufficiency, with the resultant potential for recurrent vancomycin use. In recognition of the contribution of injudicious use of vancomycin to the development of vancomycin resistance in gram-positive organisms, the Advisory Committee on Peritonitis Management of the International Society for Peritoneal Dialysis[110] recommended that traditional empiric therapy of catheter-associated peritonitis be changed from the regimen of vancomycin and gentamicin to a first-generation cephalosporin (eg, cefazolin or cephalothin in a loading dose of 500 mg/L and a maintenance dose of 125 mg/L) in combination with an aminoglycoside. The committee stated further that modifications to this regimen could be made on the basis of the organism isolated or on sensitivity patterns. In its more recent iteration of recommendations for treatment of adult peritoneal dialysis-related peritonitis,[111] the International Society for Peritoneal Dialysis suggested the substitution of ceftazidime for the aminoglycoside. Residual renal function is an independent predictor of patient survival. It is especially noteworthy that use of any aminoglycoside,[112] even when given for short periods, and the rate of peritonitis,[113] are independent risk factors for the decline of residual renal function in patients using continuous ambulatory peritoneal dialysis. A concern about ceftazidime is its risk of selecting resistant gram-negative organisms including those that produce type I β-lactamases or extended-spectrum β-lactamases.[114] The role of empiric therapy with cefazolin has also been reported in potentially infected hemodialysis patients,[115] with vancomycin being reserved for confirmed resistant organisms.[116] Many episodes of catheter-associated peritonitis may be managed without removal of the catheter but peritonitis that does not respond to antibiotic therapy and peritonitis associated with tunnel infections may be indications for catheter removal. Infection with Pseudomonas, a fungal pathogen, or mycobacteria, often requires catheter removal for cure.[117] Another entity that influences the decision for catheter removal is relapsing peritonitis, defined as an episode of peritonitis caused by the same genus/species that caused the immediately preceding episode, occurring within 4 weeks of completion of the antibiotic course. If no clinical response is noted after 96 h of therapy for relapsing peritonitis, catheter removal is indicated; if the patient responds clinically, but with subsequent relapse an additional time, catheter removal and replacement are recommended.[111]

Vascular Catheters

Of the 200,000 nosocomial bloodstream infections that occur each year in the United States, most are related to different types of intravascular devices (IVD). The IDSA, the Society of Critical Care Medicine, and the Society for Healthcare Epidemiology of America have re-

cently published guidelines for management of intravascular catheter-related infections.[118] In their review, the following recommendations were made regarding blood cultures in cases of suspected catheter-associated bacteremia: (1) two sets of blood samples for culture, with a least one drawn percutaneously, should be obtained with a new episode of suspected central venous catheter-related bloodstream infection; and (2) paired quantitative blood cultures or paired qualitative blood cultures with a continuously monitored differential time to positivity should be collected for the diagnosis of catheter-related infection, especially when the long-term catheter cannot be removed. The recommendation regarding blood cultures noted in the preceding statement is different from the recommendations in a recent *New England Journal of Medicine* review,[119] in which it was stated that "Two cultures of blood from peripheral sites should be evaluated because it is difficult to determine whether a positive culture of blood from a central venous catheter indicates contamination of the hub, catheter colonization, or a catheter-related bloodstream infection." Quantitative blood cultures simultaneously obtained through a central venous catheter and a peripheral vein, and demonstrating a 5- to 10-fold increase in concentration of an organism in catheter blood compared with peripheral blood, have been reported to correlate well with catheter-related infections; however, some studies have not supported such a correlation. For tunneled catheters, a quantitative culture of blood from the central venous catheter that yields at least 100 cfu/mL may be diagnostic without a companion culture of a peripheral blood sample.[120] A new diagnostic method has been made possible by continuous blood culture monitoring systems and compares the time to positive culture results of blood drawn from the catheter and from a peripheral vein. One study[121] has shown a sensitivity of 91% and a specificity of 94% in determining catheter-related infection when a blood culture drawn from a central venous catheter showed positivity at least 2 h earlier than the culture drawn from a peripheral vein. These data have most applicability to tunneled catheters.

During the past 2 decades, the medical literature has proposed several predictors of sepsis from a catheter. Although Gram stain of material from the tip of a catheter may be helpful with diagnosis of local infection, it is significantly less sensitive than quantitative methods. The most traditionally quoted study regarding predictors of catheter-related infection suggests that the presence of $\geq$15 colonies on a semiquantitative roll culture of the tip of a catheter or needle is most useful.[122] Although such techniques are relied on at present to assist in the determination of an infected catheter, some data have suggested that the semiquantitative culture may not be predictive of clinical outcome. When compared with qualitative cultures, quantitative methods—which include either (1) flushing the segment with broth, or (2) vortexing or sonicating the segment in broth, followed by serial dilutions and surface plating on blood agar—have greater specificity in the identification of catheter-related infections. In the recently published guidelines for management of intravascular catheter-related infections,[104] the sensitivities of these three methods were listed as follows: sonication, 80%; roll plate method, 60%; and flush culture, 40% to 50%.

