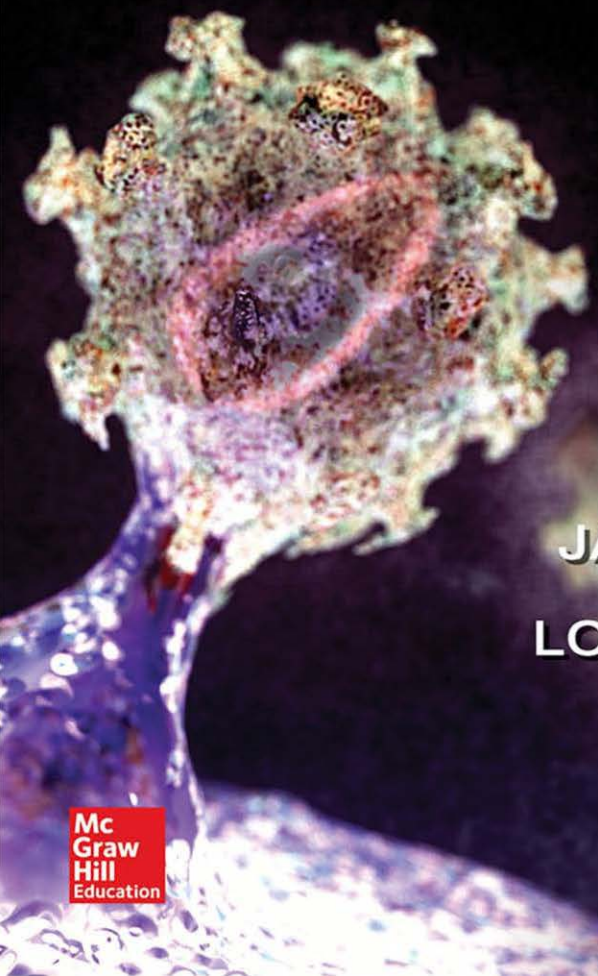
19th Edition

# HARRISON'S™ MANUAL OF MEDICINE



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# GLOSSARY

| | |
|---|---|
| **$A_2$** | aortic second sound |
| **ABGs** | arterial blood gases |
| **ACE** | angiotensin converting enzyme |
| **AF** | atrial fibrillation |
| **AIDS** | acquired immunodeficiency syndrome |
| **ALS** | amyotrophic lateral sclerosis |
| **ANA** | antinuclear antibody |
| **ARDS** | acute respiratory distress syndrome |
| **bid** | two times daily |
| **biw** | twice a week |
| **bp** | blood pressure |
| **BUN** | blood urea nitrogen |
| **CAPD** | continuous ambulatory peritoneal dialysis |
| **CBC** | complete blood count |
| **CF** | complement fixation |
| **CHF** | congestive heart failure |
| **CLL** | chronic lymphocytic leukemia |
| **CML** | chronic myeloid leukemia |
| **CMV** | cytomegalovirus |
| **CNS** | central nervous system |
| **CPK** | creatine phosphokinase |
| **CSF** | cerebrospinal fluid |
| **CT** | computed tomography |
| **CVP** | central venous pressure |
| **CXR** | chest x-ray |
| **DIC** | disseminated intravascular coagulation |
| **DVT** | deep venous thrombosis |
| **EBV** | Epstein-Barr virus |
| **ECG** | electrocardiogram |
| **EEG** | electroencephalogram |
| **ELISA** | enzyme-linked immunosorbent assay |
| **EMG** | electromyogram |
| **ENT** | ear, nose, and throat |
| **EOM** | extraocular movement |
| **ESR** | erythrocyte sedimentation rate |
| **FDA** | US Food and Drug Administration |
| **$FEV_1$** | forced expiratory volume in first second |
| **GFR** | glomerular filtration rate |
| **GI** | gastrointestinal |
| **G6PD** | glucose-6-phosphate dehydrogenase |
| **Hb** | hemoglobin |
| **Hct** | hematocrit |
| **HDL** | high-density lipoprotein |
| **HIV** | human immunodeficiency virus |
| **hs** | at bedtime |
| **HSV** | herpes simplex virus |
| **ICU** | intensive care unit |
| **IFN** | interferon |
| **Ig** | immunoglobulin |
| **IL** | interleukin |
| **IM** | intramuscular |
| **IP** | intraperitoneal |
| **IV** | intravenous |
| **IVC** | inferior vena cava |
| **IVP** | intravenous pyelogram |

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# CONTENTS

**Contributors** . . . . . xv
**Preface** . . . . . xvii
**Acknowledgments** . . . . . xix

**SECTION 1 CARE OF THE HOSPITALIZED PATIENT**

1 Electrolytes/Acid-Base Balance ..... 1
2 Diagnostic Imaging in Internal Medicine ..... 23
3 Procedures Commonly Performed by Internists ..... 26
4 Principles of Critical Care Medicine ..... 31
5 Pain and Its Management ..... 35
6 Assessment of Nutritional Status ..... 40
7 Enteral and Parenteral Nutrition ..... 43
8 Transfusion and Pheresis Therapy ..... 46
9 Palliative and End-of-Life Care ..... 48

**SECTION 2 MEDICAL EMERGENCIES**

10 Cardiovascular Collapse and Sudden Death ..... 57
11 Shock ..... 61
12 Sepsis and Septic Shock ..... 65
13 Acute Pulmonary Edema ..... 69
14 Acute Respiratory Distress Syndrome ..... 71
15 Respiratory Failure ..... 73
16 Confusion, Stupor, and Coma ..... 76
17 Stroke ..... 82
18 Subarachnoid Hemorrhage ..... 91
19 Increased Intracranial Pressure and Head Trauma ..... 93
20 Spinal Cord Compression ..... 98
21 Hypoxic-Ischemic Encephalopathy ..... 100
22 Status Epilepticus ..... 101
23 Diabetic Ketoacidosis and Hyperosmolar Coma ..... 104
24 Hypoglycemia ..... 107
25 Oncologic Emergencies ..... 109
26 Anaphylaxis ..... 114
27 Bites, Venoms, Stings, and Marine Poisonings ..... 115

## SECTION 3 COMMON PATIENT PRESENTATIONS

28 Fever, Hyperthermia, and Rash....127
29 Generalized Fatigue....131
30 Weight Loss....135
31 Chest Pain....137
32 Palpitations....141
33 Dyspnea....142
34 Cyanosis....145
35 Cough and Hemoptysis....146
36 Edema....150
37 Abdominal Pain....154
38 Nausea, Vomiting, and Indigestion....158
39 Dysphagia....162
40 Diarrhea, Malabsorption, and Constipation....167
41 Gastrointestinal Bleeding....174
42 Jaundice and Evaluation of Liver Function....178
43 Ascites....187
44 Lymphadenopathy and Splenomegaly....189
45 Anemia and Polycythemia....194
46 Azotemia and Urinary Abnormalities....197
47 Pain and Swelling of Joints....203
48 Back and Neck Pain....207
49 Headache....215
50 Syncope....222
51 Dizziness and Vertigo....226
52 Acute Visual Loss and Double Vision....229
53 Weakness and Paralysis....233
54 Tremor and Movement Disorders....236
55 Aphasia....239
56 Sleep Disorders....241
57 Dysuria and Bladder Pain....245

## SECTION 4 OTOLARYNGOLOGY

58 Sore Throat, Earache, and Upper Respiratory Symptoms....247

## SECTION 5 DERMATOLOGY

59 General Examination of the Skin ....255
60 Common Skin Conditions ....258

## SECTION 6 HEMATOLOGY AND ONCOLOGY

61 Examination of Blood Smears and Bone Marrow ....265
62 Red Blood Cell Disorders ....267
63 Leukocytosis and Leukopenia ....274
64 Bleeding and Thrombotic Disorders ....277
65 Myeloid Leukemias, Myelodysplasia, and Myeloproliferative Syndromes ....283
66 Lymphoid Malignancies ....293
67 Skin Cancer ....305
68 Head and Neck Cancer ....308
69 Lung Cancer ....310
70 Breast Cancer ....316
71 Tumors of the Gastrointestinal Tract ....321
72 Genitourinary Tract Cancer ....333
73 Gynecologic Cancer ....338
74 Prostate Hyperplasia and Carcinoma ....342
75 Cancer of Unknown Primary Site ....345
76 Paraneoplastic Endocrine Syndromes ....348
77 Neurologic Paraneoplastic Syndromes ....352

## SECTION 7 INFECTIOUS DISEASES

78 Infections Acquired in Health Care Facilities ....357
79 Infections in the Immunocompromised Host ....362
80 Infective Endocarditis ....372
81 Intraabdominal Infections ....382
82 Infectious Diarrheas ....386
83 Sexually Transmitted and Reproductive Tract Infections ....399
84 Infections of the Skin, Soft Tissues, Joints, and Bones ....415
85 Pneumococcal Infections ....422
86 Staphylococcal Infections ....425

87 Streptococcal/Enterococcal Infections, Diphtheria, and Infections Caused by Other Corynebacteria and Related Species ....434
88 Meningococcal and Listerial Infections ....443
89 Infections Caused by *Haemophilus*, *Bordetella*, *Moraxella*, and HACEK Group Organisms ....448
90 Diseases Caused by Gram-Negative Enteric Bacteria and *Pseudomonas* ....453
91 Infections Caused by Miscellaneous Gram-Negative Bacilli ....462
92 Anaerobic Infections ....469
93 Nocardiosis, Actinomycosis, and Whipple's Disease ....477
94 Tuberculosis and Other Mycobacterial Infections ....482
95 Lyme Disease and Other Nonsyphilitic Spirochetal Infections ....494
96 Rickettsial Diseases ....500
97 *Mycoplasma pneumoniae*, *Legionella* Species, and *Chlamydia pneumoniae* ....510
98 *Chlamydia trachomatis* and *C. psittaci* ....514
99 Herpesvirus Infections ....516
100 Cytomegalovirus and Epstein-Barr Virus Infections ....525
101 Influenza and Other Viral Respiratory Diseases ....530
102 Rubeola, Rubella, Mumps, and Parvovirus Infections ....538
103 Enteroviral Infections ....543
104 Insect- and Animal-Borne Viral Infections ....546
105 HIV Infection and AIDS ....554
106 Fungal Infections ....568
107 *Pneumocystis* Infections ....583
108 Protozoal Infections ....586
109 Helminthic Infections and Ectoparasite Infestations ....599

## SECTION 8 CARDIOLOGY

110 Physical Examination of the Heart ....613
111 Electrocardiography ....618
112 Noninvasive Examination of the Heart ....622
113 Congenital Heart Disease in the Adult ....627

114 Valvular Heart Disease ....632
115 Cardiomyopathies and Myocarditis ....639
116 Pericardial Disease ....644
117 Hypertension ....649
118 Metabolic Syndrome ....656
119 ST-Segment Elevation Myocardial Infarction ....658
120 Unstable Angina and Non-ST-Elevation Myocardial Infarction ....668
121 Chronic Stable Angina ....672
122 Bradyarrhythmias ....677
123 Tachyarrhythmias ....679
124 Heart Failure and Cor Pulmonale ....687
125 Diseases of the Aorta ....693
126 Peripheral Vascular Disease ....696
127 Pulmonary Hypertension ....699

SECTION 9 PULMONOLOGY

128 Respiratory Function and Pulmonary Diagnostic Procedures ....705
129 Asthma ....711
130 Environmental Lung Diseases ....715
131 Chronic Obstructive Pulmonary Disease ....718
132 Pneumonia, Bronchiectasis, and Lung Abscess ....722
133 Pulmonary Thromboembolism and Deep-Vein Thrombosis ....730
134 Interstitial Lung Disease ....734
135 Diseases of the Pleura and Mediastinum ....740
136 Disorders of Ventilation ....744
137 Sleep Apnea ....745

SECTION 10 NEPHROLOGY

138 Acute Renal Failure ....747
139 Chronic Kidney Disease and Uremia ....752
140 Dialysis ....754
141 Renal Transplantation ....756

142 Glomerular Diseases ....759
143 Renal Tubular Disease....769
144 Urinary Tract Infections and Interstitial Cystitis....775
145 Nephrolithiasis ....779
146 Urinary Tract Obstruction....782

SECTION 11 GASTROENTEROLOGY

147 Peptic Ulcer and Related Disorders ....785
148 Inflammatory Bowel Diseases ....790
149 Colonic and Anorectal Diseases ....794
150 Cholelithiasis, Cholecystitis, and Cholangitis ....799
151 Pancreatitis ....804
152 Acute Hepatitis ....809
153 Chronic Hepatitis....816
154 Cirrhosis and Alcoholic Liver Disease....826
155 Portal Hypertension ....831

SECTION 12 ALLERGY, CLINICAL IMMUNOLOGY, AND RHEUMATOLOGY

156 Diseases of Immediate-Type Hypersensitivity ....835
157 Primary Immune Deficiency Diseases ....840
158 Systemic Lupus Erythematosus, Rheumatoid Arthritis, and Other Connective Tissue Diseases....843
159 Vasculitis ....850
160 Ankylosing Spondylitis ....854
161 Psoriatic Arthritis....857
162 Reactive Arthritis....859
163 Osteoarthritis....861
164 Gout, Pseudogout, and Related Diseases ....863
165 Other Musculoskeletal Disorders....867
166 Sarcoidosis ....870
167 Amyloidosis ....873

SECTION 13 ENDOCRINOLOGY AND METABOLISM

168 Disorders of the Anterior Pituitary and Hypothalamus....877
169 Diabetes Insipidus and Syndrome of Inappropriate Antidiuretic Hormone ....883

170 Thyroid Gland Disorders ....886
171 Adrenal Gland Disorders ....895
172 Obesity ....901
173 Diabetes Mellitus ....904
174 Disorders of the Male Reproductive System ....912
175 Disorders of the Female Reproductive System ....917
176 Hypercalcemia and Hypocalcemia ....924
177 Osteoporosis and Osteomalacia ....931
178 Hypercholesterolemia and Hypertriglyceridemia ....936
179 Hemochromatosis, Porphyrias, and Wilson's Disease ....942

SECTION 14 NEUROLOGY

180 The Neurologic Examination ....947
181 Seizures and Epilepsy ....956
182 Dementia ....968
183 Parkinson's Disease ....976
184 Ataxic Disorders ....981
185 ALS and Other Motor Neuron Diseases ....984
186 Autonomic Nervous System Disorders ....988
187 Trigeminal Neuralgia, Bell's Palsy, and Other Cranial Nerve Disorders ....995
188 Spinal Cord Diseases ....1002
189 Tumors of the Nervous System ....1008
190 Multiple Sclerosis ....1012
191 Acute Meningitis and Encephalitis ....1020
192 Chronic and Recurrent Meningitis ....1031
193 Peripheral Neuropathies, Including Guillain-Barré Syndrome ....1040
194 Myasthenia Gravis ....1050
195 Muscle Diseases ....1053

SECTION 15 PSYCHIATRY AND SUBSTANCE ABUSE

196 Psychiatric Disorders ....1063
197 Psychiatric Medications ....1071
198 Eating Disorders ....1079

199 Alcohol Use Disorder ..... 1080
200 Narcotic Abuse ..... 1084

SECTION 16 DISEASE PREVENTION AND HEALTH MAINTENANCE

201 Routine Disease Screening ..... 1087
202 Cardiovascular Disease Prevention ..... 1092
203 Prevention and Early Detection of Cancer ..... 1094
204 Smoking Cessation ..... 1102
205 Women's Health ..... 1104

SECTION 17 ADVERSE DRUG REACTIONS

206 Adverse Drug Reactions ..... 1107

Index ..... 1109

# NOTICE

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# PREFACE

*Harrison's Principles of Internal Medicine (HPIM)*, the premier medical textbook for students and clinicians, provides a detailed body of information important to an understanding of the biological and clinical aspects of quality patient care. *Harrison's Manual of Medicine* aims to fulfill a different need: As a concise, fact-rich resource for bedside care, the *Manual* presents clinical information drawn from the 19th edition of *HPIM*, covering the key features of the diagnosis, clinical manifestations, and treatment of the major diseases that are likely to be encountered on a medical service.

First published in 1988, the *Manual* has become ever more useful with the rapid expansion of medical knowledge and the increasing time constraints associated with heavy patient-care responsibilities in modern health care settings. The *Manual*'s popularity and value reflect its abbreviated format, which has proven extremely useful for initial diagnosis and management in time-restricted clinical settings. In particular, the book's full-color format allows readers to locate and use information quickly. In addition, numerous tables and graphics facilitate decisions at the point of care.

The *Manual* has been written for easy and seamless reference to the full text of the 19th edition of *HPIM*, and the Editors recommend that the full textbook be consulted as soon as time allows. Although not a substitute for in-depth analysis of clinical problems, the *Manual* serves as a ready source of informative summaries that will be useful "on the spot" and that will prepare the reader for more in-depth analysis through more extensive reading at a later time. Like previous editions, this latest edition of the *Manual* is intended to keep up with the continual evolution of internal medicine practices. To this end, every chapter from the prior edition has been closely reviewed and updated, with substantial revisions and new chapters provided where appropriate. The 19th edition of the *Manual* is available in print and in portable format for the smartphone and tablet.

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# 1 Electrolytes/Acid-Base Balance

## SODIUM

Disturbances of sodium concentration [$Na^+$] result in most cases from abnormalities of $H_2O$ homeostasis, which change the relative ratio of $Na^+$ to $H_2O$. Disorders of $Na^+$ balance per se are, in contrast, associated with changes in extracellular fluid volume, either hypo- or hypervolemia. Maintenance of "arterial circulatory integrity" is achieved in large part by changes in urinary sodium excretion and vascular tone, whereas $H_2O$ balance is achieved by changes in both $H_2O$ intake and urinary $H_2O$ excretion (Table 1-1). Confusion can result from the coexistence of defects in both $H_2O$ and $Na^+$ balance. For example, a hypovolemic pt may have an appropriately low urinary $Na^+$ due to increased renal tubular reabsorption of filtered NaCl; a concomitant increase in circulating arginine vasopressin (AVP)—part of the defense of effective circulating volume (Table 1-1)—will cause the renal retention of ingested $H_2O$ and the development of hyponatremia.

### HYPONATREMIA

This is defined as a serum [$Na^+$] <135 mmol/L and is among the most common electrolyte abnormalities encountered in hospitalized pts. Symptoms include nausea, vomiting, confusion, lethargy, and disorientation; if severe (<120 mmol/L) and/or abrupt, seizures, central herniation, coma, or death may result (see Acute Symptomatic Hyponatremia, below). Hyponatremia is almost always the result of an increase

**TABLE 1-1 OSMOREGULATION VERSUS VOLUME REGULATION**

| | Osmoregulation | Volume Regulation |
|---|---|---|
| What is sensed | Plasma osmolality | Arterial filling |
| Sensors | Hypothalamic osmoreceptors | Carotid sinus |
| | | Afferent arteriole |
| | | Atria |
| Effectors | AVP | Sympathetic nervous system |
| | Thirst | Renin-angiotensin-aldosterone system |
| | | ANP/BNP |
| | | AVP |
| What is affected | Urine osmolality | Urinary sodium excretion |
| | $H_2O$ intake | Vascular tone |

***Note:*** See text for details.
***Abbreviations:*** ANP, atrial natriuretic peptide; AVP, arginine vasopressin; BNP, brain natriuretic peptide.
***Source:*** Adapted from Rose BD, Black RM (eds): *Manual of Clinical Problems in Nephrology*. Boston, Little Brown, 1988; with permission.

in circulating AVP and/or increased renal sensitivity to AVP; a notable exception is in the setting of low solute intake ("beer potomania"), wherein a markedly reduced urinary solute excretion is inadequate to support the excretion of sufficient free $H_2O$. The serum [$Na^+$] by itself does not yield diagnostic information regarding total-body $Na^+$ content; hyponatremia is primarily a disorder of $H_2O$ homeostasis. Pts with hyponatremia are thus categorized diagnostically into three groups, depending on their clinical volume status: hypovolemic, euvolemic, and hypervolemic hyponatremia (Fig. 1-1). All three forms of hyponatremia share an exaggerated, "nonosmotic" increase in circulating AVP, in the setting of reduced serum osmolality. Notably, hyponatremia is often multifactorial; clinically important nonosmotic stimuli that can cause a release of AVP and increase the risk of hyponatremia include drugs, pain, nausea, and strenuous exercise.

Laboratory investigation of a pt with hyponatremia should include a measurement of serum osmolality to exclude "pseudohyponatremia" due to hyperlipidemia or hyperproteinemia. Serum glucose also should be measured; serum $Na^+$ falls by 1.4 m*M* for every 100-mg/dL increase in glucose, due to glucose-induced $H_2O$ efflux from cells. Hyperkalemia may suggest adrenal insufficiency or hypoaldosteronism; increased blood urea nitrogen (BUN) and creatinine may suggest a renal cause. Urine electrolytes and osmolality are also critical tests in the initial evaluation of hyponatremia. In particular, a urine $Na^+$ <20 meq/L is consistent with hypovolemic hyponatremia in the clinical absence of a "hypervolemic," $Na^+$-avid syndrome such as congestive heart failure (CHF) (Fig. 1-1). Urine osmolality <100 mosmol/kg is suggestive of polydipsia or, in rare cases, of decreased solute intake; urine osmolality >400 mosmol/kg suggests that AVP excess is playing a more dominant role, whereas intermediate values are more consistent with multifactorial pathophysiology (e.g., AVP excess with a component of polydipsia). Finally, in the right clinical setting, thyroid, adrenal, and pituitary function should also be tested.

## Hypovolemic Hyponatremia

Hypovolemia from both renal and extrarenal causes is associated with hyponatremia. Renal causes of hypovolemia include primary adrenal insufficiency and hypoaldosteronism, salt-losing nephropathies (e.g., reflux nephropathy, nonoliguric acute tubular necrosis), diuretics, and osmotic diuresis. Random "spot" urine $Na^+$ is typically >20 meq/L in these cases but may be <20 meq/L in diuretic-associated hyponatremia if tested long after administration of the drug. Nonrenal causes of hypovolemic hyponatremia include GI loss (e.g., vomiting, diarrhea, tube drainage) and integumentary loss (sweating, burns); urine $Na^+$ is typically <20 meq/L in these cases.

Hypovolemia causes profound neurohumoral activation, inducing systems that preserve arterial circulatory integrity, such as the renin-angiotensin-aldosterone (RAA) axis, the sympathetic nervous system, and AVP (Table 1-1). The increase in circulating AVP serves to increase the retention of ingested free $H_2O$, leading to hyponatremia. The optimal treatment of hypovolemic hyponatremia is volume administration, generally as isotonic crystalloid, i.e., 0.9% NaCl ("normal saline"). If the history suggests that hyponatremia has been "chronic," i.e., present for 48 h, care should be taken to avoid overcorrection (see below), which can easily occur as AVP levels plummet in response to volume-resuscitation; if necessary, the administration of desmopressin (DDAVP) and free water can reinduce or arrest the correction of hyponatremia (see below).

## Hypervolemic Hyponatremia

The edematous disorders (CHF, hepatic cirrhosis, and nephrotic syndrome) are often associated with mild to moderate degrees of hyponatremia ([$Na^+$] = 125–135 mmol/L); occasionally, pts with severe CHF or cirrhosis may present with serum [$Na^+$] <120 mmol/L. The pathophysiology is similar to that in hypovolemic hyponatremia, except that arterial filling and circulatory integrity are decreased due to the specific

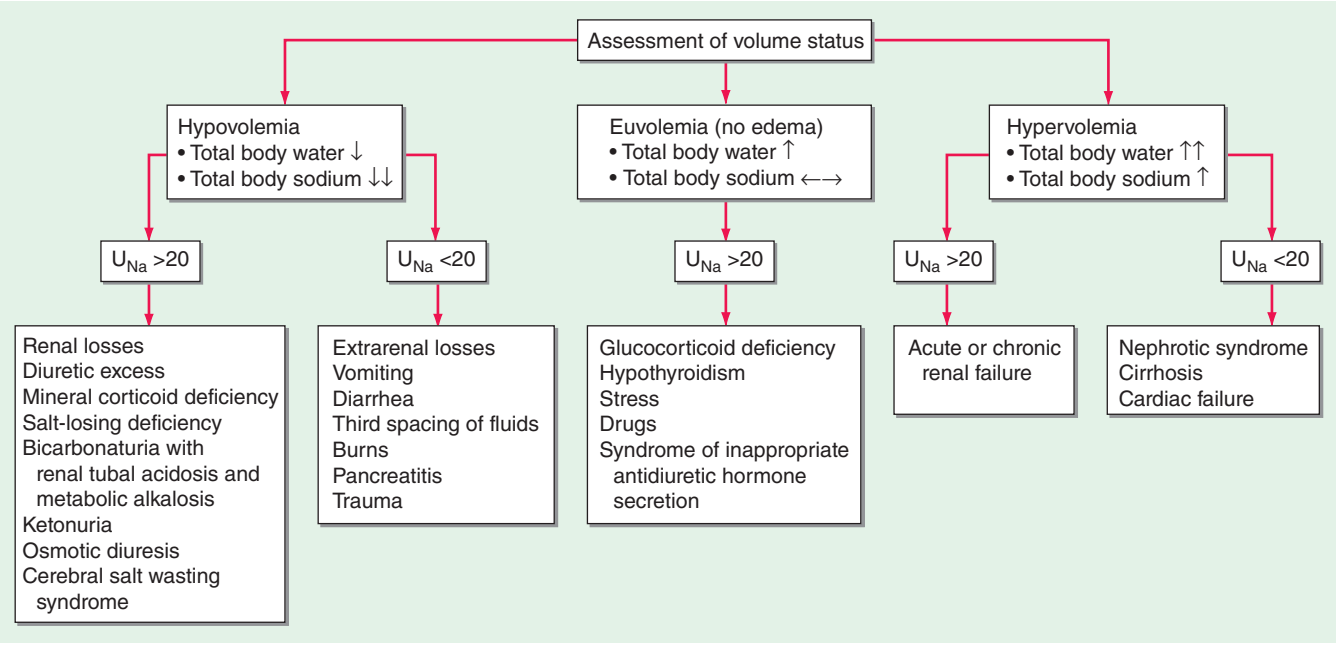



**FIGURE 1-1** The diagnostic approach to hyponatremia. See text for details. *(From S Kumar, T Berl: Diseases of water metabolism, in Atlas of Diseases of the Kidney, RW Schrier [ed]. Philadelphia, Current Medicine, Inc, 1999; with permission.)*

etiologic factors, i.e., cardiac dysfunction, peripheral vasodilation in cirrhosis, and hypoalbuminemia in nephrotic syndrome. The degree of hyponatremia is an indirect index of the associated neurohumoral activation (Table 1-1) and an important prognostic indicator in hypervolemic hyponatremia.

Management consists of treatment of the underlying disorder (e.g., afterload reduction in heart failure, large-volume paracentesis in cirrhosis, immunomodulatory therapy in some forms of nephrotic syndrome), $Na^+$ restriction, diuretic therapy, and, in some pts, $H_2O$ restriction. Vasopressin antagonists (e.g., tolvaptan and conivaptan) are also effective in normalizing hyponatremia associated with both cirrhosis and CHF.

## Euvolemic Hyponatremia

The syndrome of inappropriate ADH secretion (SIADH) characterizes most cases of euvolemic hyponatremia. Other causes of euvolemic hyponatremia include hypothyroidism and secondary adrenal insufficiency due to pituitary disease; notably, repletion of glucocorticoid levels in the latter may cause a rapid drop in circulating AVP levels and overcorrection of serum [$Na^+$] (see below).

Common causes of SIADH include pulmonary disease (e.g., pneumonia, tuberculosis, pleural effusion) and central nervous system (CNS) diseases (e.g., tumor, subarachnoid hemorrhage, meningitis); SIADH also occurs with malignancies (e.g., small cell carcinoma of the lung) and drugs (e.g., selective serotonin reuptake inhibitors, tricyclic antidepressants, nicotine, vincristine, chlorpropamide, carbamazepine, narcotic analgesics, antipsychotic drugs, cyclophosphamide, ifosfamide). Optimal treatment of euvolemic hyponatremia includes treatment of the underlying disorder. $H_2O$ restriction to <1 L/d is a cornerstone of therapy, but may be ineffective or poorly tolerated. However, vasopressin antagonists are predictably effective in normalizing serum [$Na^+$] in SIADH. Alternatives include the administration of loop diuretics to inhibit the countercurrent mechanism and reduce urinary concentration, combined with oral salt tablets to abrogate diuretic-induced salt loss and attendant hypovolemia.

## Acute Symptomatic Hyponatremia

Acute symptomatic hyponatremia is a medical emergency; a sudden drop in serum [$Na^+$] can overwhelm the capacity of the brain to regulate cell volume, leading to cerebral edema, seizures, and death. Women, particularly premenopausal women, are particularly prone to such sequelae; neurologic consequences are comparatively rare in male pts. Many of these pts develop hyponatremia from iatrogenic causes, including hypotonic fluids in the postoperative period, prescription of a thiazide diuretic, colonoscopy preparation, or intraoperative use of glycine irrigants. Polydipsia with an associated cause of increased AVP may also cause acute hyponatremia, as can increased $H_2O$ intake in the setting of strenuous exercise, e.g., a marathon. The recreational drug Ecstasy (methylenedioxymethamphetamine [MDMA]) can cause acute hyponatremia, rapidly inducing both AVP release and increased thirst.

Severe symptoms may occur at relatively modest levels of serum [$Na^+$], e.g., in the mid-120s. Nausea and vomiting are common premonitory symptoms of more severe sequelae. An important concomitant is respiratory failure, which may be hypercapnic due to CNS depression or normocapnic due to neurogenic, noncardiogenic pulmonary edema; the attendant hypoxemia amplifies the impact of hyponatremic encephalopathy.

## TREATMENT HYPONATREMIA

Three considerations are critical in the therapy of hyponatremia. First, the presence, absence, and/or severity of symptoms determine the urgency of therapy (see above for acute symptomatic hyponatremia). Second, pts with hyponatremia that has been present for >48 h ("chronic hyponatremia") are at risk for osmotic demyelination syndrome, typically central pontine myelinolysis, if serum $Na^+$ is

corrected by >10–12 m*M* within the first 24 h and/or by >18 m*M* within the first 48 h. Third, the response to interventions, such as hypertonic saline or vasopressin antagonists, can be highly unpredictable, such that frequent monitoring of serum $Na^+$ (initially every 2–4 h) is imperative.

Treatment of acute symptomatic hyponatremia should include hypertonic saline to acutely increase serum $Na^+$ by 1–2 m*M*/h to a total increase of 4–6 m*M*; this increase is typically sufficient to alleviate acute symptoms, after which corrective guidelines for "chronic" hyponatremia are appropriate (see below). A number of equations and algorithms have been developed to estimate the required rate of hypertonic solution; one popular approach is to calculate a "$Na^+$ deficit," where the $Na^+$ deficit = 0.6 × body weight × (target [$Na^+$] – starting [$Na^+$]). Regardless of the method used to determine the rate of administered hypertonic saline, the increase in serum [$Na^+$] can be highly unpredictable, due to rapid changes in the underlying physiology; serum [$Na^+$] should be monitored every 2–4 h during and after treatment with hypertonic saline. The administration of supplemental $O_2$ and ventilatory support can also be critical in acute hyponatremia, if pts develop acute pulmonary edema or hypercapnic respiratory failure. IV loop diuretics will help treat associated acute pulmonary edema and will also increase free $H_2O$ excretion by interfering with the renal countercurrent multiplier system. It is noteworthy that vasopressin antagonists do not have a role in the management of acute hyponatremia.

The rate of correction should be comparatively slow in *chronic* hyponatremia (<10–12 m*M* in the first 24 h and <18 m*M* in the first 48 h), so as to avoid osmotic demyelination syndrome. Vasopressin antagonists are highly effective in SIADH and in hypervolemic hyponatremia due to heart failure or cirrhosis. Abnormalities in liver function tests have been reported during the use of tolvaptan; hence, therapy with this agent should be restricted to 1–2 months with close monitoring of liver function. Should pts overcorrect serum [$Na^+$] in response to vasopressin antagonists, hypertonic saline, or isotonic saline (in chronic hypovolemic hyponatremia), hyponatremia can be safely reinduced or stabilized by the administration of the vasopressin *agonist* DDAVP and the administration of free $H_2O$, typically IV $D_5W$; again, close monitoring of the response of serum [$Na^+$] is essential to adjust therapy. Alternatively, the treatment of pts with marked hyponatremia can be initiated with the twice-daily administration of DDAVP to maintain constant AVP bioactivity, combined with the administration of hypertonic saline to slowly correct the serum [$Na^+$] in a more controlled fashion, thus reducing upfront the risk of overcorrection.

## HYPERNATREMIA

This is rarely associated with hypervolemia, where the association is typically iatrogenic, e.g., administration of hypertonic sodium bicarbonate. More commonly, hypernatremia is the result of a combined $H_2O$ and volume deficit, with losses of $H_2O$ in excess of $Na^+$. Elderly individuals with reduced thirst and/or diminished access to fluids are at the highest risk of hypernatremia due to decreased free $H_2O$ intake. Common causes of renal $H_2O$ loss are osmotic diuresis secondary to hyperglycemia, postobstructive diuresis, or drugs (radiocontrast, mannitol, etc.); $H_2O$ diuresis occurs in central or nephrogenic diabetes insipidus (DI) (Chap. 168). In pts with hypernatremia due to renal loss of $H_2O$, it is critical to quantify *ongoing* daily losses in addition to calculation of the baseline $H_2O$ deficit (Table 1-2).

### TREATMENT HYPERNATREMIA

The approach to correction of hypernatremia is outlined in Table 1-2. As with hyponatremia, it is advisable to correct the $H_2O$ deficit slowly to avoid neurologic compromise, decreasing the serum [$Na^+$] over 48–72 h. Depending on the blood pressure or clinical volume status, it may be appropriate to initially treat

**TABLE 1-2 CORRECTION OF HYPERNATREMIA**

**$H_2O$ Deficit**

1. Estimate TBW: 50–60% body weight (kg) depending on body composition
2. Calculate free-water deficit: $[(Na^+ - 140)/140] \times TBW$
3. Administer deficit over 48–72 h

**Ongoing $H_2O$ Losses**

4. Calculate free-water clearance, $C_eH_2O$:

$$C_eH_2O = V\left(1 - \frac{U_{Na} + U_K}{S_{Na}}\right)$$

where V is urinary volume, $U_{Na}$ is urinary $[Na^+]$, $U_K$ is urinary $[K^+]$, and SNa is serum $[Na^+]$.

**Insensible Losses**

5. ~10 mL/kg per day: less if ventilated, more if febrile

**Total**

6. Add components to determine $H_2O$ deficit and ongoing $H_2O$ loss; correct the $H_2O$ deficit over 48–72 h and replace daily $H_2O$ loss.

***Abbreviation:*** TBW, total-body water.

with hypotonic saline solutions (1/4 or 1/2 normal saline); blood glucose should be monitored in pts treated with large volumes of $D_5W$, should hyperglycemia ensue. Calculation of urinary electrolyte-free $H_2O$ clearance is helpful to estimate daily, ongoing loss of free $H_2O$ in pts with nephrogenic or central DI (Table 1-2). Other forms of therapy may be helpful in selected cases of hypernatremia. Pts with central DI may respond to the administration of intranasal DDAVP. Stable pts with nephrogenic DI may reduce their polyuria with hydrochlorothiazide (12.5–50 mg/d). This diuretic is thought to increase proximal $H_2O$ reabsorption and decrease distal solute delivery, thus reducing polyuria. Pts with lithium-associated nephrogenic DI may respond to amiloride (2.5–10 mg/d), which decreases the entry of lithium into principal cells in the distal nephron by inhibiting the amiloride-sensitive epithelial sodium channel (ENaC). Notably, however, most pts with lithium-induced nephrogenic DI can adequately accommodate by increasing their $H_2O$ intake. Occasionally, nonsteroidal anti-inflammatory drugs (NSAIDs) or COX-2 inhibitors have also been used to treat polyuria associated with nephrogenic DI, reducing the negative effect of local prostaglandins on urinary concentration; however, the nephrotoxic potential of NSAIDs typically makes them a less attractive therapeutic option.

## POTASSIUM

Because potassium ($K^+$) is the major intracellular cation, discussion of disorders of $K^+$ balance must take into consideration changes in the exchange of intra- and extracellular $K^+$ stores. (Extracellular $K^+$ constitutes <2% of total-body $K^+$ content.) Insulin, $\beta_2$-adrenergic agonists, and alkalosis tend to promote $K^+$ uptake by cells; acidosis, insulinopenia, or acute hyperosmolality (e.g., after treatment with mannitol or $D_{50}W$) promotes the efflux or reduced uptake of $K^+$. A corollary is that tissue necrosis and the attendant release of $K^+$ can cause severe hyperkalemia, particularly in the setting of acute kidney injury. Hyperkalemia due to rhabdomyolysis is thus particularly common, due to the enormous store of $K^+$ in muscle; hyperkalemia may also be prominent in tumor lysis syndrome.

The kidney plays a dominant role in $K^+$ excretion. Although $K^+$ is transported along the entire nephron, it is the principal cells of the connecting segment and cortical collecting duct that play a dominant role in $K^+$ excretion. Apical $Na^+$ entry into principal cells via the amiloride-sensitive epithelial $Na^+$ channel (ENaC) generates a lumen-negative potential difference, which drives passive $K^+$ exit through apical $K^+$ channels. *This relationship is key to the bedside understanding of potassium disorders.* For example, decreased distal delivery of $Na^+$ tends to blunt the ability to excrete $K^+$, leading to hyperkalemia. Abnormalities in the renin-angiotensin-aldosterone system (RAAS) can cause both hypo- and hyperkalemia; aldosterone has a major influence on potassium excretion, increasing the activity of ENaC channels and the basolateral Na+/K+-ATPase, thus amplifying the driving force for $K^+$ secretion across the luminal membrane of principal cells.

## HYPOKALEMIA

Major causes of hypokalemia are outlined in Table 1-3. Atrial and ventricular arrhythmias are the most serious health consequences of hypokalemia. Pts with concurrent Mg deficit and/or digoxin therapy are at a particularly increased risk of arrhythmias. Hypokalemia can directly prolong the QT interval and is a significant cofactor in arrhythmias due to other causes of a prolonged QT interval. Other clinical manifestations include muscle weakness, which may be profound at serum [$K^+$]

**TABLE 1-3 CAUSES OF HYPOKALEMIA**

I. Decreased intake
   A. Starvation
   B. Clay ingestion
II. Redistribution into cells
   A. Acid-base
      1. Metabolic alkalosis
   B. Hormonal
      1. Insulin
      2. Increased $\beta_2$-adrenergic sympathetic activity: post–myocardial infarction, head injury, theophylline
      3. $\beta_2$-Adrenergic agonists: bronchodilators, tocolytics
      4. α-Adrenergic antagonists
      5. Thyrotoxic periodic paralysis
      6. Downstream stimulation of $Na^+/K^+$-ATPase: theophylline, caffeine
   C. Anabolic state
      1. Vitamin $B_{12}$ or folic acid administration (red blood cell production)
      2. Granulocyte-macrophage colony-stimulating factor (white blood cell production)
      3. Total parenteral nutrition
   D. Other
      1. Pseudohypokalemia
      2. Hypothermia
      3. Familial hypokalemic periodic paralysis
      4. Barium toxicity: systemic inhibition of "leak" $K^+$ channels

(*Continued*)

**TABLE 1-3 CAUSES OF HYPOKALEMIA (*CONTINUED*)**

III. Increased loss
- A. Nonrenal
  1. Gastrointestinal loss (diarrhea)
  2. Integumentary loss (sweat)
- B. Renal
  1. Increased distal flow and distal $Na^+$ delivery: diuretics, osmotic diuresis, salt-wasting nephropathies
  2. Increased secretion of potassium
     - a. Mineralocorticoid excess: primary hyperaldosteronism (APAs), PAH or UAH, IHA due to bilateral adrenal hyperplasia and adrenal carcinoma, familial hyperaldosteronism (FH-I, FH-II, congenital adrenal hyperplasias), secondary hyperaldosteronism (malignant hypertension, renin-secreting tumors, renal artery stenosis, hypovolemia), Cushing's syndrome, Bartter's syndrome, Gitelman's syndrome
     - b. Apparent mineralocorticoid excess: genetic deficiency of 11β-dehydrogenase-2 (syndrome of apparent mineralocorticoid excess), inhibition of 11β-dehydrogenase-2 (glycyrrhetinic/glycyrrhizinic acid and/or carbenoxolone; licorice, food products, drugs), Liddle's syndrome (genetic activation of ENaC)
     - c. Distal delivery of nonreabsorbed anions: vomiting, nasogastric suction, proximal renal tubular acidosis, diabetic ketoacidosis, glue sniffing (toluene abuse), penicillin derivatives (penicillin, nafcillin, dicloxacillin, ticarcillin, oxacillin, and carbenicillin)
  3. Magnesium deficiency, amphotericin B, Liddle's syndrome

***Abbreviations:*** APA, aldosterone-producing adenoma; ENaC, epithelial $Na^+$ channels; IHA, idiopathic hyperaldosteronism; PAH, primary adrenal hyperplasia; UAH, unilateral adrenal hyperplasia.

<2.5 mmol/L, and, if hypokalemia is sustained, hypertension, ileus, polyuria, renal cysts, and even renal failure.

The cause of hypokalemia is usually obvious from history, physical examination, and/or basic laboratory tests. However, persistent hypokalemia may require a more thorough, systematic evaluation (Fig. 1-2). Initial laboratory evaluation should include electrolytes, BUN, creatinine, serum osmolality, $Mg^{2+}$, and $Ca^{2+}$, a complete blood count, and urinary pH, osmolality, creatinine, and electrolytes. Serum and urine osmolality are required for calculation of the transtubular $K^+$ gradient (TTKG), which should be <3 in the presence of hypokalemia (see also Hyperkalemia). Alternatively, a urinary $K^+$-to-creatinine ratio of >13-mmol/g creatinine (>1.5-mmol/mmol creatinine) is compatible with excessive $K^+$ excretion. Further tests such as urinary $Mg^{2+}$ and $Ca^{2+}$ and/or plasma renin and aldosterone levels may be necessary in specific cases.

## TREATMENT HYPOKALEMIA

The goals of therapy in hypokalemia are to prevent life-threatening and/or serious chronic consequences, to replace the associated $K^+$ deficit, and to correct the underlying cause and/or mitigate future hypokalemia. The urgency of therapy depends on the severity of hypokalemia, associated clinical factors (cardiac disease, digoxin therapy, etc.), and the rate of decline in serum $K^+$. Pts with a

prolonged QT interval and/or other risk factors for arrhythmia should be monitored by continuous cardiac telemetry during repletion. Urgent but cautious $K^+$ replacement should be considered in pts with severe redistributive hypokalemia (plasma $K^+$ concentration <2.5 m*M*) and/or when serious complications ensue; however, this approach has a risk of rebound hyperkalemia following acute resolution of the underlying cause. When excessive activity of the sympathetic nervous system is thought to play a dominant role in redistributive hypokalemia, as in thyrotoxic periodic paralysis, theophylline overdose, and acute head injury, high-dose propranolol (3 mg/kg) should be considered; this nonspecific β-adrenergic blocker will correct hypokalemia without the risk of rebound hyperkalemia. It should be noted that hypokalemia is refractory to correction in the presence of $Mg^{++}$ deficiency, which also should be corrected when present; renal wasting of both cations may be particularly prominent after renal tubular injury, e.g., from cisplatin nephrotoxicity.

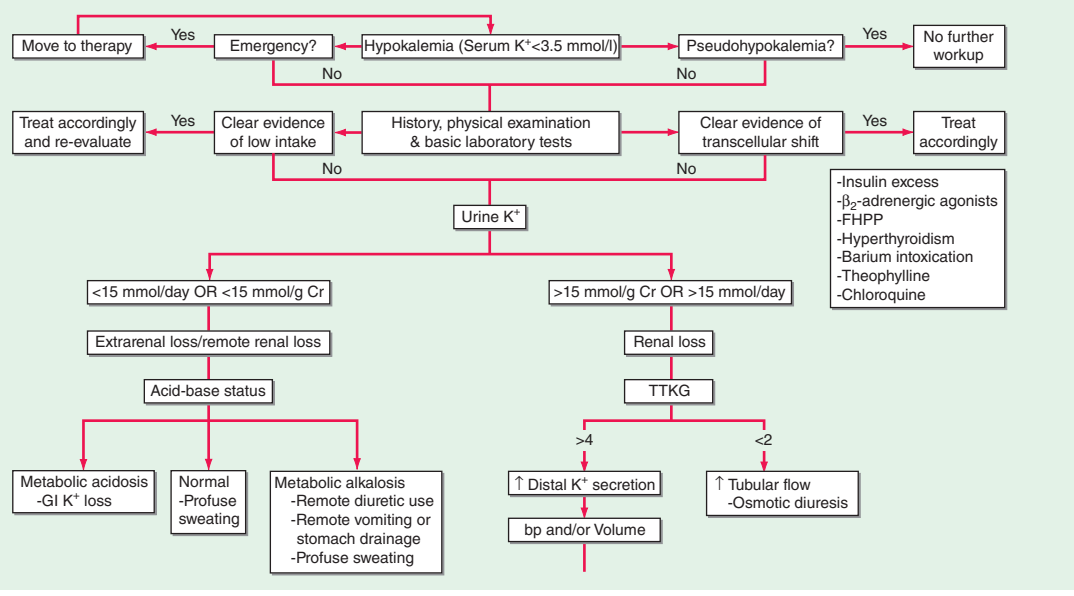
Oral replacement with $K^+$-$Cl^-$ is the mainstay of therapy in hypokalemia. Potassium phosphate, oral or IV, may be appropriate in pts with combined hypokalemia and hypophosphatemia. Potassium bicarbonate or potassium citrate should be considered in pts with concomitant metabolic acidosis. The deficit of $K^+$ and the rate of correction should be estimated as accurately as possible; renal function, medications, and comorbid conditions such as diabetes should also be considered so as to gauge the risk of overcorrection. In the absence of abnormal $K^+$ redistribution, the total deficit correlates with serum $K^+$ such that serum $K^+$ drops by approximately 0.27 m*M* for every 100-mmol reduction in total-body stores. Notably, given the delay in redistributing potassium into intracellular compartments, this deficit must be replaced gradually over 24–48 h, with frequent monitoring of plasma $K^+$ concentration to avoid transient over-repletion and transient hyperkalemia if otherwise appropriate. If hypokalemia is severe (<2.5 mmol/L) and/or if oral supplementation is not feasible or tolerated, IV KCl can be administered through a central vein with cardiac monitoring in an intensive care setting, at rates that should not exceed 20 mmol/h. KCl should always be administered in saline solutions, rather than dextrose; the dextrose-induced increase in insulin can acutely exacerbate hypokalemia.

Strategies to minimize $K^+$ losses should also be considered. These measures may include minimizing the dose of non-$K^+$-sparing diuretics, restricting $Na^+$ intake, and using clinically appropriate combinations of non-$K^+$-sparing and $K^+$-sparing medications (e.g., loop diuretics with angiotensin-converting enzyme inhibitors).

## HYPERKALEMIA

Causes are outlined in Table 1-4; in most cases, hyperkalemia is due to decreased renal $K^+$ excretion. However, increases in dietary $K^+$ intake can have a major effect in susceptible pts, e.g., diabetics with hyporeninemic hypoaldosteronism and chronic kidney disease (CKD). Drugs that impact on the RAA axis are also a major cause of hyperkalemia.