A review[123] of 51 English-language studies published from 1966 to July 2004 studied the eight diagnostic methods that are most frequently used in clinical practice and for which performance data have been published: qualitative catheter segment culture, semiquantitative catheter segment culture (roll-plate method), or quantitative catheter segment culture, each combined with demonstrated concordance with results of concomitant blood cultures; qualitative blood culture drawn through an IVD; paired quantitative peripheral and IVD-drawn blood cultures; acridine orange leukocyte cytospin testing of IVD-drawn blood; and differential time to positivity of concomitant qualitative IVD-drawn and peripheral blood cultures (>2 h). In this analysis, paired quantitative blood culture was the most accurate test for diagnosis of IVD-related bloodstream infection. However, most other methods studied showed acceptable sensitivity and specificity (both >0.75) and negative predictive value.

In the IDSA guidelines[118] for the management of catheter-related infections, alternative routes of antibiotic administration were also discussed. An important consideration is whether the infection is intraluminal or extraluminal. Catheters that have been in place for <2 weeks are most often infected extraluminally, whereas catheters in place for a longer duration are more likely to have intraluminal infection. Antibiotic solutions that contain the desired antimicrobial agent in a concentration of 1 to 5 mg/mL are usually mixed with 50 to 100 units of heparin (or normal saline) and are installed or locked into the catheter lumen during periods when the catheter is not used (eg, for a 12-h period each night). The volume of installed antibiotic is removed before infusion of the next dose of an antibiotic or IV medication or solution and the most often used duration of such therapy is 2 weeks. Summarized in this review are some reports of cure of patients with infected tunneled catheters who were treated with both parenteral and lock therapy.

Of the pathogens most characteristically isolated as a complication of indwelling vascular catheters, coagulase-negative staphylococci, *S aureus,* and *Candida* spp have been most frequently reported. In immunocompromised patients with long-term indwelling catheters, *Corynebacterium jeikeium* and *Bacillus* spp are important, and notably both have vancomycin as the drug of choice for therapy. Gram-negative bacilli and atypical mycobacteria are also included as possible pathogens in this setting.

An important and common clinical question is whether a catheter-related intravascular infection can be cured with a long-term indwelling catheter left in place. The medical literature suggests that catheter-related coagulase-negative staphylococcal bacteremia may be successfully treated without recurrence in up to 80% of patients whose catheters have remained in place and who received antibiotics.[124] In the 20% of patients who remained bacteremic while taking antibiotics with their catheters in place, metastatic infection was not a significant problem. For patients with vascular catheter-associated coagulase-negative staphylococcal bacteremia, the following recommendations have been made[118]: (1) if a central venous catheter is removed, appropriate systemic antibiotic therapy is recommended for 5 to 7 days; (2) if a nontunneled central venous catheter is retained and intraluminal infection is suspected, systemic antibiotic therapy for 10 to 14 days and antibiotic lock therapy are recommended; and (3) if a tunneled central venous catheter or an IVD is retained in patients with uncomplicated, catheter-related, bloodstream infection, patients should be treated with systemic antibiotic therapy for 7 days and with antibiotic lock therapy for 14 days.

Although some authors have suggested that infections caused by *S aureus* in the setting of a vascular catheter may respond to treatment with the catheter left in place, there are increasing reports of metastatic sites of infection by this organism when the catheter is not removed. As a result, it seems most prudent to remove the catheter when *S aureus* is isolated from the bloodstream.[125] A scoring system based on the presence or absence of four risk factors (community acquisition, skin examination findings suggesting acute systemic infection, persistent fever at 72 h, and positive follow-up blood culture results at 48 to 96 h) has been suggested as a means of clinically identifying complicated *S aureus* bacteremia.[126] With this system, the strongest predictor was a positive follow-up blood culture finding at 48 to 96 h. Because of the potentially devastating complications that may occur when *S aureus* seeds heart valves or bone, the issue of duration of therapy for bacteremia due to this pathogen in catheter-associated bacteremia is exceedingly important. It is well accepted that individuals with endocarditis or osteomyelitis occurring as complications of metastatic *S aureus* infection should receive a prolonged course of parenteral antimicrobial therapy, with 6 weeks as the frequently stated duration in these settings. The duration of therapy for patients with *S aureus* bacteremia that is catheter related may be similar to that for *S aureus* bacteremia due to a drainable focus. Discussed frequently in the medical literature, therapy for this clinical problem has not been definitively established by clinical trials.