The first priority in the management of hyperkalemia is to assess the need for emergency treatment (ECG changes and/or $K^+$ ≥6.0 m*M*). This should be followed by a comprehensive workup to determine the cause (Fig. 1-3). History and physical examination should focus on medications (e.g., ACE inhibitors, NSAIDs, trimethoprim/sulfamethoxazole), diet and dietary supplements (e.g., salt substitute), risk factors for acute kidney failure, reduction in urine output, blood pressure, and volume status. Initial laboratory tests should include electrolytes, BUN, creatinine, serum osmolality, $Mg^{2+}$, and $Ca^{2+}$, a complete blood count, and urinary pH, osmolality, creatinine, and electrolytes. A urine [$Na^+$] <20 meq/L suggests that distal $Na^+$ delivery is a limiting factor in $K^+$ excretion;


Hypokalemia (Serum K+<3.5 mmol/l)
Emergency?
Yes
Move to therapy
No
Pseudohypokalemia?
Yes
No further workup
No
History, physical examination & basic laboratory tests
Clear evidence of low intake
Yes
Treat accordingly and re-evaluate
No
Clear evidence of transcellular shift
Yes
Treat accordingly
No
-Insulin excess
-β2-adrenergic agonists
-FHPP
-Hyperthyroidism
-Barium intoxication
-Theophylline
-Chloroquine
Urine K+
<15 mmol/day OR <15 mmol/g Cr
>15 mmol/g Cr OR >15 mmol/day
Extrarenal loss/remote renal loss
Renal loss
Acid-base status
TTKG
>4
<2
Metabolic acidosis
-GI K+ loss
Normal
-Profuse sweating
Metabolic alkalosis
-Remote diuretic use
-Remote vomiting or stomach drainage
-Profuse sweating
↑ Distal K+ secretion
↑ Tubular flow
-Osmotic diuresis
bp and/or Volume

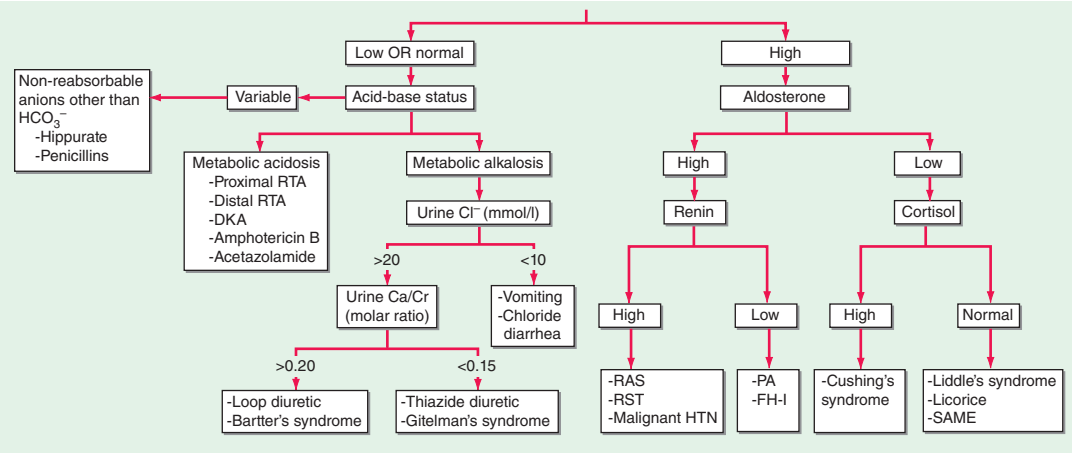



**FIGURE 1-2** The diagnostic approach to hypokalemia. See text for details. bp, blood pressure; DKA, diabetic ketoacidosis; FH-I, familial hyperaldosteronism type I; FHPP, familial hypokalemic periodic paralysis; HTN, hypertension; PA, primary aldosteronism; RAS, renal artery stenosis; RST, renin-secreting tumor; RTA, renal tubular acidosis; SAME, syndrome of apparent mineralocorticoid excess; TTKG, transtubular potassium gradient. *(From Mount DB, Zandi-Nejad K: Disorders of potassium balance, in The Kidney, 8th ed, BM Brenner [ed]. Philadelphia, Saunders, 2008; with permission.)*

**TABLE 1-4 CAUSES OF HYPERKALEMIA**

I. "Pseudo" hyperkalemia
   A. Cellular efflux: thrombocytosis, erythrocytosis, leukocytosis, in vitro hemolysis
   B. Hereditary defects in red cell membrane transport

II. Intra- to extracellular shift
   A. Acidosis
   B. Hyperosmolality; radiocontrast, hypertonic dextrose, mannitol
   C. β-Adrenergic antagonists (noncardioselective agents)
   D. Digoxin and related glycosides (yellow oleander, foxglove, bufadienolide)
   E. Hyperkalemic periodic paralysis
   F. Lysine, arginine, and ε-aminocaproic acid (structurally similar, positively charged)
   G. Succinylcholine; thermal trauma, neuromuscular injury, disuse atrophy, mucositis, or prolonged immobilization
   H. Rapid tumor lysis

III. Inadequate excretion
   A. Inhibition of the renin-angiotensin-aldosterone axis; ↑ risk of hyperkalemia when used in combination or at higher than recommended dosages
      1. ACE inhibitors
      2. Renin inhibitors: aliskiren (in combination with ACE inhibitors or ARBs)
      3. ARBs
      4. Blockade of the mineralocorticoid receptor: spironolactone, eplerenone, drospirenone
      5. Blockade of ENaC: amiloride, triamterene, trimethoprim, pentamidine, nafamostat
   B. Decreased distal delivery
      1. Congestive heart failure
      2. Volume depletion
   C. Hyporeninemic hypoaldosteronism
      1. Tubulointerstitial diseases: SLE, sickle cell anemia, obstructive uropathy
      2. Diabetes, diabetic nephropathy
      3. Drugs: nonsteroidal anti-inflammatory drugs, COX-2 inhibitors, β blockers, cyclosporine, tacrolimus
      4. Chronic kidney disease, advanced age
      5. Pseudohypoaldosteronism type II: defects in WNK1 or WNK4 kinases, Kelch-like 3 (KLHL3), or Cullin 3 (CUL3)
   D. Renal resistance to mineralocorticoid
      1. Tubulointerstitial diseases: SLE, amyloidosis, sickle cell anemia, obstructive uropathy, post–acute tubular necrosis
      2. Hereditary: pseudohypoaldosteronism type I: defects in the mineralocorticoid receptor or ENaC

(*Continued*)

**TABLE 1-4 CAUSES OF HYPERKALEMIA (*CONTINUED*)**

E. Advanced renal insufficiency with low GFR
   1. Chronic kidney disease
   2. End-stage renal disease
   3. Acute oliguric kidney injury
F. Primary adrenal insufficiency
   1. Autoimmune: Addison's disease, polyglandular endocrinopathy
   2. Infectious: HIV, cytomegalovirus, tuberculosis, disseminated fungal infection
   3. Infiltrative: amyloidosis, malignancy, metastatic cancer
   4. Drug-associated: heparin, low-molecular-weight heparin
   5. Hereditary: adrenal hypoplasia congenita, congenital lipoid adrenal hyperplasia, aldosterone synthase deficiency
   6. Adrenal hemorrhage or infarction, including in antiphospholipid syndrome

***Abbreviations:*** ARB, angiotensin receptor blocker; COX-2, cyclooxygenase 2; ENaC, epithelial $Na^+$ channels.

volume repletion with 0.9% saline or treatment with furosemide may then be effective in reducing serum $[K^+]$ by increasing distal $Na^+$ delivery. Serum and urine osmolality are required for calculation of the TTKG. The expected values of the TTKG are largely based on historic data: <3 in the presence of hypokalemia and >7–8 in the presence of hyperkalemia.

$$\text{TTKG} = \frac{[K^+]_{urine} \times OSM_{serum}}{[K^+]_{serum} \times OSM_{urine}}$$

## TREATMENT HYPERKALEMIA

The most important consequence of hyperkalemia is altered cardiac conduction, with the risk of bradycardic cardiac arrest. Figure 1-4 shows serial ECG patterns of hyperkalemia; ECG manifestations of hyperkalemia should be considered a true medical emergency and treated urgently. However, ECG changes of hyperkalemia are notoriously insensitive, particularly in pts with CKD; given these limitations, pts with significant hyperkalemia ($K^+$ ≥6–6.5 mmol/L) in the absence of ECG changes should also be aggressively managed.

Urgent management of hyperkalemia constitutes a 12-lead ECG, admission to the hospital, continuous cardiac monitoring, and immediate treatment. Treatment of hyperkalemia is divided into three categories: (1) antagonism of the cardiac effects of hyperkalemia, (2) rapid reduction in $[K^+]$ by redistribution into cells, and (3) removal of $K^+$ from the body. Treatment of hyperkalemia is summarized in Table 1-5.

## ACID-BASE DISORDERS (FIG. 1-5)

Regulation of normal pH (7.35–7.45) depends on both the lungs and kidneys. By the Henderson-Hasselbalch equation, pH is a function of the ratio of $HCO_3^-$ (regulated by the kidney) to $PCO_2$ (regulated by the lungs). The $HCO_3/PCO_2$ relationship is

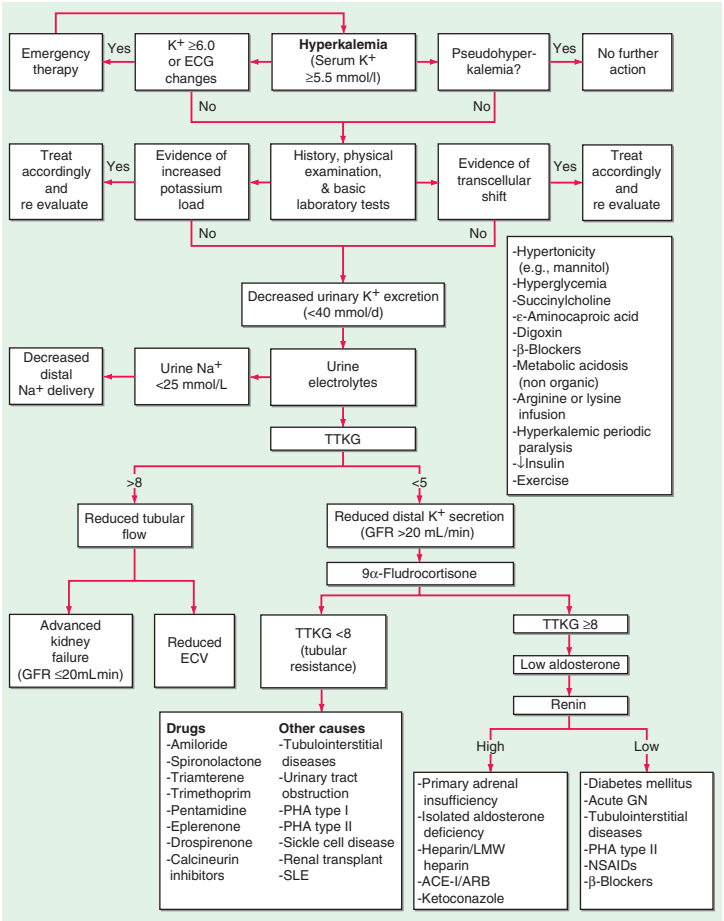



**FIGURE 1-3** The diagnostic approach to hyperkalemia. See text for details. ACEI, angiotensin-converting enzyme inhibitor; acute GN, acute glomerulonephritis; ARB, angiotensin II receptor blocker; ECV, effective circulatory volume; LMW heparin, low-molecular-weight heparin; PHA, pseudohypoaldosteronism; TTKG, transtubular potassium gradient. *(From Mount DB, Zandi-Nejad K: Disorders of potassium balance, in The Kidney, 8th ed, BM Brenner [ed]. Philadelphia, Saunders, 2008; with permission.)*

useful in classifying disorders of acid-base balance. Acidosis is due to gain of acid or loss of alkali; causes may be metabolic (fall in serum $HCO_3^-$) or respiratory (rise in $PCO_2$). Alkalosis is due to loss of acid or addition of base and is either metabolic (↑ serum [$HCO_3^-$]) or respiratory (↓ $PCO_2$).

To limit the change in pH, metabolic disorders evoke an immediate compensatory response in ventilation; full renal compensation for respiratory disorders is a slower process, such that "acute" compensations are of lesser magnitude than "chronic" compensations. Simple acid-base disorders consist of one primary disturbance and

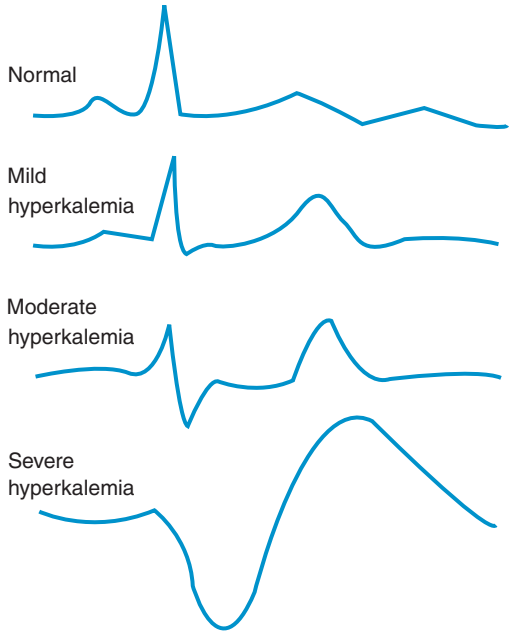



**FIGURE 1-4** Diagrammatic ECGs at normal and high serum K. Peaked T waves (precordial leads) are followed by diminished R wave, wide QRS, prolonged P-R, loss of P wave, and ultimately a sine wave.

its compensatory response. In mixed disorders, a combination of primary disturbances is present.

The cause of simple acid-base disorders is usually obvious from history, physical examination, and/or basic laboratory tests. Initial laboratory evaluation depends on the dominant acid-base disorder, but for metabolic acidosis and alkalosis this should include electrolytes, BUN, creatinine, albumin, urinary pH, and urinary electrolytes. An arterial blood gas (ABG) is not always required for pts with a simple acid-base disorder, e.g., mild metabolic acidosis in the context of chronic renal failure. However, concomitant ABG and serum electrolytes are necessary to fully evaluate more complex acid-base disorders. The compensatory response should be estimated from the ABG; Winter's formula [$PaCO_2 = (1.5 \times [HCO_3^-]) + 8 \pm 2$] is particularly useful for assessing the respiratory response to metabolic acidosis. The anion gap should also be calculated; the anion gap = $[Na^+] - ([HCO_3^-] + [Cl^-])$ = unmeasured anions - unmeasured cations. The anion gap should be adjusted for changes in the concentration of albumin, a dominant unmeasured anion; the "adjusted anion gap" = anion gap + ~2.5 × (4 - albumin mg/dL). Other supportive tests will elucidate the specific form of anion-gap acidosis (see below).

## METABOLIC ACIDOSIS

The low $HCO_3^-$ in metabolic acidosis results from the addition of acids (organic or inorganic) or from a loss of $HCO_3^-$; causes of metabolic acidosis are classically categorized by presence or absence of an increase in the anion gap (Table 1-6). Increased anion-gap acidosis (>12 mmol/L) is due to addition of acid (other than HCl) and unmeasured anions to the body. Common causes include ketoacidosis

**TABLE 1-5 TREATMENT OF HYPERKALEMIA**

| Mechanism | Therapy | Dose | Onset | Duration | Comments |
|---|---|---|---|---|---|
| Stabilize membrane potential | Calcium | 10% Ca gluconate, 10 mL over 10 min | 1–3 min | 30–60 min | Repeat in 5 min if persistent electrocardiographic changes; avoid in digoxin toxicity. |
| Cellular $K^+$ uptake | Insulin | 10 U R with 50 mL of $D_{50}$, if blood sugar <250 | 30 min | 4–6 h | Can repeat in 15 min; initiate $D_{10}W$ IV at 50–75 mL/h to avoid rebound hypoglycemia. |
| | $\beta_2$-Agonist | Nebulized albuterol, 10–20 mg in 4-mL saline | 30 min | 2–4 h | Can be synergistic/additive to insulin; should not be used as sole therapy; use with caution in cardiac disease; may cause tachycardia/hyperglycemia. |
| $K^+$ removal | Kayexalate | 30–60 g PO in 20% sorbitol | 6 h | ? | For sustained efficacy may need more than one dose. May cause fatal colonic necrosis, particularly in enema form and postoperative state. |
| | Furosemide | 20–250 mg IV | 15 min | 4–6 h | Depends on adequate renal response/function. |
| | Hemodialysis | | Immediate | | Efficacy depends on pretreatment of hyperkalemia (with attendant decrease in serum $K^+$), the dialyzer used, blood flow and dialysate flow rates, duration, and serum to dialysate $K^+$ gradient. |

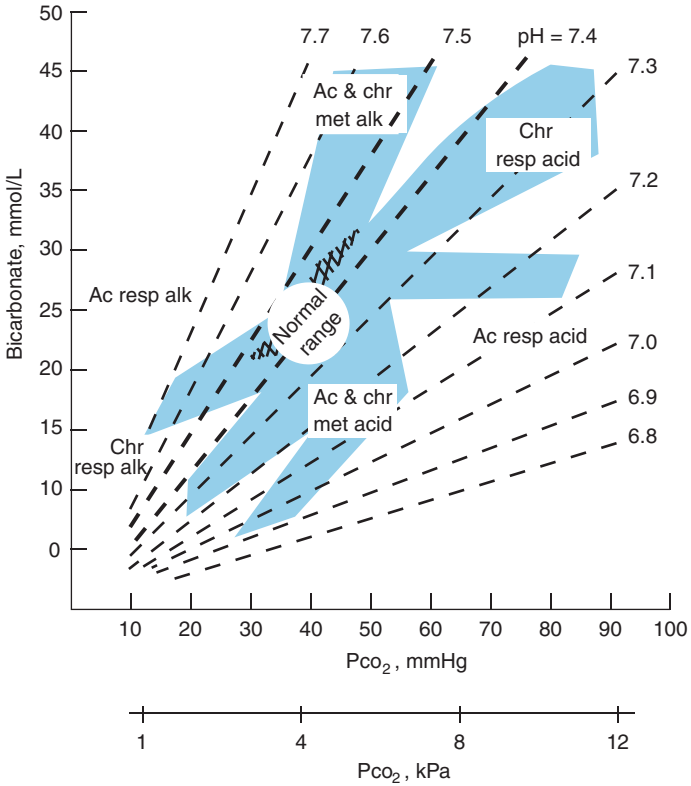



**FIGURE 1-5** Nomogram showing bands for uncomplicated respiratory or metabolic acid-base disturbances in intact subjects. Each confidence band represents the mean ±2 SD for the compensatory response of normal subjects or pts to a given primary disorder. Ac, acute; acid, acidosis; alk, alkalosis; chr, chronic; met, metabolic; resp, respiratory. *(From Levinsky NG: HPIM-12, p. 290; modified from Arbus GS: Can Med Assoc J 109:291, 1973.)*

(diabetes mellitus [DKA], starvation, alcohol), lactic acidosis, poisoning (salicylates, ethylene glycol, and methanol), and renal failure.

Rare and newly appreciated causes of anion-gap acidosis include D-lactic acidosis, propylene glycol toxicity, and 5-oxoprolinuria (also known as pyroglutamic aciduria). D-Lactic acidosis (an increase in the D-enantiomer of lactate) can occur in pts with removal, disease, or bypass of the short bowel, leading to increased delivery of carbohydrates to colon. Intestinal overgrowth of organisms that metabolize carbohydrate to D-lactate results in D-lactic acidosis; a wide variety of neurologic symptoms can ensue, with resolution following treatment with appropriate antibiotics to change the intestinal flora. Propylene glycol is a common solvent for IV preparations of a number of drugs, most prominently lorazepam. Pts receiving high rates of these drugs may develop a hyperosmolar anion-gap metabolic acidosis, due mostly to increased lactate, often accompanied by acute kidney failure. Pyroglutamic aciduria (5-oxoprolinuria) is a high anion-gap acidosis caused by dysfunction of the γ-glutamyl cycle that replenishes intracellular glutathione; 5-oxoproline is an

**TABLE 1-6 METABOLIC ACIDOSIS**

| Non-Anion-Gap Acidosis | | Anion-Gap Acidosis | |
|---|---|---|---|
| **Cause** | **Clue** | **Cause** | **Clue** |
| Diarrhea enterostomy | Hx; ↑ $K^+$ drainage | DKA | Hyperglycemia, ketones |
| RF | Early chronic kidney disease | RF | Late chronic kidney disease |
| RTA | | Lactic acidosis | Clinical setting + ↑ serum lactate |
| Proximal | ↓ $K^+$, presence of other proximal tubular defects (Fanconi syndrome) | (L-lactate) | |
| | | Alcoholic ketoacidosis | Hx; weak + ketones; + osm gap |
| Distal—hypokalemic | ↓ $K^+$; hypercalciuria; UpH >5.5 | Starvation | Hx; mild acidosis; + ketones |
| Distal—hyperkalemic | ↑ $K^+$; nl PRA/aldo; UpH >5.5 | Salicylates | Hx; tinnitus; high serum level; + ketones; + lactate |
| Distal—hyporeninemic hypoaldosteronism | ↑ $K^+$; ↓ PRA/aldo; UpH <5.5 | Methanol | Large AG; concomitant respiratory alkalosis; retinitis; + toxic screen; + osm gap |
| Dilutional | Massive volume expansion with saline | | |
| Ureterosigmoidostomy | Obstructed ileal loop | Ethylene glycol | RF; CNS symptoms; + toxic screen; crystalluria; + osm gap |
| Hyperalimentation | Amino acid infusion | D-lactic acidosis | Small-bowel disease; prominent neuro symptoms |
| Acetazolamide, $NH_4Cl$, lysine HCl, arginine HCl, sevelamer-HCl | Hx of administration of these agents | Propylene glycol | IV infusions, e.g., lorazepam; + osm gap; RF |
| | | Pyroglutamic aciduria, 5-oxoprolinuria | Large AG; chronic acetaminophen |

***Abbreviations:*** AG, anion gap; DKA, diabetic ketoacidosis; osm gap, osmolar gap; PRA, plasma renin activity; RF, renal failure; RTA, renal tubular acidosis; UpH, urinary pH.

intermediate product of the cycle. Hereditary defects in the γ-glutamyl cycle are associated with 5-oxoprolinuria; acquired defects occur in the context of acetaminophen therapy, due to derepression of the cycle by reduced glutathione and overproduction of 5-oxoproline. Resolution occurs after withdrawal of acetaminophen; treatment with *N*-acetyl cysteine to replenish glutathione stores may hasten recovery.

The differentiation of the various anion-gap acidoses depends on the clinical scenario and routine laboratory tests (Table 1-6) in conjunction with measurement of serum lactate, ketones, toxicology screens (if ethylene glycol or methanol ingestion are suspected), and serum osmolality. D-Lactic acidosis can be diagnosed by a specific assay for the D-enantiomer; 5-oxoprolinuria can be diagnosed by the clinical scenario and confirmed by gas chromatographic/mass spectroscopic (GC/MS) analysis of urine, a widely available pediatric screening test for inborn errors of metabolism (typically "urine for organic acids").

Pts with ethylene glycol, methanol, or propylene glycol toxicity may have an "osmolar gap," defined as a >10-mosmol/kg difference between calculated and measured serum osmolality. Calculated osmolality = $2 \times Na^+$ + glucose/18 + BUN/2.8. Of note, pts with alcoholic ketoacidosis and lactic acidosis may also exhibit a modest elevation in the osmolar gap; pts may alternatively metabolize ethylene glycol or methanol to completion by presentation, with an increased anion gap and no increase in the osmolar gap. However, the rapid availability of a measured serum osmolality may aid in the urgent assessment and management of pts with these medical emergencies.

Normal anion-gap acidosis can result from $HCO_3^-$ loss from the GI tract. Diarrhea is by far the most common cause, but other GI conditions associated with external losses of bicarbonate-rich fluids may lead to large alkali losses—e.g., in ileus secondary to intestinal obstruction, in which liters of alkaline fluid may accumulate within the intestinal lumen. Various forms of kidney disease are associated with non-anion-gap acidosis due to reduced tubular reabsorption of filtered bicarbonate and/or reduced excretion of ammonium ($NH_4^+$). The early stages of progressive renal disease are frequently associated with a non-anion-gap acidosis, with development of an anion-gap component in more advanced renal failure. Non-anion-gap acidosis is also seen in renal tubular acidosis or in the context of tubulointerstitial injury, e.g., after acute tubular necrosis, allergic interstitial nephritis, or urinary tract obstruction. Finally, non-anion-gap acidosis due to exogenous acid loads may occur after rapid volume expansion with saline-containing solutions, the administration of $NH_4Cl$ (a component of cough syrup), lysine HCl, or treatment with the phosphate binder sevelamer hydrochloride.

Calculation of the urinary anion gap may be helpful in the evaluation of hyperchloremic metabolic acidosis, along with a measurement of urine pH. The urinary anion gap is defined as urinary ($[Na^+] + [K^+]$) - $[Cl^-]$ = [unmeasured anions] - [unmeasured cations]); the $NH_4^+$ ion is the major unmeasured urinary cation in metabolic acidosis, wherein the urinary anion gap should be strongly negative. A negative anion gap thus suggests GI losses of bicarbonate, with appropriate renal response and increased $NH_4^+$ excretion; a positive anion gap suggests altered urinary acidification, as seen in renal failure or distal renal tubular acidoses. An important caveat is that the rapid renal excretion of unmeasured anions in anion-gap acidosis, classically seen in DKA, may reduce the serum anion gap and generate a positive value for the urinary anion gap, despite the adequate excretion of urinary $NH_4^+$; this may lead to misdiagnosis as a renal tubular acidosis.

## TREATMENT METABOLIC ACIDOSIS

Treatment of metabolic acidosis depends on the cause and severity. DKA responds to insulin therapy and aggressive hydration; close attention to serum $[K^+]$ and administration of KCl is essential, given that the correction of insulinopenia can

cause profound hypokalemia. The administration of alkali in anion-gap acidoses is controversial and is rarely appropriate in DKA. It is reasonable to treat severe lactic acidosis with IV $HCO_3^-$ at a rate sufficient to maintain a pH >7.20; treatment of moderate lactic acidosis with $HCO_3^-$ is controversial. IV $HCO_3$ is however appropriate to reduce acidosis in D-lactic acidosis, ethylene glycol and methanol toxicity, and 5-oxoprolinuria.

Chronic metabolic acidosis should be treated when $HCO_3^-$ is <18–20 mmol/L. In pts with CKD, there is some evidence that acidosis promotes protein catabolism and may worsen bone disease. There is also evidence that correction of metabolic acidosis in CKD leads to a reduced rate of progression to end-stage renal disease (ESRD). Sodium citrate may be more palatable than oral $NaHCO_3$. Oral therapy with $NaHCO_3$ usually begins with 650 mg tid and is titrated upward to maintain serum [$HCO_3^-$].

## METABOLIC ALKALOSIS

Metabolic alkalosis is due to a primary increase in serum [$HCO_3^-$], distinguished from chronic respiratory acidosis—with a compensatory increase in renal $HCO_3^-$ reabsorption—by the associated increase in arterial pH (normal or decreased in chronic respiratory acidosis). Administered, exogenous alkali ($HCO_3^-$, acetate, citrate, or lactate) may cause alkalosis if the normal capacity to excrete $HCO_3^-$ is reduced or if renal $HCO_3^-$ reabsorption is enhanced. A recently resurgent problem is "milk alkali syndrome," a triad of hypercalcemia, metabolic alkalosis, and acute renal failure due to ingested calcium carbonate, typically taken for the treatment or prevention of osteoporosis or for symptomatic relief of peptic ulcer disease.

Metabolic alkalosis is primarily caused by renal retention of $HCO_3^-$ and is due to a variety of underlying mechanisms. Pts are typically separated into two major subtypes: $Cl^-$ responsive and $Cl^-$ resistant. Measurement of urine $Cl^-$ affords this separation in the clinical setting (Fig. 1-6). The quintessential causes of $Cl^-$-responsive alkalosis are GI induced from vomiting or gastric aspiration through a nasogastric tube, and renal induced from diuretic therapy. Hypovolemia, chloride deficiency, activation of the RAA axis, and hypokalemia play interrelated roles in the maintenance of this hypochloremic or "contraction" alkalosis. The various syndromes of true or apparent mineralocorticoid excess cause $Cl^-$-resistant metabolic alkalosis (Fig. 1-6); most of these pts are hypokalemic, volume expanded, and/or hypertensive.

Common forms of metabolic alkalosis are generally diagnosed from the history, physical examination, and/or basic laboratory tests. ABGs will help determine whether an elevated [$HCO_3^-$] is reflective of metabolic alkalosis or chronic respiratory acidosis; ABGs are required for the diagnosis of mixed acid-base disorders. Measurement of urinary electrolytes will aid in separating $Cl^-$-responsive and $Cl^-$-resistant forms. Urinary [$Na^+$] may thus be >20 meq/L in $Cl^-$-responsive alkalosis despite the presence of hypovolemia; however, urinary [$Cl^-$] will typically be very low, except in pts with severe hypokalemia. Notably, urinary [$Cl^-$] may be variable in pts with diuretic-associated alkalosis, depending on the temporal relationship to diuretic administration. Other diagnostic tests—e.g., plasma renin, aldosterone, cortisol—may be appropriate in $Cl^-$-resistant forms with high urinary [$Cl^-$] (Fig. 1-6).

## TREATMENT METABOLIC ALKALOSIS

The acid-base disorder in $Cl^-$-responsive alkalosis will typically respond to saline infusion; however, the associated hypokalemia should also be corrected. Pts with true or apparent mineralocorticoid excess require specific treatment of the underlying disorder. For example, hyperactive amiloride-sensitive ENaC channels cause Liddle's syndrome, which can respond to therapy with amiloride and related drugs; pts with hyperaldosteronism may in turn respond to blockade of

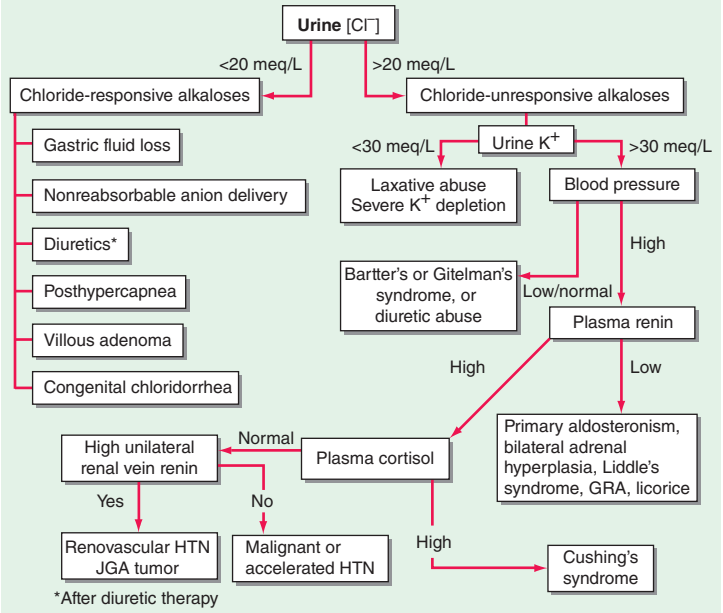



**FIGURE 1-6** The diagnostic approach to metabolic alkalosis. See text for details. GRA, glucocorticoid-remediable aldosteronism; HTN, hypertension; JGA, juxtaglomerular apparatus. *(Modified from Dubose TD: Disorders of acid-base balance, in The Kidney, 8th ed, BM Brenner [ed]. Philadelphia, Saunders, 2008; with permission.)*

the mineralocorticoid receptor with spironolactone or eplerenone. Finally, severe alkalosis in the critical care setting may require treatment with acidifying agents such as acetazolamide.

## RESPIRATORY ACIDOSIS

Respiratory acidosis is characterized by $CO_2$ retention due to ventilatory failure. Causes include sedatives, stroke, chronic pulmonary disease, airway obstruction, severe pulmonary edema, neuromuscular disorders, and cardiopulmonary arrest. Symptoms include confusion, asterixis, and obtundation.

### TREATMENT RESPIRATORY ACIDOSIS

The goal is to improve ventilation through pulmonary toilet and reversal of bronchospasm. Intubation or noninvasive positive pressure ventilation (NPPV) may be required in severe acute cases. Acidosis due to hypercapnia is usually mild; however, combined respiratory and metabolic acidosis may cause a profound reduction in pH. Respiratory acidosis may accompany low tidal volume ventilation in ICU pts and may require metabolic "overcorrection" to maintain a neutral pH.

## RESPIRATORY ALKALOSIS

Excessive ventilation causes a primary reduction in $CO_2$ and ↑ pH in pneumonia, pulmonary edema, interstitial lung disease, and asthma. Pain and psychogenic causes

are common; other etiologies include fever, hypoxemia, sepsis, delirium tremens, salicylates, hepatic failure, mechanical overventilation, and CNS lesions. Pregnancy is associated with a mild respiratory alkalosis. Severe respiratory alkalosis may acutely cause seizures, tetany, cardiac arrhythmias, or loss of consciousness.

## TREATMENT RESPIRATORY ALKALOSIS

Treatment should be directed at the underlying disorders. In psychogenic cases, sedation or a rebreathing bag may be required.

## "MIXED" DISORDERS

In many circumstances, more than a single acid-base disturbance exists. Examples include combined metabolic and respiratory acidosis with cardiogenic shock; metabolic alkalosis and anion-gap acidosis in pts with vomiting and diabetic ketoacidosis; and anion-gap metabolic acidosis with respiratory alkalosis in pts with salicylate toxicity. The diagnosis may be clinically evident and/or suggested by relationships between the $PCO_2$ and $[HCO_3^-]$ that diverge from those found in simple disorders. For example, the $PCO_2$ in a pt with metabolic acidosis and respiratory alkalosis will be considerably less than that predicted from the $[HCO_3^-]$ and Winter's formula $[PaCO_2 = (1.5 \times [HCO_3^-]) + 8 + 2]$.

In "simple" anion-gap acidosis, the anion gap increases in proportion to the fall in $[HCO_3^-]$. A lesser drop in serum $[HCO_3^-]$ than in the anion gap suggests a coexisting metabolic alkalosis. Conversely, a proportionately *larger* drop in $[HCO_3^-]$ than in the anion gap suggests the presence of a mixed anion-gap and non-anion-gap metabolic acidosis. Notably, however, these interpretations assume 1:1 relationships between unmeasured anions and the fall in $[HCO_3^-]$, which are not uniformly present in individual pts or as acidoses evolve. For example, volume resuscitation of pts with DKA will typically increase glomerular filtration and the urinary excretion of ketones, resulting in a decrease in the anion gap in the absence of a supervening non-anion-gap acidosis.

For a more detailed discussion, see Mount DB: Fluid and Electrolyte Disturbances, Chap. 63, p. 295; and DuBose TD Jr: Acidosis and Alkalosis, Chap. 66, p. 315, in HPIM-19. See also Mount DB, Zandi-Nejad K: Disorders of potassium balance, in The Kidney, 9th ed, BM Brenner (ed). Philadelphia, Saunders, 2011; and Ellison DH, Berl T: Clinical practice. The syndrome of inappropriate antidiuresis. N Engl J Med 356:2064, 2007; Perianayagam A et al: DDAVP is effective in preventing and reversing inadvertent overcorrection of hyponatremia. Clin J Am Soc Nephrol 3:331, 2008; Sood L et al: Hypertonic saline and desmopressin: a simple strategy for safe correction of severe hyponatremia. Am J Kidney Dis 61:571-578, 2013.

# 2 Diagnostic Imaging in Internal Medicine

Clinicians have a wide array of radiologic modalities at their disposal to aid them in noninvasive diagnosis. Despite the introduction of highly specialized imaging modalities, radiologic tests such as chest radiographs and ultrasound continue to serve a vital role in the diagnostic approach to pt care. At most institutions, CT is available on an emergent basis and is invaluable for initial evaluation of pts with trauma, suspected CNS hemorrhage, or ischemic stroke. MRI and related techniques (MR angiography, functional MRI, MR spectroscopy) provide remarkable resolution of many tissues including the brain, vascular system, joints, and most large organs. Radionuclide scans including positron emission tomography (PET) can provide functional assessment of organs or specific regions within organs. Combination of PET with MRI or CT scanning provides highly informative images of the location and configuration of metabolically active lesions, such as cancers. Increasingly, internists are being trained in the use of ultrasound to assist with line placement, thyroid nodules, cardiac sounds, and abdominal abnormalities.

This chapter will review the indications and utility of the most commonly utilized radiologic studies used by internists.

## CHEST RADIOGRAPHY (FIG. 2-1)

- Can be obtained quickly and should be part of the standard evaluation for pts with cardiopulmonary complaints.
- Is able to identify life-threatening conditions such as pneumothorax, intraperitoneal air, pulmonary edema, pneumonia, and aortic dissection.
- Is most often normal in a pt with an acute pulmonary embolus.
- Should be repeated in 4–6 weeks in a pt with an acute pneumonic process to document resolution of the radiographic infiltrate.
- Is used in conjunction with the physical examination to support the diagnosis of congestive heart failure. Radiographic findings supporting the diagnosis of heart failure include cardiomegaly, cephalization, Kerley B lines, and pleural effusions.
- Should be repeated frequently in intubated pts to examine endotracheal tube position and the possibility of barotrauma.
- Helps to identify alveolar or airspace disease. Radiographic features of such diseases include inhomogeneous, patchy opacities and air-bronchograms.
- Helps to document the free-flowing nature of pleural effusions. Decubitus views should be obtained to exclude loculated pleural fluid prior to attempts to extract such fluid.

## ABDOMINAL RADIOGRAPHY

- Should be the initial imaging modality in a pt with suspected bowel obstruction. Signs of small-bowel obstruction on plain radiographs include multiple air-fluid levels, absence of colonic distention, and a “stepladder” appearance of small-bowel loops.
- Should not be performed with barium enhancement when perforated bowel, portal venous gas, or toxic megacolon is suspected.
- Is used to evaluate the size of bowel:
  1. Normal small bowel is <3 cm in diameter.
  2. Normal caliber of the cecum is up to 9 cm, with the rest of the large bowel up to 6 cm in diameter.

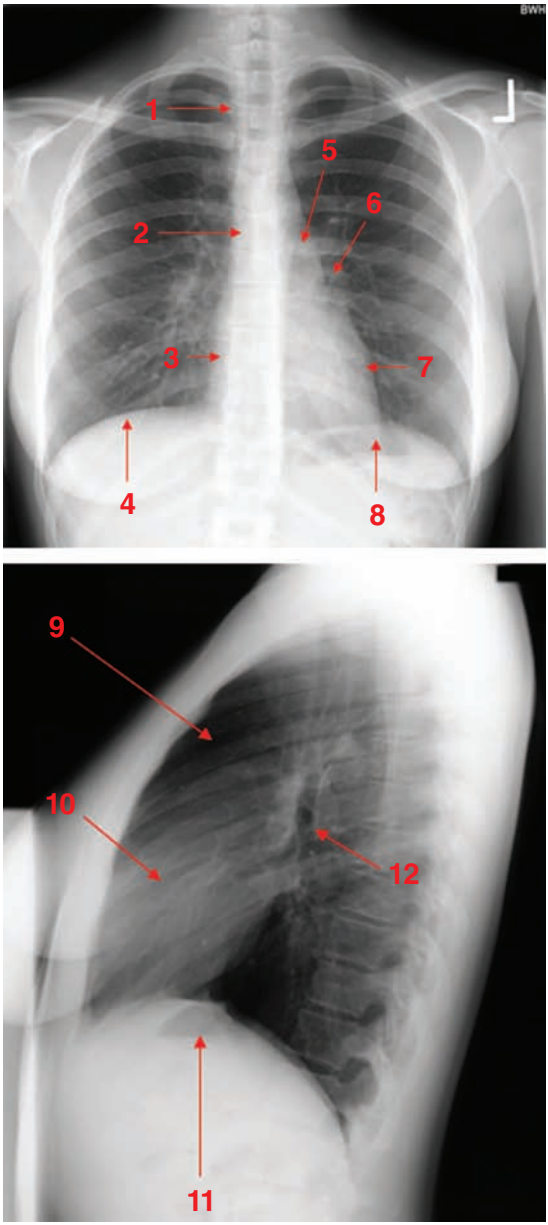



**FIGURE 2-1** Normal chest radiograph-review of anatomy. **1.** Trachea. **2.** Carina. **3.** Right atrium. **4.** Right hemidiaphragm. **5.** Aortic knob. **6.** Left hilum. **7.** Left ventricle. **8.** Left hemidiaphragm (with stomach bubble). **9.** Retrosternal clear space. **10.** Right ventricle. **11.** Left hemidiaphragm (with stomach bubble). **12.** Left upper lobe bronchus.

## ULTRASOUND

- Is more sensitive and specific than CT scanning in evaluating for the presence of gallstone disease.
- Can be used to assist with central line placement and with peripheral access when challenging.
- Can readily identify the size of the kidneys in a pt with renal insufficiency and can exclude the presence of hydronephrosis.
- Can expeditiously evaluate for the presence of peritoneal fluid in a pt with blunt abdominal trauma.
- Is used in conjunction with Doppler studies to evaluate for the presence of arterial atherosclerotic disease.
- Is used to evaluate cardiac valves and wall motion.
- Should be used to localize loculated pleural and peritoneal fluid prior to draining such fluid.
- Can determine the size of thyroid nodules and guide fine-needle aspiration biopsy.
- Can determine the size and location of enlarged lymph nodes, especially in superficial locations such as in the neck.
- Is the modality of choice for assessing known or suspected scrotal pathology.
- Should be the first imaging modality utilized when evaluating the ovaries.

## COMPUTED TOMOGRAPHY

- CT delivers a substantially higher radiation dose than conventional radiography; it should therefore be used judiciously.
- CT of the brain should be the initial radiographic modality in evaluating a pt with a potential stroke.
- Is highly sensitive for diagnosing an acute subarachnoid hemorrhage and, in the acute setting, is more sensitive than MRI.
- CT of the brain is an essential test in evaluating a pt with mental status changes to exclude entities such as intracranial bleeding, mass effect, subdural or epidural hematomas, and hydrocephalus.
- Is better than MRI for evaluating osseous lesions of the skull and spine.
- CT of the chest should be considered in the evaluation of a pt with chest pain to rule out entities such as pulmonary embolus or aortic dissection.
- CT of the chest is essential for evaluating lung nodules to assess for the presence of thoracic lymphadenopathy.
- CT, with high-resolution cuts through the lungs, is the imaging modality of choice for evaluating the lung interstitium in a pt with interstitial lung disease.
- Can be used to evaluate for the presence of pleural and pericardial fluid and to localize loculated effusions.
- Is useful in a pt with unexplained abdominal pain to evaluate for conditions such as appendicitis, mesenteric ischemia or infarction, diverticulitis, or pancreatitis.
- CT of the abdomen is also the test of choice for evaluating for nephrolithiasis in a pt with renal colic.
- Is the test of choice for evaluating for the presence of an abscess in the chest or abdomen.
- In conjunction with abdominal radiography, CT can help identify the cause of bowel obstruction.
- Can identify abdominal conditions such as intussusception and volvulus in a pt with abdominal pain.
- Is the imaging modality of choice for evaluating the retroperitoneum.
- Should be obtained expeditiously in a pt with abdominal trauma to evaluate for the presence of intraabdominal hemorrhage and to assess injury to abdominal organs.

### MAGNETIC RESONANCE IMAGING

- Is more useful than CT in the evaluation of ischemic infarction, dementia, mass lesions, demyelinating diseases, and most nonosseous spinal disorders.
- Provides excellent imaging of large joints including the knee, hip, and shoulder.
- Can be used, often with CT or angiography, to assess possible dissecting aortic aneurysms and congenital anomalies of the cardiovascular system.
- Cardiac MRI is proving useful to evaluate cardiac wall motion and for assessing cardiac muscle viability in ischemic heart disease.
- Is preferable to CT for evaluating adrenal masses such as pheochromocytoma and for helping to distinguish benign and malignant adrenal masses.
- Is preferable to CT for evaluating pituitary lesions and parasellar pathology.

### RADIONUCLIDE IMAGING

- Radionuclides can be used in the form of radioactive ions (iodide, gallium, thallium) or radiolabeled substances with affinity for specific tissues (radiopharmaceuticals, e.g., bisphosphonates, sestamibi, octreotide, metaiodobenzylguanidine [MIBG], iodocholesterol, etc.), or in the form of fluorodeoxyglucose for PET scanning.
- Radionuclide scintigraphy can be combined/merged with CT or MRI for precise anatomic localization of the radionuclide-imaged tissue.
- Tomographic radionuclide scintigraphy (single-photon emission computed tomography [SPECT]) is analogous to CT, using radionuclide emissions instead of x-rays. It permits visualization of sequential slices that can be computer manipulated to yield a three-dimensional reconstruction.
- PET is very useful for detection of metabolically active tissues, such as cancers and their metastases, and has largely supplanted older modalities of radionuclide scanning (e.g., gallium scintigraphy).
- Radionuclide scans frequently ordered by the general internist are: (1) bone scans to identify metastatic disease in bone or osteomyelitis, (2) sestamibi scans for preoperative localization of parathyroid adenomas, (3) thyroid scans (technetium or iodine) to identify hot or cold thyroid nodules.
- Specialized radionuclide scans include thallium or sestamibi myocardial perfusion scans, pulmonary ventilation/perfusion scans, octreotide scans for neuroendocrine tumors, MIBG scans for pheochromocytoma, iodocholesterol scans for adrenocortical adenomas, and whole-body radioiodine scans for disseminated thyroid cancer.
- Radioiodine scanning of the thyroid can be used to obtain quantitative information on iodine uptake by the thyroid, which is useful to differentiate subacute thyroiditis from Graves' disease.

## 3 Procedures Commonly Performed by Internists

Internists perform a wide range of medical procedures, although practices vary widely among institutions and by specialty. Internists, nurses, or other ancillary health care professionals perform venipuncture for blood testing, arterial puncture for blood gases, endotracheal intubation, and flexible sigmoidoscopy, and insert IV lines, nasogastric (NG) tubes, and urinary catheters. These procedures are not

covered here, but require skill and practice to minimize pt discomfort and potential complications. Here, we review more invasive diagnostic and therapeutic procedures performed by internists—thoracentesis, lumbar puncture, and paracentesis. Many additional procedures are performed by specialists and require additional training and credentialing, including the following:

- Allergy: skin testing, rhinoscopy
- Cardiology: stress testing, echocardiograms, coronary catheterization, angioplasty, stent insertion, pacemakers, electrophysiology testing and ablation, implantable defibrillators, cardioversion
- Endocrinology: thyroid biopsy, dynamic hormone testing, bone densitometry
- Gastroenterology: upper and lower endoscopy, esophageal manometry, endoscopic retrograde cholangiopancreatography, stent insertion, endoscopic ultrasound, liver biopsy
- Hematology/oncology: bone marrow biopsy, stem cell transplant, lymph node biopsy, plasmapheresis
- Pulmonary: intubation and ventilator management, bronchoscopy
- Renal: kidney biopsy, dialysis
- Rheumatology: joint aspiration

Increasingly, ultrasound, CT, and MRI are being used to guide invasive procedures, and flexible fiberoptic instruments are extending the reach into the body. For most invasive medical procedures, including those reviewed below, informed consent should be obtained in writing before beginning the procedure.

## THORACENTESIS

Drainage of the pleural space can be performed at the bedside. Indications for this procedure include diagnostic evaluation of pleural fluid, removal of pleural fluid for symptomatic relief, and instillation of sclerosing agents in pts with recurrent, usually malignant pleural effusions.

### PREPARATORY WORK

Familiarity with the components of a thoracentesis tray is a prerequisite to performing a thoracentesis successfully. Recent posterior-anterior (PA) and lateral chest radiographs with bilateral decubitus views should be obtained to document the free-flowing nature of the pleural effusion. Loculated pleural effusions should be localized by ultrasound or CT prior to drainage. Management should be individualized in pts with a coagulopathy of thrombocytopenia. Thoracentesis is more challenging in pts with mechanical ventilation and should be performed with ultrasound guidance if possible.

### TECHNIQUE

A posterior approach is the preferred means of accessing pleural fluid. Comfortable positioning is a key to success for both pt and physician. The pt should sit on the edge of the bed, leaning forward with the arms abducted onto a pillow on a bedside stand. Pts undergoing thoracentesis frequently have severe dyspnea, and it is important to assess if they can maintain this positioning for at least 10 min. The entry site for the thoracentesis is based on the physical examination and radiographic findings. Percussion of dullness is utilized to ascertain the extent of the pleural effusion with the site of entry being the first or second highest interspace in this area. The entry site for the thoracentesis is at the superior aspect of the rib, thus avoiding the intercostal nerve, artery, and vein, which run along the inferior aspect of the rib (Fig. 3-1).

The site of entry should be marked with a pen to guide the thoracentesis. The skin is then prepped and draped in a sterile fashion with the operator observing sterile technique at all times. A small-gauge needle is used to anesthetize the skin, and a larger-gauge needle is used to anesthetize down to the superior aspect of the rib. The

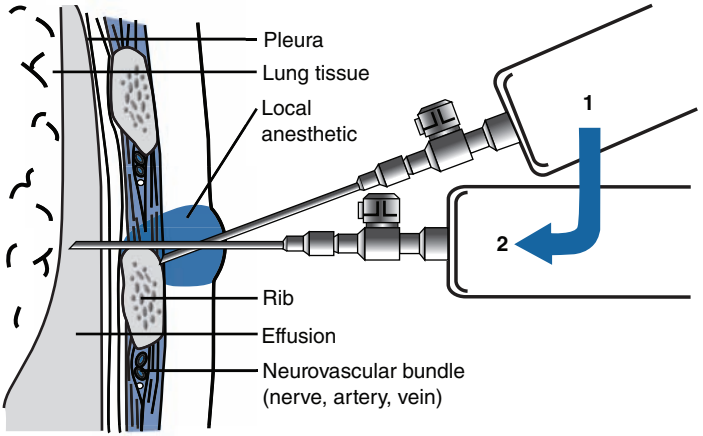



**FIGURE 3-1** In thoracentesis, the needle is passed over the top of the rib to avoid the neurovascular bundle. *(From LG Gomella, SA Haist: Clinician's Pocket Reference, 11th ed. New York, McGraw-Hill, 2007.)*

needle should then be directed over the upper margin of the rib to anesthetize down to the parietal pleura. The pleural space should be entered with the anesthetizing needle, all the while using liberal amounts of lidocaine.

A dedicated thoracentesis needle with an attached syringe should next be utilized to penetrate the skin. This needle should be advanced to the superior aspect of the rib. While maintaining gentle negative pressure, the needle should be slowly advanced into the pleural space. If a diagnostic tap is being performed, aspiration of only 30–50 mL of fluid is necessary before termination of the procedure. If a therapeutic thoracentesis is being performed, a three-way stopcock is utilized to direct the aspirated pleural fluid into collection bottles or bags. No more than 1 L of pleural fluid should be withdrawn at any given time, because quantities >1–1.5 L can result in re-expansion pulmonary edema.

After all specimens have been collected, the thoracentesis needle should be withdrawn and the needle site occluded for at least 1 min.

### SPECIMEN COLLECTION

The diagnostic evaluation of pleural fluid depends on the clinical situation. All pleural fluid samples should be sent for cell count and differential, Gram stain, and bacterial cultures. LDH and protein determinations should also be made to differentiate between exudative and transudative pleural effusions. The pH should be determined if empyema is a diagnostic consideration. Other studies on pleural fluid include mycobacterial and fungal cultures, glucose, triglyceride level, amylase, and cytologic determination.

### POSTPROCEDURE

A postprocedural chest radiograph should be obtained to evaluate for a pneumothorax, and the pt should be instructed to notify the physician if new shortness of breath develops.

## LUMBAR PUNCTURE

Evaluation of CSF is essential for the diagnosis of suspected meningeal infection, subarachnoid hemorrhage, leptomeningeal neoplastic disease, and noninfectious meningitis. Relative contraindications to LP include local skin infection in the

lumbar area, suspected spinal cord mass lesion, and a suspected intracranial mass lesion. Any bleeding diathesis should also be corrected prior to performing LP to prevent the possible occurrence of an epidural hematoma. A functional platelet count >50,000/μL and an international normalized ratio (INR) <1.5 are advisable to perform LP safely.

In pts with an altered level of consciousness, focal neurologic deficits, or evidence of papilledema, an imaging study should generally be obtained prior to performing LP.

## TECHNIQUE

Proper positioning of the pt is essential; either the lateral decubitus or the sitting position can be used. Most routine LPs should be performed using the lateral decubitus position (Fig. 3-2). The sitting position may be preferable in obese pts. With either position, the pt should be instructed to flex the spine as much as possible. In the lateral decubitus position, the pt assumes a fetal position with the knees flexed toward the abdomen; the shoulders and pelvis should be vertically aligned without forward or backward tilt. In the sitting position, the pt should bend over a bedside table with the head resting on folded arms.

The entry site for an LP is below the level of the conus medullaris, which extends to L1–L2 in most adults. Thus, either the L3–L4 or L4–L5 interspace can be utilized as the entry site. The posterior superior iliac crest should be identified and the spine palpated at this level. This represents the L3–L4 interspace, with the other interspaces referenced from this landmark. The midpoint of the interspace between the spinous processes represents the entry point for the spinal needle. For elective LPs, topical anaesthesia can be achieved by application of lidocaine 4% cream 30 min prior to the procedure. The skin is then prepped and draped in a sterile fashion with the operator observing sterile technique at all times. A small-gauge needle is then used to anesthetize the skin and subcutaneous tissue; this is usually performed with multiple small (0.5–1 mL), serial injections of 1% lidocaine as the needle is progressively advanced. The spinal needle should be introduced perpendicular to the skin in the midline and advanced slowly. The needle stylet can be withdrawn periodically as the spinal needle is advanced to assess if the subarachnoid space has been reached. As the needle enters the subarachnoid space, a "popping" sensation can sometimes be felt. If bone is encountered, the needle should be withdrawn to just below the skin and then redirected more caudally. Once CSF begins to flow, the opening pressure should be measured in the lateral decubitus position with the pt shifted to this position if the

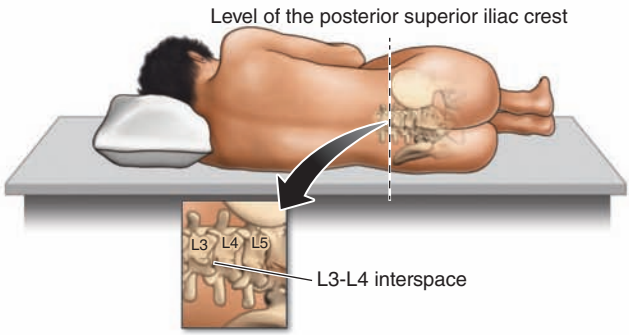



**FIGURE 3-2** Proper positioning of a pt in the lateral decubitus position. Note that the shoulders and hips are in a vertical plane; the torso is perpendicular to the bed. *(From RP Simon et al [eds]: Clinical Neurology, 7th ed. New York, McGraw-Hill, 2009.)*

procedure was begun in the sitting position. The CSF can then be collected in a series of specimen tubes. A minimum of 10–15 mL of CSF is usually obtained. The stylet is then replaced and the spinal needle removed.

### SPECIMEN COLLECTION

Diagnostic evaluation of CSF is based on the clinical scenario. In general, spinal fluid should always be sent for cell count with differential, protein, and glucose. Other studies that can be obtained on CSF include bacterial mycobacterial fungal, viral cultures, polymerase chain reaction (PCR) tests for microorganisms, smears (Gram and acid-fast stains), VDRL, cryptococcal antigen, gamma globulins, oligoclonal bands, and cytology.

### POSTPROCEDURE

The pt is often instructed to lie in the recumbent position for 30–60 min, although this practice does not appear to reduce the risk (estimated at 10–30%) of post-LP headache, caused by a fall in CSF pressure. The post-LP headache is dramatically positional; it begins when the pt sits or stands upright and is relieved upon reclining. Bedrest, hydration, and oral analgesics are often helpful; IV caffeine (500 mg in 500-mL saline given over 2 h) is sometimes tried. For post-LP headaches lasting more than a few days, consultation with an anesthesiologist should be considered for placement of an epidural blood patch; this usually provides rapid relief.

## PARACENTESIS

Removal and analysis of peritoneal fluid is invaluable in evaluating pts with new-onset ascites or ascites of unknown etiology. It is also indicated in pts with known ascites who have a decompensation in their clinical status. Relative contraindications include bleeding diathesis, prior abdominal surgery, distended bowel, or known loculated ascites.

### PREPARATORY WORK

Prior to performing a paracentesis, any severe bleeding diathesis should be corrected. Bowel distention should also be relieved by placement of a NG tube, and the bladder should also be emptied before beginning the procedure. If a large-volume paracentesis is being performed, large vacuum bottles with the appropriate connecting tubing should be obtained.

### TECHNIQUE

Proper pt positioning greatly improves the ease with which a paracentesis can be performed. The pt should be instructed to lie supine with the head of the bed elevated to 45°. This position should be maintained for ~15 min to allow ascitic fluid to accumulate in the dependent portion of the abdomen. Although not generally needed, ultrasound can be helpful for documenting ascites and identifying the locations of peritoneal fluid.

The preferred entry site for paracentesis is a midline puncture halfway between the pubic symphysis and the umbilicus; this correlates with the location of the relatively avascular linea alba. The midline puncture should be avoided if there is a previous midline surgical scar, because neovascularization may have occurred. Alternative sites of entry include the lower quadrants, lateral to the rectus abdominis, but caution should be used to avoid collateral blood vessels that may have formed in pts with portal hypertension.

The skin is prepped and draped in a sterile fashion. The skin, the subcutaneous tissue, and the abdominal wall down to the peritoneum should be infiltrated with an anesthetic agent. The paracentesis needle with an attached syringe is then introduced in the midline perpendicular to the skin. To prevent leaking of ascitic fluid, "Z-tracking" can sometimes be helpful: After penetrating the skin, the needle

is inserted 1–2 cm before advancing further. The needle is then advanced slowly while continuous aspiration is performed. As the peritoneum is pierced, the needle will "give" noticeably. Fluid should flow freely into the syringe soon thereafter. For a diagnostic paracentesis, removal of 50 mL of ascitic fluid is adequate. For a large-volume paracentesis, direct drainage into large vacuum containers using connecting tubing is a commonly utilized option.

After all samples have been collected, the paracentesis needle should be removed and firm pressure applied to the puncture site.

### SPECIMEN COLLECTION

Peritoneal fluid should be sent for cell count with differential, Gram stain, and bacterial cultures. Albumin measurement of ascitic fluid is also necessary for calculating the serum–ascitic albumin gradient. Depending on the clinical scenario, other studies that can be obtained include mycobacterial cultures, amylase, adenosine deaminase, triglycerides, and cytology.

### POSTPROCEDURE

The pt should be monitored carefully after paracentesis and should be instructed to lie supine in bed for several hours. If persistent fluid leakage occurs, continued bedrest with pressure dressings at the puncture site can be helpful. For pts with hepatic dysfunction undergoing large-volume paracentesis, the sudden reduction in intravascular volume can precipitate hepatorenal syndrome. Administration of 25-g IV albumin following large-volume paracentesis has been shown to decrease the incidence of postprocedure renal failure. Finally, if the ascites fluid analysis shows evidence of spontaneous bacterial peritonitis, then antibiotics (directed toward gram-negative gut bacteria) and IV albumin should be administered as soon as possible.

For a more detailed discussion, see Robbins E, Hauser SL: Technique of Lumbar Puncture, Chap. 443e, and the Clinical Procedure Tutorial videos in Chaps. 481e-486e in HPIM-19.

# 4 Principles of Critical Care Medicine

### INITIAL EVALUATION OF THE CRITICALLY ILL PATIENT

Initial care of critically ill pts must often be performed rapidly and before a thorough medical history has been obtained. Physiologic stabilization begins with the principles of advanced cardiovascular life support and frequently involves invasive techniques such as mechanical ventilation and renal replacement therapy to support organ systems that are failing. A variety of severity-of-illness scoring systems, such as APACHE (acute physiology and chronic health evaluation), have been developed. Although these tools are useful for ensuring similarity among groups of pts involved in clinical trials, guiding resource allocation, or monitoring quality assurance, their

relevance to individual pts is less clear. These scoring systems are not typically used to guide clinical management.

## SHOCK

Shock, which is characterized by multisystem end-organ hypoperfusion and tissue hypoxia, is a frequent problem requiring ICU admission. A variety of clinical indicators of shock exist, including reduced mean arterial pressure, tachycardia, tachypnea, cool extremities, altered mental status, oliguria, and lactic acidosis. Although hypotension is usually observed in shock, there is not a specific blood pressure threshold that is used to define it. Shock can result from decreased cardiac output, decreased systemic vascular resistance, or both. The three main categories of shock are hypovolemic, cardiogenic, and high cardiac output/low systemic vascular resistance. Clinical evaluation can be useful to assess the adequacy of cardiac output, with narrow pulse pressure, cool extremities, and delayed capillary refill suggestive of reduced cardiac output. Indicators of high cardiac output (e.g., widened pulse pressure, warm extremities, and rapid capillary refill) associated with shock suggest reduced systemic vascular resistance. Reduced cardiac output can be due to intravascular volume depletion (e.g., hemorrhage) or cardiac dysfunction. Intravascular volume depletion can be assessed through changes in right atrial pressure with spontaneous respirations or changes in pulse pressure during positive pressure mechanical ventilation. Reduced systemic vascular resistance is often caused by sepsis, but high cardiac output hypotension is also seen in pancreatitis, liver failure, burns, anaphylaxis, peripheral arteriovenous shunts, and thyrotoxicosis. Early resuscitation of septic and cardiogenic shock may improve survival; objective assessments such as echocardiography and/or invasive vascular monitoring should be used to complement clinical evaluation and minimize end-organ damage. The approach to the pt in shock is outlined in Fig. 4-1.

## MECHANICAL VENTILATORY SUPPORT

Critically ill pts often require mechanical ventilation. During initial resuscitation, standard principles of advanced cardiovascular life support should be followed. Mechanical ventilation should be considered for acute hypoxemic respiratory failure, which may occur with cardiogenic shock, pulmonary edema (cardiogenic or noncardiogenic), or pneumonia. Mechanical ventilation should also be considered for treatment of ventilatory failure, which can result from an increased load on the respiratory system—often manifested by lactic acidosis or decreased lung compliance. Mechanical ventilation may decrease respiratory work, improve arterial oxygenation with improved tissue $O_2$ delivery, and reduce acidosis. Reduction in mean arterial pressure after institution of mechanical ventilation commonly occurs due to reduced venous return from positive pressure ventilation, reduced endogenous catecholamine secretion, and administration of drugs used to facilitate intubation (such as propofol and opiates). Because hypovolemia often contributes to post-intubation hypotension, IV volume administration should be considered. The major types of respiratory failure are discussed in Chap. 15.

### TREATMENT THE MECHANICALLY VENTILATED PATIENT

Many pts receiving mechanical ventilation require treatment for pain (typically with opiates) and for anxiety (typically with benzodiazepines, which also have the benefit of providing amnesia). Protocol-driven approaches to sedation or daily interruption of sedative infusions can prevent excessive sedative drug accumulation. Less commonly, neuromuscular blocking agents are required to facilitate ventilation when there is extreme dyssynchrony between the pt's respiratory efforts and the ventilator that cannot be corrected with manipulation of the ventilator settings; aggressive sedation is required during treatment with

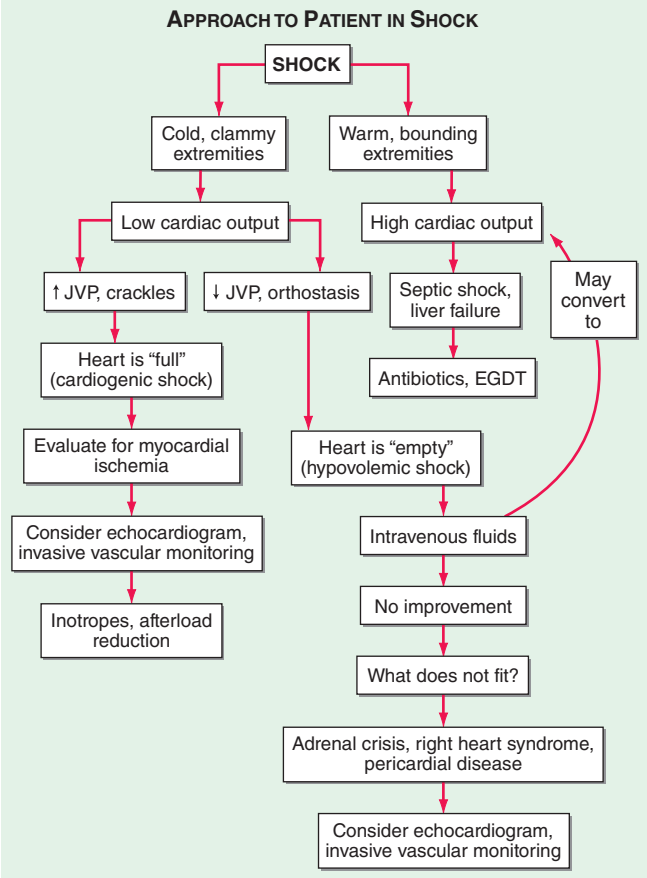



**FIGURE 4-1** Approach to pt in shock. EGDT, early goal-directed therapy; JVP, jugular venous pulse.

neuromuscular blockers. Neuromuscular blocking agents should be used with caution because a myopathy associated with prolonged weakness can result.

Weaning from mechanical ventilation should be considered when the disease process prompting intubation has improved. Daily screening of intubated pts for weaning potential should be performed. Stable oxygenation (with oxygen supplementation levels that are achievable off of mechanical ventilation and at low positive end-expiratory pressure [PEEP] levels), intact cough and airway reflexes, and lack of requirement for vasopressor agents are required before considering a trial of weaning from mechanical ventilation. The most effective approach for weaning is usually a spontaneous breathing trial, which involves 30–120 min of breathing without significant ventilatory support. Either an open T-piece breathing system or minimal amounts of ventilatory support (pressure support to overcome resistance of the endotracheal tube and/or low levels of continuous positive airway pressure [CPAP]) can be used. Failure of a spontaneous breathing trial has occurred if tachypnea (respiratory rate >35 breaths/min for >5 min),

hypoxemia ($O_2$ saturation <90%), tachycardia (>140 beats/min or 20% increase from baseline), bradycardia (20% reduction from baseline), hypotension (<90 mmHg), hypertension (>180 mmHg), increased anxiety, or diaphoresis develops. At the end of the spontaneous breathing trial, the *rapid shallow breathing index* (RSBI or f/VT), which is calculated as respiratory rate in breaths/min divided by tidal volume in liters, can be used to predict weanability. A f/VT value <105 at the end of the spontaneous breathing test warrants a trial of extubation. Daily interruption of sedative infusions in conjunction with spontaneous breathing trials can limit excessive sedation and shorten the duration of mechanical ventilation. Despite careful weaning protocols, up to 10% of pts develop respiratory distress after extubation and may require reintubation.

## MULTIORGAN SYSTEM FAILURE

Multiorgan system failure is a syndrome defined by the simultaneous dysfunction or failure of two or more organs in pts with critical illness. Multiorgan system failure is a common consequence of systemic inflammatory conditions (e.g., sepsis, pancreatitis, and trauma). To meet the criteria for multiorgan system failure, organ failure must persist for >24 h. Prognosis worsens with increased duration of organ failure and increased number of organ systems involved.

## MONITORING IN THE ICU

With critical illness, close and often continuous monitoring of multiple organ systems is required. In addition to pulse oximetry, frequent arterial blood gas analysis can reveal evolving acid-base disturbances and assess the adequacy of ventilation. Intra-arterial pressure monitoring is frequently performed to follow blood pressure and to provide arterial blood gases and other blood samples. Pulmonary artery (Swan-Ganz) catheters can provide pulmonary artery pressure, cardiac output, systemic vascular resistance, and oxygen delivery measurements. However, no morbidity or mortality benefit from pulmonary artery catheter use has been demonstrated, and rare but significant complications from placement of central venous access (e.g., pneumothorax, infection) or the pulmonary artery catheter (e.g., cardiac arrhythmias, pulmonary artery rupture) can result. Thus, routine pulmonary artery catheterization in critically ill pts is not recommended.

For intubated pts receiving volume-controlled modes of mechanical ventilation, respiratory mechanics can be followed easily. The peak airway pressure is regularly measured by mechanical ventilators, and the plateau pressure can be assessed by including an end-inspiratory pause. The inspiratory airway resistance is calculated as the difference between the peak and plateau airway pressures (with adjustment for flow rate). Increased airway resistance can result from bronchospasm, respiratory secretions, or a kinked endotracheal tube. Static compliance of the respiratory system is calculated as the tidal volume divided by the gradient in airway pressure (plateau pressure minus PEEP). Reduced respiratory system compliance can result from pleural effusions, pneumothorax, pneumonia, pulmonary edema, or auto-PEEP (elevated end-expiratory pressure related to insufficient time for alveolar emptying before the next inspiration).

## PREVENTION OF CRITICAL ILLNESS COMPLICATIONS

Critically ill pts are prone to a number of complications, including the following:

- Sepsis: Often nosocomial infections related to the invasive monitoring devices used in critically ill pts.
- Anemia: Usually due to chronic inflammation as well as iatrogenic blood loss. A conservative approach to providing blood transfusions is recommended unless pts have active hemorrhage.

- Deep-vein thrombosis: May occur despite standard prophylaxis with subcutaneous (SC) heparin or lower extremity sequential compression devices and may occur at the site of central venous catheters. Low-molecular-weight heparins (e.g., enoxaparin) are more effective for high-risk pts than unfractionated heparin.
- GI bleeding: Stress ulcers of the gastric mucosa frequently develop in pts with bleeding diatheses, shock, or respiratory failure, necessitating prophylactic acid neutralization in such pts.
- Acute renal failure: A frequent occurrence in ICU pts, exacerbated by nephrotoxic medications and hypoperfusion. The most common etiology is acute tubular necrosis. Low-dose dopamine treatment does not protect against the development of acute renal failure.
- Inadequate nutrition and hyperglycemia: Enteral feeding, when possible, is preferred over parenteral nutrition, because the parenteral route is associated with multiple complications including hyperglycemia, cholestasis, and sepsis. The utility of tight glucose control in the ICU is controversial.
- ICU-acquired weakness: Neuropathies and myopathies have been described—typically after at least 1 week of ICU care. These complications are especially common in sepsis.

### NEUROLOGIC DYSFUNCTION IN CRITICALLY ILL PATIENTS

A variety of neurologic problems can develop in critically ill pts. Most ICU pts develop delirium, which is characterized by acute changes in mental status, inattention, disorganized thinking, and an altered level of consciousness. Use of dexmedetomidine was associated with less ICU delirium than midazolam, one of the conventional sedatives. Less common but important neurologic complications include anoxic brain injury, stroke, and status epilepticus.

### LIMITATION OR WITHDRAWAL OF CARE

Withholding or withdrawing care commonly occurs in the ICU. Technological advances have allowed many pts to be maintained in the ICU with little or no chance of recovery. Increasingly, pts, families, and caregivers have acknowledged the ethical validity to withhold or withdraw care when the pt or surrogate decision-maker determines that the pt's goals for care are no longer achievable with the clinical situation.

For a more detailed discussion, see Kress JP, Hall JB: Approach to the Patient with Critical Illness, Chap. 321, p. 1729, in HPIM-19.

# 5 Pain and Its Management

## APPROACH TO THE PATIENT: **Pain**

Pain is the most common symptom that brings a pt to a physician's attention. Management depends on determining its cause, alleviating triggering and potentiating factors, and providing rapid relief whenever possible. Pain may be of

somatic (skin, joints, muscles), visceral, or neuropathic (injury to nerves, spinal cord pathways, or thalamus) origin. Characteristics of each are summarized in Table 5-1.

**Neuropathic Pain** Due to damage of peripheral or central nociceptive pathways. Definitions: *neuralgia*: pain in the distribution of a single nerve, as in trigeminal neuralgia; *dysesthesia*: spontaneous, unpleasant, abnormal sensation; *hyperalgesia* and *hyperesthesia*: exaggerated responses to nociceptive or touch stimulus, respectively; *allodynia*: perception of light mechanical stimuli as painful, as when vibration evokes painful sensation. Reduced pain perception is called *hypalgesia* or, when absent, *analgesia*. *Causalgia* is continuous severe burning pain with indistinct boundaries and accompanying sympathetic nervous system dysfunction (sweating; vascular, skin, and hair changes—sympathetic dystrophy) that occurs after injury to a peripheral nerve.

*Sensitization* refers to a lowered threshold for activating primary nociceptors following repeated stimulation in damaged or inflamed tissues; inflammatory mediators play a role. Sensitization contributes to tenderness, soreness, and hyperalgesia (as in sunburn).

*Referred pain* results from the convergence of sensory inputs from skin and viscera on single spinal neurons that transmit pain signals to the brain. Because of this convergence, input from deep structures is mislocalized to a region of skin innervated by the same spinal segment.

**Chronic Pain** The problem is often difficult to diagnose with certainty, and pts may appear emotionally distraught. Several factors can cause, perpetuate, or exacerbate chronic pain: (1) painful disease for which there is no cure (e.g., arthritis, cancer, chronic daily headaches, diabetic neuropathy); (2) perpetuating factors initiated by a bodily disease that persist after the disease has resolved (e.g., damaged sensory or sympathetic nerves); (3) psychological conditions. Pay special attention to the medical history and to depression. Major depression is common, treatable, and potentially fatal (suicide).

**TABLE 5-1 CHARACTERISTICS OF SOMATIC AND NEUROPATHIC PAIN**

| |
|---|
| Somatic pain |
| Nociceptive stimulus usually evident |
| Usually well localized |
| Similar to other somatic pains in pt's experience |
| Relieved by anti-inflammatory or narcotic analgesics |
| Visceral pain |
| Most commonly activated by inflammation |
| Pain poorly localized and usually referred |
| Associated with diffuse discomfort, e.g., nausea, bloating |
| Relieved by narcotic analgesics |
| Neuropathic pain |
| No obvious nociceptive stimulus |
| Associated evidence of nerve damage, e.g., sensory impairment, weakness |
| Unusual, dissimilar from somatic pain, often shooting or electrical quality |
| Only partially relieved by narcotic analgesics; may respond to antidepressants or anticonvulsants |

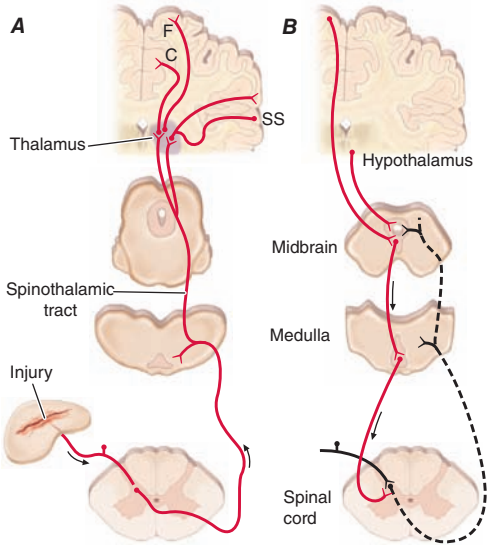



**FIGURE 5-1** Pain transmission and modulatory pathways. **A.** Transmission system for nociceptive messages. Noxious stimuli activate the sensitive peripheral ending of the primary afferent nociceptor by the process of transduction. The message is then transmitted over the peripheral nerve to the spinal cord, where it synapses with cells of origin of the major ascending pain pathway, the spinothalamic tract. The message is relayed in the thalamus to the anterior cingulate (C), frontal insular (F), and somatosensory cortex (SS). **B.** Pain-modulation network. Inputs from frontal cortex and hypothalamus activate cells in the midbrain that control spinal pain-transmission cells via cells in the medulla.

## PATHOPHYSIOLOGY: ORGANIZATION OF PAIN PATHWAYS

Pain-producing (nociceptive) sensory stimuli in skin and viscera activate peripheral nerve endings of primary afferent neurons, which synapse on second-order neurons in spinal cord or medulla (Fig. 5-1). These second-order neurons form crossed ascending pathways that reach the thalamus and project to the somatosensory cortex. Parallel ascending neurons, connecting with brainstem and thalamic nuclei, project to the limbic system and underlie the emotional aspect of pain. Pain transmission is regulated at the dorsal horn level by descending bulbospinal pathways that utilize serotonin, norepinephrine, and several neuropeptides as neurotransmitters.

Agents that modify pain perception may act by reducing tissue inflammation (NSAIDs, prostaglandin synthesis inhibitors), interfering with pain transmission (narcotics), or enhancing descending modulation (narcotics and antidepressants). Anticonvulsants (gabapentin, carbamazepine) may be effective for aberrant pain sensations arising from peripheral nerve injury.

## TREATMENT PAIN (TABLE 5-2)

### ACUTE SOMATIC PAIN

- Mild to moderate pain: Usually treated effectively with nonnarcotic analgesics, e.g., aspirin, acetaminophen, and NSAIDs, which inhibit cyclooxygenase (COX)

**TABLE 5-2 DRUGS FOR RELIEF OF PAIN**

| Generic Name | Dose, mg | Interval | Comments |
|---|---|---|---|
| **Nonnarcotic analgesics: usual doses and intervals** | | | |
| Acetylsalicylic acid | 650 PO | q4h | Enteric-coated preparations available |
| Acetaminophen | 650 PO | q4h | Side effects uncommon |
| Ibuprofen | 400 PO | q4–6h | Available without prescription |
| Naproxen | 250–500 PO | q12h | Delayed effects may be due to long half-life |
| Fenoprofen | 200 PO | q4–6h | Contraindicated in renal disease |
| Indomethacin | 25–50 PO | q8h | Gastrointestinal side effects common |
| Ketorolac | 15–60 IM/IV | q4–6h | Available for parenteral use |
| Celecoxib | 100–200 PO | q12–24h | Useful for arthritis |
| Valdecoxib | 10–20 PO | q12–24h | Removed from U.S. market in 2005 |
| **Generic Name** | **Parenteral Dose, mg** | **PO Dose, mg** | **Comments** |
| **Narcotic analgesics: usual doses and intervals** | | | |
| Codeine | 30–60 q4h | 30–60 q4h | Nausea common |
| Oxycodone | — | 5–10 q4–6h | Usually available with acetaminophen or aspirin |
| Morphine | 5 q4h | 30 q4h | |
| Morphine sustained release | — | 15–60 bid to tid | Oral slow-release preparation |
| Hydromorphone | 1–2 q4h | 2–4 q4h | Shorter acting than morphine sulfate |
| Levorphanol | 2 q6–8h | 4 q6–8h | Longer acting than morphine sulfate; absorbed well PO |
| Methadone | 5–10 q6–8h | 5–20 q6–8h | Delayed sedation due to long half-life; therapy should not be initiated with >40 mg/d, and dose escalation should be made no more frequently than every 3 days |

| | | | | |
|---|---|---|---|---|
| Meperidine | 50–100 q3–4h | 300 q4h | Poorly absorbed PO; normeperidine is a toxic metabolite; routine use of this agent is not recommended | |
| Butorphanol | — | 1–2 q4h | Intranasal spray | |
| Fentanyl | 25–100 μg/h | — | 72-h transdermal patch | |
| Buprenorphine | 5–20 μg/h | | 7-day transdermal patch | |
| Buprenorphine | 0.3 q6–8h | | Parenteral administration | |
| Tramadol | — | 50–100 q4–6h | Mixed opioid/adrenergic action | |

| | Uptake Blockade | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Generic Name** | **5-HT** | **NE** | **Sedative Potency** | **Anticholinergic Potency** | **Orthostatic Hypotension** | **Cardiac Arrhythmia** | **Average Dose, mg/d** | **Range, mg/d** |
| **Antidepressants[a]** | | | | | | | | |
| Doxepin | ++ | + | High | Moderate | Moderate | Less | 200 | 75–400 |
| Amitriptyline | ++++ | ++ | High | Highest | Moderate | Yes | 150 | 25–300 |
| Imipramine | ++++ | ++ | Moderate | Moderate | High | Yes | 200 | 75–400 |
| Nortriptyline | +++ | ++ | Moderate | Moderate | Low | Yes | 100 | 40–150 |
| Desipramine | +++ | ++++ | Low | Low | Low | Yes | 150 | 50–300 |
| Venlafaxine | +++ | ++ | Low | None | None | No | 150 | 75–400 |
| Duloxetine | +++ | +++ | Low | None | None | No | 40 | 30–60 |

| **Generic Name** | **PO Dose, mg** | **Interval** | **Generic Name** | **PO Dose, mg** | **Interval** |
|---|---|---|---|---|---|
| **Anticonvulsants and antiarrhythmics[a]** | | | | | |
| Phenytoin | 300 | daily/qhs | Clonazepam | 1 | q6h |
| Carbamazepine | 200–300 | q6h | Gabapentin[b] | 600–1200 | q8h |
| Oxcarbazepine | 300 | bid | Pregabalin | 150–600 | bid |

[a]Antidepressants, anticonvulsants, and antiarrhythmics have not been approved by the U.S. Food and Drug Administration (FDA) for the treatment of pain.
[b]Gabapentin in doses up to 1800 mg/d is FDA approved for postherpetic neuralgia.
***Abbreviations:*** 5-HT, serotonin; NE, norepinephrine.

and, except for acetaminophen, have anti-inflammatory actions, especially at high dosages. Particularly effective for headache and musculoskeletal pain.

- Parenteral NSAIDs: Ketorolac and diclofenac are sufficiently potent and rapid in onset to supplant opioids for many pts with acute severe pain.
- Narcotic analgesics in oral or parenteral form can be used for more severe pain. These are the most effective drugs available; the opioid antagonist naloxone should be readily available when narcotics are used in high doses or in unstable pts.
- Pt-controlled analgesia (PCA) permits infusion of a baseline dose plus self-administered boluses (activated by press of a button) as needed to control pain.

### CHRONIC PAIN

- Develop an explicit treatment plan including specific and realistic goals for therapy, e.g., getting a good night's sleep, being able to go shopping, or returning to work.
- A multidisciplinary approach that utilizes medications, counseling, physical therapy, nerve blocks, and even surgery may be required to improve quality of life.
- Psychological evaluation is key; behaviorally based treatment paradigms are frequently helpful.
- Some pts may require referral to a pain clinic; for others, pharmacologic management alone can provide significant help.
- Tricyclic antidepressants are useful in management of chronic pain from many causes, including headache, diabetic neuropathy, postherpetic neuralgia, chronic low back pain, cancer, and central post-stroke pain.
- Anticonvulsants or antiarrhythmics benefit pts with neuropathic pain (e.g., diabetic neuropathy, trigeminal neuralgia).
- The long-term use of opioids is accepted for pain due to malignant disease, but is controversial for chronic pain of nonmalignant origin.

For a more detailed discussion, see Rathmell HP, Fields HL: Pain: Pathophysiology and Management, Chap. 18, p. 87, in HPIM-19.

# 6 Assessment of Nutritional Status

Stability of body weight requires that energy intake and expenditures are balanced over time. The major categories of energy output are resting energy expenditure (REE) and physical activity; minor sources include the energy cost of metabolizing food (thermic effect of food or specific dynamic action) and shivering thermogenesis. The average energy intake is about 2600 kcal/d for men and about 1800 kcal/d for women, though these estimates vary with age, body size, and activity level. Basal energy expenditure (BEE), measured in kcal/d, may be estimated by the Harris and Benedict formula (Fig. 6-1).

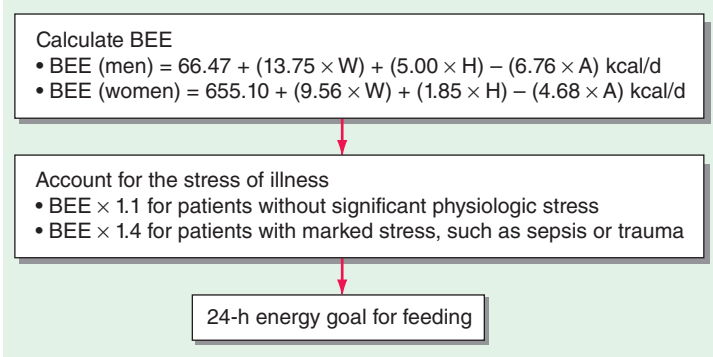



**FIGURE 6-1** Basal energy expenditure (BEE) calculation in kcal/d, estimated by the Harris and Benedict formula. A, age in years; H, height in cm; W, Weight in kg.

Dietary reference intakes (DRIs) and recommended dietary allowances (RDAs) have been defined for many nutrients, including 9 essential amino acids, 4 fat-soluble and 10 water-soluble vitamins, several minerals, fatty acids, choline, and water (see Tables 95e-1 and 95e-2 in HPIM-19). The usual water requirements are 1.0–1.5 mL/kcal energy expenditure in adults, with adjustments for excessive losses. The RDA for protein is 0.6-g/kg ideal body weight, representing 10-15% of total caloric intake. Fat should constitute ≤30% of calories, and saturated fat should be <10% of calories. At least 55% of calories should be derived from carbohydrates.

## MALNUTRITION

Malnutrition results from inadequate intake or abnormal GI assimilation of dietary calories, excessive energy expenditure, or altered metabolism of energy supplies by an intrinsic disease process.

Both outpatients and inpatients are at risk for malnutrition if they meet one or more of the following criteria:

- Unintentional loss of >10% of usual body weight in the preceding 3 months
- Body weight <90% of ideal for height (Table 6-1)
- Body mass index (BMI: weight/height$^2$ in kg/m$^2$) <18.5

Two forms of severe malnutrition can be seen: *marasmus*, which refers to generalized starvation that occurs in the setting of chronically decreased energy intake without systemic inflammation, and *kwashiorkor*, which refers to selective protein malnutrition due to decreased protein intake and catabolism in the setting of acute, life-threatening illnesses or chronic inflammatory disorders. Aggressive nutritional support is indicated in kwashiorkor to prevent infectious complications and poor wound healing.

### Etiology

The major etiologies of malnutrition are starvation, stress from surgery or severe illness, and mixed mechanisms. Starvation results from decreased dietary intake (from poverty, chronic alcoholism, anorexia nervosa, fad diets, severe depression, neurodegenerative disorders, dementia, or strict vegetarianism; abdominal pain from intestinal ischemia or pancreatitis; or anorexia associated with AIDS, disseminated cancer, heart failure, or renal failure) or decreased assimilation of the diet (from pancreatic insufficiency; short bowel syndrome; celiac disease; or esophageal, gastric,

**TABLE 6-1 IDEAL WEIGHT FOR HEIGHT**

| Men | | | | Women | | | |
|---|---|---|---|---|---|---|---|
| Height[a] | Weight[a] | Height | Weight | Height | Weight | Height | Weight |
| 145 | 51.9 | 166 | 64.0 | 140 | 44.9 | 161 | 56.9 |
| 146 | 52.4 | 167 | 64.6 | 141 | 45.4 | 162 | 57.6 |
| 147 | 52.9 | 168 | 65.2 | 142 | 45.9 | 163 | 58.3 |
| 148 | 53.5 | 169 | 65.9 | 143 | 46.4 | 164 | 58.9 |
| 149 | 54.0 | 170 | 66.6 | 144 | 47.0 | 165 | 59.5 |
| 150 | 54.5 | 171 | 67.3 | 145 | 47.5 | 166 | 60.1 |
| 151 | 55.0 | 172 | 68.0 | 146 | 48.0 | 167 | 60.7 |
| 152 | 55.6 | 173 | 68.7 | 147 | 48.6 | 168 | 61.4 |
| 153 | 56.1 | 174 | 69.4 | 148 | 49.2 | 169 | 62.1 |
| 154 | 56.6 | 175 | 70.1 | 149 | 49.8 | | |
| 155 | 57.2 | 176 | 70.8 | 150 | 50.4 | | |
| 156 | 57.9 | 177 | 71.6 | 151 | 51.0 | | |
| 157 | 58.6 | 178 | 72.4 | 152 | 51.5 | | |
| 158 | 59.3 | 179 | 73.3 | 153 | 52.0 | | |
| 159 | 59.9 | 180 | 74.2 | 154 | 52.5 | | |
| 160 | 60.5 | 181 | 75.0 | 155 | 53.1 | | |
| 161 | 61.1 | 182 | 75.8 | 156 | 53.7 | | |
| 162 | 61.7 | 183 | 76.5 | 157 | 54.3 | | |
| 163 | 62.3 | 184 | 77.3 | 158 | 54.9 | | |
| 164 | 62.9 | 185 | 78.1 | 159 | 55.5 | | |
| 165 | 63.5 | 186 | 78.9 | 160 | 56.2 | | |

[a]Values are expressed in cm for height and kg for weight. To obtain height in inches, divide by 2.54. To obtain weight in pounds, multiply by 2.2.
***Source:*** Adapted from GL Blackburn et al: Nutritional and metabolic assessment of the hospitalized patient. *J Parenter Enteral Nutr* 1:11, 1977; with permission.

or intestinal obstruction). Contributors to physical stress include fever, acute trauma, major surgery, burns, acute sepsis, hyperthyroidism, and inflammation as occurs in pancreatitis, collagen vascular diseases, and chronic infectious diseases such as tuberculosis or AIDS opportunistic infections. Mixed mechanisms occur in AIDS, disseminated cancer, chronic obstructive pulmonary disease, chronic liver disease, Crohn's disease, ulcerative colitis, and renal failure.

## Clinical Features

- *General:* weight loss, temporal and proximal muscle wasting, decreased skin-fold thickness
- *Skin, hair, and nails:* easily plucked hair (protein); sparse hair (protein, biotin, zinc); coiled hair, easy bruising, petechiae, and perifollicular hemorrhages (vit. C); "flaky paint" rash of lower extremities (zinc); hyperpigmentation of skin in exposed areas (niacin, tryptophan); spooning of nails (iron)
- *Eyes:* conjunctival pallor (anemia); night blindness, dryness, and Bitot spots (vit. A); ophthalmoplegia (thiamine)
- *Mouth and mucous membranes:* glossitis and/or cheilosis (riboflavin, niacin, vit. $B_{12}$, pyridoxine, folate), diminished taste (zinc), inflamed and bleeding gums (vit. C)

- *Neurologic:* disorientation (niacin, phosphorus); confabulation, cerebellar gait, or past pointing (thiamine); peripheral neuropathy (thiamine, pyridoxine, vit. E); lost vibratory and position sense (vit. $B_{12}$)
- *Other:* edema (protein, thiamine), heart failure (thiamine, phosphorus), hepatomegaly (protein)

Laboratory findings in protein malnutrition include a low serum albumin, low total iron-binding capacity, and anergy to skin testing. Specific vitamin deficiencies also may be present.

For a more detailed discussion, see Dwyer J: Nutritional Requirements and Dietary Assessment, Chap. 95e; Russell RM and Suter PM: Vitamin and Trace Mineral Deficiency and Excess, Chap. 96e; and Heimberger DC: Malnutrition and Nutritional Assessment, Chap. 97, p. 459 in HPIM-19.

# 7 Enteral and Parenteral Nutrition

Nutritional support should be initiated in pts with malnutrition or in those at risk for malnutrition (e.g., conditions that preclude adequate oral feeding or pts in catabolic states, such as sepsis, burns, major surgery, or trauma). An approach for deciding when to use various types of specialized nutrition support (SNS) is summarized in Fig. 7-1.

*Enteral therapy* refers to feeding via the gut, using oral supplements or infusion of formulas via various feeding tubes (nasogastric, nasoduodenal, gastrostomy, jejunostomy, or combined gastrojejunostomy). *Parenteral therapy* refers to the infusion of nutrient solutions into the bloodstream via a peripherally inserted central catheter (PICC), a centrally inserted externalized catheter, or a centrally inserted tunneled catheter or subcutaneous port. When feasible, enteral nutrition is the preferred route because it sustains the digestive, absorptive, and immunologic functions of the GI tract, and because it minimizes the risk of fluid and electrolyte imbalance. Parenteral nutrition is often indicated in severe pancreatitis, necrotizing enterocolitis, prolonged ileus, and distal bowel obstruction.

## ENTERAL NUTRITION

The components of a standard enteral formula are as follows:

- Caloric density: 1 kcal/mL
- Protein: ~14% cals; caseinates, soy, lactalbumin
- Fat: ~30% cals; corn, soy, safflower oils
- Carbohydrate: ~60% cals; hydrolyzed corn starch, maltodextrin, sucrose
- Recommended daily intake of all minerals and vitamins in ≥1500 kcal/d
- Osmolality (mosmol/kg): ~300

However, modification of the enteral formula may be required based on various clinical indications and/or associated disease states. After elevation of the head of the

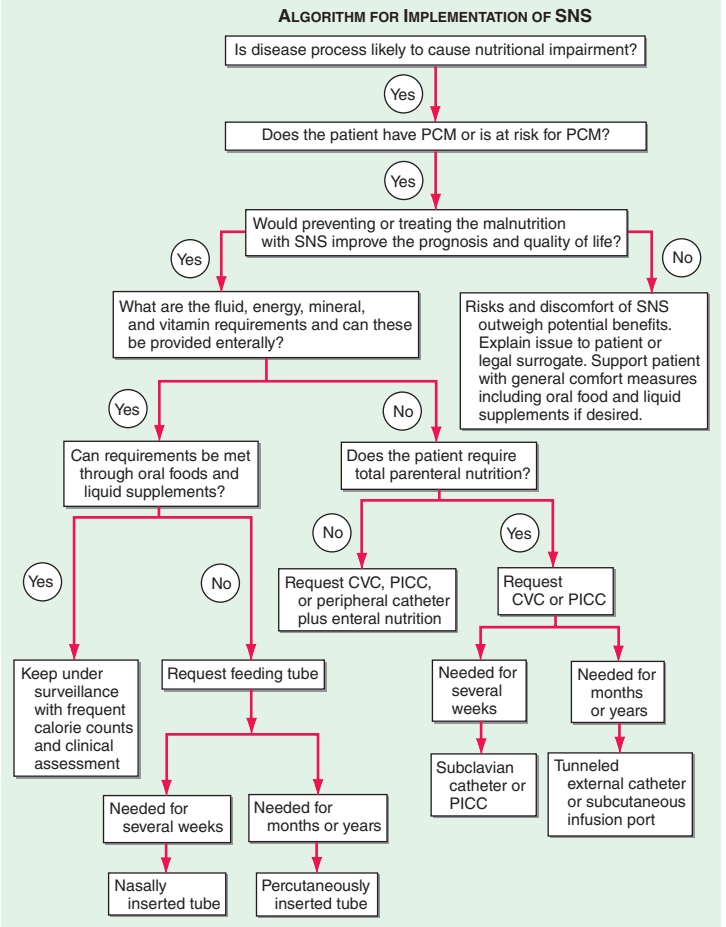



**FIGURE 7-1** Decision-making for the implementation of specialized nutrition support (SNS). CVC, central venous catheter; PCM, protein-calorie malnutrition; PICC, peripherally inserted central catheter. *(Adapted from chapter in Harrison's Principles of Internal Medicine, 16e, by Lyn Howard, MD.)*

bed and confirmation of correct tube placement, continuous gastric infusion is initiated using a half-strength diet at a rate of 25–50 mL/h. This can be advanced to full strength as tolerated to meet the energy target. The major risks of enteral tube feeding are aspiration, diarrhea, electrolyte imbalance, warfarin resistance, sinusitis, and esophagitis.

## PARENTERAL NUTRITION

The components of parenteral nutrition include adequate fluid (30-mL/kg body weight/24 h for adults, plus any abnormal loss); energy from glucose, amino acids, and lipid solutions; nutrients essential in severely ill pts, such as glutamine, nucleotides, and products of methionine metabolism; and electrolytes, vitamins, and minerals. The risks of parenteral therapy include mechanical complications from insertion of the infusion catheter, catheter sepsis, fluid overload, hyperglycemia, hypophosphatemia, hypokalemia, acid-base and electrolyte imbalance, cholestasis, metabolic bone disease, and micronutrient deficiencies.

**TABLE 7-1 THERAPY FOR COMMON VITAMIN AND MINERAL DEFICIENCIES**

| Nutrient | Therapy |
|---|---|
| Vitamin A[a,b,c] | 60 mg PO, repeated 1 and 14 days later if ocular changes; 30 mg for ages 6–11 months<br>15 mg PO qd × 1 month if chronic malabsorption |
| Vitamin C | 200 mg PO qd |
| Vitamin D[a,d] | Encourage sun exposure if possible<br>50,000 units PO once weekly for 4–8 weeks, then 400–800 units PO qd<br>Substantially higher dose may be required in chronic malabsorption |
| Folic acid | 0.4 mg PO qd prenatally and during pregnancy<br>Confirm normal $B_{12}$ levels in pts with megaloblastic anemia |
| Vitamin $B_{12}$ | 1000 µg IM x 6 doses to replenish stores, then 1000 µg IM monthly |
| Vitamin E[a] | 800–1200 mg PO qd |
| Vitamin K[a] | 10 mg IV × 1<br>1–2 mg PO qd or 1–2 mg IV weekly in chronic malabsorption |
| Thiamine[b] | 300 mg IV qd × 3 days, followed by 10 mg PO qd until recovery |
| Niacin | 100–200 mg PO tid for 5 days |
| Pyridoxine | 50 mg PO qd, 100–200 mg PO qd if deficiency related to medications |
| Zinc[b,c] | 60 mg PO bid |

[a]Associated with fat malabsorption.
[b]Associated with chronic alcoholism; always replete thiamine before carbohydrates in alcoholics to avoid precipitation of acute thiamine deficiency.
[c]Associated with protein-calorie malnutrition.
[d]Therapy must be monitored by serum calcium measurements.

The following parameters should be monitored in all pts receiving supplemental nutrition, whether enteral or parenteral:

- Fluid balance (weight, intake vs. output)
- Glucose, electrolytes, BUN (daily until stable, then 2× per week)
- Serum creatinine, albumin, phosphorus, calcium, magnesium, Hb/Hct, WBC (baseline, then 2× per week)
- International normalized ratio (INR) (baseline, then weekly)
- Micronutrient tests as indicated

## SPECIFIC MICRONUTRIENT DEFICIENCY

Appropriate therapies for micronutrient deficiencies are outlined in Table 7-1.

For a more detailed discussion, see Russell RM and Suter PM: Vitamin and Trace Mineral Deficiency and Excess, Chap. 96e; and Bistrian BR, Hoffer LJ, and Driscoll DF: Enteral and Parenteral Nutrition Therapy, Chap. 98e, HPIM-19.

# 8 Transfusion and Pheresis Therapy

## TRANSFUSIONS

### WHOLE BLOOD TRANSFUSION

Indicated when acute blood loss is sufficient to produce hypovolemia, whole blood provides both oxygen-carrying capacity and volume expansion. In acute blood loss, hematocrit may not accurately reflect degree of blood loss for 48 h until fluid shifts occur.

### RED BLOOD CELL TRANSFUSION

Indicated for symptomatic anemia unresponsive to specific therapy or requiring urgent correction. Packed red blood cell (RBC) transfusions may be indicated in pts who are symptomatic from cardiovascular or pulmonary disease when Hb is between 70 and 90 g/L (7 and 9 g/dL). Transfusion is usually necessary when Hb is <70 g/L (<7 g/dL). One unit of packed RBCs raises the Hb by ~10 g/L (1 g/dL). In the setting of acute hemorrhage, packed RBCs, fresh frozen plasma (FFP), and platelets in an approximate ratio of 3:1:10 units are an adequate replacement for whole blood. Removal of leukocytes reduces risk of alloimmunization and transmission of cytomegalovirus. Washing to remove donor plasma reduces risk of allergic reactions. Irradiation prevents graft-versus-host disease in immunocompromised recipients by killing alloreactive donor lymphocytes. Avoid related donors.

#### Other Indications

(1) *Hypertransfusion therapy* to block production of defective cells, e.g., thalassemia, sickle cell anemia; (2) *exchange transfusion*—hemolytic disease of newborn, sickle cell crisis; (3) *transplant recipients*—decreases rejection of cadaveric kidney transplants.

#### Complications (Table 8-1)

(1) *Transfusion reaction*—immediate or delayed, seen in 1–4% of transfusions; IgA-deficient pts at particular risk for severe reaction; (2) *infection*—bacterial (rare); hepatitis C, 1 in 1,800,000 transfusions; HIV transmission, 1 in 2,300,000; (3) *circulatory overload*; (4) *iron overload*—each unit contains 200- to 250-mg iron; hemochromatosis may develop after 100 U of RBCs (less in children), in absence of blood loss; iron chelation therapy with deferoxamine indicated; (5) *graft-versus-host disease*; (6) *alloimmunization*.

### AUTOLOGOUS TRANSFUSION

Use of pt's own stored blood avoids hazards of donor blood; also useful in pts with multiple RBC antibodies. Pace of autologous donation may be accelerated using erythropoietin (50–150 U/kg SC three times a week) in the setting of normal iron stores.

### RED CELL EXCHANGE

The main goal of red cell exchange transfusions is to remove sickle cells and replace them with normal red cells to interrupt the vicious cycle of sickling, stasis, vasoocclusion, and hypoxemia that propagate sickle cell crises. The usual target is 70% hemoglobin A.