Based on the available data, the most frequently noted minimum duration of parenteral therapy in such settings is 2 weeks. However, before one makes the decision to limit parenteral therapy to this short course, all four of the following criteria should probably be met: (1)

there is removal of the intravascular catheter or drainage of the abscess that was presumed to be the source of the bacteremia; (2) the bacteremia is demonstrated to promptly resolve with the removal or drainage; (3) there is prompt clinical response, including resolution of fever; and (4) heart valves are demonstrated to be normal. Some have suggested that transesophageal echocardiography (TEE) may be a cost-effective means of stratifying patients with catheter-associated *S aureus* bacteremia to a specific duration of therapy.[127] With infectious disease consultation as one of the six components of the evaluation, it was suggested that a 7-day course of antibiotics may be appropriate for patients with what has been termed *simple bacteremia* with *S aureus* if all of the other criteria are met: (1) negative TEE findings on day 5 to 7 of therapy for both vegetations and predisposing valvular abnormalities; (2) negative surveillance culture results of blood obtained 2 to 4 days after beginning appropriate antibiotic therapy and removal of focus; (3) removable focus of infection; (4) clinical resolution (afebrile and no localizing complaints attributable to metastatic staphylococcal infections within 72 h of initiating therapy and removal of focus); and (5) no indwelling prosthetic devices.[128] Even in such settings, patients with diabetes mellitus may still be at an increased risk for developing *S aureus* endocarditis, and some experts have suggested 4 weeks of therapy in this patient population even if heart valves are normal. Removal is suggested in the following settings of *S aureus* bacteremia: (1) nontunneled central vascular catheters and (2) tunneled central vascular catheters or IVDs when there is evidence of tunnel, pocket, or exit-site infection.[118] In the recommendations just cited, it was noted that tunneled central vascular catheters or IVDs with uncomplicated intraluminal infection and *S aureus* bacteremia should be removed or, in selected cases, retained and treated with appropriate systemic and antibiotic lock therapy for 14 days. For patients who remain febrile and/or have bacteremia for >3 days after catheter removal and/or initiation of antibiotic therapy, a longer course of therapy and an aggressive workup for septic thrombosis and infective endocarditis should be instituted. Because the sensitivity of transthoracic echocardiography is low, it is not recommended for excluding a diagnosis of catheter-related endocarditis if TEE can be done.[118] It is important to reiterate that not all of the recommendations listed in this discussion of *S aureus* bacteremia have been definitively validated by clinical trials.

In a retrospective review of 51 patients with prosthetic heart valves in whom *S aureus* bacteremia developed, 26 (51%) had definite endocarditis, using the modified Duke criteria for the diagnosis of endocarditis.[129] The risk of endocarditis was independent of the type, location, or age of the prosthetic valve. Because of the high mortality of prosthetic valve endocarditis, it has been recommended that all patients with a prosthetic valve in whom *S aureus* bacteremia develops should be aggressively screened and followed up for endocarditis.[129]

Like *S aureus* and enterococci, *Candida* spp have a predilection to cause metastatic infection on heart valves and in bone when these organisms are bloodborne. In addition to the complications of endocarditis and osteomyelitis, *Candida* may seed the retina of the eye to cause retinal abscesses that proliferate into the vitreous and result in the clinical entity of *Candida* endophthalmitis. Because of the significant complications associated with candidemia, there are now two basic recommendations for patients with a positive blood culture finding for *Candida*: (1) the patient should receive a course of antifungal therapy[130] and (2) intravascular lines should be removed.[131]

Risk factors cited for candidemia vary by reports, but the following is a representative list from international experts in the field: antibiotics; indwelling catheters; hyperalimentation; cancer therapy; immunosuppressive therapy after organ transplant; hospitalization in ICUs; candiduria; and colonization with *Candida* spp.[132]

A clinical trial conducted by the Mycoses Study Group of the NIH[133] compared amphotericin B with fluconazole in the treatment of candidemia in nonneutropenic and nonimmunocompromised patients. In the 194 patients who had a single species of *Candida* isolated, 69% of the organisms were *C albicans*. The study concluded that fluconazole and amphotericin B were not significantly different in their effectiveness in treating candidemia. Since that study was

performed, there has been an increasing prevalence of non-*albicans* strains of *Candida* in the bloodborne isolates from certain hospitals, and some of these strains may not respond to traditional doses of fluconazole. In their guidelines for the treatment of candidemia, the IDSA presented options for the treatment of candidemia based on the presence or absence of neutropenia.[134] In nonneutropenic patients, fluconazole, amphotericin B, and caspofungin were offered as options for therapy. In neutropenic patients, amphotericin B, a lipid preparation of amphotericin B, or caspofungin was recommended, with the absence of fluconazole in this patient population acknowledging the role of azole exposure as a risk factor for non-*albicans* strains of *Candida*. In a trial comparing the echinocandin caspofungin to amphotericin B in patients with *Candida* infection involving blood or another sterile body site, caspofungin was shown to be superior, with significantly fewer drug-related adverse events than in the amphotericin B group.[135] Because echinocandins are more likely to have activity against non-*albicans* strains of *Candida*, they are potentially useful in patients who have previously been exposed to azole therapy or in whom empiric therapy is needed for presumed life-threatening fungal infection.

Other clinical situations for which catheter removal is necessary for cure of a catheter-related infection include the following: (1) bacteremia due to *C jeikeium* and Bacillus spp; (2) bacteremia with gram-negative bacilli; (3) fungemia; (4) persistence of fever or bacteremia during therapy; (5) evidence of tunnel infection; and (6) rapid relapse after treatment. Currently available data do not support the need for scheduled replacement of short-term central venous catheters, either by guidewire exchange or through insertion at a new site.[136]

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Notes