**TABLE 8-1 RISKS OF TRANSFUSION COMPLICATIONS**

| | Frequency, Episodes: Unit |
|---|---|
| **Reactions** | |
| Febrile (FNHTR) | 1–4:100 |
| Allergic | 1–4:100 |
| Delayed hemolytic | 1:1000 |
| TRALI | 1:5000 |
| Acute hemolytic | 1:12,000 |
| Fatal hemolytic | 1:100,000 |
| Anaphylactic | 1:150,000 |
| **Infections**[a] | |
| Hepatitis B | 1:220,000 |
| Hepatitis C | 1:1,800,000 |
| HIV-1, HIV-2 | 1:2,300,000 |
| HTLV-I, HTLV-II | 1:2,993,000 |
| Malaria | 1:4,000,000 |
| **Other complications** | |
| RBC allosensitization | 1:100 |
| HLA allosensitization | 1:10 |
| Graft-versus-host disease | Rare |

[a]Infectious agents rarely associated with transfusion, theoretically possible, or of unknown risk include West Nile virus, hepatitis A virus, parvovirus B-19, *Babesia microti* (babesiosis), *Borrelia burgdorferi* (Lyme disease), *Anaplasma phagocytophilum* (human granulocytic ehrlichiosis), *Trypanosoma cruzi* (Chagas' disease), *Treponema pallidum*, and human herpesvirus 8.
***Abbreviations:*** FNHTR, febrile nonhemolytic transfusion reaction; HLA, human leukocyte antigen; HTLV, human T lymphotropic virus; TRALI, transfusion-related acute lung injury.

### PLATELET TRANSFUSION

Prophylactic transfusions usually reserved for platelet count <10,000/μL (<20,000/μL in acute leukemia). One unit elevates the count by about 10,000/μL if no platelet antibodies are present as a result of prior transfusions. Efficacy assessed by 1- and 24-h posttransfusion platelet counts. HLA-matched single-donor platelets may be required in pts with platelet alloantibodies.

### TRANSFUSION OF PLASMA COMPONENTS

Fresh frozen plasma (FFP) is a source of coagulation factors, fibrinogen, antithrombin, and proteins C and S. It is used to correct coagulation factor deficiencies, rapidly reverse warfarin effects, and treat thrombotic thrombocytopenic purpura (TTP). Cryoprecipitate is a source of fibrinogen, factor VIII, and von Willebrand factor; it may be used when recombinant factor VIII or factor VIII concentrates are not available.

## THERAPEUTIC HEMAPHERESIS

*Hemapheresis* is removal of a cellular or plasma constituent of blood; the specific procedure is referred to by the blood fraction removed.

### LEUKAPHERESIS

Removal of WBCs; most often used in acute leukemia, esp. acute myeloid leukemia (AML) in cases complicated by marked elevation (>100,000/μL) of the peripheral blast count, to lower risk of leukostasis (blast-mediated vasoocclusive events resulting in central nervous system or pulmonary infarction, hemorrhage). Leukapheresis is replacing bone marrow aspiration to obtain hematopoietic stem cells. After treatment with a chemotherapeutic agent and granulocyte-macrophage colony-stimulating factor, hematopoietic stem cells are mobilized from marrow to the peripheral blood; such cells are leukapheresed and then used for hematopoietic reconstitution after high-dose myeloablative therapy. A third emerging medical use of leukapheresis is to harvest lymphocytes to use as adoptive immunotherapy.

### PLATELETPHERESIS

Used in some pts with thrombocytosis associated with myeloproliferative disorders with bleeding and/or thrombotic complications. Other treatments are generally used first. Plateletpheresis also enhances platelet yield from blood donors.

### PLASMAPHERESIS

#### Indications

(1) *Hyperviscosity states*—e.g., Waldenström's macroglobulinemia; (2) *TTP*; (3) *immune-complex* and *autoantibody disorders*—e.g., Goodpasture's syndrome, rapidly progressive glomerulonephritis, myasthenia gravis; possibly Guillain-Barré, systemic lupus erythematosus, idiopathic thrombocytopenic purpura; (4) cold agglutinin disease, cryoglobulinemia. In plasma exchange, abnormal proteins are removed and normal plasma or plasma components are replaced; useful in TTP to remove anti-ADAMTS13 antibody and provide normal ADAMTS13 levels.

For a more detailed discussion, see Dzieczkowski JS, Anderson KC: Transfusion Biology and Therapy, Chap. 138e, in HPIM-19.

# 9 Palliative and End-of-Life Care

In 2014, 2,596,993 people died in the United States; death rates are declining. Nearly three-fourth of all deaths occur in people >65 years old. Heart disease and cancer are the two leading causes of death and together account for nearly half of all deaths. About 70% of deaths occur in people who have a condition that is known to be leading to their death; thus, planning for terminal care is relevant and important. An increasing fraction of deaths are occurring in hospices or at home rather than in the hospital.

Optimal care depends on a comprehensive assessment of pt needs in all four domains affected by illness: physical, psychological, social, and spiritual. A variety of assessment tools are available to assist in the process.

Communication and continuous assessment of management goals are key components to addressing end-of-life care. Physicians must be clear about the likely

outcome of the illness(es) and provide an anticipated schedule with goals and landmarks in the care process. When the goals of care have changed from cure to palliation, that transition must be clearly explained and defended. Seven steps are involved in establishing goals:

1. Ensure that the medical information is as complete as possible and understood by all relevant parties.
2. Explore the pt's goals while making sure the goals are achievable.
3. Explain the options.
4. Show empathy as the pt and the family adjust to changing expectations.
5. Make a plan with realistic goals.
6. Follow-through with the plan.
7. Review and revise the plan periodically as the pt's situation changes.

## ADVANCE DIRECTIVES

About 70% of pts lack decision-making capacity in their final days. Advance directives define ahead of time the level of intervention the pt is willing to accept. Two types of legal documents can be used: the advance directive, in which specific instructions from the pt may be made known; and the durable attorney for health care, in which a person is designated as having the pt's authority to make health decisions on pt's behalf. Forms are available free of charge from the National Hospice and Palliative Care Organization (www.nhpco.org). Physicians also should complete these forms for themselves.

## PHYSICAL SYMPTOMS AND THEIR MANAGEMENT

The most common physical and psychological symptoms among terminally ill pts are shown in Table 9-1. Studies of pts with advanced cancer have shown that pts experience an average of 11.5 symptoms.

**TABLE 9-1 COMMON PHYSICAL AND PSYCHOLOGICAL SYMPTOMS OF TERMINALLY ILL PATIENTS**

| Physical Symptoms | Psychological Symptoms |
|---|---|
| Pain | Anxiety |
| Fatigue and weakness | Depression |
| Dyspnea | Hopelessness |
| Insomnia | Meaninglessness |
| Dry mouth | Irritability |
| Anorexia | Impaired concentration |
| Nausea and vomiting | Confusion |
| Constipation | Delirium |
| Cough | Loss of libido |
| Swelling of arms or legs | |
| Itching | |
| Diarrhea | |
| Dysphagia | |
| Dizziness | |
| Fecal and urinary incontinence | |
| Numbness/tingling in hands/feet | |

## Pain

Pain is noted in 36–90% of terminally ill pts. The various types of pain and their management are discussed in Chap. 5.

## Constipation

Constipation is noted in up to 87% of terminally ill pts. Medications that commonly contribute to constipation include opioids used to manage pain and dyspnea and tricyclic antidepressants with their anticholinergic effects. Inactivity, poor diet, and hypercalcemia may contribute. GI tract obstruction also may play a role in some settings.

**Interventions** Improved physical activity (if possible), adequate hydration; opioid effects can be antagonized by the μ-opioid receptor blocker methylnaltrexone (8–12 mg SC daily); rule out surgically correctable obstruction; laxatives and stool softeners (Table 9-2).

## Nausea

Up to 70% of pts with advanced cancer have nausea. Nausea may result from uremia, liver failure, hypercalcemia, bowel obstruction, severe constipation, infection, gastroesophageal reflux disease, vestibular disease, brain metastases, medications (cancer chemotherapy, antibiotics, nonsteroidal anti-inflammatory drugs, opioids, proton pump inhibitors), and radiation therapy.

**Interventions** Treatment should be tailored to the cause. Offending medications should be stopped. Underlying conditions should be alleviated, if possible. If

**TABLE 9-2 MEDICATIONS FOR THE MANAGEMENT OF CONSTIPATION**

| Intervention | Dose | Comment |
|---|---|---|
| Stimulant laxatives | | These agents directly stimulate peristalsis and may reduce colonic absorption of water. Work in 6–12 h. |
| Prune juice | 120–240 mL/d | |
| Senna (Senokot) | 2–8 tablets PO bid | |
| Bisacodyl | 5–15 mg/d PO, PR | |
| Osmotic laxatives | | These agents are not absorbed. They attract and retain water in the gastrointestinal tract. |
| Lactulose | 15–30 mL PO q4–8h | Lactulose may cause flatulence and bloating. |
| Magnesium hydroxide (Milk of Magnesia) | 15–30 mL/d PO | Lactulose works in 1 day, magnesium products in 6 h. |
| Magnesium citrate | 125–250 mL/d PO | |
| Stool softeners | | These agents work by increasing water secretion and as detergents, increasing water penetration into the stool. Work in 1–3 days. |
| Sodium docusate (Colace) | 300–600 mg/d PO | |
| Calcium docusate | 300–600 mg/d PO | |
| Suppositories and enemas | | |
| Bisacodyl | 10–15 PR qd | |
| Sodium phosphate enema | PR qd | Fixed dose, 4.5 oz, Fleet's. |

decreased bowel motility is suspected, metoclopramide may help. Nausea from cancer chemotherapy agents can generally be prevented with glucocorticoids and serotonin receptor blockers like ondansetron or dolasetron. Aprepitant is useful in controlling nausea from highly emetogenic agents like cisplatin. Vestibular nausea may respond to antihistamines (meclizine) or anticholinergics (scopolamine). Anticipatory nausea may be prevented with a benzodiazepine such as lorazepam. Haloperidol is sometimes useful when the nausea does not have a single specific cause.

## Dyspnea

Up to 75% of dying pts experience dyspnea. Dyspnea exerts perhaps the greatest adverse effect on the pt, often even more distressing than pain. It may be caused by parenchymal lung disease, infection, effusions, pulmonary emboli, pulmonary edema, asthma, or compressed airway. While many of the causes may be treated, often the underlying cause cannot be reversed.

**Interventions** Underlying causes should be reversed, where possible, as long as the intervention is not more unpleasant (e.g., repeated thoracenteses) than the dyspnea. Most often the treatment is symptomatic (Table 9-3).

## Fatigue

Fatigue is nearly a universal symptom in terminally ill pts. It is often a direct consequence of the disease process (and the cytokines produced in response to that process) and may be complicated by inanition, dehydration, anemia, infection, hypothyroidism, and drug effects. Depression may also contribute to fatigue. Functional assessments include the Karnofsky performance status or the Eastern Cooperative Oncology Group system based on how much time the pt spends in bed each day: 0, normal activity; 1, symptomatic without being bedridden; 2, in bed <50% of the day; 3, in bed >50% of the day; 4, bedbound.

**TABLE 9-3 MEDICATIONS FOR THE MANAGEMENT OF DYSPNEA**

| Intervention | Dose | Comments |
|---|---|---|
| Weak opioids | | For pts with mild dyspnea |
| Codeine (or codeine with 325-mg acetaminophen) | 30 mg PO q4h | For opioid-naïve pts |
| Hydrocodone | 5 mg PO q4h | |
| Strong opioids | | For opioid-naïve pts with moderate to severe dyspnea |
| Morphine | 5–10 mg PO q4h<br>30–50% of baseline opioid dose q4h | For pts already taking opioids for pain or other symptoms |
| Oxycodone | 5–10 mg PO q4h | |
| Hydromorphone | 1–2 mg PO q4h | |
| Anxiolytics | | Give a dose every hour until the pt is relaxed, then provide a dose for maintenance |
| Lorazepam | 0.5–2.0 mg PO/SL/IV qh then q4–6h | |
| Clonazepam | 0.25–2.0 mg PO q12h | |
| Midazolam | 0.5 mg IV q15min | |

**Interventions** Modest exercise and physical therapy may reduce muscle wasting and depression and improve mood; discontinue medications that worsen fatigue, if possible; glucocorticoids may increase energy and enhance mood; dextroamphetamine (5–10 mg/d) or methylphenidate (2.5–5 mg/d) in the morning may enhance energy levels but should be avoided at night because they may produce insomnia; modafinil and L-carnitine have shown some promise.

## Depression

Up to 75% of terminally ill pts experience depression. The inexperienced physician may feel that depression is an appropriate response to terminal illness; however, in a substantial fraction of pts the depression is more intense and disabling than usual. Pts with a previous history of depression are at greater risk. A number of treatable conditions can cause depression-like symptoms including hypothyroidism, Cushing's syndrome, electrolyte abnormalities (e.g., hypercalcemia), and drugs including dopamine blockers, interferon, tamoxifen, interleukin 2, vincristine, and glucocorticoids.

**Interventions** Dextroamphetamine or methylphenidate (see above); serotonin reuptake inhibitors such as fluoxetine, paroxetine, and citalopram; modafinil 100 mg/d; pemoline 18.75 mg in the A.M. and at noon.

## Delirium

Delirium is a global cerebral dysfunction associated with altered cognition and consciousness; it is frequently preceded by anxiety. Unlike dementia, it is of sudden onset, is characterized by fluctuating consciousness and inattention, and may be reversible. It is generally manifested in the hours before death. It may be caused by metabolic encephalopathy in renal or liver failure, hypoxemia, infection, hypercalcemia, paraneoplastic syndromes, dehydration, constipation, urinary retention, and central nervous system spread of cancer. It is also a common medication side effect; offending agents include those commonly used in dying pts including opioids, glucocorticoids, anticholinergics, antihistamines, antiemetics, and benzodiazepines. Early recognition is key because the pt should be encouraged to use the periods of lucidity for final communication with loved ones. Day-night reversal with changes in mentation may be an early sign.

**Interventions** Stop any and all unnecessary medications that may have this side effect; provide a calendar, clock, newspaper, or other orienting signals; gently correct hallucinations or cognitive mistakes; pharmacologic interventions are shown in Table 9-4.

**TABLE 9-4 MEDICATIONS FOR THE MANAGEMENT OF DELIRIUM**

| Interventions | Dose |
|---|---|
| Neuroleptics | |
| Haloperidol | 0.5–5 mg q2–12h, PO/IV/SC/IM |
| Thioridazine | 10–75 mg q4–8h, PO |
| Chlorpromazine | 12.5–50 mg q4–12h, PO/IV/IM |
| Atypical neuroleptics | |
| Olanzapine | 2.5–5 mg qd or bid, PO |
| Risperidone | 1–3 mg q12h, PO |
| Quetiapine | 50 mg qd, PO |
| Anxiolytics | |
| Lorazepam | 0.5–2 mg q1–4h, PO/IV/IM |
| Midazolam | 1–5 mg/h continuous infusion, IV/SC |
| Anesthetics | |
| Propofol | 0.3–2.0 mg/h continuous infusion, IV |

## CARE DURING THE LAST HOURS

The clinical course of a dying pt may largely be predictable. Figure 9-1 shows common and uncommon changes during the last days of life. Informing families that these changes might occur can help minimize the distress that they cause. In particular, the physician needs to be sensitive to the sense of guilt and helplessness that family members feel. They should be reassured that the illness is taking its course and their care of the pt is not at fault in any way. The pt stops eating because they are dying; they are not dying because they have stopped eating. Families and caregivers should be encouraged to communicate directly with the dying pt whether or not the pt is unconscious. Holding the pt's hand may be a source of comfort to both the pt and the family member/caregiver. Table 9-5 provides a listing of some changes in the pt's condition in the final hours and advice on how to manage the changes.

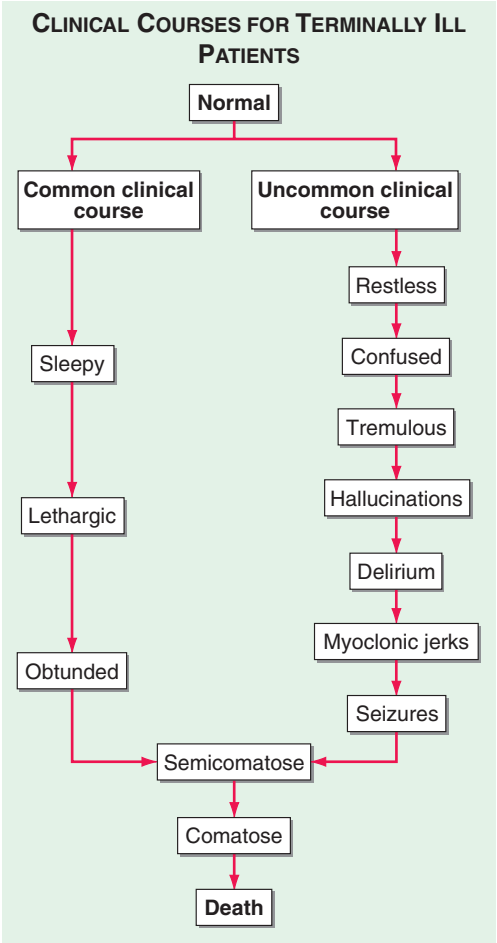



**FIGURE 9-1** Common and uncommon clinical courses in the last days of terminally ill pts. *(Adapted from FD Ferris et al: Module 4: Palliative care, in Comprehensive Guide for the Care of Persons with HIV Disease. Toronto: Mt. Sinai Hospital and Casey Hospice, 1995.)*

**TABLE 9-5 MANAGING CHANGES IN THE PATIENT'S CONDITION DURING THE FINAL DAYS AND HOURS**

| Changes in the Patient's Condition | Potential Complication | Family's Possible Reaction and Concern | Advice and Intervention |
|---|---|---|---|
| Profound fatigue | Bedbound with development of pressure ulcers that are prone to infection, malodor, and pain, and joint pain | Pt is lazy and giving up. | Reassure family and caregivers that terminal fatigue will not respond to interventions and should not be resisted.<br>Use an air mattress if necessary. |
| Anorexia | None | Pt is giving up; pt will suffer from hunger and will starve to death. | Reassure family and caregivers that the pt is not eating because he or she is dying; not eating at the end of life does not cause suffering or death.<br>Forced feeding, whether oral, parenteral, or enteral, does not reduce symptoms or prolong life. |
| Dehydration | Dry mucosal membranes (see below) | Pt will suffer from thirst and die of dehydration. | Reassure family and caregivers that dehydration at the end of life does not cause suffering because pts lose consciousness before any symptom distress.<br>IV hydration can worsen symptoms of dyspnea by pulmonary edema and peripheral edema as well as prolong dying process. |
| Dysphagia | Inability to swallow oral medications needed for palliative care | | Do not force oral intake.<br>Discontinue unnecessary medications that may have been continued, including antibiotics, diuretics, antidepressants, and laxatives.<br>If swallowing pills is difficult, convert essential medications (analgesics, antiemetics, anxiolytics, and psychotropics) to oral solutions, buccal, sublingual, or rectal administration. |

(*Continued*)

**TABLE 9-5 MANAGING CHANGES IN THE PATIENT'S CONDITION DURING THE FINAL DAYS AND HOURS (*CONTINUED*)**

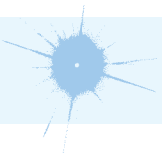
| Changes in the Patient's Condition | Potential Complication | Family's Possible Reaction and Concern | Advice and Intervention |
|---|---|---|---|
| "Death rattle"—noisy breathing | | Pt is choking and suffocating. | Reassure the family and caregivers that this is caused by secretions in the oropharynx and the pt is not choking.<br>Reduce secretions with scopolamine (0.2–0.4 mg SC q4h or 1–3 patches q3d).<br>Reposition pt to permit drainage of secretions.<br>Do not suction. Suction can cause pt and family discomfort and is usually ineffective. |
| Apnea, Cheyne-Stokes respirations, dyspnea | | Pt is suffocating. | Reassure family and caregivers that unconscious pts do not experience suffocation or air hunger.<br>Apneic episodes are frequently a premorbid change.<br>Opioids or anxiolytics may be used for dyspnea.<br>Oxygen is unlikely to relieve dyspneic symptoms and may prolong the dying process. |
| Urinary or fecal incontinence | Skin breakdown if days until death<br>Potential transmission of infectious agents to caregivers | Pt is dirty, malodorous, and physically repellent. | Remind family and caregivers to use universal precautions.<br>Frequent changes of bedclothes and bedding.<br>Use diapers, urinary catheter, or rectal tube if diarrhea or high urine output. |

(*Continued*)

**TABLE 9-5 MANAGING CHANGES IN THE PATIENT'S CONDITION DURING THE FINAL DAYS AND HOURS (*CONTINUED*)**

| Changes in the Patient's Condition | Potential Complication | Family's Possible Reaction and Concern | Advice and Intervention |
|---|---|---|---|
| Agitation or delirium | Day/night reversal | Pt is in horrible pain and going to have a horrible death. | Reassure family and caregivers that agitation and delirium do not necessarily connote physical pain. |
| | Hurt self or caregivers | | Depending on the prognosis and goals of treatment, consider evaluating for causes of delirium and modify medications. |
| | | | Manage symptoms with haloperidol, chlorpromazine, diazepam, or midazolam. |
| Dry mucosal membranes | Cracked lips, mouth sores, and candidiasis can also cause pain. | Pt may be malodorous, physically repellent. | Use baking soda mouthwash or saliva preparation q15–30min. |
| | Odor | | Use topical nystatin for candidiasis. |
| | | | Coat lips and nasal mucosa with petroleum jelly q60–90min. |
| | | | Use ophthalmic lubricants q4h or artificial tears q30min. |

Additional resources for managing terminally ill pts may be found at the following websites: www.epec.net, www.eperc.mcw.edu, www.capc.org, and www.nhpco.org.



For a more detailed discussion, see Emanuel EJ: Palliative and End-of-Life Care, Chap. 10, p. 55, in HPIM-19.

# 10 Cardiovascular Collapse and Sudden Death

Unexpected cardiovascular collapse and death most often result from ventricular fibrillation in pts with acute or chronic atherosclerotic coronary artery disease. Other common etiologies are listed in Table 10-1. Arrhythmic causes may be provoked by electrolyte disorders (primarily hypokalemia), hypoxemia, acidosis, or massive sympathetic discharge, as may occur in CNS injury. Immediate institution of cardiopulmonary resuscitation (CPR) followed by advanced life support measures (see below) is mandatory. Ventricular fibrillation, or asystole, without institution of CPR within 4–6 min is usually fatal.

## MANAGEMENT OF CARDIAC ARREST

**Basic life support (BLS)** must commence immediately (Fig. 10-1):

1. Phone emergency line (e.g., 911); retrieve automated external defibrillator (AED) if quickly available.
2. If respiratory stridor is present, assess for aspiration of a foreign body and perform Heimlich maneuver.

**TABLE 10-1 CARDIAC ARREST AND SUDDEN CARDIAC DEATH**

**Structural Associations and Causes**

1. Coronary heart disease (chronic, or acute coronary syndromes)
2. Myocardial hypertrophy (e.g., hypertrophic cardiomyopathy)
3. Dilated cardiomyopathy
4. Inflammatory (e.g., myocarditis) and infiltrative disorders
5. Valvular heart diseases
6. Electrophysiologic abnormalities (e.g., Wolff-Parkinson-White syndrome)
7. Inherited disorders associated with electrophysiological abnormalities (e.g., congenital long QT syndromes, right ventricular dysplasia, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia)

**Functional Contributing Factors**

1. Transient ischemia
2. Low cardiac output states (heart failure, shock)
3. Systemic metabolic abnormalities
   a. Electrolyte imbalance (e.g., hypokalemia)
   b. Hypoxemia, acidosis
4. Neurologic disturbances (e.g., CNS injury)
5. Toxic responses
   a. Proarrhythmic drug effects
   b. Cardiac toxins (e.g., cocaine, digitalis intoxication)

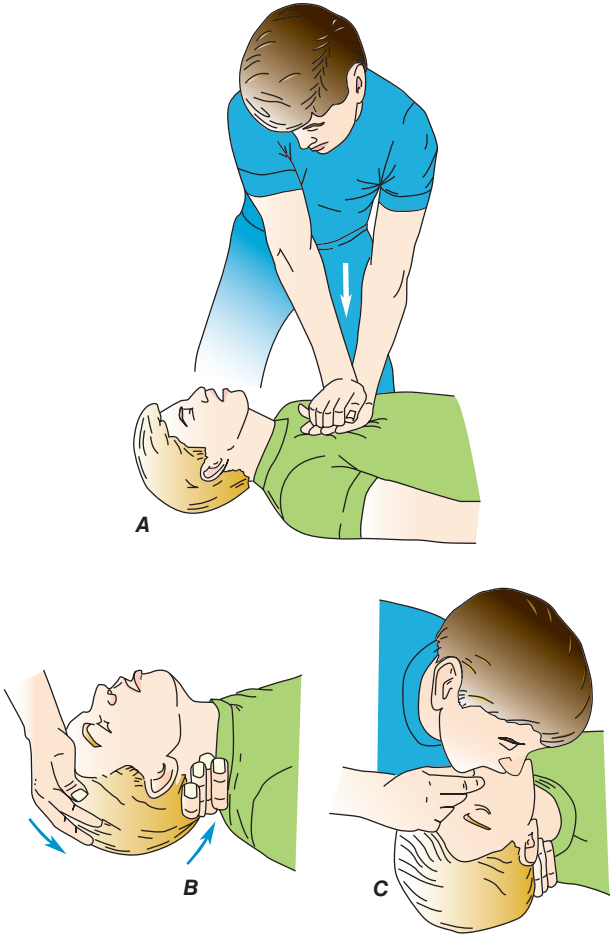



**FIGURE 10-1** Major steps in cardiopulmonary resuscitation. **A.** Begin cardiac compressions at 100 compressions/min. **B.** Confirm that victim has an open airway. **C.** Trained rescuers begin ventilation if advanced life support equipment is not available (pocket mask preferred if available). *(Modified from J Henderson, Emergency Medical Guide, 4th ed, New York, McGraw-Hill, 1978.)*

3. Perform chest compressions (depressing sternum 4–5 cm) at rate of 100 per min without interruption. A second rescuer should attach and utilize AED if available.
4. If second *trained* rescuer available, tilt pt's head backward, lift chin, and begin rescue breathing (pocket mask is preferable to mouth-to-mouth respiration to prevent transmission of infection), while chest compressions continue. The lungs should be inflated twice in rapid succession for every 30 chest compressions. For *untrained* lay rescuers, chest compression only, without ventilation, is recommended until advanced life support capability arrives.
5. As soon as resuscitation equipment is available, begin **advanced life support** with continued chest compressions and ventilation. Although performed as

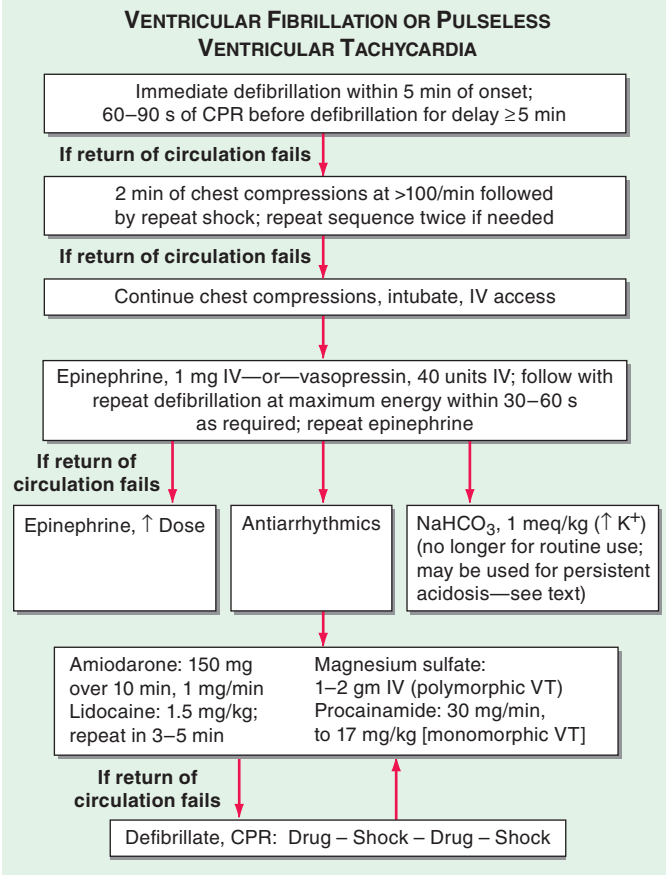



**FIGURE 10-2** Management of cardiac arrest. The algorithm of ventricular fibrillation or hypotensive ventricular tachycardia begins with defibrillation attempts, separated by 2 min of chest compressions. If that fails, it is followed by epinephrine or vasopressin (intravenous or intraosseous) and then antiarrhythmic drugs. CPR, cardiopulmonary resuscitation; VT, ventricular tachycardia. *(Modified from Myerburg RJ, Castellanos A. Chap. 327, HPIM-19.)*

simultaneously as possible, defibrillation (150–200 J biphasic, or 360 J monophasic) takes highest priority (Fig. 10-2), followed by placement of IV access and intubation (if pt is less than fully conscious). One hundred percent $O_2$ should be administered by endotracheal tube or, if rapid intubation cannot be accomplished, by bag-valve-mask device. Once an advanced airway is placed, ventilate at rate of 1 breath every 6–8 s without interrupting chest compressions. Use quantitative capnography to confirm and monitor appropriate endotracheal tube placement.

6. Initial IV access should be through the antecubital vein, but if drug administration is ineffective, an intraosseous or central line (internal jugular or subclavian) should be placed. IV $NaHCO_3$ should be administered only if there is persistent

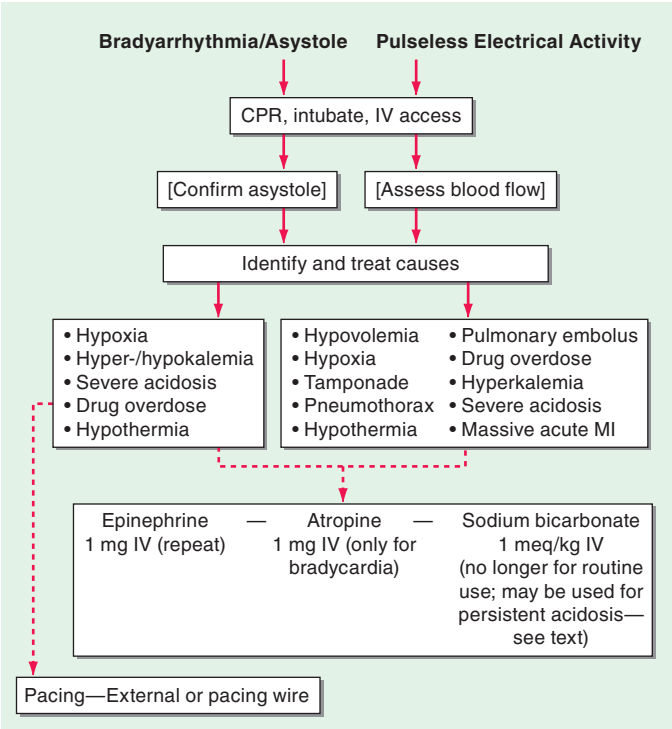



**FIGURE 10-3** The algorithms for bradyarrhythmia/asystole (left) or pulseless electrical activity (right) are dominated first by continued life support and a search for reversible causes. CPR, cardiopulmonary resuscitation; MI, myocardial infarction. *(Modified from Myerburg RJ, Castellanos A. Chap. 327, HPIM-19.)*

severe acidosis (pH <7.15) despite adequate ventilation. Calcium is not routinely administered but should be given to pts with known hypocalcemia, those who have received toxic doses of calcium channel antagonists, or if acute hyperkalemia is thought to be the triggering event for resistant ventricular fibrillation.

7. The approach to cardiovascular collapse caused by bradyarrhythmias, asystole, or pulseless electrical activity is shown in Fig. 10-3.
8. Therapeutic hypothermia (cooling to 32–34°C [89.6–93.2°F] for 12–24 h) should be considered for unconscious survivors of cardiac arrest.

## FOLLOW-UP

If cardiac arrest resulted from ventricular fibrillation in initial hours of an acute MI, follow-up is standard post-MI care (Chap. 119). For other survivors of a ventricular fibrillation arrest, further assessment, including evaluation of coronary anatomy, and left ventricular function, is typically recommended. In absence of a transient or reversible cause, placement of an implantable cardioverter defibrillator is usually indicated.

For a more detailed discussion, see Myerburg RJ, Castellanos A: Cardiovascular Collapse, Cardiac Arrest, and Sudden Cardiac Death, Chap. 327, p. 1764, in HPIM-19.

# 11 Shock

## DEFINITION

Condition of severe impairment of tissue perfusion leading to cellular injury and dysfunction. Rapid recognition and treatment are essential to prevent irreversible organ damage and death. Common causes are listed in Table 11-1.

## CLINICAL MANIFESTATIONS

- Hypotension (mean arterial bp <60 mmHg), tachycardia, tachypnea, pallor, restlessness, and altered sensorium.
- Signs of intense peripheral vasoconstriction, with weak pulses and cold clammy extremities. In distributive (e.g., septic) shock, vasodilation predominates and extremities are warm.
- Oliguria (<20 mL/h) and metabolic acidosis common.

**TABLE 11-1 CATEGORIES OF SHOCK**

| |
|---|
| Hypovolemic shock |
| Hemorrhage |
| Intravascular volume depletion (e.g., vomiting, diarrhea, ketoacidosis) |
| Internal sequestration (ascites, pancreatitis, intestinal obstruction) |
| Cardiogenic shock |
| Myopathic (acute MI, fulminant myocarditis) |
| Mechanical (e.g., acute mitral regurgitation, ventricular septal defect, severe aortic stenosis, aortic dissection with aortic insufficiency) |
| Arrhythmic |
| Extracardiac obstructive shock |
| Pericardial tamponade |
| Massive pulmonary embolism |
| Tension pneumothorax |
| Distributive shock (profound decrease in systemic vascular tone) |
| Sepsis |
| Toxic overdoses |
| Anaphylaxis |
| Neurogenic (e.g., spinal cord injury) |
| Endocrinologic (Addison's disease, myxedema) |

- Acute lung injury and acute respiratory distress syndrome (ARDS; see Chap. 14) with noncardiogenic pulmonary edema, hypoxemia, and diffuse pulmonary infiltrates.

## APPROACH TO THE PATIENT: **Shock**

Obtain history for underlying causes, including cardiac disease (coronary disease, heart failure, pericardial disease), recent fever or infection leading to sepsis, drug effects (e.g., excess diuretics or antihypertensives), conditions leading to pulmonary embolism (Chap. 133), and potential sources of bleeding.

### PHYSICAL EXAMINATION

Jugular veins are flat in oligemic or distributive (septic) shock; jugular venous distention (JVD) suggests cardiogenic shock; JVD in presence of paradoxical pulse (Chap. 110) may reflect cardiac tamponade (Chap. 116). Check for asymmetry of pulses (aortic dissection—Chap. 125). Assess for evidence of heart failure (Chap. 124), murmurs of aortic stenosis, acute mitral or aortic regurgitation, and ventricular septal defect. Tenderness or rebound in abdomen may indicate peritonitis or pancreatitis; high-pitched bowel sounds suggest intestinal obstruction. Perform stool guaiac to rule out GI bleeding.

Fever and chills typically accompany septic shock. Sepsis may not cause fever in elderly, uremic, or alcoholic pts. Skin lesions may suggest specific pathogens in septic shock: petechiae or purpura (*Neisseria meningitidis* or *Haemophilus influenzae*), ecthyma gangrenosum (*Pseudomonas aeruginosa*), generalized erythroderma (toxic shock due to *Staphylococcus aureus* or *Streptococcus pyogenes*).

### LABORATORY

Obtain hematocrit, WBC, electrolytes, platelet count, PT, PTT, DIC screen, electrolytes. Arterial blood gas usually shows metabolic acidosis (in septic shock, respiratory alkalosis precedes metabolic acidosis). If sepsis suspected, draw blood cultures, perform urinalysis, and obtain Gram stain and cultures of sputum, urine, and other suspected sites.

Obtain ECG (myocardial ischemia or acute arrhythmia) and chest x-ray (heart failure, tension pneumothorax, pneumonia). Echocardiogram is often helpful (cardiac tamponade, left/right ventricular dysfunction, aortic dissection).

CVP or pulmonary capillary wedge (PCW) pressure measurements may be necessary to distinguish between different categories of shock (Table 11-2): Mean PCW <6 mmHg suggests oligemic or distributive shock; PCW >20 mmHg suggests left

**TABLE 11-2 PHYSIOLOGIC CHARACTERISTICS OF FORMS OF SHOCK**

| Type of Shock | CVP and PCWP | Cardiac Output | Systemic Vascular Resistance | Venous $O_2$ Saturation |
|---|---|---|---|---|
| Hypovolemic | ↓ | ↓ | ↑ | ↓ |
| Cardiogenic | ↑ | ↓ | ↑ | ↓ |
| Septic | | | | |
| Hyperdynamic | ↓↑ | ↑ | ↓ | ↑ |
| Hypodynamic | ↓↑ | ↓ | ↑ | ↑↓ |
| Traumatic | ↓ | ↓↑ | ↑↓ | ↓ |
| Neurogenic | ↓ | ↓ | ↓ | ↓ |
| Hypoadrenal | ↓ | ↓ | =↓ | ↓ |

***Abbreviations:*** PCWP, pulmonary capillary wedge pressure.

ventricular failure. Cardiac output (thermodilution) is decreased in cardiogenic and oligemic shock, and usually increased initially in septic shock.

## TREATMENT SHOCK (FIG. 11-1)

Aimed at rapid improvement of tissue hypoperfusion and respiratory impairment:

- Serial measurements of bp (intraarterial line preferred), heart rate, continuous ECG monitor, urine output, pulse oximetry, blood studies: Hct, electrolytes, creatinine, BUN, ABGs, pH, calcium, phosphate, lactate, urine Na concentration (<20 mmol/L suggests volume depletion). Consider monitoring of CVP and/or pulmonary artery pressure/PCW pressures in pts with ongoing blood loss,

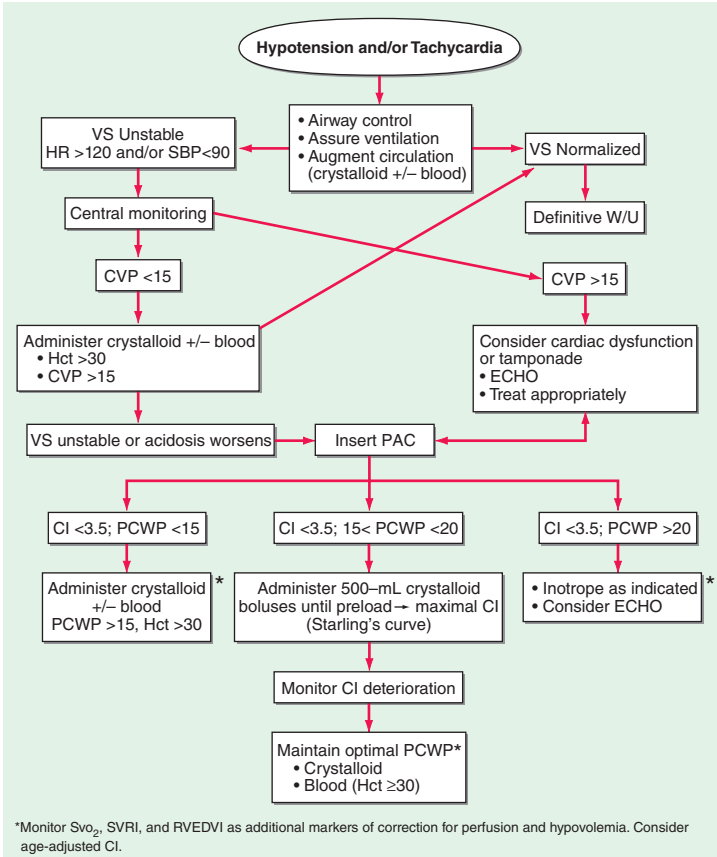



**FIGURE 11-1** An algorithm for the resuscitation of the pt in shock. $Svo_2$, saturation of hemoglobin with $O_2$ in venous blood; SVRI, systemic vascular resistance index; RVEDVI, right-ventricular end-diastolic volume index. CI, cardiac index in (L/min) per $m^2$; ECHO, echocardiogram; Hct, hematocrit; HR, heart rate; PAC, pulmonary artery catheter; PCWP, pulmonary capillary wedge pressure in mmHg; SBP, systolic blood pressure; VS, vital signs; W/U, work up.

marked fluid shifts, or suspected cardiac dysfunction (the majority of pts do *not* require pulmonary artery catheter monitoring).

- Insert Foley catheter to monitor urine flow.
- Assess mental status frequently.
- Augment systolic bp to >100 mmHg: (1) Place in reverse Trendelenburg position; (2) IV volume infusion (500- to 1000-mL bolus), unless cardiogenic shock suspected (begin with normal saline or Ringer's lactate, then whole blood, or packed RBCs, if anemic); continue volume replacement as needed to restore vascular volume.
- Add vasoactive drugs after intravascular volume is optimized; administer vasopressors (Table 11-3) if systemic vascular resistance (SVR) is decreased (begin with norepinephrine [preferred] or dopamine; for persistent hypotension add phenylephrine or vasopressin).
- If heart failure is present, add inotropic agents (usually dobutamine) (Table 11-3); aim to maintain cardiac index >2.2(L/m$^2$)/min [>4.0(L/m$^2$)/min in septic shock].
- Administer 100% $O_2$; intubate with mechanical ventilation if $PO_2$ <70 mmHg.
- If severe metabolic acidosis present (pH <7.15), administer $NaHCO_3$.

**TABLE 11-3 VASOPRESSORS USED IN SHOCK STATES[a]**

| Drug | Dose | Notes |
|---|---|---|
| Dopamine | 1–2 μg/kg per min | Facilitates diuresis |
| | 2–10 μg/kg per min | Positive inotropic and chronotropic effects; may increase $O_2$ consumption as well as $O_2$ delivery; use may be limited by tachycardia |
| | 10–20 μg/kg per min | Generalized vasoconstriction (decrease renal perfusion) |
| Norepinephrine | 0.5–30 μg/min | Potent vasoconstrictor; moderate inotropic effect; in septic shock is thought to increase tissue $O_2$ consumption as well as $O_2$ delivery; may be chosen over dopamine in sepsis due to less chronotropic and adverse effects; may be useful in cardiogenic shock with reduced SVR but should generally be reserved for refractory hypotension |
| Dobutamine | 2–20 μg/kg per min | Primarily for cardiogenic shock (Chap. 119): positive inotrope; lacks vasoconstrictor activity; most useful when only mild hypotension present and avoidance of tachycardia desired |
| Phenylephrine | 40–180 μg/min | Potent vasoconstrictor without inotropic effect; may be useful in distributive (septic) shock |
| Vasopressin | 0.01–0.04 U/min | Occasionally used in refractory septic (distributive) shock; restores vascular tone in vasopressin-deficient states (e.g., sepsis) |

[a]Isoproterenol not recommended in shock states because of potential hypotension and arrhythmogenic effects.
***Abbreviation:*** SVR, systemic vascular resistance.

- Identify and treat underlying cause of shock. Cardiogenic shock in acute MI is discussed in Chap. 119. Emergent coronary revascularization may be lifesaving if persistent ischemia is present.

## SEPTIC SHOCK (SEE CHAP. 11)

For a more detailed discussion, see Maier RV: Approach to the Patient with Shock, Chap. 324, p.1744, and Hochman JS, Ingbar DH: Cardiogenic Shock and Pulmonary Edema, Chap. 326, p. 1759, in HPIM-19.

# 12 Sepsis and Septic Shock

## DEFINITIONS

- *Possibly harmful systemic response:* Two or more of the following:
  - Fever (oral temperature >38°C [100.4°F]) or hypothermia (oral temperature <36°C [96.8°F])
  - Tachypnea (>24 breaths/min)
  - Tachycardia (>90 beats/min)
  - Leukocytosis (>12,000/μL), leukopenia (<4000/μL), or >10% bands; may have a noninfectious etiology
- *Sepsis (or severe sepsis):* Harmful systemic response (including some degree of organ hypofunction) with a proven or suspected microbial etiology
- *Septic shock:* Sepsis with hypotension (arterial bp <90 mmHg or 40 mmHg below pt's normal bp for at least 1 h despite fluid resuscitation) or need for vasopressors to maintain systolic bp ≥90 mmHg or mean arterial bp ≥70 mmHg

## ETIOLOGY

- Blood cultures are positive in 20–40% of sepsis cases and in 40–70% of septic shock cases.
- For infected pts in ICUs, respiratory infections have been most common (64%). Microbiologic results have revealed that 62% of isolates are gram-negative bacteria (most commonly *Pseudomonas* spp. and *Escherichia coli*), 47% are gram-positive bacteria (most commonly *Staphylococcus aureus*), and 19% are fungi (most commonly *Candida* spp.), with some cultures being polymicrobial.

## EPIDEMIOLOGY

- The incidence of severe sepsis and septic shock in the United States continues to increase, with >750,000 cases each year contributing to >200,000 deaths.
- Invasive bacterial infections are a prominent cause of death around the world, especially among young children.

- Sepsis-related incidence and mortality rates increase with age and preexisting comorbidity, with two-thirds of cases occurring in pts with significant underlying disease.
- The increasing incidence of sepsis has been attributable to the aging of the population, longer survival of pts with chronic diseases, a relatively high frequency of sepsis among AIDS pts, and medical treatments that circumvent host defenses (e.g., immunosuppressive agents, indwelling catheters, and mechanical devices).

## PATHOPHYSIOLOGY

### Local and Systemic Host Responses

- Hosts have numerous receptors that recognize highly conserved microbial molecules (e.g., lipopolysaccharide, lipoproteins, double-stranded RNA), triggering the release of cytokines and other host molecules that increase blood flow and neutrophil migration to the infected site, enhance local vascular permeability, and elicit pain.
- Many local and systemic control mechanisms diminish cellular responses to microbial molecules, including intravascular thrombosis (which prevents spread of infection and inflammation) and an increase in anti-inflammatory cytokines (e.g., IL-4 and IL-10).

### Organ Dysfunction and Shock

- Widespread vascular endothelial injury is believed to be the major mechanism for multiorgan dysfunction.
- Septic shock is characterized by compromised oxygen delivery to tissues followed by a vasodilatory phase (a decrease in peripheral vascular resistance despite increased levels of vasopressor catecholamines).

## CLINICAL FEATURES

- Hyperventilation that produces respiratory alkalosis
- Encephalopathy (disorientation, confusion)
- Acrocyanosis and ischemic necrosis of peripheral tissues (e.g., digits) due to hypotension and DIC
- Skin: hemorrhagic lesions, bullae, cellulitis, pustules. Skin lesions may suggest specific pathogens; e.g., petechiae and purpura suggest *Neisseria meningitidis*, and ecthyma gangrenosum suggests *Pseudomonas aeruginosa*.
- GI: nausea, vomiting, diarrhea, ileus, cholestatic jaundice

### Major Complications

- *Cardiopulmonary manifestations*
  - Ventilation-perfusion mismatch, increased alveolar capillary permeability, increased pulmonary water content, and decreased pulmonary compliance impede oxygen exchange and lead to ARDS (progressive diffuse pulmonary infiltrates and arterial hypoxemia) in ~50% of pts.
  - Hypotension: Normal or increased cardiac output and decreased systemic vascular resistance distinguish septic shock from cardiogenic and hypovolemic shock.
  - The ejection fraction is decreased, but ventricular dilation allows maintenance of a normal stroke volume.
- *Adrenal insufficiency:* may be difficult to diagnose in critically ill pts
- *Renal manifestations*: oliguria or polyuria, azotemia, proteinuria, and renal failure due to acute tubular necrosis
- *Neurologic manifestations*: delirium in the acute phase, polyneuropathy with distal motor weakness in prolonged sepsis. Survivors may have long-term cognitive impairment.
- *Immunosuppression*: Pts may have reactivation of HSV, CMV, or VZV.

## Laboratory Findings

- *CBC:* leukocytosis with a left shift, thrombocytopenia
- *Coagulation:* prolonged thrombin time, decreased fibrinogen, presence of D-dimers suggestive of DIC. With DIC, platelet counts usually fall below 50,000/μL.
- *Chemistries:* metabolic acidosis, elevated anion gap, elevated lactate levels
- *LFTs:* transaminitis, hyperbilirubinemia, azotemia, hypoalbuminemia

## DIAGNOSIS

Definitive diagnosis requires isolation of the microorganism from blood or a local site of infection. Culture of infected cutaneous lesions may help establish the diagnosis.

## TREATMENT SEPSIS AND SEPTIC SHOCK

Pts in whom sepsis is suspected must be managed expeditiously, if possible within 1 h of presentation.

1. Antibiotic treatment: See Table 12-1.
2. Removal or drainage of a focal source of infection
   a. Remove indwelling intravascular catheters; replace Foley and other drainage catheters; drain local sources of infection.
   b. Rule out sinusitis in pts with nasal intubation.
   c. Image the chest, abdomen, and/or pelvis to evaluate for abscess.
3. Hemodynamic, respiratory, and metabolic support
   a. Initiate treatment with 1–2 L of normal saline administered over 1–2 h, keeping the CVP at 8–12 $cmH_2O$, urine output at >0.5 mL/kg per hour, and mean arterial bp at >65 mmHg. Add vasopressor therapy if needed.
   b. If hypotension does not respond to fluid replacement therapy, hydrocortisone (50 mg IV q6h) should be given. If clinical improvement results within 24–48 h, most experts would continue hydrocortisone treatment for 5–7 days.
   c. Maintain oxygenation with ventilator support as indicated. Recent studies favor the use of low tidal volumes—typically 6 mL/kg of ideal body weight—provided the plateau pressure is ≤30 $cmH_2O$.
   d. Erythrocyte transfusion is recommended when the blood Hb level decreases to ≤7 g/dL, with a target level of 9 g/dL.
4. General support: Nutritional supplementation should be given to pts with prolonged sepsis (i.e., that lasting >2–3 days), with available evidence suggesting an enteral delivery route. Prophylactic heparin should be administered to prevent deep-venous thrombosis if no active bleeding or coagulopathy is present. Insulin should be used only if it is needed to maintain the blood glucose concentration below ~180 mg/dL.

## PROGNOSIS

In all, 20–35% of pts with severe sepsis and 40–60% of pts with septic shock die within 30 days, and further deaths occur within 6 months. Prognostic stratification systems (e.g., APACHE II) can estimate the risk of dying of severe sepsis.

**TABLE 12-1 INITIAL ANTIMICROBIAL THERAPY FOR SEVERE SEPSIS WITH NO OBVIOUS SOURCE IN ADULTS WITH NORMAL RENAL FUNCTION**

| Clinical Condition | Antimicrobial Regimens (Intravenous Therapy) |
|---|---|
| Immunocompetent adult | The many acceptable regimens include (1) piperacillin-tazobactam (3.375 g q4–6h); (2) imipenem-cilastatin (0.5 g q6h), ertapenem (1 g q24h), or meropenem (1 g q8h); or (3) cefepime (2 g q12h). If the pt is allergic to β-lactam agents, use ciprofloxacin (400 mg q12h) or levofloxacin (500–750 mg q12h) plus clindamycin (600 mg q8h). Vancomycin (15 mg/kg q12h) should be added to each of the above regimens. |
| Neutropenia (<500 neutrophils/μL) | Regimens include (1) imipenem-cilastatin (0.5 g q6h) or meropenem (1 g q8h) or cefepime (2 g q8h) or (2) piperacillin-tazobactam (3.375 g q4h) plus tobramycin (5–7 mg/kg q24h). Vancomycin (15 mg/kg q12h) should be added if the pt has an indwelling vascular catheter, has received quinolone prophylaxis, or has received intensive chemotherapy that produces mucosal damage; if staphylococci are suspected; if the institution has a high incidence of MRSA infections; or if there is a high prevalence of MRSA isolates in the community. Empirical antifungal therapy with an echinocandin (for caspofungin: a 70-mg loading dose, then 50 mg daily), voriconazole (6 mg/kg q12h for 2 doses, then 3 mg/kg q12h), or a lipid formulation of amphotericin B should be added if the pt is hypotensive, has been receiving broad-spectrum antibacterial drugs, or remains febrile 5 days after initiation of empirical antibacterial therapy. |
| Splenectomy | Cefotaxime (2 g q6–8h) or ceftriaxone (2 g q12h) should be used. If the local prevalence of cephalosporin-resistant pneumococci is high, add vancomycin. If the pt is allergic to β-lactam drugs, vancomycin (15 mg/kg q12h) plus either moxifloxacin (400 mg q24h) or levofloxacin (750 mg q24h) should be used. |
| IV drug user | Vancomycin (15 mg/kg q12h) is essential. |
| AIDS | Cefepime alone (2 g q8h) or piperacillin-tazobactam (3.375 g q4h) plus tobramycin (5–7 mg/kg q24h) should be used. If the pt is allergic to β-lactam drugs, ciprofloxacin (400 mg q12h) or levofloxacin (750 mg q12h) plus vancomycin (15 mg/kg q12h) plus tobramycin should be used. |

***Abbreviation:*** MRSA, methicillin-resistant *Staphylococcus aureus*.
***Source:*** Adapted in part from DN Gilbert et al: *The Sanford Guide to Antimicrobial Therapy,* 43rd ed, 2013, Antimicrobial Therapy, Inc., Sperryville, VA.

## PREVENTION

Nosocomial infections cause most episodes of severe sepsis and septic shock in the United States. Measures to reduce those infections could reduce the incidence of sepsis.

For a more detailed discussion, see Munford RS: Severe Sepsis and Septic Shock, Chap. 325, p. 1751, in HPIM-19.

# 13 Acute Pulmonary Edema

Life-threatening, acute development of alveolar lung edema due to one or more of the following:

1. Elevation of hydrostatic pressure in the pulmonary capillaries (left heart failure, mitral stenosis).
2. Specific precipitants (Table 13-1), resulting in cardiogenic pulmonary edema in pts with previously compensated heart failure or without previous cardiac history.
3. Increased permeability of pulmonary alveolar-capillary membrane (noncardiogenic pulmonary edema). For common causes, see Table 13-2.

## PHYSICAL FINDINGS

Pt appears severely ill, often diaphoretic, sitting bolt upright, tachypneic, and cyanosis may be present. Bilateral pulmonary rales; third heart sound may be present. Frothy, blood-tinged sputum may occur.

## LABORATORY

Early arterial blood gases show reductions of both $PaO_2$ and $PaCO_2$. With progressive respiratory failure, hypercapnia develops with acidemia. CXR shows pulmonary vascular redistribution, diffuse haziness in lung fields with perihilar "butterfly" appearance.

## TREATMENT ACUTE PULMONARY EDEMA

Immediate, aggressive therapy is mandatory for survival. The following measures should be instituted as simultaneously as possible for cardiogenic pulmonary edema:

**TABLE 13-1 PRECIPITANTS OF ACUTE PULMONARY EDEMA**

| |
|---|
| Acute tachy- or bradyarrhythmia |
| Infection, fever |
| Acute MI |
| Severe hypertension |
| Acute mitral or aortic regurgitation |
| Increased circulating volume ($Na^+$ ingestion, blood transfusion, pregnancy) |
| Increased metabolic demands (exercise, hyperthyroidism) |
| Pulmonary embolism |
| Noncompliance (sudden discontinuation) of chronic CHF medications |

**TABLE 13-2 COMMON CAUSES OF NONCARDIOGENIC PULMONARY EDEMA**

| | |
|---|---|
| **Direct Injury to Lung** | |
| Chest trauma, pulmonary contusion | Pneumonia |
| Aspiration | Oxygen toxicity |
| Smoke inhalation | Pulmonary embolism, reperfusion |
| **Hematogenous Injury to Lung** | |
| Sepsis | Multiple transfusions |
| Pancreatitis | IV drug use, e.g., heroin |
| Nonthoracic trauma | Cardiopulmonary bypass |
| **Possible Lung Injury Plus Elevated Hydrostatic Pressures** | |
| High-altitude pulmonary edema | Reexpansion pulmonary edema |
| Neurogenic pulmonary edema | |

1. Administer 100% $O_2$ by mask to achieve $PaO_2$ >60 mmHg; if inadequate, use positive-pressure ventilation by face or nasal mask, and if necessary, proceed to endotracheal intubation.
2. Reduce preload:
   a. Seat pt upright to reduce venous return, if not hypotensive.
   b. Intravenous loop diuretic (e.g., furosemide, initially 0.5–1.0 mg/kg); use lower dose if pt does not take diuretics chronically.
   c. Nitroglycerin (sublingual 0.4 mg × 3 q5min) followed by 5–20 μg/ min IV if needed.
   d. Morphine 2–4 mg IV; assess frequently for hypotension or respiratory depression; naloxone should be available to reverse effects of morphine if necessary.
   e. Consider ACE inhibitor if pt is hypertensive, or in setting of acute MI with heart failure.
   f. Consider nesiritide (2-μg/kg bolus IV followed by 0.01 μg/kg per min) for refractory symptoms—do not use in acute MI or cardiogenic shock.
3. Inotropic agents are indicated in cardiogenic pulmonary edema and severe LV dysfunction: dopamine, dobutamine, milrinone (Chap. 11).
4. The precipitating cause of cardiogenic pulmonary edema (Table 13-1) should be sought and treated, particularly acute arrhythmias or infection. For refractory pulmonary edema associated with persistent cardiac ischemia, early coronary revascularization may be life-saving. For noncardiac pulmonary edema, identify and treat/remove cause (Table 13-2).

For a more detailed discussion, see Schwartzstein RM: Dyspnea, Chap. 47e; and Hochman JS, Ingbar DH: Cardiogenic Shock and Pulmonary Edema, Chap. 326, p. 1759, in HPIM-19.

# 14 Acute Respiratory Distress Syndrome

## DEFINITION AND ETIOLOGY

Acute respiratory distress syndrome (ARDS) develops rapidly and includes severe dyspnea, diffuse pulmonary infiltrates, and hypoxemia; it typically causes respiratory failure. Key diagnostic criteria for ARDS include (1) diffuse bilateral pulmonary infiltrates on CXR; (2) $PaO_2$ (arterial partial pressure of oxygen in mmHg)/$FIO_2$ (inspired $O_2$ fraction) ≤200 mmHg; and (3) absence of elevated left atrial pressure (pulmonary capillary wedge pressure ≤18 mmHg). Acute lung injury is a related but milder syndrome, with less profound hypoxemia ($PaO_2/FIO_2$ ≤300 mmHg), that can develop into ARDS. Although many medical and surgical conditions can cause ARDS, most cases (>80%) result from sepsis, bacterial pneumonia, trauma, multiple blood transfusions, gastric acid aspiration, and drug overdose. Individuals with more than one predisposing factor have a greater risk of developing ARDS. Other risk factors include older age, chronic alcohol abuse, metabolic acidosis, and overall severity of critical illness.

## CLINICAL COURSE AND PATHOPHYSIOLOGY

There are three phases in the natural history of ARDS:

1. *Exudative phase:* Characterized by alveolar edema and neutrophil inflammation, with subsequent development of hyaline membranes from diffuse alveolar damage. The alveolar edema, which is most prominent in the dependent portions of the lung, causes atelectasis and reduced lung compliance. Hypoxemia, tachypnea, and progressive dyspnea develop, and increased pulmonary dead space can also lead to hypercarbia. Respiratory failure frequently develops during this phase. CXR reveals bilateral, diffuse alveolar, and interstitial opacities. The differential diagnosis is broad, but common alternative etiologies to consider are cardiogenic pulmonary edema, pneumonia, and alveolar hemorrhage. Unlike cardiogenic pulmonary edema, the CXR in ARDS rarely shows cardiomegaly, pleural effusions, or pulmonary vascular redistribution. The exudative phase duration is typically up to 7 days in length and usually begins within 12–36 h after the inciting insult.
2. *Proliferative phase:* This phase typically lasts from approximately days 7 to 21 after the inciting insult. Although most pts recover, some will develop progressive lung injury and evidence of pulmonary fibrosis. Even among pts who show rapid improvement allowing removal of mechanical ventilatory support, dyspnea and hypoxemia often persist during this phase.
3. *Fibrotic phase:* Although the majority of pts recover within 3–4 weeks of the initial pulmonary injury, some experience progressive fibrosis, necessitating prolonged ventilatory support and/or supplemental $O_2$. Increased risk of pneumothorax, reductions in lung compliance, and increased pulmonary dead space are observed during this phase.

## TREATMENT ARDS

Progress in recent therapy has emphasized the importance of general critical care of pts with ARDS in addition to lung protective ventilatory strategies. General care requires treatment of the underlying medical or surgical problem that caused lung injury, minimizing iatrogenic complications, prophylaxis to prevent venous thromboembolism and GI hemorrhage, prompt treatment of nosocomial

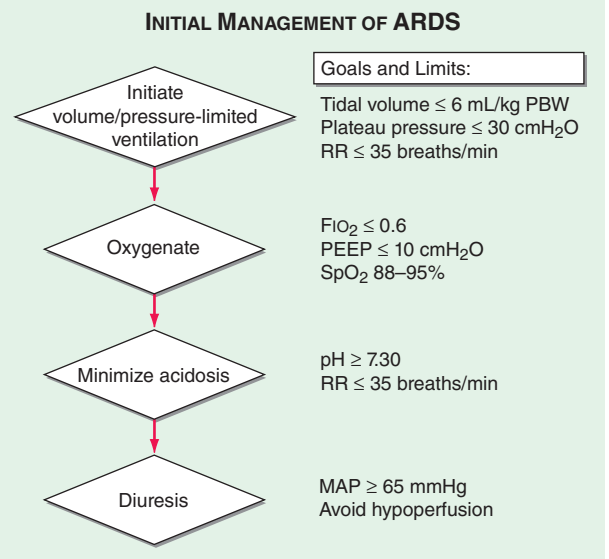



**FIGURE 14-1** Algorithm for the initial management of acute respiratory distress syndrome (ARDS). Clinical trials have provided evidence-based therapeutic goals for a stepwise approach to the early mechanical ventilation, oxygenation, and correction of acidosis and diuresis of critically ill pts with ARDS. $FIO_2$, inspired $O_2$ percentage; MAP, mean arterial pressure; PBW, predicted body weight; PEEP, positive end-expiratory pressure; RR, respiratory rate; $SpO_2$, arterial oxyhemoglobin saturation measured by pulse oximetry.

infections, and adequate nutritional support. An algorithm for the initial management of ARDS is presented in Fig. 14-1.

**MECHANICAL VENTILATORY SUPPORT** Pts with ARDS typically require mechanical ventilatory support due to hypoxemia and increased work of breathing. A substantial improvement in outcomes from ARDS occurred with the recognition that mechanical ventilator–related overdistention of normal lung units with positive pressure can produce or exacerbate lung injury, causing or worsening ARDS. Currently recommended ventilator strategies limit alveolar distention but maintain adequate tissue oxygenation.

It has been clearly shown that low tidal volumes (≤6-mL/kg predicted body weight) provide reduced mortality compared with higher tidal volumes (12-mL/kg predicted body weight). In ARDS, alveolar collapse can occur due to alveolar/interstitial fluid accumulation and loss of surfactant, thus worsening hypoxemia. Therefore, low tidal volumes are combined with the use of positive end-expiratory pressure (PEEP) at levels that strive to minimize alveolar collapse and achieve adequate oxygenation with the lowest required $FIO_2$. Use of PEEP levels higher than necessary to optimize oxygenation has not been proven to reduce ARDS mortality. Measurement of esophageal pressures to estimate transpulmonary pressure may help to identify an optimal level of PEEP. Other techniques that may improve oxygenation while limiting alveolar distention include extending the time of inspiration on the ventilator (inverse ratio ventilation) and placing the pt in the prone position. However, these approaches are not of proven benefit in reducing mortality from ARDS.

**ANCILLARY THERAPIES** Pts with ARDS have increased pulmonary vascular permeability leading to interstitial and alveolar edema. Therefore, they should receive IV fluids only as needed to achieve adequate cardiac output and tissue $O_2$ delivery as assessed by urine output, acid-base status, and arterial pressure. A recent study suggested that neuromuscular blockage with cisatracurium for 48 h could potentially reduce mortality in severe ARDS. There is not convincing evidence currently to support the use of glucocorticoids or nitric oxide in ARDS.

## OUTCOMES

Mortality from ARDS has declined with improvements in general critical care treatment and with the introduction of low tidal volume ventilation. Current mortality from ARDS is 26–44%, with most deaths due to sepsis and nonpulmonary organ failure. Increased risk of mortality from ARDS is associated with advanced age, preexisting organ dysfunction (e.g., chronic conditions of liver disease, alcohol abuse, immunosuppression, or renal disease). Increased mortality has also been associated with ARDS related to direct lung injury (e.g., pneumonia, pulmonary contusion, and aspiration) compared with indirect lung injury (e.g., sepsis, trauma, and pancreatitis). Most surviving ARDS pts do not have significant long-term pulmonary disability.

For a more detailed discussion, see Levy BD, Choi AMK: Acute Respiratory Distress Syndrome, Chap. 322, p. 1736, in HPIM-19.

# 15 Respiratory Failure

## DEFINITION AND CLASSIFICATION OF RESPIRATORY FAILURE

Respiratory failure is defined as inadequate gas exchange due to malfunction of one or more components of the respiratory system. There are two main types of acute respiratory failure: hypoxemic and hypercarbic. Hypoxemic respiratory failure is defined by arterial $O_2$ saturation <90% while receiving an increased inspired $O_2$ fraction. Acute hypoxemic respiratory failure can result from pneumonia, pulmonary edema (cardiogenic or noncardiogenic), and alveolar hemorrhage. Hypoxemia results from ventilation-perfusion mismatch and intrapulmonary shunting.

Hypercarbic respiratory failure is characterized by alveolar hypoventilation and respiratory acidosis. Hypercarbic respiratory failure results from decreased minute ventilation and/or increased physiologic dead space. Conditions associated with hypercarbic respiratory failure include neuromuscular diseases (e.g., myasthenia gravis), disease processes causing diminished respiratory drive (e.g., drug overdose, brainstem injury), and respiratory diseases associated with respiratory muscle fatigue (e.g., exacerbations of asthma and chronic obstructive pulmonary disease [COPD]). In acute hypercarbic respiratory failure, $PaCO_2$ is typically >50 mmHg. With acute-on-chronic respiratory failure, as is often seen with COPD exacerbations, considerably higher $PaCO_2$ values may be observed. The degree of respiratory acidosis, the

pt's mental status, and the pt's degree of respiratory distress are better indicators of the need for mechanical ventilation than a specific $PaCO_2$ level in acute-on-chronic respiratory failure. Two other types of respiratory failure are commonly considered: (1) perioperative respiratory failure related to atelectasis, and (2) hypoperfusion of respiratory muscles related to shock.

## MODES OF MECHANICAL VENTILATION

Respiratory failure often requires treatment with mechanical ventilation to decrease the work of breathing and reverse severe hypoxemia and respiratory acidosis. There are two general classes of mechanical ventilation: noninvasive ventilation (NIV) and conventional mechanical ventilation. NIV, administered through a tightly fitting nasal or facial mask, is widely used in acute-on-chronic respiratory failure related to COPD exacerbations. NIV typically involves a preset positive pressure applied during inspiration and a lower pressure applied during expiration; it is associated with fewer complications such as nosocomial pneumonia than conventional mechanical ventilation through an endotracheal tube. However, NIV is contraindicated in cardiopulmonary arrest, severe encephalopathy, severe GI hemorrhage, hemodynamic instability, unstable coronary artery disease, facial surgery or trauma, upper airway obstruction, inability to protect the airway, and inability to clear secretions.

Most pts with acute respiratory failure require conventional mechanical ventilation via a cuffed endotracheal tube. The goal of mechanical ventilation is to optimize oxygenation while avoiding ventilator-induced lung injury. Various modes of conventional mechanical ventilation are commonly used; different modes are characterized by a trigger (what the ventilator senses to initiate a machine-delivered breath), a cycle (what determines the end of inspiration), and limiting factors (operator-specified values for key parameters that are monitored by the ventilator and not allowed to be exceeded). Three of the common modes of mechanical ventilation are described below; additional information is provided in Table 15-1.

- Assist-control ventilation: The trigger for a machine-delivered breath is the pt's inspiratory effort, which causes a synchronized breath to be delivered. If no effort is detected over a prespecified time interval, a timer-triggered machine breath is delivered. Assist-control is volume-cycled with an operator-determined tidal volume. Limiting factors include the minimum respiratory rate, which is specified by the operator; pt efforts can lead to higher respiratory rates. Other limiting factors include the airway pressure limit, which is also set by the operator. Because the pt will receive a full tidal breath with each inspiratory effort, tachypnea due to nonrespiratory factors, such as pain, can lead to respiratory alkalosis. In pts with airflow obstruction (e.g., asthma or COPD), auto-PEEP (positive end-expiratory pressure) can develop.
- Synchronized intermittent mandatory ventilation (SIMV): As with assist-control, SIMV is volume-cycled, with similar limiting factors. As with assist-control, the trigger for a machine-delivered breath can be either pt effort or a specified time interval. However, if the pt's next inspiratory effort occurs before the time interval for another mandatory breath has elapsed, only their spontaneous respiratory effort (without machine support) is delivered. Thus, the number of machine-delivered breaths is limited in SIMV, allowing pts to exercise their inspiratory muscles between assisted breaths.
- Pressure-support ventilation (PSV): PSV is triggered by the pt's inspiratory effort. The cycle of PSV is determined by the inspiratory flow rate. Because a specific respiratory rate is not provided, this mode of ventilation may be combined with SIMV to ensure that an adequate respiratory rate is achieved in pts with respiratory depression.

**TABLE 15-1 CLINICAL CHARACTERISTICS OF COMMONLY USED MODES OF MECHANICAL VENTILATION**

| Ventilator Mode | Independent Variables (Set by User) | Dependent Variables (Monitored by User) | Trigger/Cycle Limit | Advantages | Disadvantages |
|---|---|---|---|---|---|
| ACMV | $FIO_2$<br>Tidal volume<br>Ventilator rate<br>Level of PEEP<br>Inspiratory flow pattern<br>Peak inspiratory flow<br>Pressure limit | Peak airway pressure<br>Minute ventilation<br>Plateau pressure<br>Mean airway pressure<br>I/E ratio | Pt effort<br>Timer<br>Pressure limit | Timer backup<br>Pt-vent synchrony<br>Pt controls minute ventilation | Not useful for weaning<br>Potential for dangerous respiratory alkalosis due to hyperventilation<br>Barotrauma risk |
| SIMV | Same as for ACMV | Same as for ACMV | Same as for ACMV | Timer backup is useful for weaning<br>Comfort from spontaneous breaths | Potential dyssynchrony |
| PSV | $FIO_2$<br>Inspiratory pressure level<br>PEEP pressure limit | Tidal volume<br>Respiratory rate<br>Minute ventilation<br>ABG | Inspiratory flow<br>Pressure limit | Assures synchrony<br>Good for weaning | No timer backup; may result in hypoventilation |
| NIV | Inspiratory and expiratory pressure levels<br>$FIO_2$ | Tidal volume<br>Respiratory rate<br>I/E ratio<br>Minute ventilation<br>ABG | Pressure limit<br>Inspiratory flow | Pt control | Discomfort and bruising from mask<br>Leaks are common<br>Hypoventilation risk |

***Abbreviations:*** ACMV, assist-control mandatory ventilation; I/E, inspiration/expiration; $FIO_2$, inspired $O_2$; NIV, noninvasive ventilation; PEEP, positive end-expiratory pressure; PSV, pressure-support ventilation; SIMV, synchronized intermittent mandatory ventilation.

Other modes of ventilation may be appropriate in specific clinical situations; for example, pressure-control ventilation is helpful to regulate airway pressures in pts with barotrauma or in the postoperative period from thoracic surgery.

### MANAGEMENT OF MECHANICALLY VENTILATED PATIENTS

General care of mechanically ventilated pts is reviewed in Chap. 4, along with weaning from mechanical ventilation. A cuffed endotracheal tube is often used to provide positive pressure ventilation with conditioned gas. A protective ventilation approach is generally recommended, including the following elements: (1) target tidal volume of ~6 mL/kg of ideal body weight; (2) avoid plateau pressures >30 cm $H_2O$; (3) use the lowest fraction of inspired oxygen ($FIO_2$) to maintain arterial oxygen saturation ≥90%; and (4) apply PEEP to maintain alveolar patency while avoiding overdistention. This approach may result in a permissible degree of hypercapnia. After an endotracheal tube has been in place for an extended period of time, tracheostomy should be considered, primarily to improve pt comfort, reduce needs for sedative medications, and provide a more secure airway. No absolute time frame for tracheostomy placement exists, but pts who are likely to require mechanical ventilatory support for >2 weeks should be considered for a tracheostomy.

A variety of complications can result from mechanical ventilation. Barotrauma—overdistention and damage of lung tissue—can cause pneumomediastinum, subcutaneous emphysema, and pneumothorax. Ventilator-related pneumothorax typically requires treatment with tube thoracostomy. Ventilator-associated pneumonia is a major complication in intubated pts; common pathogens include *Pseudomonas aeruginosa* and other gram-negative bacilli, as well as *Staphylococcus aureus*.

For a more detailed discussion, see Celli BR: Mechanical Ventilatory Support, Chap. 323, p. 1740; and Kress JP, Hall JB: Approach to the Patient with Critical Illness, Chap. 321, p. 1729, in HPIM-19.

# 16 Confusion, Stupor, and Coma

## APPROACH TO THE PATIENT: Disorders of Consciousness

Disorders of consciousness are common; these always signify a disorder of the nervous system. Assessment should determine the level of consciousness (drowsy, stuporous, comatose) and/or content of consciousness (confusion, perseveration, hallucinations). *Confusion* is a lack of clarity in thinking with inattentiveness; *delirium* is used to describe an acute confusional state; *stupor*, a state in which vigorous stimuli are needed to elicit a response; *coma*, a condition of unresponsiveness. Pts in such states are usually seriously ill, and etiologic factors must be assessed (Tables 16-1 and 16-2).

**TABLE 16-1 COMMON ETIOLOGIES OF DELIRIUM**

| |
|---|
| Toxins |
| Prescription medications: especially those with anticholinergic properties, narcotics, and benzodiazepines |
| Drugs of abuse: alcohol intoxication and alcohol withdrawal, opiates, ecstasy, LSD, GHB, PCP, ketamine, cocaine, "bath salts," marijuana and its synthetic forms |
| Poisons: inhalants, carbon monoxide, ethylene glycol, pesticides |
| Metabolic conditions |
| Electrolyte disturbances: hypoglycemia, hyperglycemia, hyponatremia, hypernatremia, hypercalcemia, hypocalcemia, hypomagnesemia |
| Hypothermia and hyperthermia |
| Pulmonary failure: hypoxemia and hypercarbia |
| Liver failure/hepatic encephalopathy |
| Renal failure/uremia |
| Cardiac failure |
| Vitamin deficiencies: $B_{12}$, thiamine, folate, niacin |
| Dehydration and malnutrition |
| Anemia |
| Infections |
| Systemic infections: urinary tract infections, pneumonia, skin and soft tissue infections, sepsis |
| CNS infections: meningitis, encephalitis, brain abscess |
| Endocrine conditions |
| Hyperthyroidism, hypothyroidism |
| Hyperparathyroidism |
| Adrenal insufficiency |
| Cerebrovascular disorders |
| Global hypoperfusion states |
| Hypertensive encephalopathy |
| Focal ischemic strokes and hemorrhages (rare): especially nondominant parietal and thalamic lesions |
| Autoimmune disorders |
| CNS vasculitis |
| Cerebral lupus |
| Neurologic paraneoplastic syndromes |
| Seizure-related disorders |
| Nonconvulsive status epilepticus |
| Intermittent seizures with prolonged postictal states |
| Neoplastic disorders |
| Diffuse metastases to the brain |
| Gliomatosis cerebri |
| Carcinomatous meningitis |
| CNS lymphoma |
| Hospitalization |
| Terminal end-of-life delirium |

***Abbreviations:*** GHB, γ-hydroxybutyrate; LSD, lysergic acid diethylamide; PCP, phencyclidine.

**TABLE 16-2 STEPWISE EVALUATION OF A PATIENT WITH DELIRIUM**

| |
|---|
| Initial evaluation |
| History with special attention to medications (including over-the-counter and herbals) |
| General physical examination and neurologic examination |
| Complete blood count |
| Electrolyte panel including calcium, magnesium, phosphorus |
| Liver function tests, including albumin |
| Renal function tests |
| First-tier further evaluation guided by initial evaluation |
| Systemic infection screen |
| Urinalysis and culture |
| Chest radiograph |
| Blood cultures |
| Electrocardiogram |
| Arterial blood gas |
| Serum and/or urine toxicology screen (perform earlier in young persons) |
| Brain imaging with MRI with diffusion and gadolinium (preferred) or CT |
| Suspected CNS infection: lumbar puncture after brain imaging |
| Suspected seizure-related etiology: EEG (if high suspicion, should be performed immediately) |
| Second-tier further evaluation |
| Vitamin levels: $B_{12}$, folate, thiamine |
| Endocrinologic laboratories: TSH and free $T_4$; cortisol |
| Serum ammonia |
| Sedimentation rate |
| Autoimmune serologies: ANA, complement levels; p-ANCA, c-ANCA. consider paraneoplastic serologies |
| Infectious serologies: RPR; fungal and viral serologies if high suspicion; HIV antibody |
| Lumbar puncture (if not already performed) |
| Brain MRI with and without gadolinium (if not already performed) |

***Abbreviations:*** c-ANCA, cytoplasmic antineutrophil cytoplasmic antibody; CNS, central nervous system; p-ANCA, perinuclear antineutrophil cytoplasmic antibody; RPR, rapid plasmin reagin; TSH, thyroid-stimulating hormone.

## DELIRIUM

Delirium is a clinical diagnosis made at the bedside; a careful history and physical examination are necessary, focusing on common etiologies of delirium, especially toxins and metabolic conditions. Observation will usually reveal an altered level of consciousness or a deficit of attention. Attention can be assessed through a simple bedside test of digits forward—pts are asked to repeat successively longer random strings of digits beginning with two digits in a row; a digit span of four digits or less usually indicates an attentional deficit unless hearing or language barriers are present. Delirium is vastly underrecognized, especially in pts presenting with a quiet, hypoactive state and those in the ICU.

A cost-effective approach to the evaluation of delirium allows the history and physical examination to guide tests. No single algorithm will fit all pts due to the large number of potential etiologies, but one step-wise approach is shown in Table 16-2.

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Management begins with treatment of the underlying inciting factor (e.g., pts with systemic infections should be given appropriate antibiotics, and electrolyte disturbances judiciously corrected). Relatively simple methods of supportive care can be quite effective, such as frequent reorientation by staff, preservation of sleep-wake cycles, and attempting to mimic the home environment as much as possible. Chemical restraints exacerbate delirium and should be used only when necessary to protect pt or staff from possible injury; antipsychotics at low dose are usually the treatment of choice.

## COMA (TABLE 16-3)

Because coma demands immediate attention, the physician must employ an organized approach. Almost all instances of coma can be traced to either widespread abnormalities of the bilateral cerebral hemispheres or to reduced activity of the reticular activating system in the brainstem.

### History

History should be obtained from witnesses or family members regarding use of insulin, narcotics, anticoagulants, other prescription drugs, suicidal intent, recent trauma, headache, epilepsy, significant medical problems, and preceding symptoms. History of sudden headache followed by loss of consciousness suggests intracranial hemorrhage; preceding vertigo, nausea, diplopia, ataxia, hemisensory disorder suggest basilar artery involvement; chest pain, palpitations, and faintness suggest a cardiovascular cause.

### Immediate Assessment

Acute respiratory and cardiovascular problems should be attended to prior to the neurologic assessment. Vital signs should be evaluated, and appropriate support initiated. Thiamine, glucose, and naloxone should be administered if the etiology of coma is not immediately apparent. Blood should be drawn for glucose, electrolytes, calcium, and renal (BUN, creatinine) and hepatic (ammonia, transaminases) function; also screen for presence of alcohol and other toxins, and obtain blood cultures if infection is suspected. Arterial blood-gas analysis is helpful in pts with lung disease and acid-base disorders. Fever, especially with petechial rash, suggests meningitis. Examination of CSF is essential in diagnosis of meningitis and encephalitis; lumbar puncture should not be deferred if meningitis is a possibility, but CT scan should be obtained first if a mass lesion is suspected. Empirical antibiotic and glucocorticoid coverage for meningitis should be instituted until CSF results are available. Fever with dry skin suggests heat shock or intoxication with anticholinergics. Hypothermia suggests myxedema, intoxication, sepsis, exposure, or hypoglycemia. Marked hypertension occurs with increased intracranial pressure (ICP) and hypertensive encephalopathy.

### Neurologic Examination

Focus on establishing pt's best level of function and uncovering signs that enable a specific diagnosis. Comatose pt's best motor and sensory function should be assessed by testing responses to noxious stimuli; carefully note any asymmetric responses, which suggest a focal lesion. Multifocal myoclonus indicates that a metabolic disorder is likely; intermittent twitching or subtle eye movements may be the only sign of a seizure.

### Responsiveness

Stimuli of increasing intensity are applied to gauge the degree of unresponsiveness and any asymmetry in sensory or motor function. Motor responses may be purposeful or reflexive. Spontaneous flexion of elbows with leg extension, termed *decorticate posturing*, accompanies severe damage to contralateral hemisphere above midbrain. Internal rotation of the arms with extension of elbows, wrists, and legs, termed

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**TABLE 16-3 DIFFERENTIAL DIAGNOSIS OF COMA**

1. Diseases that cause no focal or lateralizing neurologic signs, usually with normal brainstem functions; CT scan and cellular content of the CSF are normal.
   a. Intoxications: alcohol, sedative drugs, opiates, etc.
   b. Metabolic disturbances: anoxia, hyponatremia, hypernatremia, hypercalcemia, diabetic acidosis, nonketotic hyperosmolar hyperglycemia, hypoglycemia, uremia, hepatic coma, hypercarbia, Addisonian crisis, hypo- and hyperthyroid states, profound nutritional deficiency
   c. Severe systemic infections: pneumonia, septicemia, typhoid fever, malaria, Waterhouse-Friderichsen syndrome
   d. Shock from any cause
   e. Postseizure states, status epilepticus, nonconvulsive status epilepticus
   f. Hypertensive encephalopathy, eclampsia
   g. Severe hyperthermia, hypothermia
   h. Concussion
   i. Acute hydrocephalus
2. Diseases that cause meningeal irritation with or without fever, and with an excess of WBCs or RBCs in the CSF, usually without focal or lateralizing cerebral or brainstem signs; CT or MRI shows no mass lesion.
   a. Subarachnoid hemorrhage from ruptured aneurysm, arteriovenous malformation, trauma
   b. Acute bacterial meningitis
   c. Viral encephalitis
   d. Miscellaneous: fat embolism, cholesterol embolism, carcinomatous and lymphomatous meningitis, etc.
3. Diseases that cause focal brainstem or lateralizing cerebral signs, with or without changes in the CSF; CT and MRI are abnormal
   a. Hemispheral hemorrhage (basal ganglionic, thalamic) or infarction (large middle cerebral artery territory) with secondary brainstem compression
   b. Brainstem infarction due to basilar artery thrombosis or embolism
   c. Brain abscess, subdural empyema
   d. Epidural and subdural hemorrhage, brain contusion
   e. Brain tumor with surrounding edema
   f. Cerebellar and pontine hemorrhage and infarction
   g. Widespread traumatic brain injury
   h. Metabolic coma (see above) with preexisting focal damage
   i. Miscellaneous: Cortical vein thrombosis, herpes simplex encephalitis, multiple cerebral emboli due to bacterial endocarditis, acute hemorrhagic leukoencephalitis, acute disseminated (postinfectious) encephalomyelitis, thrombotic thrombocytopenic purpura, cerebral vasculitis, neurologic paraneoplastic syndromes, gliomatosis cerebri, pituitary apoplexy, intravascular lymphoma, etc.

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*decerebrate posturing*, suggests damage to midbrain or caudal diencephalon. These postural reflexes occur in profound encephalopathic states.

## Pupillary Signs

In comatose pts, equal, round, reactive pupils exclude midbrain damage as cause and suggest a metabolic abnormality. Pinpoint pupils occur in narcotic overdose, pontine damage, hydrocephalus, or thalamic hemorrhage; the response to naloxone and presence of reflex eye movements (usually intact with drug overdose) can distinguish these. A unilateral, enlarged, often oval, poorly reactive pupil is caused by midbrain lesions or compression of third cranial nerve, as occurs in transtentorial herniation. Bilaterally dilated, unreactive pupils indicate severe bilateral midbrain damage, anticholinergic overdose, or ocular trauma.

## Ocular Movements

Examine spontaneous and reflex eye movements. Intermittent horizontal divergence is common in drowsiness. Slow, to-and-fro horizontal movements suggest bihemispheric dysfunction. Conjugate eye deviation to one side indicates damage to the pons on the opposite side or a lesion in the frontal lobe on the same side ("*The eyes look toward a hemispheral lesion and away from a brainstem lesion*"). An adducted eye at rest with impaired ability to turn eye laterally indicates an abducens (VI) nerve palsy, common in raised ICP or pontine damage. The eye with a dilated, unreactive pupil is often abducted at rest and cannot adduct fully due to third nerve dysfunction, as occurs with transtentorial herniation. Vertical separation of ocular axes (skew deviation) occurs in pontine or cerebellar lesions. Doll's head maneuver (oculocephalic reflex) and cold caloric–induced eye movements allow diagnosis of gaze or cranial nerve palsies in pts who do not move their eyes purposefully. Doll's head maneuver is tested by observing eye movements in response to lateral rotation of head (this should not be performed in pts with possible neck injury); full conjugate movement of eyes occurs in bihemispheric dysfunction. In comatose pts with intact brainstem function, raising head to 60° above the horizontal and irrigating external auditory canal with cool water causes tonic deviation of gaze to side of irrigated ear ("cold calorics"). In conscious pts, it causes nystagmus, vertigo, and emesis.

## Respiratory Patterns

Cheyne-Stokes (periodic) breathing occurs in bihemispheric dysfunction and is common in metabolic encephalopathies. Respiratory patterns composed of gasps or other irregular breathing patterns are indicative of lower brainstem damage; such pts usually require intubation and ventilatory assistance.

## Radiologic Examination

Lesions causing raised ICP commonly cause impaired consciousness. CT or MRI scan of the brain is often abnormal in coma but may not be diagnostic; appropriate therapy should not be postponed while awaiting a CT or MRI scan. Pts with disordered consciousness due to high ICP can deteriorate rapidly; emergent CT study is necessary to confirm the presence of mass effect and guide surgical decompression. CT scan is normal in some pts with subarachnoid hemorrhage; the diagnosis then rests on clinical history combined with RBCs or xanthochromia in spinal fluid. CT, MR, or conventional angiography may be necessary to establish basilar artery thrombosis as cause of coma in pts with brainstem signs. The EEG is useful in metabolic or drug-induced states but is rarely diagnostic except in coma due to seizures or herpes simplex encephalitis.

# BRAIN DEATH

This results from total cessation of cerebral function while somatic function is maintained by artificial means and the heart continues to pump. It is legally and ethically equivalent to cardiorespiratory death. The pt is unresponsive to all forms of

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stimulation (widespread cortical destruction), brainstem reflexes are absent (global brainstem damage), and there is complete apnea (destruction of the medulla). Demonstration of apnea requires that the $PCO_2$ be high enough to stimulate respiration, while $PO_2$ and bp are maintained. EEG is isoelectric at high gain. The absence of deep tendon reflexes is not required because the spinal cord may remain functional. Special care must be taken to exclude drug toxicity and hypothermia prior to making a diagnosis of brain death. Diagnosis should be made only if the state persists for some agreed-upon period, usually 6–24 h.

For a more detailed discussion, see Josephson SA, Miller BL: Confusion and Delirium, Chap. 34, p. 166, and Ropper AH: Coma, Chap. 328, p. 1771, in HPIM-19.

# 17 Stroke

Sudden onset of a neurologic deficit from a vascular mechanism: ~85% are ischemic; ~15% are primary hemorrhages (subarachnoid [Chap. 18] and intraparenchymal). An ischemic deficit that resolves rapidly without radiologic evidence of an infarction is termed a *transient ischemic attack* (TIA); 24 h is a commonly used boundary between TIA and stroke, although most TIAs last between 5 and 15 min. Stroke is a leading cause of neurologic disability in adults; 200,000 deaths annually in the United States. Much can be done to limit morbidity and mortality through prevention and acute intervention.

## PATHOPHYSIOLOGY

Ischemic stroke can be due to embolic occlusion of large cerebral vessels; source of emboli may be heart, aortic arch, or other arteries such as the internal carotids. Small, deep ischemic lesions are most often related to intrinsic small-vessel disease (lacunar strokes). Low-flow strokes are occasionally seen with severe proximal stenosis and inadequate collaterals challenged by systemic hypotensive episodes. Hemorrhages most frequently result from rupture of aneurysms or small vessels within brain tissue. Variability in stroke recovery is influenced by collateral vessels, blood pressure, and the specific site and mechanism of vessel occlusion; if blood flow is restored prior to significant cell death, the pt may experience only transient symptoms, i.e., a TIA.

## CLINICAL FEATURES

### Ischemic Stroke

Abrupt and dramatic onset of focal neurologic symptoms is typical. Pts may not seek assistance on their own because they are rarely in pain and may lose appreciation that something is wrong (*anosognosia*). Symptoms reflect the vascular territory involved (Table 17-1). Transient monocular blindness (amaurosis fugax) is a particular form of TIA due to retinal ischemia; pts describe a shade descending over the visual field.

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**TABLE 17-1 ANATOMIC LOCALIZATION IN STROKE**

| Signs and Symptoms |
|---|
| **Cerebral Hemisphere, Lateral Aspect (Middle Cerebral A.)** |
| Hemiparesis |
| Hemisensory deficit |
| Motor aphasia (Broca's)—hesitant speech with word-finding difficulty and preserved comprehension |
| Sensory aphasia (Wernicke's)—anomia, poor comprehension, jargon speech |
| Unilateral neglect, apraxias |
| Homonymous hemianopia or quadrantanopia |
| Gaze preference with eyes deviated toward side of lesion |
| **Cerebral Hemisphere, Medial Aspect (Anterior Cerebral A.)** |
| Paralysis of foot and leg with or without paresis of arm |
| Cortical sensory loss over leg |
| Grasp and sucking reflexes |
| Urinary incontinence |
| Gait apraxia |
| **Cerebral Hemisphere, Posterior Aspect (Posterior Cerebral A.)** |
| Homonymous hemianopia |
| Cortical blindness |
| Memory deficit |
| Dense sensory loss, spontaneous pain, dysesthesias, choreoathetosis |
| **Brainstem, Midbrain (Posterior Cerebral A.)** |
| Third nerve palsy and contralateral hemiplegia |
| Paralysis/paresis of vertical eye movement |
| Convergence nystagmus, disorientation |
| **Brainstem, Pontomedullary Junction (Basilar A.)** |
| Facial paralysis |
| Paresis of abduction of eye |
| Paresis of conjugate gaze |
| Hemifacial sensory deficit |
| Horner's syndrome |
| Diminished pain and thermal sense over half body (with or without face) |
| Ataxia |
| **Brainstem, Lateral Medulla (Vertebral A.)** |
| Vertigo, nystagmus |
| Horner's syndrome (miosis, ptosis, decreased sweating) |
| Ataxia, falling toward side of lesion |
| Impaired pain and thermal sense over half body with or without face |

## Lacunar Syndromes (Small-Vessel Strokes)

Most common are:

- Pure motor hemiparesis of face, arm, and leg (internal capsule or pons)
- Pure sensory stroke (ventral thalamus)
- Ataxic hemiparesis (pons or internal capsule)
- Dysarthria—clumsy hand (pons or genu of internal capsule)

## Intracranial Hemorrhage

Vomiting and drowsiness occur in some cases with increased intracranial pressure (ICP), and headache is common. Signs and symptoms are often not confined to a

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**TABLE 17-2 CAUSES OF INTRACRANIAL HEMORRHAGE**

| Cause | Location | Comments |
|---|---|---|
| Head trauma | Intraparenchymal: frontal lobes, anterior temporal lobes; subarachnoid; extra-axial (subdural, epidural) | Coup and contrecoup injury during brain deceleration |
| Hypertensive hemorrhage | Putamen, globus pallidus, thalamus, cerebellar hemisphere, pons | Chronic hypertension produces hemorrhage from small (~30–100 μm) vessels in these regions |
| Transformation of prior ischemic infarction | Basal ganglion, subcortical regions, lobar | Occurs in 1–6% of ischemic strokes with predilection for large hemispheric infarctions |
| Metastatic brain tumor | Lobar | Lung, choriocarcinoma, melanoma, renal cell carcinoma, thyroid, atrial myxoma |
| Coagulopathy | Any | Risk for ongoing hematoma expansion |
| Drug | Any, lobar, subarachnoid | Cocaine, amphetamine |
| Arteriovenous malformation | Lobar, intraventricular, subarachnoid | Risk is ~2–3% per year for bleeding if previously unruptured |
| Aneurysm | Subarachnoid, intraparenchymal, rarely subdural | Mycotic and nonmycotic forms of aneurysms |
| Amyloid angiopathy | Lobar | Degenerative disease of intracranial vessels; associated with dementia, rare in patients <60 years |
| Cavernous angioma | Intraparenchymal | Multiple cavernous angiomas linked to mutations in *KRIT1*, *CCM2*, and *PDCD10* genes |
| Dural arteriovenous fistula | Lobar, subarachnoid | Produces bleeding by venous hypertension |
| Capillary telangiectasias | Usually brainstem | Rare cause of hemorrhage |

single vascular territory. Etiologies are diverse but hypertension related is the most common (Table 17-2). Hypertensive hemorrhages typically occur in the following locations:

- Putamen: contralateral hemiparesis often with homonymous hemianopia
- Thalamus: hemiparesis with prominent sensory deficit
- Pons: quadriplegia, "pinpoint" pupils, impaired horizontal eye movements
- Cerebellum: headache, vomiting, gait ataxia

A neurologic deficit that evolves gradually over 30–90 min strongly suggests intracerebral bleeding.

## TREATMENT STROKE

Principles of management are outlined in Fig. 17-1. Stroke needs to be distinguished from potential mimics, including seizure, migraine, tumor, and metabolic derangements.

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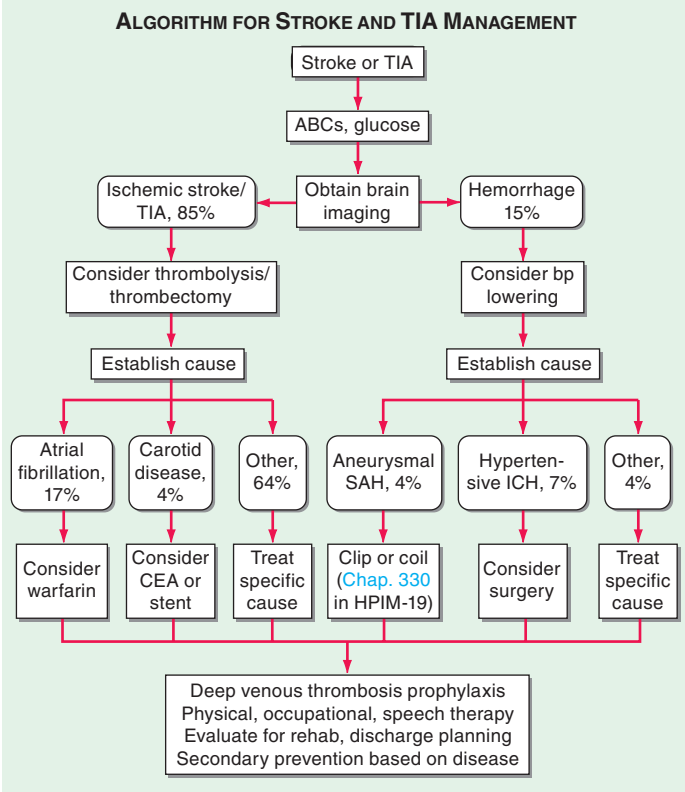


**FIGURE 17-1** Medical management of stroke and TIA. *Rounded boxes* are diagnoses; *rectangles* are interventions. Numbers are percentages of stroke overall. ABCs, airway, breathing, circulation; bp, blood pressure; CEA, carotid endarterectomy; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; TIA, transient ischemic attack.

- Imaging. After initial stabilization, an emergency noncontrast head CT scan is necessary to differentiate ischemic from hemorrhagic stroke. With large ischemic strokes, CT abnormalities are usually evident within the first few hours, but small infarcts can be difficult to visualize by CT. CT or MR angiography (CTA/MRA) may help reveal vascular occlusions. Diffusion-weighted MRI has a high sensitivity for identifying ischemic stroke even minutes after onset.

**ACUTE ISCHEMIC STROKE** Treatments designed to reverse or lessen tissue infarction include: (1) medical support, (2) intravenous thrombolysis, (3) endovascular revascularization, (4) antiplatelet agents, (5) anticoagulation, and (6) neuroprotection.

**MEDICAL SUPPORT** Optimize perfusion in ischemic penumbra surrounding the infarct.

- Blood pressure should never be lowered precipitously (exacerbates the underlying ischemia), and only in the most extreme situations should gradual lowering

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be undertaken (e.g., malignant hypertension with bp > 220/120 mmHg or, if thrombolysis planned, bp > 185/110 mmHg).

- Intravascular volume should be maintained with isotonic fluids because volume restriction is rarely helpful. Osmotic therapy with mannitol may be necessary to control edema in large infarcts, but isotonic volume must be replaced to avoid hypovolemia.
- In cerebellar infarction (or hemorrhage), rapid deterioration can occur from brainstem compression and hydrocephalus, requiring neurosurgical intervention.

## INTRAVENOUS THROMBOLYSIS

- Ischemic deficits of <3 h duration, with no hemorrhage by CT criteria, may benefit from thrombolytic therapy with IV recombinant tissue plasminogen activator (Table 17-3).
- Based on trial data, IV rtPA is used in many centers for deficits of 3–4.5 h duration, but is not yet approved for this window in the United States.

**TABLE 17-3 ADMINISTRATION OF INTRAVENOUS RTPA FOR AIS[a]**

| Indication | Contraindication |
|---|---|
| Clinical diagnosis of stroke | Sustained bp >185/110 mmHg despite treatment |
| Onset of symptoms to time of drug administration ≤4.5 h[b] | Platelets <100,000; Hct <25%; glucose <50 or >400 mg/dL |
| CT scan showing no hemorrhage or edema of >1/3 of the MCA territory | Use of heparin within 48 h and prolonged PTT, or elevated INR |
| Age 18 ≥ years | Rapidly improving symptoms |
| Consent by patient or surrogate | Prior stroke or head injury within 3 months; prior intracranial hemorrhage |
| | Major surgery in preceding 14 days |
| | Minor stroke symptoms |
| | Gastrointestinal bleeding in preceding 21 days |
| | Recent myocardial infarction |
| | Coma or stupor |
| **Administration of rtPA** | |
| IV access with two peripheral IV lines (avoid arterial or central line placement). | |
| Review eligibility for rtPA. | |
| Administer 0.9 mg/kg IV (maximum 90 mg) IV as 10% of total dose by bolus, followed by remainder of total dose over 1 h. | |
| Frequent cuff blood pressure monitoring. | |
| No other antithrombotic treatment for 24 h. | |
| For decline in neurologic status or uncontrolled blood pressure, stop infusion, give cryoprecipitate, and reimage brain emergently. | |
| Avoid urethral catheterization for ≥2 h. | |

[a]See Activase (tissue plasminogen activator) package insert for complete list of contraindications and dosing.
[b]Depending on the country, IV rtPA may be approved for up to 4.5 h with additional restrictions.
***Abbreviations:*** AIS, acute ischemic stroke; INR, international normalized ratio; MCA, middle cerebral artery; rtPA, recombinant tissue plasminogen activator; PTT, partial thromboplastin time.

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## ENDOVASCULAR REVASCULARIZATION

- Ischemic stroke from large-vessel intracranial occlusion results in high rates of morbidity and mortality; pts with such occlusions likely benefit from embolectomy (<6 h duration) administered at the time of an urgent cerebral angiogram at specialized centers. CT angiography is becoming more commonly used as part of initial imaging protocols to identify these patients rapidly.

## ANTIPLATELET AGENTS

- Aspirin (up to 325 mg/d) is safe and has a small but definite benefit in acute ischemic stroke.

## ANTICOAGULATION

- Trials do not support the use of heparin or other anticoagulants acutely for pts with acute stroke.

## NEUROPROTECTION

- Hypothermia is effective in coma following cardiac arrest but has not been shown to benefit stroke patients. Other neuroprotective agents have shown no efficacy in human trials despite promising animal data.

## STROKE CENTERS AND REHABILITATION

- Pt care in comprehensive stroke units followed by rehabilitation services improves neurologic outcomes and reduces mortality.

## ACUTE INTRACEREBRAL HEMORRHAGE

- Noncontrast head CT will confirm diagnosis.
- Rapidly identify and correct any coagulopathy.
- 35–45% of pts die in the first month; prognosis is determined by volume and location of hematoma.
- Stuporous or comatose pts generally are treated presumptively for elevated ICP. Treatment for edema and mass effect with osmotic agents may be necessary; glucocorticoids not helpful.
- Neurosurgical consultation should be sought for possible urgent evacuation of cerebellar hematoma; in other locations, data do not support surgical intervention.

## EVALUATION: DETERMINING THE CAUSE OF STROKE

Although initial management of acute ischemic stroke or TIA does not depend on the etiology, establishing a cause is essential to reduce risk of recurrence (Table 17-4); particular attention should be on atrial fibrillation and carotid atherosclerosis because these etiologies have proven secondary prevention strategies. Nearly 30% of strokes remain unexplained despite extensive evaluation.

Clinical examination should be focused on the peripheral and cervical vascular system. Routine studies include CXR and ECG, urinalysis, CBC/platelets, electrolytes, glucose, ESR, lipid profile, PT, and PTT. If a hypercoagulable state is suspected, further studies of coagulation are indicated.

Imaging evaluation may include brain MRI (compared with CT, increased sensitivity for small infarcts of cortex and brainstem); MR or CT angiography (evaluate patency of intracranial vessels and extracranial carotid and vertebral vessels); noninvasive carotid ultrasound; or cerebral angiography ("gold standard" for evaluation of intracranial and extracranial vascular disease). For suspected cardiogenic source, cardiac echocardiogram with attention to right-to-left shunts, and inpatient cardiac telemetry and long-term cardiac event monitoring indicated.

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**TABLE 17-4 CAUSES OF ISCHEMIC STROKE**

| Common Causes | Uncommon Causes |
|---|---|
| Thrombosis | Hypercoagulable disorders |
| Lacunar stroke (small vessel) | Protein C deficiency[a] |
| Large-vessel thrombosis | Protein S deficiency[a] |
| Dehydration | Antithrombin III deficiency[a] |
| Embolic occlusion | Antiphospholipid syndrome |
| Artery-to-artery | Factor V Leiden mutation[a] |
| Carotid bifurcation | Prothrombin G20210 mutation[a] |
| Aortic arch | Systemic malignancy |
| Arterial dissection | Sickle cell anemia |
| Cardioembolic | β Thalassemia |
| Atrial fibrillation | Polycythemia vera |
| Mural thrombus | Systemic lupus erythematosus |
| Myocardial infarction | Homocysteinemia |
| Dilated cardiomyopathy | Thrombotic thrombocytopenic purpura |
| Valvular lesions | Disseminated intravascular coagulation |
| Mitral stenosis | Dysproteinemias[a] |
| Mechanical valve | Nephrotic syndrome[a] |
| Bacterial endocarditis | Inflammatory bowel disease[a] |
| Paradoxical embolus | Oral contraceptives |
| Atrial septal defect | Venous sinus thrombosis[b] |
| Patent foramen ovale | Fibromuscular dysplasia |
| Atrial septal aneurysm | Vasculitis |
| Spontaneous echo contrast | Systemic vasculitis (PAN, granulomatosis with polyangiitis [Wegener's], Takayasu's, giant cell arteritis) |
| Stimulant drugs: cocaine, amphetamine | Primary CNS vasculitis |
| | Meningitis (syphilis, tuberculosis, fungal, bacterial, zoster) |
| | Noninflammatory vasculopathy |
| | Reversible vasoconstriction syndrome |
| | Fabry's disease |
| | Angiocentric lymphoma |
| | Cardiogenic |
| | Mitral valve calcification |
| | Atrial myxoma |
| | Intracardiac tumor |
| | Marantic endocarditis |
| | Libman-Sacks endocarditis |
| | Subarachnoid hemorrhage vasospasm |
| | Moyamoya disease |
| | Eclampsia |

[a]Chiefly cause venous sinus thrombosis.
[b]May be associated with any hypercoagulable disorder.
***Abbreviations:*** PAN, polyarteritis nodosa.

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## PRIMARY AND SECONDARY PREVENTION OF STROKE

### Risk Factors

Atherosclerosis is a systemic disease affecting arteries throughout the body. Multiple factors including hypertension, diabetes, hyperlipidemia, and family history influence stroke and TIA risk (Table 17-5). Cardioembolic risk factors include atrial fibrillation/flutter, MI, valvular heart disease, and cardiomyopathy. Hypertension and diabetes are also specific risk factors for lacunar stroke and intraparenchymal hemorrhage. Smoking is a potent risk factor for all vascular mechanisms of stroke. *Identification of modifiable risk factors and prophylactic interventions to lower risk is probably the best approach to stroke overall.*

### Antiplatelet Agents

Platelet antiaggregation agents can prevent atherothrombotic events, including TIA and stroke, by inhibiting formation of intraarterial platelet aggregates. Aspirin (50–325 mg/d) inhibits thromboxane $A_2$, a platelet aggregating and vasoconstricting prostaglandin. Aspirin, clopidogrel (blocks the platelet adenosine diphosphate [ADP] receptor), and the combination of aspirin plus extended-release dipyridamole (inhibits platelet uptake of adenosine) are the antiplatelet agents most commonly used. In general, antiplatelet agents reduce new stroke events by 25–30%. Every pt who has experienced an atherothrombotic stroke or TIA and has no contraindication

**TABLE 17-5 RECOMMENDATIONS ON CHRONIC USE OF ANTITHROMBOTICS FOR VARIOUS CARDIAC CONDITIONS**

| Condition | Recommendation |
|---|---|
| Nonvalvular atrial fibrillation | Calculate CHADS2[a] score |
| • CHADS2 score 0 | Aspirin or no antithrombotic |
| • CHADS2 score 1 | Aspirin or OAC |
| • CHADS2 score >1 | OAC |
| Rheumatic mitral valve disease | |
| • With atrial fibrillation, previous embolization, or atrial appendage thrombus, or left atrial diameter >55 mm | OAC |
| • Embolization or appendage clot despite OAC | OAC plus aspirin |
| Mitral valve prolapse | |
| • Asymptomatic | No therapy |
| • With otherwise cryptogenic stroke or TIA | Aspirin |
| • Atrial fibrillation | OAC |
| Mitral annular calcification | |
| • Without atrial fibrillation but systemic embolization, or otherwise cryptogenic stroke or TIA | Aspirin |
| • Recurrent embolization despite aspirin | OAC |
| • With atrial fibrillation | OAC |
| Aortic valve calcification | |
| • Asymptomatic | No therapy |
| • Otherwise cryptogenic stroke or TIA | Aspirin |
| Aortic arch mobile atheroma | |
| • Otherwise cryptogenic stroke or TIA | Aspirin or OAC |
| Patent foramen ovale | |
| • Otherwise cryptogenic ischemic stroke or TIA | Aspirin |
| • Indication for OAC (deep venous thrombosis or hypercoagulable state) | OAC |

(*Continued*)

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**TABLE 17-5 RECOMMENDATIONS ON CHRONIC USE OF ANTITHROMBOTICS FOR VARIOUS CARDIAC CONDITIONS (*CONTINUED*)**

| Condition | Recommendation |
|---|---|
| Mechanical heart value | |
| • Aortic position, bileaflet or Medtronic Hall tilting disk with normal left atrial size and sinus rhythm | VKA INR 2.5, range 2–3 |
| • Mitral position tilting disk or bileaflet valve | VKA INR 3.0, range 2.5–3.5 |
| • Mitral or aortic position, anterior-apical myocardial infarct, or left atrial enlargement | VKA INR 3.0, range 2.5–3.5 |
| • Mitral or aortic position, with atrial fibrillation, or hypercoagulable state, or low ejection fraction, or atherosclerotic vascular disease | Aspirin plus VKA INR 3.0, range 2.5–3.5 |
| • Systemic embolization despite target INR | Add aspirin and/or increase INR: prior target was 2.5 increase to 3.0, range 2.5–3.5; prior target was 3.0 increase to 3.5, range 3–4 |
| Bioprosthetic valve | |
| • No other indication for VKA therapy | Aspirin |
| Infective endocarditis | Avoid antithrombotic agents |
| Nonbacterial thrombotic endocarditis | |
| • With systemic embolization | Full-dose unfractionated heparin or SC LMWH |

[a]CHADS2 score calculated as follows: 1 point for age >75 years, 1 point for hypertension, 1 point for congestive heart failure, 1 point for diabetes, and 2 points for stroke or TIA; sum of points is the total CHADS2 score.
***Note:*** Dose of aspirin is 50–325 mg/d; target INR for OAC is between 2 and 3 unless otherwise specified.
***Abbreviations:*** INR, international normalized ratio; LMWH, low-molecular-weight heparin; OAC, oral anticoagulant (VKA, thrombin inhibitor, oral factor Xa inhibitors); TIA, transient ischemic attack; VKA, vitamin K antagonist.
***Sources:*** Modified from DE Singer et al: *Chest* 133:546S, 2008; DN Salem et al: *Chest* 133:593S, 2008.

should take an antiplatelet agent regularly because the average annual risk of another stroke is 8–10%. The choice of aspirin, clopidogrel, or dipyridamole plus aspirin must balance the fact that the latter are marginally more effective than aspirin but the cost is higher.

## Embolic Stroke

In pts with atrial fibrillation and stroke, anticoagulants are generally the treatment of choice.

## Anticoagulation Therapy for Noncardiogenic Stroke

Data do not support the use of long-term warfarin for preventing atherothrombotic stroke for either intracranial or extracranial cerebrovascular disease.

## Carotid Revascularization

Carotid endarterectomy benefits many pts with *symptomatic* severe (>70%) *carotid stenosis*; the relative risk reduction is ~65%. However, if the perioperative stroke

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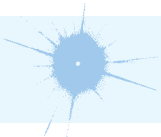
rate is >6% for any surgeon, the benefit is questionable. Endovascular stenting is an emerging option; there remains controversy as to who should receive a stent or undergo endarterectomy. Surgical results in pts with *asymptomatic carotid stenosis* are less robust, and medical therapy for reduction of atherosclerosis risk factors plus antiplatelet medications is generally recommended in this group.



For a more detailed discussion, see Smith WS, Johnston SC, Hemphill JC III: Cerebrovascular Diseases, Chap. 446, p. 2559, in HPIM-19.

# 18 Subarachnoid Hemorrhage

Excluding head trauma, the most common cause of subarachnoid hemorrhage (SAH) is rupture of an intracranial (saccular) aneurysm; other etiologies include bleeding from a vascular malformation (arteriovenous malformation or dural arteriovenous fistula) and extension into the subarachnoid space from a primary intracerebral hemorrhage. Approximately 2% of the population harbor aneurysms, and 25,000–30,000 cases of aneurysmal rupture producing SAH occur each year in the United States; rupture risk for aneurysms <10 mm in size is 0.1% per year; for unruptured aneurysms, the surgical morbidity rate far exceeds the percentage.

## CLINICAL PRESENTATION

Sudden, severe headache, often with transient loss of consciousness at onset; vomiting is common. Bleeding may injure adjacent brain tissue and produce focal neurologic deficits. A progressive third nerve palsy, usually involving the pupil, along with headache, suggests posterior communicating artery aneurysm. In addition to dramatic presentations, aneurysms can undergo small ruptures with leaks of blood into the subarachnoid space (sentinel bleeds). The initial clinical manifestations of SAH can be graded using established scales (Table 18-1); prognosis for good outcome falls as the grade increases.

## INITIAL EVALUATION

- Noncontrast CT is initial study of choice and usually demonstrates hemorrhage if obtained within 72 h. LP is required for diagnosis of suspected SAH if CT is nondiagnostic; xanthochromia of the spinal fluid is seen within 6–12 h after rupture and lasts for 1–4 weeks.
- Cerebral angiography is necessary to localize and define the anatomic details of the aneurysm and to determine if other unruptured aneurysms exist; angiography should be performed as soon as possible after diagnosis of SAH.
- ECG may reveal ST-segment and T-wave changes similar to cardiac ischemia; caused by circulating catecholamines and excessive discharge of sympathetic neurons. A reversible cardiomyopathy producing shock or congestive heart failure may result.
- Studies of coagulation and platelet count should be obtained, with rapid correction indicated if SAH is documented.

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**TABLE 18-1 GRADING SCALES FOR SUBARACHNOID HEMORRHAGE**

| Grade | Hunt-Hess Scale | WFNS Scale |
|---|---|---|
| 1 | Mild headache, normal mental status, no cranial nerve or motor findings | GCS[a] score 15, no motor deficits |
| 2 | Severe headache, normal mental status, may have cranial nerve deficit | GCS score 13–14, no motor deficits |
| 3 | Somnolent, confused, may have cranial nerve or mild motor deficit | GCS score 13–14, with motor deficits |
| 4 | Stupor, moderate to severe motor deficit, may have intermittent reflex posturing | GCS score 7–12, with or without motor deficits |
| 5 | Coma, reflex posturing or flaccid | GCS score 3–6, with or without motor deficits |

[a]Glasgow Coma Scale; see Table 19-2.
***Abbreviation:*** WFNS, World Federation of Neurosurgical Societies.

## TREATMENT SUBARACHNOID HEMORRHAGE

### ANEURYSM REPAIR

- Early aneurysm repair prevents rerupture.
- The International Subarachnoid Aneurysm Trial (ISAT) demonstrated improved outcomes with endovascular therapy compared to surgery; however, some aneurysms have morphology not amenable to endovascular treatment, and therefore surgery is still an important treatment option for some pts.

### MEDICAL MANAGEMENT

- Closely follow serum electrolytes and osmolality; hyponatremia ("cerebral salt wasting") frequently develops several days after SAH, and supplemental oral salt plus IV normal saline or hypertonic saline may be needed to overcome renal losses.
- Anticonvulsants are sometimes begun until the aneurysm is treated, although most experts reserve this therapy only for pts in whom a seizure has occurred.
- Blood pressure should be carefully controlled, while preserving cerebral blood flow, in order to decrease the risk of rerupture until the aneurysm is repaired.
- All pts should have pneumatic compression stockings applied to prevent pulmonary embolism; unfractionated heparin administered subcutaneously for deep-vein thrombosis prophylaxis can be initiated immediately following endovascular treatment and within days following craniotomy and surgical clipping.

### HYDROCEPHALUS

- Severe hydrocephalus may require urgent placement of a ventricular catheter for external CSF drainage; some pts will require permanent shunt placement.
- Deterioration of a SAH pt in the first hours to days should prompt repeat CT scanning to evaluate ventricular size.

### VASOSPASM

- The leading cause of mortality and morbidity following initial rupture; may appear 4–14 days after the initial hemorrhage, leading to focal ischemia and stroke.

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- Treatment with the calcium channel antagonist nimodipine (60 mg PO q4h) improves outcomes, perhaps by preventing ischemic injury rather than reducing risk of vasospasm.
- Cerebral perfusion can be improved in symptomatic vasospasm by increasing mean arterial pressure with vasopressor agents such as phenylephrine or norepinephrine, and intravascular volume can be expanded with crystalloid, augmenting cardiac output and reducing blood viscosity by reducing the hematocrit; this so-called "triple-H" (hypertension, hemodilution, and hypervolemic) therapy is widely used.
- If symptomatic vasospasm persists despite optimal medical therapy, intraarterial vasodilators and angioplasty of the cerebral vessels can be effective.

For a more detailed discussion, see Hemphill JC III, Smith WS, and Gress DR: Neurologic Critical Care, Including Hypoxic-Ischemic Encephalopathy and Subarachnoid Hemorrhage. Chap. 330, p. 1777, in HPIM-19.

# 19 Increased Intracranial Pressure and Head Trauma

## INCREASED INTRACRANIAL PRESSURE

A limited volume of extra tissue, blood, CSF, or edema can be added to the intracranial contents without raising the intracranial pressure (ICP). Clinical deterioration or death may follow increases in ICP that shift intracranial contents, distort vital brainstem centers, or compromise cerebral perfusion. Cerebral perfusion pressure (CPP), defined as the mean arterial pressure (MAP) minus the ICP, is the driving force for circulation across capillary beds of the brain; decreased CPP is a fundamental mechanism of secondary ischemic brain injury and constitutes an emergency that requires immediate attention. In general, ICP should be maintained at <20 mmHg and CPP should be maintained at ≥60 mmHg.

### CLINICAL FEATURES

Elevated ICP may occur in a wide range of disorders including head trauma, intracerebral hemorrhage, subarachnoid hemorrhage (SAH) with hydrocephalus, and fulminant hepatic failure.

Symptoms of high ICP include drowsiness, headache (especially a constant ache that is worse upon awakening), nausea, emesis, diplopia, and blurred vision. Papilledema and sixth nerve palsies are common. If not controlled, cerebral hypoperfusion, pupillary dilation, coma, focal neurologic deficits, posturing, abnormal respirations, systemic hypertension, and bradycardia may result.

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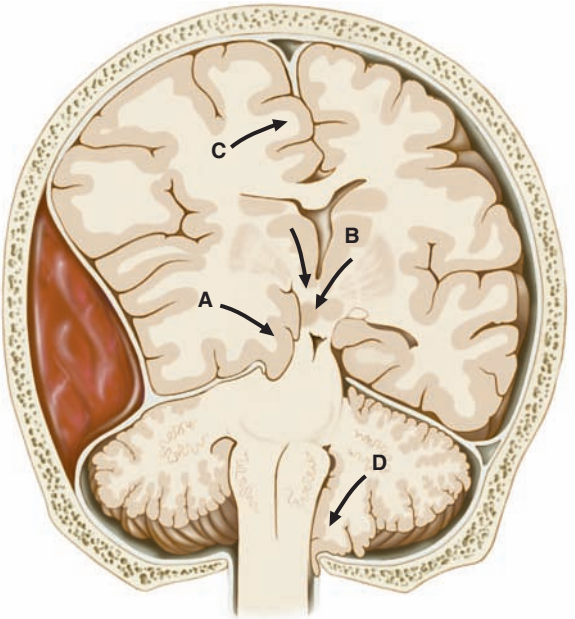


**FIGURE 19-1** Types of cerebral herniation. **A.** uncal; **B.** central; **C.** transfalcial; **D.** foraminal.

Masses that cause raised ICP also distort midbrain and diencephalic anatomy, leading to stupor and coma. Brain tissue is pushed away from the mass against fixed intracranial structures and into spaces not normally occupied. Posterior fossa masses, which may initially cause ataxia, stiff neck, and nausea, are especially dangerous because they can both compress vital brainstem structures and cause obstructive hydrocephalus.

Herniation syndromes (Fig. 19-1) include:

- *Uncal:* Medial temporal lobe displaced through the tentorium, compressing the third cranial nerve and pushing the cerebral peduncle of the midbrain against the tentorium, leading to ipsilateral pupillary dilation, contralateral hemiparesis, and posterior cerebral artery compression.
- *Central:* Downward displacement of the thalamus through the tentorium; miotic pupils and drowsiness are early signs.
- *Transfalcial:* Cingulate gyrus displaced under the midline falx, leading to anterior cerebral artery compression.
- *Foraminal:* Cerebellar tonsils displaced into the foramen magnum, causing medullary compression and respiratory arrest.

## TREATMENT INCREASED INTRACRANIAL PRESSURE

- A number of different interventions may lower ICP, and ideally the selection of treatment will be based on the underlying mechanism responsible for the elevated ICP (Table 19-1).
- With hydrocephalus, the principal cause of elevated ICP is impaired CSF drainage; in this setting, ventricular drainage of CSF may be sufficient.

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**TABLE 19-1 STEPWISE APPROACH TO TREATMENT OF ELEVATED ICP[a]**

Insert ICP monitor—ventriculostomy versus parenchymal device

General goals: maintain ICP <20 mmHg and CPP ≥60 mmHg. For ICP >20–25 mmHg for >5 min:

1. Elevate head of the bed; midline head position
2. Drain CSF via ventriculostomy (if in place)
3. Osmotherapy—mannitol 25–100 g q4h as needed (maintain serum osmolality <320 mosmol) or hypertonic saline (30 mL, 23.4% NaCl bolus)
4. Glucocorticoids—dexamethasone 4 mg q6h for vasogenic edema from tumor, abscess (avoid glucocorticoids in head trauma, ischemic and hemorrhagic stroke)
5. Sedation (e.g., morphine, propofol, or midazolam); add neuromuscular paralysis if necessary (patient will require endotracheal intubation and mechanical ventilation at this point, if not before)
6. Hyperventilation—to $PaCO_2$ 30–35 mmHg (short-term use or skip this step)
7. Pressor therapy—phenylephrine, dopamine, or norepinephrine to maintain adequate MAP to ensure CPP ≥60 mmHg (maintain euvolemia to minimize deleterious systemic effects of pressors). May adjust target CPP in individual patients based on autoregulation status.
8. Consider second-tier therapies for refractory elevated ICP
   a. Decompressive craniectomy
   b. High-dose barbiturate therapy ("pentobarb coma")
   c. Hypothermia to 33°C (91.4°F)

[a]Throughout ICP treatment algorithm, consider repeat head computed tomography to identify mass lesions amenable to surgical evacuation. May alter order of steps based on directed treatment to specific cause of elevated ICP.

***Abbreviations:*** CPP, cerebral perfusion pressure; ICP, intracranial pressure; MAP, mean arterial pressure; $PaCO_2$, arterial partial pressure of carbon dioxide.

- If cytotoxic edema is responsible, as in head trauma or stroke, use of osmotic diuretics such as mannitol or hypertonic saline is an appropriate early step.
- Elevated ICP may cause tissue ischemia; resulting vasodilation can lead to a cycle of worsening ischemia. Paradoxically, administration of vasopressor agents to increase MAP may actually lower ICP by increasing perfusion; therefore, hypertension should be treated carefully, if at all.
- Free water should be restricted.
- Fever should be treated aggressively.
- Hyperventilation is best used for only short periods of time until a more definitive treatment can be instituted.
- ICP monitoring may help guide medical and surgical decisions in selected pts with cerebral edema (Fig. 19-2).

After stabilization and initiation of the above therapies, a CT scan (or MRI, if feasible) is performed to delineate the cause of the elevated ICP. Emergency surgery is sometimes necessary to decompress the intracranial contents in cerebellar stroke with edema, surgically accessible tumor, and subdural or epidural hemorrhage.

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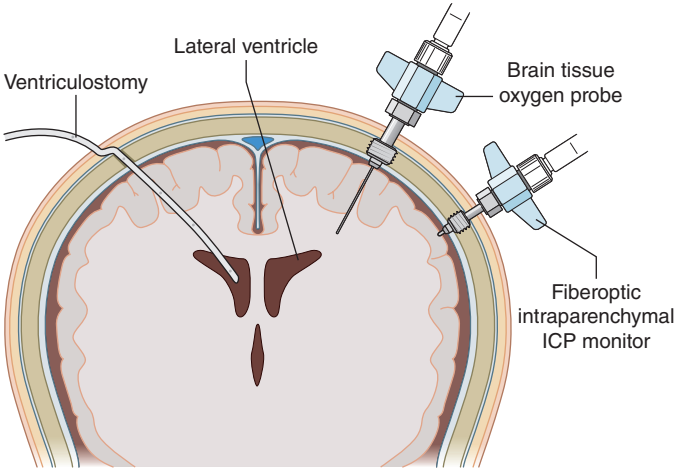


**FIGURE 19-2** Intracranial pressure (ICP) and brain tissue oxygen monitoring. A ventriculostomy allows for drainage of cerebrospinal fluid to treat elevated ICP. Fiberoptic ICP and brain tissue oxygen monitors are usually secured using a screwlike skull bolt. Cerebral blood flow and microdialysis probes (not shown) may be placed in a manner similar to the brain tissue oxygen probe.

## HEAD TRAUMA

Almost 10 million head injuries occur annually in the United States, about 20% of which are serious enough to cause brain damage.

### CLINICAL FEATURES

Head trauma can cause immediate loss of consciousness. Prolonged alterations in consciousness may be due to parenchymal, subdural, or epidural hematoma or to diffuse shearing of axons in the white matter. The term "*concussion*" is now applied to all cognitive and perceptual changes experienced after a blow to the head, whether or not consciousness is lost. Skull fracture should be suspected in pts with CSF rhinorrhea, hemotympanum, and periorbital or mastoid ecchymoses. Glasgow Coma Scale (Table 19-2) is useful for grading severity of brain injury.

### APPROACH TO THE PATIENT: **Head Injury**

Medical personnel caring for head injury pts should be aware that:

- Spinal injury often accompanies head injury and care must be taken to prevent compression of the spinal cord due to instability of the spinal column.
- Intoxication is a frequent accompaniment of traumatic brain injury; when appropriate, testing should be carried out for drugs and alcohol.
- Accompanying systemic injuries, including ruptures of abdominal organs, may produce vascular collapse or respiratory compromise requiring immediate attention.

**Minor Head Injury** The pt with minor head injury who is alert and attentive after a short period of unconsciousness (<1 min) may have headache, dizziness,

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**TABLE 19-2 GLASGOW COMA SCALE FOR HEAD INJURY**

| Eye Opening (E) | | Verbal Response (V) | |
|---|---|---|---|
| Spontaneous | 4 | Oriented | 5 |
| To loud voice | 3 | Confused, disoriented | 4 |
| To pain | 2 | Inappropriate words | 3 |
| Nil | 1 | Incomprehensible sounds | 2 |
| | | Nil | 1 |
| **Best Motor Response (M)** | | | |
| Obeys | 6 | | |
| Localizes | 5 | | |
| Withdraws (flexion) | 4 | | |
| Abnormal flexion posturing | 3 | | |
| Extension posturing | 2 | | |
| Nil | 1 | | |

***Note:*** Coma score = E + M + V. Patients scoring 3 or 4 have an 85% chance of dying or remaining vegetative, whereas scores >11 indicate only a 5–10% likelihood of death or vegetative state and 85% chance of moderate disability or good recovery. Intermediate scores correlate with proportional chances of recovery.

faintness, nausea, a single episode of emesis, difficulty with concentration, or slight blurring of vision. Such pts have usually sustained a concussion and are expected to have a brief amnestic period.

Two studies have indicated that older age, two or more episodes of vomiting, >30 min of retrograde or persistent anterograde amnesia, seizure, and concurrent drug or alcohol intoxication are sensitive (but not specific) indicators of intracranial hemorrhage that justify CT scanning. It may be appropriate to be more liberal in obtaining CT scans in children, although the risks of radiation must be considered.

In the current absence of adequate data, a common sense approach to athletic concussion has been to remove the individual from play immediately and avoid contact sports for at least several days after a mild injury and for a longer period if there are more severe injuries or if there are protracted neurologic symptoms such as headache and difficulty concentrating.

**Injury Of Intermediate Severity** Pts who are not comatose but who have persistent confusion, behavioral changes, subnormal alertness, extreme dizziness, or focal neurologic signs such as hemiparesis should be hospitalized and have a CT scan. A cerebral contusion or subdural hematoma is often found. Pts with intermediate head injury require medical observation to detect increasing drowsiness, respiratory dysfunction, pupillary enlargement, or other changes in the neurologic examination. Abnormalities of attention, intellect, spontaneity, and memory tend to return to normal weeks or months after the injury, although some cognitive deficits may be persistent.

**Severe Injury** Pts who are comatose from onset require immediate neurologic attention and resuscitation. After intubation, with care taken to immobilize the cervical spine, the depth of coma, pupillary size and reactivity, limb movements, and plantar responses are assessed. As soon as vital functions permit and cervical spine x-rays and a CT scan have been obtained, the pt should be transported to

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a critical care unit. CT scan may be normal in comatose pts with axonal shearing lesions in cerebral white matter.

The finding of an epidural or subdural hematoma or large intracerebral hemorrhage requires prompt decompressive surgery in otherwise salvageable pts. Measurement of ICP with a ventricular catheter or fiberoptic device in order to guide treatment has been favored by many units but has not improved outcome. Use of prophylactic anticonvulsants has been recommended but there is little supportive data.

For a more detailed discussion, see Hemphill JC III, Smith WS, Gress DR: Neurologic Critical Care, Including Hypoxic-Ischemic Encephalopathy and Subarachnoid Hemorrhage, Chap. 330, p. 1777; Ropper AH: Concussion and Other Traumatic Head Injuries, Chap. 457e; and Ropper AH: Coma, Chap. 328, p. 1771; in HPIM-19.

# 20 Spinal Cord Compression

## APPROACH TO THE PATIENT: Spinal Cord Compression

Initial symptoms of focal neck or back pain may evolve over days to weeks; followed by combinations of paresthesias, sensory loss, motor weakness, and sphincter disturbance evolving over hours to several days. Partial lesions may selectively involve one or more tracts and may be limited to one side of the cord. In severe or abrupt cases, areflexia reflecting spinal shock may be present, but hyperreflexia supervenes over days to weeks. With thoracic lesions, a sensory level to pain may be present on the trunk, indicating localization to the cord at that dermatomal level.

In pts with spinal cord symptoms, the first priority is to exclude treatable compression by a mass. Compression is more likely to be preceded by warning signs of neck or back pain, bladder disturbances, and sensory symptoms prior to development of weakness; noncompressive etiologies such as infarction and hemorrhage are more likely to produce myelopathy without antecedent symptoms.

MRI with gadolinium, centered on the clinically suspected level, is the initial diagnostic procedure. CT myelography can be helpful in pts who have contraindications to MRI. It is important to image the entire spine to search for additional clinically silent lesions. Infectious etiologies, unlike tumor, often cross the disc space to involve adjacent vertebral bodies.

### NEOPLASTIC SPINAL CORD COMPRESSION

Occurs in 5–10% of pts with cancer; epidural tumor may be the initial manifestation of malignancy. Most neoplasms are epidural in origin and result from metastases to

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the adjacent spinal bones. Almost any malignant tumor can metastasize to the spinal column with lung, breast, prostate, kidney, lymphoma, and plasma cell dyscrasia being particularly frequent. The thoracic cord is most commonly involved; exceptions include prostate and ovarian tumors, which preferentially involve the lumbar and sacral segments from spread through veins in the anterior epidural space. Urgent MRI is indicated when the diagnosis is suspected; up to 40% of pts with neoplastic cord compression at one level are found to have asymptomatic epidural disease elsewhere. Plain radiographs will miss 15–20% of metastatic vertebral lesions.

## TREATMENT NEOPLASTIC SPINAL CORD COMPRESSION

- Glucocorticoids to reduce edema (dexamethasone, up to 40 mg daily) can be administered before the imaging study if the clinical suspicion is high, and continued at a lower dose until radiotherapy (generally 3000 cGy administered in 15 daily fractions) and/or surgical decompression is completed.
- Early surgery, either decompression by laminectomy or vertebral body resection, followed by radiotherapy is more effective than radiotherapy alone for pts with a single area of spinal cord compression by extradural tumor.
- Time is of the essence; fixed motor deficits (paraplegia or quadriplegia) once established for >12 h do not usually improve, and beyond 48 h the prognosis for substantial motor recovery is poor.
- Biopsy is needed if there is no history of underlying malignancy; a simple systemic workup including chest imaging, mammography, measurement of prostate-specific antigen (PSA), and abdominal CT usually reveals the diagnosis.

## SPINAL EPIDURAL ABSCESS

Presents as a triad of pain, fever, and progressive limb weakness. Aching pain is almost always present, either over the spine or in a radicular pattern. The duration of pain prior to presentation is generally <2 weeks but may be several months or longer. Fever is usually present along with elevated white blood cell count, sedimentation rate, and C-reactive protein. Risk factors include an impaired immune status (diabetes mellitus, HIV, renal failure, alcoholism, malignancy), intravenous drug abuse, and infections of skin or other soft tissues. Most cases are due to *Staphylococcus aureus*; other causes include gram-negative bacilli, *Streptococcus*, anaerobes, fungi, and tuberculosis.

MRI localizes the abscess. Lumbar puncture (LP) is required only if encephalopathy or other clinical signs raise question of associated meningitis, a feature found in <25% of cases. The level of the LP should be planned to minimize risk of meningitis due to passage of the needle through infected tissue.

## TREATMENT SPINAL EPIDURAL ABSCESS

- Decompressive laminectomy with debridement combined with long-term antibiotic treatment.
- Surgical evacuation is unlikely to improve deficits of more than several days duration.
- Broad-spectrum antibiotics should be started empirically before surgery, modified on the basis of culture results, and continued for at least 6 weeks.
- With prompt diagnosis and treatment, up to two-thirds of pts experience significant recovery.

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### SPINAL EPIDURAL HEMATOMA

Hemorrhage into the epidural (or subdural) space causes acute focal or radicular pain followed by variable signs of a spinal cord disorder. Therapeutic anticoagulation, trauma, tumor, or blood dyscrasia is a predisposing condition; rarely, hematomas complicate LP or epidural anesthesia. Treatment consists of prompt reversal of any underlying bleeding disorder and surgical decompression.

For a more detailed discussion, see Gucalp R, Dutcher J: Oncologic Emergencies, Chap. 331, p. 1787; and Hauser SL, Ropper AH: Diseases of the Spinal Cord, Chap. 456, p. 2650, in HPIM-19.

# 21 Hypoxic-Ischemic Encephalopathy

Results from lack of delivery of oxygen to the brain because of extreme hypotension or respiratory failure. Most common causes are MI, cardiac arrest, shock, asphyxiation, paralysis of respiration, and carbon monoxide or cyanide poisoning. In some circumstances, hypoxemia may predominate. Carbon monoxide and cyanide poisoning are termed *histotoxic hypoxemia* because they cause a direct impairment of the respiratory chain.

### CLINICAL MANIFESTATIONS

Mild degrees of pure hypoxemia (e.g., at high altitude) cause impaired judgment, inattentiveness, motor incoordination, and, at times, euphoria. However, with hypoxia-ischemia, such as occurs with circulatory arrest, consciousness is lost within seconds. If circulation is restored within 3–5 min, full recovery may occur, but with longer periods permanent cerebral damage usually results. It may be difficult to judge the precise degree of hypoxia-ischemia, and some pts make a relatively full recovery even after 8–10 min of global ischemia. The distinction between pure hypoxemia and hypoxia-ischemia is important, because a $PaO_2$ as low as 2.7 kPa (20 mmHg) can be well tolerated if it develops gradually and normal blood pressure is maintained, but short durations of very low or absent cerebral circulation may result in permanent impairment.

Clinical examination at different time points after an insult (especially cardiac arrest) helps to assess prognosis. The prognosis is better for pts with intact brainstem function, as indicated by normal pupillary light responses, intact oculocephalic (doll's eyes), oculovestibular (caloric), and corneal reflexes. Absence of these reflexes and the presence of persistently dilated pupils that do not react to light are grave prognostic signs. A low likelihood of a favorable outcome is suggested by the absence of a pupillary light reflex or an extensor or absent motor response to pain on day 3 following the injury. Bilateral absence of the cortical somatosensory evoked potentials (SSEP) in the first several days also conveys a poor prognosis, as does a very elevated serum level (>33 μg/L) of the biochemical marker neuron-specific enolase (NSE). Usefulness of SSEP and NSE is often limited: difficult to obtain in a timely fashion, need for expert interpretation (SSEP), and lack of standardization

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(NSE measurements). Administration of mild hypothermia after cardiac arrest may change the time points when these clinical and electrophysiologic predictors become reliable in identifying patients with a very low likelihood of clinically meaningful recovery.

Long-term consequences include persistent coma or vegetative state, dementia, visual agnosia, parkinsonism, choreoathetosis, ataxia, myoclonus, seizures, and an amnestic state. Delayed postanoxic encephalopathy is an uncommon phenomenon in which pts appear to make an initial recovery following an insult and then have a relapse with a progressive course often characterized by widespread demyelination on imaging studies.

### TREATMENT HYPOXIC-ISCHEMIC ENCEPHALOPATHY

- Initial treatment is directed at restoring normal cardiorespiratory function. This includes securing a clear airway, ensuring adequate oxygenation and ventilation, and restoring cerebral perfusion, whether by cardiopulmonary resuscitation, fluids, pressors, or cardiac pacing.
- Mild hypothermia (33°C [91°F]), initiated as early as possible and continued for 12–24 h, may improve outcome in pts who remain comatose after cardiac arrest, based on trials in pts whose initial rhythm was primarily ventricular fibrillation or pulseless ventricular tachycardia. Potential complications include coagulopathy and an increased risk of infection.
- Anticonvulsants are not usually given prophylactically but may be used to control seizures.
- Posthypoxic myoclonus can be controlled with clonazepam (1.5–10 mg/d) or valproate (300–1200 mg/d) in divided doses.
- Myoclonic status epilepticus within 24 h after a hypoxic-ischemic insult portends a very poor prognosis, even if seizures are controlled.

For a more detailed discussion, see Hemphill JC III, Smith WS, Gress DR: Neurologic Critical Care, Including Hypoxic-Ischemic Encephalopathy and Subarachnoid Hemorrhage, Chap. 330, p. 1777, in HPIM-19.

# 22 Status Epilepticus

Defined as continuous seizures or repetitive, discrete seizures with impaired consciousness in the interictal period. The duration of seizure activity to meet the definition has traditionally been 15–30 min. A more practical definition is any situation requiring the acute use of anticonvulsants; in generalized convulsive status epilepticus (GCSE), this is typically when seizures last >5 min.

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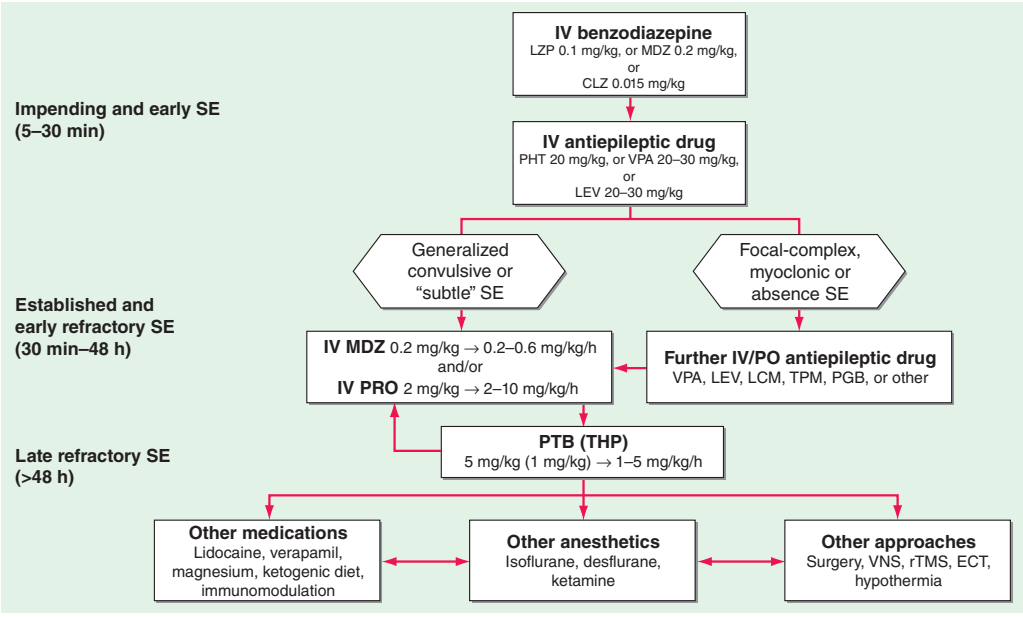


**FIGURE 22-1** Pharmacologic treatment of generalized tonic-clonic status epilepticus (SE) in adults. CLZ, clonazepam; ECT, electroconvulsive therapy; LCM, lacosamide; LEV, levetiracetam; LZP, lorazepam; MDZ, midazolam; PGB, pregabalin; PHT, phenytoin or fos-phenytoin; PRO, propofol; PTB, pentobarbital; rTMS, repetitive transcranial magnetic stimulation; THP, thiopental; TPM, topiramate; VNS, vagus nerve stimulation; VPA, valproic acid. *(From AO Rossetti, DH Lowenstein: Lancet Neurol 10:922, 2011.)*

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## CLINICAL FEATURES

Has numerous subtypes: GCSE (e.g., persistent, generalized electrographic seizures, coma, and tonic-clonic movements), and nonconvulsive status epilepticus (e.g., persistent absence seizures or focal seizures with confusion or partially impaired consciousness, and minimal motor abnormalities). GCSE is obvious when overt convulsions are present, but after 30–45 min of uninterrupted seizures, the signs may become increasingly subtle (mild clonic movements of the fingers; fine, rapid movements of the eyes; or paroxysmal episodes of tachycardia, pupillary dilatation, and hypertension). EEG may be the only method of diagnosis with these subtle signs; therefore, if a pt remains comatose after a seizure, EEG should be performed to exclude ongoing status epilepticus. GCSE is life threatening when accompanied by cardiorespiratory dysfunction, hyperthermia, and metabolic derangements such as acidosis (from prolonged muscle activity). Irreversible neuronal injury may occur from persistent seizures, even when a pt is paralyzed from neuromuscular blockade.

## ETIOLOGY

Principal causes of GCSE are antiepileptic drug withdrawal or noncompliance, metabolic disturbances, drug toxicity, CNS infections, CNS tumors, refractory epilepsy, and head trauma.

## TREATMENT STATUS EPILEPTICUS

GCSE is a medical emergency and must be treated immediately.

- First attend to any acute cardiorespiratory problems or hyperthermia.
- Perform a brief medical and neurologic examination, establish venous access, and send laboratory tests results to screen for metabolic abnormalities including anticonvulsant levels if pt has a history of epilepsy.
- Anticonvulsant therapy should then begin without delay (Fig. 22-1)
- In parallel, it is essential to determine the cause of the seizures to prevent recurrence and treat any underlying abnormalities.

The treatment of nonconvulsive status epilepticus is somewhat less urgent because the ongoing seizures are not accompanied by the severe metabolic disturbances of GCSE; however, evidence suggests cellular injury in the region of the seizure focus, so the condition should be treated as promptly as possible using the general approach for GCSE.

## PROGNOSIS

The mortality rate is 20% in GCSE, and the incidence of permanent neurologic sequelae is 10–50%.

For a more detailed discussion, see Lowenstein DH: Seizures and Epilepsy, Chap. 445, p. 2542, in HPIM-19.

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# 23 Diabetic Ketoacidosis and Hyperosmolar Coma

Diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) are acute complications of diabetes mellitus (DM). DKA is seen primarily in individuals with type 1 DM and HHS in individuals with type 2 DM. Both disorders are associated with absolute or relative insulin deficiency, volume depletion, and altered mental status. The metabolic similarities and differences in DKA and HHS are summarized in Table 23-1.

## DIABETIC KETOACIDOSIS

### ETIOLOGY

DKA results from insulin deficiency with a relative or absolute increase in glucagon and may be caused by inadequate insulin administration, infection (pneumonia, urinary tract infection, gastroenteritis, sepsis), infarction (cerebral, coronary, mesenteric, peripheral), surgery, trauma, drugs (cocaine), or pregnancy. A common precipitating scenario is the pt with type 1 DM who erroneously stops administering insulin because of anorexia/lack of food intake caused by a minor illness, followed by lipolysis and progressive ketosis leading to DKA.

### CLINICAL FEATURES

The initial symptoms of DKA include anorexia, nausea, vomiting, polyuria, and thirst. Abdominal pain, altered mental function, or frank coma may ensue. Classic signs of DKA include Kussmaul respirations and an acetone odor on the pt's breath. Volume depletion can lead to dry mucous membranes, tachycardia, and hypotension. Fever and abdominal tenderness may also be present. Laboratory evaluation reveals hyperglycemia, ketosis (β-hydroxybutyrate > acetoacetate), and metabolic acidosis (arterial pH 6.8–7.3) with an increased anion gap (Table 23-1). The fluid deficit is often 3–5 L and can be greater. Despite a total-body potassium deficit, the serum potassium at presentation may be normal or mildly high as a result of acidosis. Similarly, phosphate may be normal at presentation despite total-body phosphate depletion. Leukocytosis, hypertriglyceridemia, and hyperlipoproteinemia are common. Hyperamylasemia is usually of salivary origin but may suggest a diagnosis of pancreatitis. The measured serum sodium is reduced as a consequence of osmotic fluid shifts due to hyperglycemia (1.6-meq reduction for each 5.6-mmol/L [100-mg/dL] rise in the serum glucose).

**TREATMENT DIABETIC KETOACIDOSIS**

The management of DKA is outlined in Table 23-2.

## HYPERGLYCEMIC HYPEROSMOLAR STATE

### ETIOLOGY

Relative insulin deficiency and inadequate fluid intake are the underlying causes of HHS. Hyperglycemia induces an osmotic diuresis that leads to profound intravascular volume depletion. HHS is often precipitated by a serious, concurrent illness such as myocardial infarction or sepsis and compounded by conditions that impede access to water.

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**TABLE 23-1 LABORATORY VALUES IN DKA AND HHS (REPRESENTATIVE RANGES AT PRESENTATION)**

| | DKA | HHS |
|---|---|---|
| Glucose,[a] mmol/L (mg/dL) | 13.9–33.3 (250–600) | 33.3–66.6 (600–1200)[c] |
| Sodium, meq/L | 125–135 | 135–145 |
| Potassium,[a] meq/L | Normal to ↑[b] | Normal |
| Magnesium[a] | Normal[b] | Normal |
| Chloride[a] | Normal | Normal |
| Phosphate[a] | Normal to ↓[b] | Normal |
| Creatinine, μmol/L (mg/dL) | Slightly ↑ | Moderately ↑ |
| Osmolality (mosmol/mL) | 300–320 | 330–380 |
| Plasma ketones[a] | ++++ | ± |
| Serum bicarbonate,[a] meq/L | <15 meq/L | Normal to slightly ↓ |
| Arterial pH | 6.8–7.3 | >7.3 |
| Arterial $PCO_2$,[a] mmHg | 20–30 | Normal |
| Anion gap[a] [Na – (Cl + $HCO_3$)], meq/L | ↑ | Normal to slightly ↑ |

[a]Large changes occur during treatment of DKA.
[b]Although plasma levels may be normal or high at presentation, total-body stores are usually depleted.
[c]Large changes occur during treatment
***Abbreviations:*** DKA, diabetic ketoacidosis; HHS, hyperglycemic hyperosmolar state.

## CLINICAL FEATURES

Presenting symptoms include polyuria, thirst, and altered mental state, ranging from lethargy to coma. Notably absent are symptoms of nausea, vomiting, and abdominal pain and the Kussmaul respirations characteristic of DKA. The prototypical pt is an elderly individual with a several week history of polyuria, weight loss, and diminished oral intake. The laboratory features are summarized in Table 23-1. In contrast to DKA, acidosis and ketonemia are usually not found; however, a small anion gap may be due to lactic acidosis, and moderate ketonuria may occur from starvation. Prerenal azotemia is typically present. Although the measured serum sodium may be normal or slightly low, the corrected serum sodium is usually increased (add 1.6 meq to measured sodium for each 5.6-mmol/L [100-mg/dL] rise in the serum glucose). HHS, even when adequately treated, has a significant mortality rate (up to 15%), which is in part explained by comorbidities and pt age.

## TREATMENT HYPERGLYCEMIC HYPEROSMOLAR STATE

The precipitating problem should be sought and treated. Sufficient IV fluids (1–3 L of 0.9% normal saline over the first 2–3 h) should be given to stabilize the hemodynamic status. The calculated free water deficit (usually 9–10 L) should be reversed over the next 1–2 days, using 0.45% saline initially then 5% dextrose in water. Overly rapid fluid replacement should be avoided to prevent worsening of neurologic status. Potassium repletion is usually necessary. The plasma glucose may drop precipitously with hydration alone, though insulin therapy with an IV bolus of 0.1 units/kg followed by a constant infusion rate (0.1 units/kg per hour) is usually required. If the serum glucose does not fall, the insulin infusion rate should be doubled. Glucose should be added to IV fluid, and the insulin infusion

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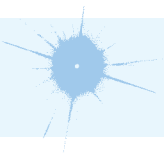
**TABLE 23-2 MANAGEMENT OF DIABETIC KETOACIDOSIS**

1. Confirm diagnosis (plasma glucose, positive serum ketones, metabolic acidosis).
2. Admit to hospital; intensive-care setting may be necessary for frequent monitoring or if pH <7.00 or unconscious.
3. Assess: Serum electrolytes ($K^+$, $Na^+$, $Mg^{2+}$, $Cl^-$, bicarbonate, phosphate) Acid-base status—pH, $HCO_3^-$, $PCO_2$, β-hydroxybutyrate renal function (creatinine, urine output)
4. Replace fluids: 2–3 L of 0.9% saline over first 1–3 h (10–15 mL/kg per hour); subsequently, 0.45% saline at 150–300 mL/h; change to 5% glucose and 0.45% saline at 100–200 mL/h when plasma glucose reaches 14 mmol/L (250 mg/dL).
5. Administer short-acting insulin: IV (0.1 units/kg) or IM (0.3 units/kg), then 0.1 units/kg per hour by continuous IV infusion; increase two- to threefold if no response by 2–4 h. If initial serum potassium is <3.3 meq/L, do not administer insulin until the potassium is corrected to >3.3 meq/L. If the initial serum potassium is >5.2 meq/L, do not supplement $K^+$ until the potassium is corrected.
6. Assess pt: What precipitated the episode (noncompliance, infection, trauma, infarction, cocaine)? Initiate appropriate workup for precipitating event (cultures, chest x-ray, ECG).
7. Measure capillary glucose every 1–2 h; measure electrolytes (especially $K^+$, bicarbonate, phosphate) and anion gap every 4 h for first 24 h.
8. Monitor blood pressure, pulse, respirations, mental status, fluid intake and output every 1–4 h.
9. Replace $K^+$: 10 meq/h when plasma $K^+$ <5.0–5.2 meq/L, ECG normal, urine flow and normal creatinine documented; administer 40–80 meq/h when plasma $K^+$ <3.5 meq/L or if bicarbonate is given. If initial serum potassium is >5.2 mmol/L (5.2 meq/L), do not supplement $K^+$ until the potassium is corrected.
10. Continue above until pt is stable, glucose goal is 150–250 mg/dL, and acidosis is resolved. Insulin infusion may be decreased to 0.05–0.1 units/kg per hour.
11. Administer intermediate or long-acting insulin as soon as pt is eating. Allow for overlap in insulin infusion and SC insulin injection.

***Source:*** Adapted from M Sperling, in *Therapy for Diabetes Mellitus and Related Disorders*, American Diabetes Association, Alexandria, VA, 1998; and AE Kitabchi et al: *Diabetes Care* 29:2739, 2006.

rate decreased when the plasma glucose falls to 13.9 mmol/L (250 mg/dL). The insulin infusion should be continued until the pt has resumed eating and can be transitioned to a subcutaneous insulin regimen.



For a more detailed discussion, see Powers AC: Diabetes Mellitus: Management and Therapies, Chap. 418, p. 2407 in HPIM-19.

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# 24 Hypoglycemia

Glucose is an obligate metabolic fuel for the brain. Hypoglycemia should be considered in any pt with confusion, altered level of consciousness, or seizures. Counterregulatory responses to hypoglycemia include insulin suppression and the release of catecholamines, glucagon, growth hormone, and cortisol.

The laboratory diagnosis of hypoglycemia is usually defined as a plasma glucose level <2.5–2.8 mmol/L (<45–50 mg/dL), although the absolute glucose level at which symptoms occur varies among individuals. For this reason, *Whipple's triad* should be present: (1) symptoms consistent with hypoglycemia, (2) a low plasma glucose concentration measured by a method capable of accurately measuring low glucose levels (not a glucose monitor), and (3) relief of symptoms after the plasma glucose level is raised.

## ETIOLOGY

Hypoglycemia occurs most commonly as a result of treating pts with diabetes mellitus. Additional factors to be considered in any pt with hypoglycemia are listed below.

1. Drugs: insulin, insulin secretagogues (especially chlorpropamide, repaglinide, nateglinide), alcohol, high doses of salicylates, sulfonamides, pentamidine, quinine, quinolones
2. Critical illness: hepatic, renal, or cardiac failure; sepsis; prolonged starvation
3. Hormone deficiencies: adrenal insufficiency, hypopituitarism (particularly in young children)
4. Insulinoma (pancreatic β cell tumor), β cell hyperplasia (nesidioblastosis; congenital or after gastric or bariatric surgery)
5. Other rare etiologies: non–β cell tumors (large mesenchymal or epithelial tumors producing an incompletely processed IGF-II, other nonpancreatic tumors), antibodies to insulin or the insulin receptor, inherited enzymatic defects such as hereditary fructose intolerance and galactosemia

## CLINICAL FEATURES

Symptoms of hypoglycemia can be divided into autonomic (adrenergic: palpitations, tremor, and anxiety; cholinergic: sweating, hunger, and paresthesia) and neuroglycopenic (behavioral changes, confusion, fatigue, seizure, loss of consciousness, and, if hypoglycemia is severe and prolonged, death). Signs of autonomic discharge, such as tachycardia, elevated systolic blood pressure, pallor, and diaphoresis, are typically present in a pt with hypoglycemia awareness but may be absent in a pt with pure neuroglycopenia.

Recurrent hypoglycemia shifts thresholds for the autonomic symptoms and counterregulatory responses to lower glucose levels, leading to hypoglycemic unawareness. Under these circumstances, the first manifestation of hypoglycemia is neuroglycopenia, placing pts at risk of being unable to treat themselves.

## DIAGNOSIS

Diagnosis of the hypoglycemic mechanism is critical for choosing a treatment that prevents recurrent hypoglycemia (Fig. 24-1). Urgent treatment is often necessary in pts with suspected hypoglycemia. Nevertheless, blood should be drawn at the time of symptoms, whenever possible before the administration of glucose, to allow documentation of hypoglycemia as the cause of symptoms. If the glucose level is low and the cause of hypoglycemia is unknown, additional assays should be performed

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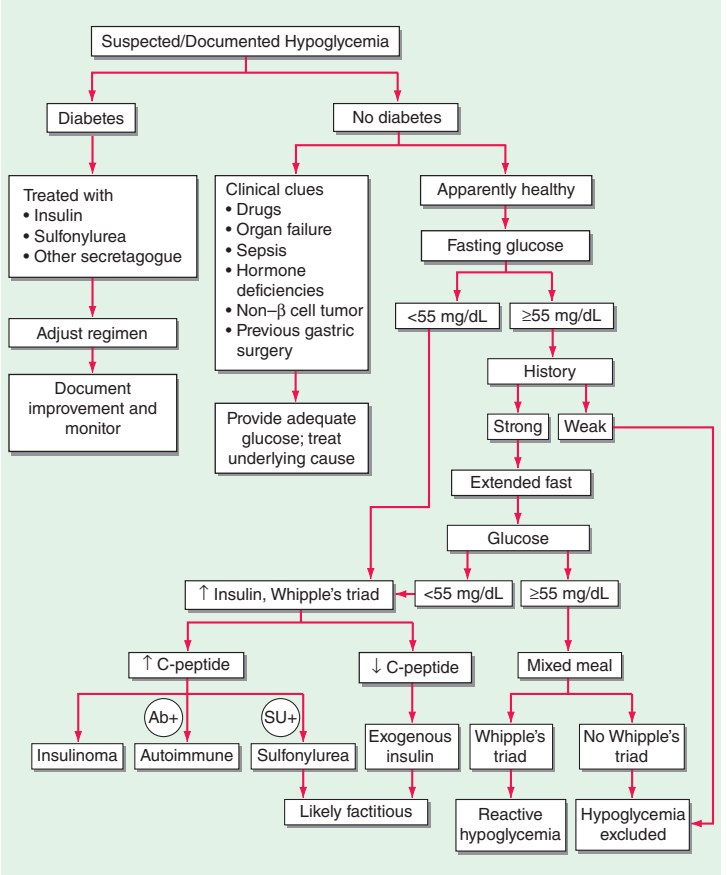


**FIGURE 24-1** Diagnostic approach to a pt with suspected hypoglycemia based on a history of symptoms, a low plasma glucose concentration, or both. AB+, positive for antibodies against insulin or the insulin receptor; SU+, positive for sulfonylurea.

on blood obtained at the time of a low plasma glucose. These should include insulin, proinsulin, C-peptide, sulfonylurea levels, cortisol, and ethanol. In the absence of documented spontaneous hypoglycemia, overnight fasting or food deprivation during observation in the outpatient setting will sometimes elicit hypoglycemia and allow diagnostic evaluation. An extended (up to 72 h) fast under careful supervision in the hospital may be required—the test should be terminated if plasma glucose drops below 2.5 mmol/L (45 mg/dL) and the pt has symptoms.

Interpretation of fasting test results is shown in Table 24-1.

## TREATMENT HYPOGLYCEMIA

The syndrome of hypoglycemic unawareness in pts with diabetes mellitus is reversible after as little as 2 weeks of scrupulous avoidance of hypoglycemia. This involves a shift of glycemic thresholds for sympathetic autonomic symptoms back to higher glucose concentrations.

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**TABLE 24-1 DIAGNOSTIC INTERPRETATION OF HYPOGLYCEMIA**

| Diagnosis | Glucose, mmol/L (mg/dL) | Insulin, μU/mL | C-Peptide, pmol/L | Proinsulin, pmol/L | Urine or Plasma Sulfonylurea |
|---|---|---|---|---|---|
| Nonhypoglycemic | ≥2.2 (≥40) | <3 | <200 | <5 | No |
| Insulinoma | ≤2.5 (≤45) | ≥3 | ≥200 | ≥5 | No |
| Exogenous insulin | ≤2.5 (≤45) | ≥3[a] | <200 | <5 | No |
| Sulfonylurea | ≤2.5 (≤45) | ≥3 | ≥200 | ≥5 | Yes |
| Non-insulin mediated | ≤2.5 (≤45) | <3 | <200 | <5 | No |

[a]Often very high.

Acute therapy of hypoglycemia requires administration of oral glucose or, if unavailable, rapidly absorbable sugar (e.g., fruit juice), or 25 g of a 50% solution IV followed by a constant infusion of 5% or 10% dextrose if parenteral therapy is necessary. Hypoglycemia from sulfonylureas is often prolonged, requiring treatment and monitoring for 24 h or more. SC or IM glucagon can be used in diabetics. Prevention of recurrent hypoglycemia requires treatment of the underlying cause of hypoglycemia, including discontinuation or dose reduction of offending drugs, treatment of critical illnesses, replacement of hormonal deficiencies, and surgery of insulinomas or other tumors. Diazoxide or octreotide therapy can be used to control hypoglycemia in inoperable metastatic insulinoma or nesidioblastosis. Treatment of other forms of hypoglycemia is dietary, with avoidance of fasting and ingestion of frequent small meals.

For a more detailed discussion, see Cryer PE, Davis SN: Hypoglycemia, Chap. 420, p. 2430, in HPIM-19.

# 25 Oncologic Emergencies

Emergencies in the cancer pt may be classified into three categories: effects from tumor expansion, metabolic or hormonal effects mediated by tumor products, and treatment complications.

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## STRUCTURAL/OBSTRUCTIVE ONCOLOGIC EMERGENCIES

The most common problems are superior vena cava syndrome; pericardial effusion/tamponade; spinal cord compression; seizures (Chap. 181) and/or increased intracranial pressure; and intestinal, urinary, or biliary obstruction. The last three conditions are discussed in Chap. 331 in HPIM-19.

### SUPERIOR VENA CAVA SYNDROME

Obstruction of the superior vena cava reduces venous return from the head, neck, and upper extremities. About 85% of cases are due to lung cancer; lymphoma and thrombosis of central venous catheters are also causes. Pts often present with facial swelling, dyspnea, and cough. In severe cases, the mediastinal mass lesion may cause tracheal obstruction. Dilated neck veins and increased collateral veins on anterior chest wall are noted on physical examination. Chest x-ray (CXR) documents widening of the superior mediastinum; 25% of pts have a right-sided pleural effusion.

**TREATMENT SUPERIOR VENA CAVA SYNDROME**

Radiation therapy is the treatment of choice for non-small-cell lung cancer; addition of chemotherapy to radiation therapy is effective in small-cell lung cancer and lymphoma. Symptoms recur in 10–30% and can be palliated by venous stenting. Clotted central catheters producing this syndrome should be removed and anticoagulation therapy initiated.

### PERICARDIAL EFFUSION/TAMPONADE

Accumulation of fluid in the pericardium impairs filling of the heart and decreases cardiac output. Most commonly seen in pts with lung or breast cancers, leukemias, or lymphomas, pericardial tamponade may also develop as a late complication of mediastinal radiation therapy (constrictive pericarditis). Common symptoms are dyspnea, cough, chest pain, orthopnea, and weakness. Pleural effusion, sinus tachycardia, jugular venous distention, hepatomegaly, and cyanosis are frequent physical findings. Paradoxical pulse, decreased heart sounds, pulsus alternans, and friction rub are less common with malignant than nonmalignant pericardial disease. Echocardiography is diagnostic; pericardiocentesis may show serous or bloody exudate, and cytology usually shows malignant cells.

**TREATMENT PERICARDIAL EFFUSION/TAMPONADE**

Drainage of fluid from the pericardial sac may be lifesaving until a definitive surgical procedure (pericardial stripping or window) can be performed.

### SPINAL CORD COMPRESSION

Primary spinal cord tumors occur rarely, and cord compression is most commonly due to epidural metastases from vertebral bodies involved with tumor, especially from prostate, lung, breast, lymphoma, and myeloma primaries. Pts present with back pain, worse when recumbent, with local tenderness. Loss of bowel and bladder control may occur. On physical examination, pts have a loss of sensation below a horizontal line on the trunk, called a *sensory level*, which usually corresponds to one or two vertebrae below the site of compression. Weakness and spasticity of the legs and hyperactive reflexes with upgoing toes on Babinski testing are often noted. Spine radiographs may reveal erosion of the pedicles (winking owl sign), lytic or sclerotic vertebral body lesions, and vertebral collapse. Collapse alone is not a reliable indicator of tumor; it is a common manifestation of a more common disease, osteoporosis. MRI can visualize the cord throughout its length and define the extent of tumor involvement.

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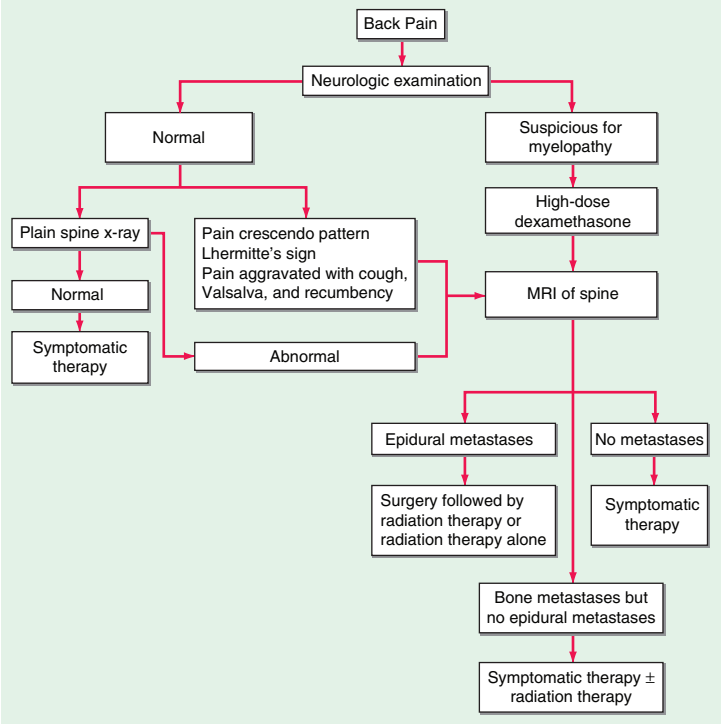


**FIGURE 25-1** Management of cancer pts with back pain.

## TREATMENT SPINAL CORD COMPRESSION (FIG. 25-1)

Radiation therapy plus dexamethasone, 4 mg IV or PO q4h, is successful in arresting and reversing symptoms in about 75% of pts who are diagnosed while still ambulatory. Surgery results in better recovery rates but may be extensive (vertebral body resection with spine stabilization). Only 10% of pts made paraplegic by the tumor recover the ability to ambulate.

## EMERGENT PARANEOPLASTIC SYNDROMES

Most paraneoplastic syndromes have an insidious onset (Chap. 76). Hypercalcemia, syndrome of inappropriate antidiuretic hormone secretion (SIADH), and adrenal insufficiency may present as emergencies.

### HYPERCALCEMIA

The most common paraneoplastic syndrome, hypercalcemia occurs in about 10% of cancer pts, particularly those with lung, breast, head and neck, and kidney cancer and myeloma. Bone resorption mediated by parathyroid hormone–related protein is the most common mechanism; interleukin 1 (IL-1), IL-6, tumor necrosis factor, and transforming growth factor β may act locally in tumor-involved bone. Pts usually present with nonspecific symptoms: fatigue, anorexia, constipation, weakness. Hypoalbuminemia associated with malignancy may make symptoms worse for any

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given serum calcium level because more calcium will be free rather than protein bound.

**TREATMENT HYPERCALCEMIA**

Saline hydration, antiresorptive agents (e.g., pamidronate, 60–90 mg IV over 4 h, or zoledronate, 4–8 mg IV), and glucocorticoids usually lower calcium levels significantly within 1–3 days. Treatment effects usually last several weeks. Treatment of the underlying malignancy is also important.

### SIADH

Induced by the action of arginine vasopressin produced by certain tumors (especially small cell cancer of the lung), SIADH is characterized by hyponatremia, inappropriately concentrated urine, and high urine sodium excretion in the absence of volume depletion. Most pts with SIADH are asymptomatic. When serum sodium falls to <115 meq/L, pts may experience anorexia, depression, lethargy, irritability, confusion, weakness, and personality changes.

**TREATMENT SIADH**

Water restriction controls mild forms. Demeclocycline (150–300 mg PO tid or qid) inhibits the effects of vasopressin on the renal tubule but has a slow onset of action (1 week). Conivaptan can be given PO (20–120 mg bid) or IV (10–40 mg); tolvaptan (15 mg PO daily) is a vasopressin agonist that can be used. Treatment of the underlying malignancy is also important. If the pt has mental status changes with sodium levels <115 meq/L, normal saline infusion plus furosemide to increase free water clearance may provide more rapid improvement. Rate of correction should not exceed 0.5–1 meq/L per h. More rapid change can produce fluid shifts that lead to brain damage.

### ADRENAL INSUFFICIENCY

The infiltration of the adrenals by tumor and their destruction by hemorrhage are the two most common causes. In addition, the immunologic checkpoint inhibiting antibodies, ipilimumab, nivolumab, and pembrolizumab can produce an autoimmune hypophysitis that leads to adrenal insufficiency. Symptoms such as nausea, vomiting, anorexia, and orthostatic hypotension may be attributed to progressive cancer or to treatment side effects. Certain treatments (e.g., ketoconazole, aminoglutethimide) may directly interfere with steroid synthesis in the adrenal.

**TREATMENT ADRENAL INSUFFICIENCY**

In emergencies, a bolus of 100-mg IV hydrocortisone is followed by a continuous infusion of 10 mg/h. In nonemergent but stressful circumstances, 100–200 mg/d oral hydrocortisone is the beginning dose, tapered to maintenance of 15–37.5 mg/d. Fludrocortisone (0.1 mg/d) may be required in the presence of hyperkalemia.

## TREATMENT COMPLICATIONS

Complications from treatment may occur acutely or emerge only many years after treatment. Toxicity may be either related to the agents used to treat the cancer or from the response of the cancer to the treatment (e.g., leaving a perforation in a

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hollow viscus or causing metabolic complications such as tumor lysis syndrome). Several treatment complications present as emergencies. Fever and neutropenia and tumor lysis syndrome will be discussed here; others are discussed in Chap. 331 in HPIM-19.

## FEVER AND NEUTROPENIA

Many cancer pts are treated with myelotoxic agents. When peripheral blood granulocyte counts are <1000/μL, the risk of infection is substantially increased (48 infections/100 pts). A neutropenic pt who develops a fever (>38°C [100.4°F]) should undergo physical examination with special attention to skin lesions, mucous membranes, IV catheter sites, and perirectal area. Two sets of blood cultures from different sites should be drawn and a CXR performed, and any additional tests should be guided by findings from the history and physical examination. Any fluid collections should be tapped, and urine and/or fluids should be examined under the microscope for evidence of infection.

### TREATMENT FEVER AND NEUTROPENIA

After cultures are obtained, all pts should receive IV broad-spectrum antibiotics (e.g., ceftazidime, 1 g q8h). If an obvious infectious site is found, the antibiotic regimen is designed to cover organisms that may cause the infection. Usually therapy should be started with an agent or agents that cover both gram-positive and -negative organisms. If the fever resolves, treatment should continue until neutropenia resolves. Persistence of febrile neutropenia after 7 days should lead to addition of amphotericin B (or another broad-spectrum antifungal agent like posaconazole) to the antibiotic regimen.

## TUMOR LYSIS SYNDROME

When rapidly growing tumors are treated with effective chemotherapy regimens, the dying tumor cells can release large amounts of nucleic acid breakdown products (chiefly uric acid), potassium, phosphate, and lactic acid. The phosphate elevations can lead to hypocalcemia. The increased uric acid, especially in the setting of acidosis, can precipitate in the renal tubules and lead to renal failure. The renal failure can exacerbate the hyperkalemia.

### TREATMENT TUMOR LYSIS SYNDROME

Prevention is the best approach. Maintain hydration with 3 L/d of saline, keep urine pH > 7.0 with bicarbonate administration, and start allopurinol, 300 mg/m$^2$ per day, 24 h before starting chemotherapy. Once chemotherapy is given, monitor serum electrolytes every 6 h. If after 24 h, uric acid (>8 mg/dL) and serum creatinine (>1.6 mg/dL) are elevated, rasburicase (recombinant urate oxidase), 0.2 mg/kg IV daily, may lower uric acid levels. If serum potassium is >6.0 meq/L and renal failure ensues, hemodialysis may be required. Maintain normal calcium levels.

For a more detailed discussion, see Finberg RW: Infections in Patients with Cancer, Chap. 104, p. 484; Jameson JL, Longo DL: Paraneoplastic Syndromes: Endocrinologic/Hematologic, Chap. 121, p. 608, and Gucalp R, Dutcher J: Oncologic Emergencies, Chap. 331, p. 1787, in HPIM-19.

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# 26 Anaphylaxis

## DEFINITION

A life-threatening systemic hypersensitivity reaction to contact with an allergen; it may appear within minutes of exposure to the offending substance. Manifestations include respiratory distress, pruritus, urticaria, mucous membrane swelling, GI disturbances (including nausea, vomiting, abdominal pain, and diarrhea), and vascular collapse. Virtually any allergen may trigger an anaphylactic reaction, but among the more common agents are proteins such as antisera, hormones, pollen extracts, Hymenoptera venom, and foods; drugs (especially antibiotics); and diagnostic agents such as IV contrast material. Atopy does not seem to predispose to anaphylaxis from penicillin or venom exposures. Anaphylactic transfusion reactions are covered in Chap. 8.

## CLINICAL PRESENTATION

Time to onset is variable, but symptoms usually occur within seconds to minutes of exposure to the offending antigen:

- Respiratory: mucous membrane swelling, hoarseness, stridor, wheezing
- Cardiovascular: tachycardia, hypotension
- Cutaneous: pruritus, urticaria, angioedema

## DIAGNOSIS

Made by obtaining history of exposure to offending substance with subsequent development of characteristic complex of symptoms.

## TREATMENT ANAPHYLAXIS

Mild symptoms such as pruritus and urticaria can be controlled by administration of 0.3–0.5 mL of 1:1000 (1.0 mg/mL) epinephrine SC or IM, with repeated doses as required at 5- to 20-min intervals for a severe reaction.

An IV infusion should be initiated for administration of 2.5 mL of 1:10,000 epinephrine solution at 5- to 10-min intervals, and volume expanders such as normal saline, and vasopressor agents, e.g., dopamine, if intractable hypotension occurs.

Epinephrine provides both α- and β-adrenergic effects, resulting in vasoconstriction and bronchial smooth-muscle relaxation. Beta blockers are relatively contraindicated in persons at risk for anaphylactic reactions.

The following should also be used as necessary:

- Antihistamines such as diphenhydramine 50–100 mg IM or IV.
- Nebulized albuterol or aminophylline 0.25–0.5 g IV for bronchospasm.
- Oxygen; endotracheal intubation or tracheostomy may be necessary for progressive hypoxemia.
- Glucocorticoids (methylprednisolone 0.5–1.0 mg/kg IV); not useful for acute manifestations but may help alleviate later recurrence of hypotension, bronchospasm, or urticaria.
- For antigenic material injected into an extremity consider: use of a tourniquet proximal to the site, 0.2 mL of 1:1000 epinephrine into the site, removal without compression of an insect stinger if present.

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## PREVENTION

Avoidance of offending antigen, where possible; skin testing and desensitization to materials such as penicillin and Hymenoptera venom, if necessary. Individuals should wear an informational bracelet and have immediate access to an unexpired epinephrine kit.

For a more detailed discussion, see Boyce JA, Austen KF: Allergies, Anaphylaxis, and Systemic Mastocytosis, Chap. 376, p. 2113, in HPIM-19.

# 27 Bites, Venoms, Stings, and Marine Poisonings

## MAMMALIAN BITES

- Each year, there are ~300 dog and cat bites per 100,000 population in the United States, with most bites inflicted by pet animals.
- The microbiology of bite wounds typically reflects the oral flora of the biting animal.
- Bites from many different animals can transmit rabies and tularemia.

## DOG BITES

- **Epidemiology:** Dogs bite ≥4.7 million people per year, causing 80% of all animal bites; 15–20% of dog bites become infected.
- **Bacteriology (Table 27-1):** includes aerobic and anaerobic organisms, such as β-hemolytic streptococci; *Eikenella corrodens*; *Capnocytophaga canimorsus*; and *Pasteurella*, *Staphylococcus*, *Actinomyces*, and *Fusobacterium* species
- **Clinical features:** typically manifest within 8–24 h after the bite as local cellulitis with purulent, sometimes foul-smelling discharge. Systemic spread (e.g., bacteremia, endocarditis, brain abscess) can occur. *C. canimorsus* infection can present as sepsis syndrome, DIC, and renal failure, particularly in pts who are splenectomized, have hepatic dysfunction, or are otherwise immunosuppressed.

## CAT BITES

- **Epidemiology:** Cat bites and scratches result in infection in >50% of cases.
- **Bacteriology (Table 27-1):** includes organisms similar to those involved in dog bites. *Pasteurella multocida* and *Bartonella henselae* (the agent of cat-scratch disease) are important cat-associated pathogens.
- **Clinical features:** *P. multocida* infections can cause rapidly advancing inflammation and purulent discharge within a few hours after the bite. Because of deep tissue penetration by narrow, sharp feline incisors, cat bites are more likely than dog bites to cause septic arthritis or osteomyelitis.

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**TABLE 27-1 MANAGEMENT OF WOUND INFECTIONS FOLLOWING ANIMAL AND HUMAN BITES**

| Biting Species | Commonly Isolated Pathogens | Preferred Antibiotic(s)[a] | Alternative in Penicillin-Allergic Pt | Prophylaxis Advised for Early Uninfected Wounds | Other Considerations |
|---|---|---|---|---|---|
| Dog | *Staphylococcus aureus*, *Pasteurella multocida*, anaerobes, *Capnocytophaga canimorsus* | Amoxicillin/clavulanate (250–500 mg PO tid) or ampicillin/sulbactam (1.5–3.0 g IV q6h) | Clindamycin (150–300 mg PO qid) plus either TMP-SMX (1 DS tablet PO bid) or ciprofloxacin (500 mg PO bid) | Sometimes[b] | Consider rabies prophylaxis. |
| Cat | *P. multocida*, *S. aureus*, anaerobes | Amoxicillin/clavulanate or ampicillin/sulbactam as above | Clindamycin plus TMP-SMX as above or a fluoroquinolone | Usually | Consider rabies prophylaxis. Carefully evaluate for joint/bone penetration. |
| Human, occlusional | Viridans streptococci, *S. aureus*, *Haemophilus influenzae*, anaerobes | Amoxicillin/clavulanate or ampicillin/sulbactam as above | Erythromycin (500 mg PO qid) or a fluoroquinolone | Always | |
| Human, clenched-fist | As for occlusional, plus *Eikenella corrodens* | Ampicillin/sulbactam as above or imipenem (500 mg q6h) | Cefoxitin[c] | Always | Examine for tendon, nerve, or joint involvement. |

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| | | | | | |
|---|---|---|---|---|---|
| Monkey | As for human bite | As for human bite | As for human bite | Always | For macaque monkeys, consider B virus prophylaxis with acyclovir. |
| Snake | *Pseudomonas aeruginosa*, *Proteus* spp., *Bacteroides fragilis*, *Clostridium* spp. | Ampicillin/sulbactam as above | Clindamycin plus TMP-SMX as above or a fluoroquinolone | Sometimes, especially with venomous snakes | Administer antivenin for venomous snakebite. |
| Rodent | *Streptobacillus moniliformis*, *Leptospira* spp., *P. multocida* | Penicillin VK (500 mg PO qid) | Doxycycline (100 mg PO bid) | Sometimes | — |

[a]Antibiotic choices should be based on culture data when available. These suggestions for empirical therapy need to be tailored to individual circumstances and local conditions. IV regimens should be used for hospitalized pts. A single IV dose of antibiotics may be given to pts who will be discharged after initial management.

[b]Prophylactic antibiotics are suggested for severe or extensive wounds, facial wounds, and crush injuries; when bone or joint may be involved; and when comorbidity is present (see text).

[c]May be hazardous in pts with immediate-type hypersensitivity to penicillin.

***Abbreviations:*** DS, double-strength; TMP-SMX, trimethoprim-sulfamethoxazole.



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## OTHER NONHUMAN MAMMALIAN BITES

- Old World monkeys (*Macaca* species): Bites may transmit herpes B virus (*Herpesvirus simiae*), which can cause CNS infections with high mortality rates.
- Seals, walruses, polar bears: Bites may cause a chronic suppurative infection known as *seal finger*, which is probably due to *Mycoplasma* species.
- Small rodents (and their predators): Bites may transmit *rat-bite fever*, caused by *Streptobacillus moniliformis* (in the United States) or *Spirillum minor* (in Asia).
  - Rat-bite fever occurs after the initial wound has healed, a feature distinguishing it from an acute bite-wound infection.
  - *S. moniliformis* infections manifest 3–10 days after the bite as fever, chills, myalgias, headache, and severe migratory arthralgias followed by a maculopapular rash involving the palms and soles. Disease can progress to metastatic abscesses, endocarditis, meningitis, and pneumonia.
    - Haverhill fever is an *S. moniliformis* infection acquired from contaminated milk or drinking water and has manifestations similar to those described above.
  - *S. minor* infections cause local pain, purple swelling at the bite site, and associated lymphangitis and regional lymphadenopathy 1–4 weeks after the bite, with evolution into a nonspecific systemic illness.

## HUMAN BITES

- **Epidemiology:** Human bites become infected 10–15% of the time.
  - *Occlusional* injuries are inflicted by actual biting; *clenched-fist* injuries result when the fist of one individual strikes the teeth of another.
  - *Clenched-fist* injuries are more common and typically result in more serious infections (e.g., septic arthritis, tenosynovitis).
- **Bacteriology:** See Table 27-1.

## TREATMENT MAMMALIAN BITES

- *Wound management:* Wound closure is controversial in bite injuries. After thorough cleansing, facial wounds are usually sutured for cosmetic reasons and because the abundant facial blood supply lessens the risk of infection. For wounds elsewhere on the body, many authorities do not attempt primary closure, preferring instead to irrigate the wound copiously, debride devitalized tissue, remove foreign bodies, and approximate the margins. Delayed primary closure may be undertaken after the risk of infection has passed. Puncture wounds due to cat bites should be left unsutured because of the high rate at which they become infected.
- *Antibiotic therapy:* See Table 27-1. Antibiotics are typically given for 3–5 days (as prophylaxis in pts presenting within 8 h of the bite) or for 10–14 days (as treatment for established infections).
- *Other prophylaxis:* Rabies prophylaxis (passive immunization with rabies immune globulin and active immunization with rabies vaccine) should be given in consultation with local and regional public health authorities. A tetanus booster for pts immunized previously but not boosted within 5 years should be considered, as should primary immunization and tetanus immune globulin administration for pts not previously immunized against tetanus.

## VENOMOUS SNAKEBITES

- **Epidemiology:** Worldwide, 1.2–5.5 million snakebites are sustained each year, with 421,000–1,841,000 envenomations and 20,000–94,000 deaths.
  - Bite rates are highest in temperate and tropical climates where populations subsist by manual agriculture and fishing.

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– Differentiation of venomous from nonvenomous snake species can be difficult; color pattern is notoriously misleading.

- **Clinical features:** Snake venoms are complex mixtures of enzymes and other substances that promote vascular leaking, cause tissue necrosis, affect the coagulation cascade, and impair organ function.
  – Specific presentations differ somewhat with the particular snake species.
  – Systemic symptoms may include hypotension, pulmonary edema, hemorrhage, altered mental status, or paralysis (including muscles of respiration).
- **Prognosis:** The overall mortality rate for venomous snakebite is <1% among U.S. victims who receive antivenom; the incidence of permanent functional loss in a bitten extremity is substantial.

## TREATMENT VENOMOUS SNAKEBITES

### FIELD MANAGEMENT

- Get the victim to definitive care as soon as possible.
- Splint a bitten extremity and keep it at heart level to lessen bleeding and discomfort.
- *Avoid* incisions into the bite wound, cooling, consultation with traditional healers, tourniquets, and electric shock because these measures are ineffective and may increase local tissue damage.
- If the offending snake is reliably identified and known to be primarily neurotoxic, pressure immobilization (wrapping of the entire limb in a bandage at a pressure of 40–70 mmHg for upper limbs or 55–70 mmHg for lower limbs) may be used. The victim must be carried to medical care, because walking will disperse venom from the bite site regardless of its anatomic location.

### HOSPITAL MANAGEMENT

- Monitor vital signs, cardiac rhythm, urine output, and $O_2$ saturation closely, and watch for evidence of cranial nerve dysfunction (e.g., ptosis), which may precede difficulty swallowing or respiratory insufficiency.
- Note the level of swelling and the circumference of the affected limb every 15 min until swelling has stabilized.
- Treat shock initially with isotonic saline (20–40 mL/kg IV); if hypotension persists, try 5% albumin (10–20 mL/kg IV) and vasopressors.
- Begin the search for appropriate, specific antivenom early in all cases of known venomous snakebite. In the United States, round-the-clock assistance is available from regional poison control centers.
  1. Any evidence of systemic envenomation (systemic symptoms or signs, laboratory abnormalities) and significant, progressive local findings (e.g., swelling that crosses a joint or involves more than half of the bitten limb) are indications for antivenom administration.
  2. Treating physicians should seek advice from snakebite experts regarding indications for and dosing of antivenom. The duration of antivenom administration depends on the offending snake species, but multiple doses are not effective in reversing bite responses that have already been established (e.g., renal failure, established paralysis, necrosis).
  3. Worldwide, antivenom quality varies; rates of anaphylactoid reaction can exceed 50%, prompting some authorities to recommend pretreatment with IV antihistamines (diphenhydramine, 1 mg/kg to a maximum of 100 mg; and cimetidine, 5–10 mg/kg to a maximum of 300 mg) or even a prophylactic SC or IM dose of epinephrine (0.01 mg/kg, up to 0.3 mg). CroFab, an antivenom

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used in the United States against North American pit viper species, poses a low risk of allergy elicitation.

4. A trial of acetylcholinesterase inhibitors should be undertaken for pts with objective evidence of neurologic dysfunction because this treatment may cause neurologic improvement in pts bitten by snakes with postsynaptic neurotoxins.

- Elevate the bitten extremity above heart level once antivenom administration has been initiated.
- Update tetanus immunization.
- Observe pts for muscle-compartment syndrome.
- Observe pts with signs of envenomation in the hospital for at least 24 h. Pts with "dry" bites should be watched for at least 8 h because symptoms are commonly delayed.

## MARINE ENVENOMATIONS

- Much of the management of envenomation by marine creatures is supportive in nature. Specific marine antivenom can be used when appropriate.

### INVERTEBRATES

- **Etiology:** Injuries from cnidocysts (stinging cells) of hydroids, fire coral, jellyfish, Portuguese man-of-wars, and sea anemones cause similar clinical symptoms that differ in severity. Other invertebrates (e.g., sea sponges, annelid worms, sea urchins) have spines that can inflict painful stings.
- **Clinical features:** Pain (prickling, burning, and throbbing), pruritus, and paresthesia develop immediately at the site of the bite. Neurologic, GI, renal, cardiovascular, respiratory, rheumatologic, and ocular symptoms have been described.

### TREATMENT MARINE INVERTEBRATE ENVENOMATIONS

- Decontaminate the skin immediately with lidocaine (up to 4%). Vinegar (5% acetic acid), rubbing alcohol (40–70% isopropanol), baking soda, papain (unseasoned meat tenderizer), lemon or lime juice, household ammonia, olive oil, or sugar may be effective, depending on the species of the stinging creature.
- Shaving the skin may help remove remaining nematocysts.
- After decontamination, topical anesthetics, antihistamines, or steroid lotions may be helpful.
- Narcotics may be necessary for persistent pain.
- Muscle spasms may respond to diazepam (2–5 mg titrated upward as needed) or IV 10% calcium gluconate (5–10 mL).

### VERTEBRATES

- **Etiology:** Many marine vertebrates, including stingrays, scorpionfish (e.g., lionfish and stonefish), marine catfish, and horned venomous sharks are capable of envenomating humans.
- **Clinical features:** depend on the offending fish
  - Stingrays: represent both an envenomation and a traumatic wound. The venom causes immediate, intense pain that may last up to 48 h. The wound often becomes ischemic and heals poorly. Systemic effects can include weakness, dysrhythmias, hypotension, paralysis, and rare deaths.

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– Stonefish: Because of the neuromuscular toxicity of the venom, stings may be life-threatening, and death may occur within 6–8 h. Local pain is immediate and intense and may last for days. Systemic effects are similar to those of stingray envenomations.

### TREATMENT MARINE VERTEBRATE ENVENOMATIONS

- Immerse the affected part immediately in nonscalding hot water (113°F/45°C) for 30–90 min or until there is significant pain relief. Repeated hot-water therapy may help with recurrent pain.
- Explore, debride, and vigorously irrigate the wound after local/regional anesthetics are given.
- Antivenom is available for stonefish and serious scorpionfish envenomations. In the United States, contact the nearest regional poison control center for assistance.
- Leave wounds to heal by secondary intention or to be treated by delayed primary closure.
- Update tetanus immunization.
- Consider empirical antibiotics to cover *Staphylococcus* and *Streptococcus* species for serious wounds or envenomations in immunocompromised hosts. Coverage should be broadened to include *Vibrio* species if the wound is primarily closed.

## MARINE POISONINGS

### CIGUATERA

- **Epidemiology:** the most common fish-associated nonbacterial food poisoning in the United States, with most cases occurring in Florida and Hawaii
  – In all, 20,000–50,000 people are affected annually.
  – Three-quarters of cases involve barracuda, snapper, jack, or grouper found in the Indian Ocean, the South Pacific, and the Caribbean Sea.
- **Pathogenesis:** Ciguatera toxin is created by microalgae, whose consumption by fish allows the toxin to accumulate in the food chain. Three major ciguatoxins—CTX-1, -2, and -3—are found in the flesh and viscera of ciguateric fish, are typically unaffected by external factors (e.g., heat, cold, freeze-drying, gastric acid), and do not generally affect the fish (e.g., odor, color, or taste).
- **Clinical features:** Virtually all pts are affected within 24 h; most experience symptoms within 2–6 h. The diagnosis is made on clinical grounds.
  – Symptoms can be numerous (>150 reported) and include diarrhea, vomiting, abdominal pain, neurologic signs (e.g., paresthesias, weakness, fasciculations, ataxia), maculopapular or vesicular rash, and hemodynamic instability.
  – A pathognomonic symptom—reversal of hot and cold tactile perception—develops within 3–5 days and can last for months.

### TREATMENT CIGUATERA POISONING

- Therapy is supportive and based on symptoms.
- Cool showers, hydroxyzine (25 mg PO q6–8h), or amitriptyline (25 mg PO bid) may ameliorate pruritus and dysesthesias.
- For 6 months after disease onset, the pt should avoid ingestion of fish (fresh or preserved), shellfish, fish oils, fish or shellfish sauces, alcohol, nuts, and nut oils.

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### PARALYTIC SHELLFISH POISONING

- **Etiology:** induced by ingestion of contaminated filter-feeding organisms (e.g., clams, oysters, scallops, mussels) that concentrate water-soluble, heat- and acid-stable chemical toxins
  - The best-characterized and most frequently identified paralytic shellfish toxin is saxitoxin.
  - Paralytic shellfish toxins cannot be destroyed by ordinary cooking.
- **Clinical features:** Oral paresthesias (initially tingling and burning, later numbness) develop within minutes to hours after ingestion of contaminated shellfish and progress to involve the neck and distal extremities. Flaccid paralysis and respiratory insufficiency may follow 2–12 h later; 12% of pts die, usually within 18 h.

**TREATMENT PARALYTIC SHELLFISH POISONING**

- If pts present within hours of ingestion, gastric lavage and stomach irrigation with 2 L of a 2% sodium bicarbonate solution may be of benefit, as may administration of activated charcoal (50–100 g) and non-magnesium-based cathartics (e.g., sorbitol, 20–50 g).
- The pt should be monitored for respiratory paralysis for at least 24 h.

### SCOMBROID

- **Etiology:** histamine intoxication due to bacterial decomposition of inadequately preserved or refrigerated scombroid fish (e.g., tuna, mackerel, saury, needlefish, wahoo, skipjack, and bonito)
  - This syndrome can also occur with nonscombroid fish (e.g., sardines, herring, dolphinfish, amberjack, and bluefish).
  - Affected fish typically have a sharply metallic or peppery taste but may be normal in appearance and flavor.
  - Because of uneven distribution of decay within the fish, not all people who eat an affected fish will become ill.
- **Clinical features:** Within 15–90 min of ingestion, pts present with oral tingling, mild abdominal pain, and nausea. Pts with severe cases develop flushing (exacerbated by UV exposure), pruritus, urticaria, angioneurotic edema, bronchospasm, GI symptoms, and hypotension.
  - Symptoms generally resolve within 8–12 h.
  - May be worse in pts concurrently taking isoniazid because of inhibition of GI tract histaminases

**TREATMENT SCOMBROID POISONING**

- Treatment consists of antihistamine ($H_1$ or $H_2$) administration.
- If bronchospasm is severe, an inhaled bronchodilator or injected epinephrine may be used.

## ARTHROPOD BITES AND STINGS

### TICK BITES AND TICK PARALYSIS

- **Epidemiology:** Ticks are important carriers of vector-borne diseases (e.g., Lyme disease, babesiosis, anaplasmosis, ehrlichiosis) in the United States.
- **Etiology:** While ticks feed on blood from their hosts, their secretions may produce local reactions, transmit diverse pathogens, induce a febrile illness, or cause paralysis. Soft ticks attach for <1 h; hard ticks can feed for >1 week.
- **Clinical features:** Except for tick-borne diseases, most manifestations of tick bites are self-limited following tick removal.

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– Tick-induced fever, in the absence of pathogen transmission, is associated with headache, nausea, and malaise and usually resolves ≤36 h after the tick is removed.
– Tick paralysis is an ascending flaccid paralysis due to a toxin in tick saliva that causes neuromuscular block and decreased nerve conduction.
  - Weakness begins symmetrically in the lower extremities ≤6 days after the tick's attachment and ascends symmetrically, causing complete paralysis of the extremities and cranial nerves.
  - Deep tendon reflexes are decreased or absent, but sensory examination and LP yield normal findings.
  - Tick removal results in improvement within hours; failure to remove the tick may lead ultimately to respiratory paralysis and death.

**TREATMENT TICK BITES AND TICK PARALYSIS**

- Ticks should be removed with forceps applied close to the point of attachment, which should then be disinfected.
- Pts bitten by a deer tick in Lyme disease–endemic regions can receive a prophylactic oral dose of doxycycline (200 mg) within 72 h of tick removal.
- Tick removal within 36 h of attachment usually prevents transmission of the agents of Lyme disease, babesiosis, anaplasmosis, and ehrlichiosis.

## SPIDER BITES

### Recluse Spider Bites

**Epidemiology:** Brown recluse spiders occur mainly in the south-central United States, and their close relatives are found in the Americas, Africa, and the Middle East. These spiders only infrequently bite humans, typically if threatened or pressed against the skin.

**Clinical Features**

- Most bites by the brown recluse spider result in only minor injury with edema and erythema, although severe necrosis of the skin and SC tissue and systemic hemolysis may occur.
- Within hours, the site of the bite becomes painful and pruritic, with central induration surrounded by zones of ischemia and erythema.
- Fever and other nonspecific systemic symptoms may develop within 3 days of the bite.
- Lesions typically resolve within a few days, but severe cases can leave a large ulcer and a depressed scar that take months or years to heal.

**TREATMENT RECLUSE SPIDER BITES**

- Initial management includes RICE (rest, ice, compression, elevation); administration of analgesics, antihistamines, antibiotics, and tetanus prophylaxis should be undertaken as indicated.
- Early debridement or surgical excision of the wound without closure delays healing.

### Widow Spider Bites

**Epidemiology:** Black widow spiders, recognized by a red hourglass marking on a shiny black ventral abdomen, are most abundant in the southeastern United States. Other *Latrodectus* species are present in other temperate and subtropical parts of the world.

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**Pathogenesis:** Female widow spiders produce a potent neurotoxin that binds irreversibly to presynaptic nerve terminals and causes release and depletion of acetylcholine and other neurotransmitters.

**Clinical features**

- Within 60 min, painful cramps spread from the bite site to large muscles of the extremities and trunk.
- Extreme abdominal muscular rigidity and pain may mimic peritonitis, but the abdomen is nontender.
- Other features are similar to that of acetylcholine overdose (e.g., excessive salivation, lacrimation, urination, and defecation; GI upset; and emesis).
- Although pain may subside within the first 12 h, it can recur for weeks.
- Respiratory arrest, cerebral hemorrhage, or cardiac failure may occur.

**TREATMENT WIDOW SPIDER BITES**

- Treatment consists of RICE and tetanus prophylaxis.
- The use of antivenom is limited by questionable efficacy and concern about anaphylaxis and serum sickness.

## SCORPION STINGS

**Epidemiology:** Only ~30 of the ~1000 species of scorpions produce potentially lethal venoms, causing >5000 deaths worldwide each year. Among scorpions in the United States, only the bark scorpion (*Centruroides sculpturatus* or *C. exilicauda*) in the Southwest produces a potentially lethal venom.

**Clinical features:** The severity of symptoms depends on the particular scorpion species. For the U.S. bark scorpion, symptoms progress to maximal severity in ~5 h and typically subside within 1–2 days, although pain and paresthesias can last for weeks.

- Bark scorpion: Swelling generally is not apparent; tapping on the affected area (the tap test) can accentuate pain, paresthesia, and hyperesthesia. Cranial nerve dysfunction and skeletal muscle hyperexcitability develop within hours. Complications include tachycardia, arrhythmias, hypertension, hyperthermia, rhabdomyolysis, acidosis, and occasional fatal respiratory arrests.
- Outside the United States, scorpion envenomations can cause massive release of endogenous catecholamines with hypertensive crises, arrhythmias, pulmonary edema, and myocardial damage.

**TREATMENT SCORPION STINGS**

- Stings of nonlethal species require at most ice packs, analgesics, or antihistamines.
- In severe envenomations, aggressive supportive care should include pressure dressings and cold packs to decrease the absorption of venom.
- A continuous IV infusion of midazolam helps control agitation and involuntary muscle movements.
- *C. sculpturatus* antivenom administered IV rapidly reverses cranial nerve dysfunction and muscular symptoms.

## HYMENOPTERA STINGS

**Epidemiology:** The hymenoptera include bees, wasps, hornets, yellow jackets, and ants. About 100 deaths from hymenoptera stings occur annually in the United States,

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nearly all due to allergic reactions to venoms. An estimated 0.4–4.0% of the U.S. population exhibits immediate-type hypersensitivity to insect stings.

**Clinical Features**

- Uncomplicated stings cause pain, a wheal-and-flare reaction, and local edema that subside within hours.
- Multiple stings (e.g., from wasps, hornets, ants) can lead to vomiting, diarrhea, generalized edema, dyspnea, hypotension, rhabdomyolysis, renal failure, and death.
- Large (>10-cm) local reactions (e.g., with erythema, edema, warmth, tenderness) progressing over 1–2 days are not uncommon; while they resemble cellulitis, they are in fact hypersensitivity reactions. Such reactions recur on subsequent exposure but are seldom accompanied by anaphylaxis.
- Serious reactions occur within 10 min (and rarely >5 h) after the sting and include upper airway edema, bronchospasm, hypotension, shock, and death.

## TREATMENT HYMENOPTERA STINGS

- Stingers embedded in skin should be removed promptly by grasping with forceps or scraping with a blade or fingernail.
- The site should be disinfected and ice packs applied to slow the spread of venom.
- Elevation of the bite site and administration of analgesics, oral antihistamines, and topical calamine lotion may ease symptoms.
- Large local reactions may require a short course of glucocorticoids.
- Anaphylaxis is treated with epinephrine hydrochloride (0.3–0.5 mL of a 1:1000 solution, given SC q20–30min as needed). For profound shock, epinephrine (2–5 mL of a 1:10,000 solution by slow IV push) is indicated. Pts should be observed for 24 h for recurrent anaphylaxis.
- Pts with a history of allergy to insect stings should carry a sting kit and seek medical attention immediately after the kit is used.

For a more detailed discussion, see Madoff LC, Pereyra F: Infectious Complications of Bites, Chap. 167e; Lei C, Badowski NJ, Auerbach PS, Norris RL: Disorders Caused by Venomous Snakebites and Marine Animal Exposures, Chap. 474, p. 2733; and Pollack RJ, Norton SA: Ectoparasite Infestations and Arthropod Injuries, Chap. 475, p. 2744, in HPIM-19.

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# 28 Fever, Hyperthermia, and Rash

## DEFINITIONS

- *Temperature:* The hypothalamic thermoregulatory center balances excess heat production from metabolic activity in muscle and liver with heat dissipation from the skin and lungs to maintain a normal body temperature of 36.8° ± 0.4°C (98.2° ± 0.7°F), with diurnal variation (lower in A.M., higher in P.M.).
- *Fever*: an elevation of body temperature (>37.2°C/98.9°F in the morning and >37.7°C/99.9°F in the evening) in conjunction with an increase in the hypothalamic set point
- *Fever of unknown origin* (*FUO*): temperatures >38.3°C (>101°F) on two or more occasions and an illness duration of ≥3 weeks, with no known immunocompromised state and unrevealing laboratory and radiologic investigations into the cause
- *Hyperpyrexia*: temperatures >41.5°C (>106.7°F) that can occur with severe infections but more commonly occur with CNS hemorrhages
- *Hyperthermia*: an uncontrolled increase in body temperature that exceeds the body's ability to lose heat *without* a change in the hypothalamic set point. Hyperthermia does not involve pyrogenic molecules.
- *Pyrogen*: any fever-causing substance, including exogenous pyrogens (e.g., microbial toxins, lipopolysaccharide, superantigens) and pyrogenic cytokines (e.g., IL-1, IL-6, TNF)

## FEVER

- **Pathogenesis:** The hypothalamic set point increases, causing peripheral vasoconstriction (i.e., heat conservation). The pt feels cold as a result of blood shunting to the internal organs. Mechanisms of heat production (e.g., shivering, increased hepatic thermogenesis) help to raise the body temperature to the new set point. Increases in peripheral prostaglandin $E_2$ account for the nonspecific myalgias and arthralgias that often accompany fever. When the set point is lowered again by resolution or treatment of fever, processes of heat loss (e.g., peripheral vasodilation and sweating) commence.
- **Etiology:** Most fevers are associated with self-limited infections (usually viral) and have causes that are easily identified.

### APPROACH TO THE PATIENT: Fever

- *History:* A meticulous history is essential, with particular attention to the chronology of events (e.g., in the case of rash: the site of onset and the direction and rate of spread; see below) and the relation of symptoms to medications, pet exposure, sick contacts, sexual contacts, travel, trauma, and the presence of prosthetic materials.
- *Physical examination:* A thorough physical examination should be performed. A consistent site for taking temperatures should be used. Temperature–pulse dissociations (relative bradycardia) should be noted if present (sometimes present, for example, with typhoid fever, brucellosis, leptospirosis, factitious



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fever). Close attention should be paid to any rash, with precise definition of its salient features.

1. Lesion type (e.g., macule, papule, nodule, vesicle, pustule, purpura, ulcer; see Chap. 59 for details), configuration (e.g., annular or target), arrangement, distribution (e.g., central or peripheral)
2. Classification of rash
   a. Centrally distributed maculopapular eruptions (e.g., viral exanthems, exanthematous drug-induced eruptions)
   b. Peripheral eruptions (e.g., Rocky Mountain spotted fever, secondary syphilis, bacterial endocarditis)
   c. Confluent desquamative erythemas (e.g., toxic shock syndrome)
   d. Vesiculobullous eruptions (e.g., varicella, primary HSV infection, ecthyma gangrenosum)
   e. Urticaria-like eruptions: in the presence of fever, usually due to urticarial vasculitis caused by serum sickness, connective-tissue disease, infection (hepatitis B virus, enteroviral, or parasitic infection), or malignancy (particularly lymphoma)
   f. Nodular eruptions (e.g., disseminated fungal infection, erythema nodosum, Sweet's syndrome)
   g. Purpuric eruptions (e.g., meningococcemia, viral hemorrhagic fever, disseminated gonococcemia)
   h. Eruptions with ulcers or eschars (e.g., rickettsial diseases, tularemia, anthrax)

- *Laboratory tests:* CBC with differential, ESR, and C-reactive protein; other tests as indicated by history and physical examination

## TREATMENT FEVER

- The use of antipyretics is not contraindicated in common viral or bacterial infections and can relieve symptoms without slowing resolution of infection. Withholding of antipyretics may be useful, however, in evaluating the effectiveness of a particular antibiotic or in diagnosing conditions with temperature–pulse dissociations or relapsing fevers (e.g., infection with *Plasmodium* or *Borrelia* species).
- Treatment of fever in pts with preexisting impairment of cardiac, pulmonary, or CNS function is recommended to reduce oxygen demand.
- Aspirin, NSAIDs, and glucocorticoids are effective antipyretics. Acetaminophen is preferred because it does not mask signs of inflammation, does not impair platelet function, and is not associated with Reye's syndrome.
- Hyperpyretic pts should be treated with cooling blankets in addition to oral antipyretics.

## FEVER OF UNKNOWN ORIGIN

- **Etiology:** FUO is more commonly caused by an atypical presentation of a common disease than by a very rare disease. The most common causes of FUO can be categorized as infections, neoplasms, or noninfectious inflammatory diseases (NIIDs; e.g., "collagen or rheumatic diseases," vasculitis syndromes, and granulomatous disorders). The frequency of each category differs between Western countries and countries in other parts of the world: infections, neoplasms, and NIIDs account for 22%, 11%, and 23% of Western cases, respectively, and for 43%, 16%, and 23% of cases in other geographic regions.

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– Atypical presentations of endocarditis, diverticulitis, vertebral osteomyelitis, and extrapulmonary tuberculosis represent the more common infectious-disease diagnoses.
– The most common NIIDs that result in FUO are large-vessel vasculitis, polymyalgia rheumatica, sarcoidosis, familial Mediterranean fever, and adult-onset Still's disease.
– Among the neoplasms, malignant lymphoma is by far the most common cause of FUO. Fever occasionally precedes lymphadenopathy detectable by physical examination.

## APPROACH TO THE PATIENT: **FUO**

A structured approach to the pt with FUO is shown in Fig. 28-1. The most important step in the diagnostic workup is the search for potentially diagnostic clues (PDCs) through complete and repeated history taking and physical examination. $^{18}$F-fluorodeoxyglucose positron emission tomography combined with low-dose CT (FDG-PET/CT) can be used to guide additional diagnostic tests (e.g., targeted biopsies and culture) and aids in final diagnosis of FUO in 54% of cases.

## TREATMENT FUO

Empirical therapeutic trials with antibiotics, glucocorticoids, or antituberculous agents should be avoided in FUO except when a pt's condition is rapidly deteriorating after diagnostic tests have failed to provide a definitive result.

- Hemodynamic instability and neutropenia may prompt earlier empirical antiinfective therapies.
- Use of glucocorticoids and NSAIDs should be avoided unless infection and malignant lymphoma have been largely ruled out and unless inflammatory disease is both probable and debilitating or life-threatening.
- Anakinra, a recombinant form of the naturally occurring IL-1 receptor antagonist, blocks the activity of both IL-1α and IL-1β and is extremely effective in the treatment of many autoinflammatory syndromes. A therapeutic trial with anakinra can be considered in pts whose FUO has not been diagnosed after later-stage diagnostic tests.

**Prognosis**: When no underlying source of FUO is identified after prolonged observation (>6 months), the prognosis is generally good.

## HYPERTHERMIA

- **Etiology:** Exogenous heat exposure (e.g., heat stroke) and endogenous heat production (e.g., drug-induced hyperthermia, malignant hyperthermia) are two mechanisms by which hyperthermia can result in dangerously high internal temperatures.
  – *Heat stroke:* thermoregulatory failure in association with a warm environment; can be categorized as *exertional* (e.g., due to exercise in high heat or humidity) or *classic* (typically occurring in pts with chronic diseases that predispose to heat-related illnesses)
- **Clinical features:** high core temperature in association with an appropriate history (heat exposure, certain drug treatments) and dry skin, hallucinations, delirium, pupil dilation, muscle rigidity, and/or elevated levels of CPK
- **Diagnosis:** It can be difficult to distinguish fever from hyperthermia. The clinical history is often most useful (e.g., a history of heat exposure or of treatment with drugs that interfere with thermoregulation).

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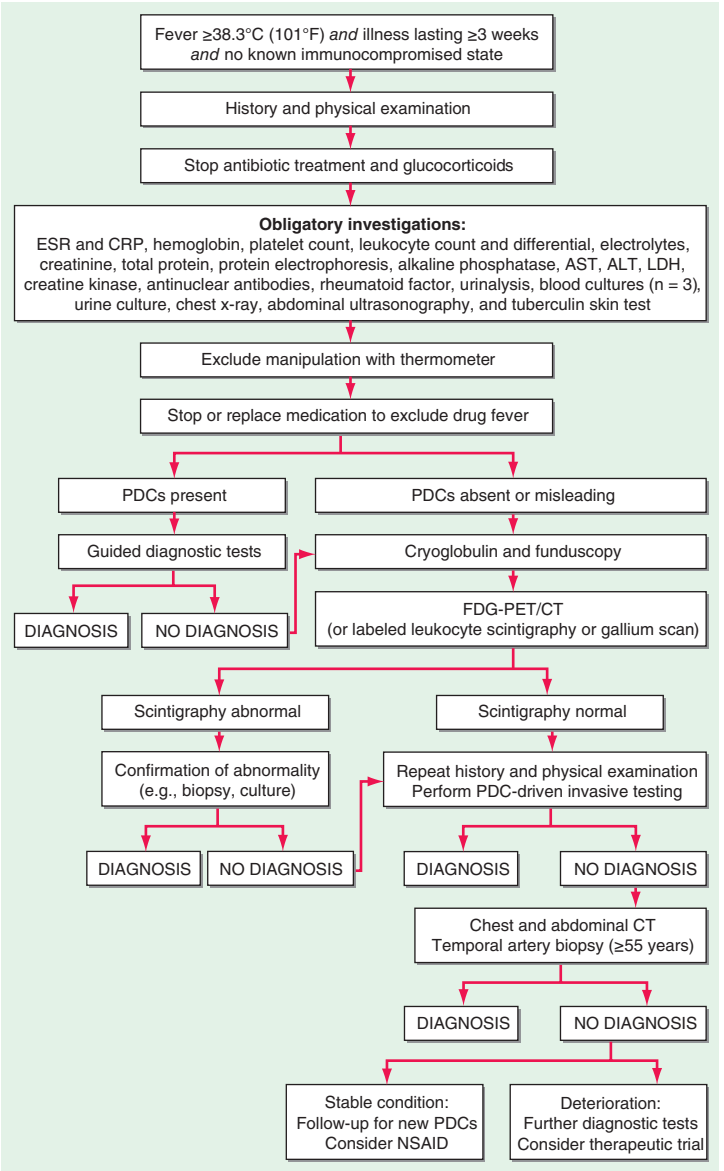


**FIGURE 28-1** Structured approach to pts with fever of unknown origin (FUO). ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FDG-PET/CT, $^{18}$F-fluorodeoxyglucose positron emission tomography combined with low-dose computed tomography; LDH, lactate dehydrogenase; PDCs, potentially diagnostic clues (all localizing signs, symptoms, and abnormalities potentially pointing toward a diagnosis); NSAID, nonsteroidal anti-inflammatory drug.

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–*Hyperthermic* pts have hot, dry skin; antipyretic agents do not lower the body temperature.
–*Febrile* pts can have cold skin (as a result of vasoconstriction) or hot, moist skin; antipyretics usually result in some lowering of the body temperature.

**TREATMENT HYPERTHERMIA**

- Before cooling is initiated, endotracheal intubation, CVP determination, and continuous core-temperature monitoring should be considered.
- Evaporative cooling (spraying cool water on exposed skin while fans direct continuous airflow over the moistened skin) is the most practical and effective technique for reducing body temperature. Invasive methods (e.g., IV infusion of cold fluids, cold thoracic and peritoneal lavage, cardiopulmonary bypass) are effective but rarely necessary.
- Given the risk of dehydration, IV fluids are necessary or at least appropriate. The CVP, particularly in classic heat stroke, may be deceptively high; rarely, measurement of wedge pressures via a pulmonary artery catheter may be necessary to guide resuscitation.

For a more detailed discussion, see Dinarello CA, Porat R: Fever and Hyperthermia, Chap. 23, p. 123; Kaye ET, Kaye KM: Fever and Rash, Chap. 24, p. 127; Kaye KM, Kaye ET: Atlas of Rashes Associated with Fever, Chap. 25e; Bleeker-Rovers CP, van der Meer JWM: Fever of Unknown Origin, Chap. 26, p. 135; and Danzl DF: Heat-Related Illnesses, Chap. 479e, in HPIM-19.

# 29 Generalized Fatigue

*Fatigue* is one of the most common complaints related by pts. It usually refers to nonspecific sense of a low energy level, or the feeling that near exhaustion is reached after relatively little exertion. Fatigue should be distinguished from true neurologic *weakness*, which describes a reduction in the normal power of one or more muscles (Chap. 53). It is not uncommon for pts, especially the elderly, to present with generalized failure to thrive, which may include components of fatigue and weakness, depending on the cause.

## CLINICAL MANIFESTATIONS

Because the causes of generalized fatigue are numerous, a thorough history, review of systems (ROS), and physical examination are paramount to narrow the focus to likely causes. The history and ROS should focus on the temporal onset of fatigue and its progression. Has it lasted days, weeks, or months? Activities of daily living, exercise, eating habits/appetite, sexual practices, and sleep habits should be reviewed. Features of depression or dementia should be sought. Travel history and

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possible exposures to infectious agents should be reviewed, along with the medication list. The ROS may elicit important clues as to organ system involvement. The past medical history may elucidate potential precursors to the current presentation, such as previous malignancy or cardiac problems. The physical examination should specifically assess weight and nutritional status, lymphadenopathy, hepatosplenomegaly, abdominal masses, pallor, rash, heart failure, new murmurs, painful joints or trigger points, and evidence of weakness or neurologic abnormalities. A finding of true weakness or paralysis should prompt consideration of neurologic disorders (Chap. 53).

## DIFFERENTIAL DIAGNOSIS

Determining the cause of fatigue can be one of the most challenging diagnostic problems in medicine because the differential diagnosis is very broad, including infection, malignancy, cardiac disease, endocrine disorders, neurologic disease, depression, or serious abnormalities of virtually any organ system, as well as side effects of many medications (Table 29-1). Symptoms of fever and weight loss will focus attention on infectious causes, whereas symptoms of progressive dyspnea might point toward cardiac, pulmonary, or renal causes. A presentation that includes arthralgia suggests the possibility of a rheumatologic disorder. A previous malignancy, thought to be

**TABLE 29-1 POTENTIAL CAUSES OF GENERALIZED FATIGUE**

| Disease Category | Examples |
|---|---|
| Infection | HIV, TB, Lyme disease, endocarditis, hepatitis, sinusitis, fungal, EBV, malaria (chronic phase) |
| Inflammatory disease | RA, polymyalgia rheumatica, chronic fatigue syndrome, fibromyalgia, sarcoidosis |
| Cancer | Lung, GI, breast, prostate, leukemia, lymphoma, metastases |
| Psychiatric | Depression, alcoholism, chronic anxiety |
| Metabolic | Hypothyroidism, hyperthyroidism, diabetes mellitus, Addison's disease, hyperparathyroidism, hypogonadism, hypopituitarism (TSH, ACTH, growth hormone deficiency), McArdle's disease |
| Electrolyte imbalance | Hypercalcemia, hypokalemia, hyponatremia, hypomagnesemia |
| Nutrition, vitamin deficiency | Starvation, obesity, iron deficiency, vitamin $B_{12}$, folic acid deficiency, vitamin C deficiency (scurvy), thiamine deficiency (beriberi) |
| Neurologic | Multiple sclerosis, myasthenia gravis, dementia |
| Cardiac | Heart failure, CAD, valvular disease, cardiomyopathy |
| Pulmonary | COPD, pulmonary hypertension, chronic pulmonary emboli, sarcoidosis |
| Sleep disturbances | Sleep apnea, insomnia, restless leg syndrome |
| Gastrointestinal | Celiac disease, Crohn's, ulcerative colitis, chronic hepatitis, cirrhosis |
| Hematologic | Anemia |
| Renal | Renal failure |
| Medication | Sedatives, antihistamines, narcotics, β blockers, and many other medications |

***Abbreviations:*** ACTH, adrenocorticotropin hormone; CAD, coronary artery disease; COPD; chronic obstructive pulmonary disorder; EBV, Epstein-Barr virus; RA, rheumatoid arthritis; TSH, thyroid-stimulating hormone.

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cured or in remission, may have recurred or metastasized widely. A previous history of valvular heart disease or cardiomyopathy may identify a condition that has decompensated. Treatment for Graves' disease may have resulted in hypothyroidism. Sleep apnea is under-recognized and is a common cause of unexplained fatigue. Changes in medication should always be pursued, whether discontinued or recently started. Almost any new medication has the potential to cause fatigue. However, a temporal association with a new medication should not eliminate other causes, because many pts may have received new medications in an effort to address their complaints. Medications and their dosages should be carefully assessed, especially in elderly pts, in whom polypharmacy and inappropriate or misunderstood dosing is a frequent cause of fatigue. The time course for presentation is also valuable. Indolent presentations over months to years are more likely to be associated with slowly progressive organ failure or endocrinopathies, whereas a more rapid course over weeks to months suggests infection or malignancy.

## LABORATORY TESTING

Laboratory testing and imaging should be guided by the history and physical examination. However, a CBC with differential, electrolytes, BUN, creatinine, glucose, calcium, and LFTs are useful in most pts with undifferentiated fatigue, because these tests will rule out many causes and may provide clues to unsuspected disorders. Similarly, a CXR is useful to evaluate many possible disorders rapidly, including heart failure, pulmonary disease, or occult malignancy that may be detected in the lungs or bony structures. Subsequent testing should be based on the initial results and clinical assessment of the likely differential diagnoses. For example, a finding of anemia would dictate the need to assess whether it has features of iron deficiency or hemolysis, thereby narrowing potential causes. Hyponatremia might be caused by syndrome of inappropriate antidiuretic hormone (SIADH), hypothyroidism, adrenal insufficiency, or medications or by underlying cardiac, pulmonary, liver, or renal dysfunction. An elevated WBC count would raise the possibility of infection or malignancy. Thus, the approach is generally one of gathering information in a serial but cost-effective manner to narrow the differential diagnosis progressively.

## TREATMENT GENERALIZED FATIGUE

Treatment should be based on the diagnosis, if known. Many conditions, such as metabolic, nutritional, or endocrine disorders, can be corrected quickly by appropriate treatment of the underlying causes. Specific treatment can also be initiated for many infections, such as TB, sinusitis, or endocarditis. Pts with chronic conditions such as chronic obstructive pulmonary disorder (COPD), heart failure, renal failure, or liver disease may benefit from interventions that enhance organ function or correct associated metabolic problems, and it may be possible to gradually improve physical conditioning. In pts with cancer, fatigue may be caused by chemotherapy or radiation and may resolve with time; treatment of associated anemia, nutritional deficiency, hyponatremia, or hypercalcemia may increase energy levels. Replacement therapy in endocrine deficiencies typically results in improvement. Treatment of depression or sleep disorders, whether a primary cause of fatigue or secondary to a medical disorder, may be beneficial. A variety of treatments are now available for sleep apnea, including continuous positive airway pressure (CPAP). Withdrawal of medications that potentially contribute to fatigue should be considered, recognizing that other medications may need to be substituted for the underlying condition. In elderly pts, appropriate medication dose adjustments (typically lowering the dose) and restricting the regimen to only essential drugs may improve fatigue.

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## CHRONIC FATIGUE SYNDROME

Chronic fatigue syndrome (CFS) is characterized by debilitating fatigue and several associated physical, constitutional, and neuropsychological complaints. The majority of pts (~75%) are women, generally 30–45 years old. The CDC has developed diagnostic criteria for CFS based upon symptoms and the exclusion of other illnesses (Table 29-2). The cause is uncertain, although clinical manifestations often follow an infectious illness (Q fever, Lyme disease, mononucleosis, or another viral illness). Many studies have attempted, without success, to link CFS to specific infectious agents such as EBV, a retrovirus (including a murine leukemia virus–related retrovirus), or an enterovirus, and many others. CFS might be caused by more than one infectious agent or by postinfectious immune responses. Physical or psychological stress is also often identified as a precipitating factor. Depression is present in half to two-thirds of pts, and some experts believe that CFS is fundamentally a psychiatric disorder.

CFS remains a diagnosis of exclusion, and no laboratory test can establish the diagnosis or measure its severity. CFS does not appear to progress but typically has a protracted course. The median annual recovery rate is 5% (range, 0–31%) with an improvement rate of 39% (range, 8–63%).

The management of CFS commences with acknowledgement by the physician that the pt's daily functioning is impaired. The pt should be informed of the current understanding of CFS (or lack thereof) and be offered general advice about disease management. NSAIDs alleviate headache, diffuse pain, and feverishness. Regular and adequate sleep is important. Antihistamines or decongestants may be helpful for symptoms of rhinitis and sinusitis. Although the pt may be averse to psychiatric diagnoses, features of depression and anxiety may justify treatment. Nonsedating antidepressants may improve mood and disordered sleep and may attenuate the fatigue. Cognitive behavioral therapy (CBT) and graded exercise therapy (GET) have been found to be effective treatment strategies in some pts.

**TABLE 29-2 CDC CRITERIA FOR DIAGNOSIS OF CFS**

Consider a diagnosis of CFS if these three criteria are met:

1. The individual has severe chronic fatigue for ≥6 consecutive months that is not due to ongoing exertion or other medical conditions associated with fatigue (these other conditions need to be ruled out by a doctor after diagnostic tests have been conducted)
2. The fatigue significantly interferes with daily activities and work.
3. The individual concurrently has four or more of the following eight symptoms:
   - postexertion malaise lasting >24 hours
   - unrefreshing sleep
   - significant impairment of short-term memory or concentration
   - muscle pain
   - multijoint pain without swelling or redness
   - headaches of a new type, pattern, or severity
   - tender cervical or axillary lymph nodes
   - sore throat that is frequent or recurring

***Abbreviations:*** CDC, Centers for Disease Control and Prevention; CFS, chronic fatigue syndrome.
***Source:*** www.cdc.gov/cfs/diagnosis/index.html

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For a more detailed discussion, see Aminoff MJ: Neurologic Causes of Weakness and Paralysis, Chap. 30, p. 154; Czeisler CA, Thomas E. Scammell TE, Saper CB: Sleep Disorders, Chap. 38, p. 184; Robertson RG, Jameson LJ: Involuntary Weight Loss, Chap. 80, p. 641; Bleijenberg G, van der Meer JWM: Chronic Fatigue Syndrome, Chap. 464e; Reus VI: Mental Disorders, Chap. 466, p. 2708, in HPIM-19.

# 30 Weight Loss

Significant unintentional weight loss in a previously healthy individual is often a harbinger of underlying systemic disease. The routine medical history should always include inquiry about changes in weight. Rapid fluctuations of weight over days suggest loss or gain of fluid, whereas long-term changes usually involve loss of tissue mass. Loss of 5% of body weight over 6–12 months should prompt further evaluation. Gradual weight loss is physiologic in persons over age 80, but this demographic group also has a high risk for malignancy or other serious illness.

## ETIOLOGY

The principal causes of involuntary weight loss can be assigned to four categories: (1) malignant neoplasms, (2) chronic inflammatory or infectious diseases, (3) metabolic disorders, or (4) psychiatric disorders (Table 30-1). In older persons the most common causes of weight loss are depression, cancer, and benign GI disease. Lung and GI cancers are the most common malignancies in pts presenting with weight loss. In younger individuals, diabetes mellitus, hyperthyroidism, anorexia nervosa, and infection, especially with HIV, should be considered.

## CLINICAL FEATURES

Before extensive evaluation is undertaken, it is important to confirm that weight loss has occurred (up to 50% of claims of weight loss cannot be substantiated). In the absence of documentation, changes in belt notch size or the fit of clothing may help to determine loss of weight.

The *history* should include questions about fever, pain, shortness of breath or cough, palpitations, and evidence of neurologic disease. A history of GI symptoms should be obtained, including difficulty eating, dysgeusia, dysphagia, anorexia, nausea, and change in bowel habits. Travel history, use of cigarettes, alcohol, and all medications should be reviewed, and pts should be questioned about previous illness or surgery as well as diseases in family members. Risk factors for HIV should be assessed. Signs of depression, evidence of dementia, and social factors, including isolation, loneliness, and financial issues that might affect food intake, should be considered.

*Physical examination* should begin with weight determination and documentation of vital signs. The skin should be examined for pallor, jaundice, turgor, surgical scars, and stigmata of systemic disease. Evaluation for oral thrush, dental disease, thyroid gland enlargement, and adenopathy and for respiratory, cardiac, or

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**TABLE 30-1 CAUSES OF WEIGHT LOSS**

- Cancer
- Endocrine and metabolic causes
  - Hyperthyroidism
  - Diabetes mellitus
  - Pheochromocytoma
  - Adrenal insufficiency
- Gastrointestinal disorders
  - Malabsorption
  - Obstruction
  - Peptic ulcer
  - Celiac disease
  - Inflammatory bowel disease
  - Pancreatitis
  - Pernicious anemia
- Cardiac disorders
  - Chronic ischemia
  - Chronic congestive heart failure
- Respiratory disorders
  - Emphysema
  - Chronic obstructive pulmonary disease
- Renal insufficiency
- Rheumatologic disease
- Infections
  - HIV
  - Tuberculosis
  - Parasitic infection
  - Subacute bacterial endocarditis
- Medications
  - Sedatives
  - Antibiotics
  - Nonsteroidal anti-inflammatory drugs
  - Serotonin reuptake inhibitors
  - Metformin
  - Levodopa
  - ACE inhibitors
  - Other drugs
- Disorders of the mouth and teeth
  - Caries
  - Dysgeusia
- Age-related factors
  - Physiologic changes
  - Decreased taste and smell
  - Functional disabilities
- Neurologic causes
  - Stroke
  - Parkinson's disease
  - Neuromuscular disorders
  - Dementia
- Social causes
  - Isolation
  - Economic hardship
- Psychiatric and behavioral causes
  - Depression
  - Anxiety
  - Bereavement
  - Alcoholism
  - Eating disorders
  - Increased activity or exercise
  - Idiopathic

***Abbreviation:*** ACE, angiotensin-converting enzyme.

abdominal abnormalities should be performed. All men should have a rectal examination, including the prostate; all women should have a pelvic examination; and both should have testing of the stool for occult blood. Neurologic examination should include mental status assessment and screening for depression.

Initial *laboratory evaluation* is shown in Table 30-2, with appropriate treatment based on the underlying cause of the weight loss. If an etiology of weight loss is not found, careful clinical follow-up, rather than persistent undirected testing, is reasonable. The absence of abnormal laboratory tests is a favorable prognostic sign.

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**TABLE 30-2 SCREENING TESTS FOR EVALUATION OF INVOLUNTARY WEIGHT LOSS**

| Initial testing | Additional testing |
|---|---|
| CBC | HIV test |
| Electrolytes, calcium, glucose | Upper and/or lower gastrointestinal endoscopy |
| Renal and liver function tests | Abdominal ultrasound |
| Urinalysis | |
| Thyroid-stimulating hormone | |
| Chest x-ray | |
| Recommended cancer screening | |

***Abbreviation:*** CBC, complete blood cell.

## TREATMENT WEIGHT LOSS

Treatment of weight loss should be directed at correcting the underlying physical cause or social circumstance. In specific situations, nutritional supplements and medications (megestrol acetate, dronabinol, or growth hormone) may be effective for stimulating appetite or increasing weight.

For a more detailed discussion, see Robertson RG, Jameson JL: Involuntary Weight Loss, Chap. 56, p. 274, in HPIM-19.

# 31 Chest Pain

There is little correlation between the severity of chest pain and the seriousness of its cause. The range of disorders that cause chest discomfort is shown in Table 31-1.

## POTENTIALLY SERIOUS CAUSES

The differential diagnosis of chest pain is shown in Figs. 31-1 and 31-2. It is useful to characterize the chest pain as (1) new, acute, and ongoing; (2) recurrent, episodic; and (3) persistent, e.g., for days at a time.

### Myocardial Ischemia: Angina Pectoris

Substernal pressure, squeezing, constriction, with radiation often to left arm; usually on exertion, especially after meals or with emotional arousal. Characteristically relieved by rest and nitroglycerin.

### Acute Myocardial Infarction (Chaps. 119 and 120)

Similar to angina but usually more severe, of longer duration (≥30 min), and not immediately relieved by rest or nitroglycerin. S3 and/or S4 may be present.

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**TABLE 31-1 DIFFERENTIAL DIAGNOSES OF PATIENTS ADMITTED TO HOSPITAL WITH ACUTE CHEST PAIN RULED NOT MYOCARDIAL INFARCTION**

| Diagnosis | Percentage |
|---|---|
| Gastroesophageal disease[a] | 42 |
| Gastroesophageal reflux | |
| Esophageal motility disorders | |
| Peptic ulcer | |
| Gallstones | |
| Ischemic heart disease | 31 |
| Chest wall syndromes | 28 |
| Pericarditis | 4 |
| Pleuritis/pneumonia | 2 |
| Pulmonary embolism | 2 |
| Lung cancer | 1.5 |
| Aortic aneurysm | 1 |
| Aortic stenosis | 1 |
| Herpes zoster | 1 |

[a]In order of frequency.
***Source:*** Fruergaard P et al: *Eur Heart J* 17:1028, 1996.

### Pulmonary Embolism (Chap. 133)

May be substernal or lateral, pleuritic in nature, and associated with hemoptysis, tachycardia, and hypoxemia.

### Aortic Dissection (Chap. 125)

Very severe, in center of chest, a sharp "ripping" quality, radiates to back, not affected by changes in position. May be associated with weak or absent peripheral pulses.

### Mediastinal Emphysema

Sharp, intense, localized to substernal region; often associated with audible crepitus.

### Acute Pericarditis (Chap. 116)

Usually steady, crushing, substernal; often has pleuritic component aggravated by cough, deep inspiration, supine position, and relieved by sitting upright; pericardial friction rub often audible.

### Pleurisy

Due to inflammation; less commonly tumor and pneumothorax. Usually unilateral, knifelike, superficial, aggravated by cough and respiration.

## LESS SERIOUS CAUSES

### Costochondral Pain

In anterior chest, usually sharply localized, may be brief and darting or a persistent dull ache. Can be reproduced by pressure on costochondral and/or chondrosternal junctions. In Tietze's syndrome (costochondritis), joints are swollen, red, and tender.

### Chest Wall Pain

Due to strain of muscles or ligaments from excessive exercise or rib fracture from trauma; accompanied by local tenderness.

### Esophageal Pain

Deep thoracic discomfort; may be accompanied by dysphagia and regurgitation.

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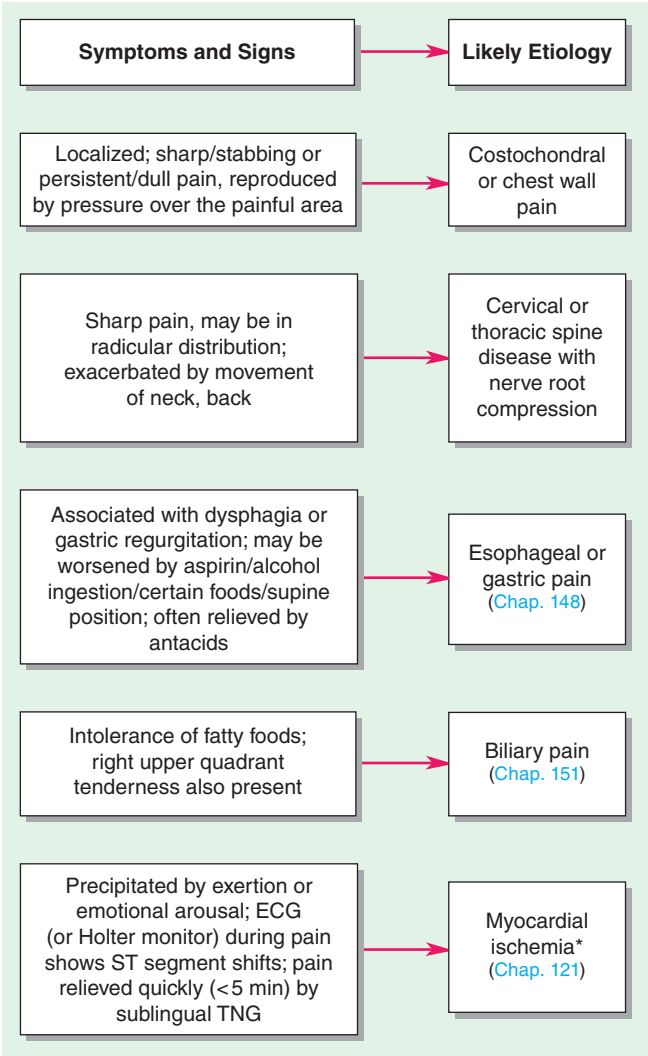


**FIGURE 31-1** Differential diagnosis of recurrent chest pain. *If myocardial ischemia suspected, also consider aortic valve disease (**Chap. 114**) and hypertrophic obstructive cardiomyopathy (**Chap. 115**) if systolic murmur present. TNG, trinitroglycerin.

## Emotional Disorders

Prolonged ache or dartlike, brief, flashing pain; associated with fatigue, emotional strain.

### OTHER CAUSES

(1) Cervical disk disease; (2) osteoarthritis of cervical or thoracic spine; (3) abdominal disorders: peptic ulcer, hiatus hernia, pancreatitis, biliary colic; (4) tracheobronchitis,

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| | | | | | | |
|---|---|---|---|---|---|---|
| **Description of pain** | Oppressive, constrictive, or squeezing; may radiate to arm(s), neck, back | "Tearing" or "ripping"; may travel from anterior chest to mid-back | Crushing, sharp, pleuritic; relieved by sitting forward | Pleuritic, sharp; possibly accompanied by cough/hemoptysis | Very sharp, pleuritic | Intense substernal and epigastric; accompanied by vomiting ± hematemesis |
| **Background history** | Less severe, similar pain on exertion; + coronary risk factors | Hypertension or Marfan syndrome (Chap. 158) | Recent upper respiratory tract infection, or other conditions which predispose to pericarditis (Chap. 116) | Recent surgery or other immobilization | Recent chest trauma, or history of chronic obstructive lung disease | Recent recurrent vomiting/retching |
| **Key physical findings** | Diaphoresis, pallor; S4 common; S3 less common | Weak, asymmetric peripheral pulses; possible diastolic murmur of aortic insufficiency (Chap. 114) | Pericardial friction rub (usually three components, best heard by sitting patient forward) | Tachypnea; possible pleural friction rub | Tachypnea; breath sounds and hyperresonance over affected lung field | Subcutaneous emphysema; audible crepitus adjacent to the sternum |
| **Consider** | **Acute coronary syndromes** (Chaps. 119 and 120) | **Aortic dissection** (Chap. 125) | **Acute pericarditis** (Chap. 116) | **Pulmonary embolism** (Chap. 133) | **Acute pneumothorax** (Chap. 135) | **Rupture of esophagus** |
| **Confirmatory tests** | • Serial ECGs<br>• Serial cardiac markers (esp. troponins,CK) | • CXR – widened mediastinal silhouette<br>• MRI, CT, or transesophageal echogram: intimal flap visualized<br>• Aortic angiogram: definitive diagnosis | • ECG: diffuse ST elevation and PR segment depression<br>• Echogram: pericardial effusion often visualized | • Normal D-dimer makes diagnosis unlikely<br>• CT angiography or lung scan: $\dot{V}/\dot{Q}$ mismatch<br>• Pulmonary angiogram: arterial luminal filling defects | • CXR: radiolucency within pleural space; poss. collapse of adjacent lung segment; if tension pneumothorax, mediastinum is shifted to opp. side | • CXR: pneumomediastinum<br>• Esophageal endoscopy is diagnostic |

**FIGURE 31-2** Differential diagnosis of serious conditions that cause acute chest pain. CK, creatine phosphokinase.

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pneumonia; (5) diseases of the breast (inflammation, tumor); (6) intercostal neuritis (herpes zoster).

## APPROACH TO THE PATIENT: **Chest Pain**

A meticulous history of the behavior of pain, what precipitates it and what relieves it, aids diagnosis of recurrent chest pain. Figure 31-2 presents clues to diagnosis and workup of acute, life-threatening chest pain.

An ECG is key to the initial evaluation to rapidly distinguish pts with acute ST-elevation MI, who typically warrant immediate reperfusion therapies (Chap. 119).

For a more detailed discussion, see Morrow DA: Chest Discomfort, Chap. 19, p. 95, in HPIM-19.

# 32 Palpitations

Palpitations represent an intermittent or sustained awareness of the heartbeat, often described by the pt as a thumping, pounding, or fluttering sensation in the chest. The symptom may reflect a cardiac etiology, an extracardiac cause (e.g., hyperthyroidism, use of stimulants [e.g., caffeine, cocaine]), or a high catecholamine state (e.g., exercise, anxiety, pheochromocytoma). Contributory cardiac dysrhythmias include atrial or ventricular premature beats or, when sustained and regular, supraventricular or ventricular tachyarrhythmias (Chap. 123). *Irregular* sustained palpitations are often due to atrial fibrillation. Asking the pt to "tap out" the sense of palpitation can help distinguish regular from irregular rhythms.

## APPROACH TO THE PATIENT: **Palpitations**

Palpitations are often benign but may represent an important dysrhythmia if associated with hemodynamic compromise (light-headedness, syncope, angina, dyspnea) or if found in pts with preexisting coronary artery disease (CAD), ventricular dysfunction, hypertrophic cardiomyopathy, aortic stenosis, or other valvular disease.

Helpful diagnostic studies include *electrocardiography* (if symptoms present at time of recording), *exercise testing* (if exertion typically precipitates the sense of palpitation or if underlying CAD is suspected), and *echocardiography* (if structural heart disease is suspected). If symptoms are episodic, ambulatory electrocardiographic monitoring can be diagnostic, including use of a Holter monitor (24–48 h of monitoring), event/loop monitor (for 2–4 weeks), or implantable loop monitor (for 1–2 years). Helpful laboratory studies may include testing for hypokalemia, hypomagnesemia, and/or hyperthyroidism.

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For pts with benign atrial or ventricular premature beats in the absence of structural heart disease, therapeutic strategies include reduction of ethanol and caffeine intake, reassurance, and consideration of beta-blocker therapy for symptomatic suppression. Treatment of more serious dysrhythmias is presented in Chaps. 122 and 123.

For a more detailed discussion, see Loscalzo J: Palpitations, Chap. 52, p. 254, in HPIM-19.

# 33 Dyspnea

## DEFINITION

Dyspnea, a subjective experience of uncomfortable breathing, is a symptom that typically results from cardiopulmonary problems that cause an increased drive to breathe, increased work of breathing, and/or stimulation of specific receptors in the heart, lungs, or vasculature. Assessment begins by determining the quality and intensity of the discomfort.

## CAUSES

### Respiratory System Dyspnea

- *Airway disease:* Asthma and chronic obstructive pulmonary disorder (COPD) are common causes of dyspnea associated with increased work of breathing. Bronchospasm can cause chest tightness and hyperventilation. Hypoxemia and hypercapnia can result from ventilation-perfusion mismatch.
- *Chest wall disorders:* Chest wall stiffness (e.g., kyphoscoliosis) and neuromuscular weakness (e.g., myasthenia gravis) cause increased work of breathing.
- *Lung parenchymal disorders:* Interstitial lung diseases (Chap. 134) cause reduced lung compliance and increased work of breathing. Ventilation-perfusion mismatch and pulmonary fibrosis may lead to hypoxemia. Stimulation of lung receptors can cause hyperventilation.

### Cardiovascular System Dyspnea

- *Left heart disorders:* Elevations of left-ventricular end-diastolic and pulmonary capillary wedge pressures lead to dyspnea related to stimulation of pulmonary receptors and hypoxemia from ventilation-perfusion mismatch.
- *Pulmonary vascular disorders:* Pulmonary emboli, primary pulmonary arterial hypertension, and pulmonary vasculitis stimulate pulmonary receptors via increased pulmonary artery pressures. Hyperventilation and hypoxemia also may contribute to dyspnea.
- *Pericardial diseases:* Constrictive pericarditis and pericardial tamponade cause increased intracardiac and pulmonary arterial pressures, leading to dyspnea.

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## Dyspnea with Normal Respiratory and Cardiovascular Systems

Anemia can cause dyspnea, especially with exertion. Obesity is associated with dyspnea due to high cardiac output and impaired ventilatory function. Deconditioning may also cause dyspnea in patients with normal respiratory and cardiovascular systems.

### APPROACH TO THE PATIENT: Dyspnea (Fig. 33-1)

*History:* Obtain description of discomfort, including the impact of position, infections, and environmental exposures. Orthopnea is commonly observed in CHF. Nocturnal dyspnea is seen in CHF and asthma. Acute intermittent dyspnea suggests myocardial ischemia, asthma, or pulmonary embolism.

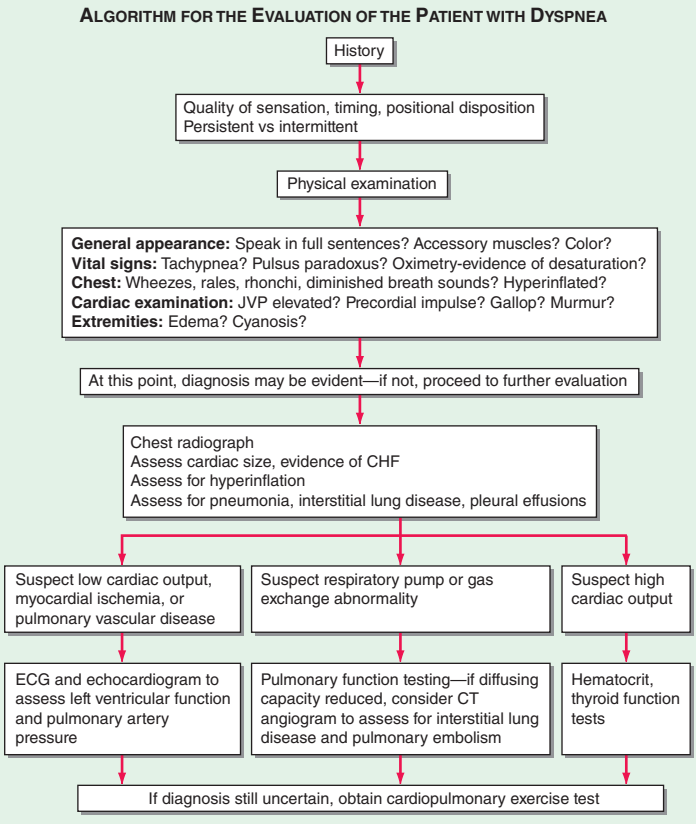


**FIGURE 33-1** An algorithm for the evaluation of the pt with dyspnea. CHF, congestive heart failure; ECG, electrocardiogram; JVP, jugular venous pulse. *(Adapted from RM Schwartzstein, D Feller-Kopman, in Primary Cardiology, 2nd ed. E Braunwald, L Goldman [eds]: Philadelphia, Saunders, 2003.)*

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*Physical examination:* Assess increased work of breathing indicated by accessory ventilatory muscle use. Determine if chest movement is symmetric. Use percussion (dullness or hyperresonance) and auscultation (decreased or adventitious breath sounds) to assess the lungs. Cardiac examination should note jugular venous distention, heart murmurs, and S3 or S4 gallops. Clubbing can relate to interstitial lung disease or lung cancer. To evaluate exertional dyspnea, reproduce the dyspnea with observation while assessing pulse oximetry.

*Radiographic studies:* Chest radiograph should be obtained as initial evaluation. Chest CT can be used subsequently to assess lung parenchyma (e.g., emphysema or interstitial lung disease) and pulmonary embolism.

*Laboratory studies:* ECG should be obtained; echocardiography can assess left ventricular dysfunction, pulmonary hypertension, and valvular disease. Pulmonary function tests to consider include spirometry, lung volumes, and diffusing capacity. Methacholine challenge testing can assess for asthma in subjects with normal spirometry. Cardiopulmonary exercise testing can determine whether pulmonary or cardiac disease limits exercise capacity.

**TREATMENT DYSPNEA**

Ideally, treatment involves correcting the underlying problem that caused dyspnea. Supplemental oxygen is required for significant oxygen desaturation at rest or with exertion. Pulmonary rehabilitation is helpful to improve exercise tolerance in COPD.

## Pulmonary Edema

Cardiogenic pulmonary edema results from cardiac abnormalities that cause increased pulmonary venous pressure leading to interstitial edema; with greater pressures, alveolar edema and pleural effusions develop. Symptoms include exertional dyspnea and orthopnea. Physical examination can reveal S3 gallop, elevated jugular venous pressure, and peripheral edema. Chest radiographs show prominent vascular markings in the upper lung zones. CXRs demonstrate perihilar alveolar opacities progressing to diffuse parenchymal abnormalities as pulmonary edema worsens.

Noncardiogenic pulmonary edema results from damage to the pulmonary capillary lining. Hypoxemia relates to intrapulmonary shunt; decreased pulmonary compliance is observed. Clinical impact can range from mild dyspnea to severe respiratory failure. Normal intracardiac pressures are typically observed. Etiologies may be direct injury (e.g., aspiration, smoke inhalation, pneumonia, oxygen toxicity, or chest trauma), indirect injury (e.g., sepsis, pancreatitis, and transfusion-related acute lung injury), or pulmonary vascular (e.g., high altitude and neurogenic pulmonary edema). Chest radiograph typically shows normal heart size and diffuse alveolar infiltrates; pleural effusions are atypical. Hypoxemia in noncardiogenic pulmonary edema often requires treatment with high concentrations of oxygen.

For a more detailed discussion, see Schwartzstein RM: Dyspnea, Chap. 47e, in HPIM-19.

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# 34 Cyanosis

Bluish discoloration of the skin and/or mucous membranes are usually due to elevated quantity of reduced hemoglobin (>40 g/L [>4 g/dL]) in the capillary blood vessels. Findings are most apparent in the lips, nail beds, ears, and malar eminences.

## CENTRAL CYANOSIS

Results from arterial desaturation or presence of an abnormal hemoglobin. Usually evident when arterial saturation is ≤85%, or ≤75% in dark-skinned individuals. Etiologies include:

1. *Impaired pulmonary function:* Poorly ventilated alveoli or impaired oxygen diffusion; most frequent in pneumonia, pulmonary edema, and chronic obstructive pulmonary disease (COPD); in COPD with cyanosis, secondary polycythemia is often present.
2. *Anatomic vascular shunting:* Shunting of desaturated venous blood into the arterial circulation may result from congenital heart disease or pulmonary atrioventricular (AV) fistula.
3. *Decreased inspired $O_2$:* Cyanosis may develop in ascents to altitudes >4000 m (>13,000 ft).
4. *Abnormal hemoglobins:* Methemoglobinemia, sulfhemoglobinemia, and mutant hemoglobins with low oxygen affinity (see Chap. 127, HPIM-19).

## PERIPHERAL CYANOSIS

Occurs with normal arterial $O_2$ saturation with increased extraction of $O_2$ from capillary blood caused by decreased localized blood flow. Contributors include vasoconstriction due to cold exposure, decreased cardiac output (e.g., in shock, Chap. 11), heart failure (Chap. 124), and peripheral vascular disease (Chap. 126) with arterial obstruction or vasospasm (Table 34-1). Local (e.g., thrombophlebitis) or central (e.g., constrictive pericarditis) venous hypertension intensifies cyanosis.

### APPROACH TO THE PATIENT: Cyanosis

- Inquire about duration (cyanosis since birth suggests congenital heart disease) and exposures (drugs or chemicals that result in abnormal hemoglobins).
- Differentiate central from peripheral cyanosis by examining nailbeds, lips, and mucous membranes. Peripheral cyanosis is most intense in nailbeds and may resolve with gentle warming of extremities.
- Check for clubbing, i.e., selective enlargement of the distal segments of fingers and toes, due to proliferation of connective tissue. Clubbing may be hereditary, idiopathic, or acquired in association with lung cancer, infective endocarditis, bronchiectasis, or hepatic cirrhosis. Combination of clubbing and cyanosis is frequent in congenital heart disease and occasionally in pulmonary disease (lung abscess, pulmonary AV shunts, but *not* with uncomplicated obstructive lung disease).
- Examine chest for evidence of pulmonary disease, pulmonary edema, or murmurs associated with congenital heart disease.
- If cyanosis is localized to an extremity, evaluate for peripheral vascular obstruction.

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**TABLE 34-1 CAUSES OF CYANOSIS**

| |
|---|
| **Central Cyanosis** |
| Decreased arterial oxygen saturation |
| Decreased atmospheric pressure—high altitude |
| Impaired pulmonary function |
| Alveolar hypoventilation |
| Inhomogeneity in pulmonary ventilation and perfusion (perfusion of hypoventilated alveoli) |
| Impaired oxygen diffusion |
| Anatomic shunts |
| Certain types of congenital heart disease |
| Pulmonary arteriovenous fistulas |
| Multiple small intrapulmonary shunts |
| Hemoglobin with low affinity for oxygen |
| Hemoglobin abnormalities |
| Methemoglobinemia—hereditary, acquired |
| Sulfhemoglobinemia—acquired |
| Carboxyhemoglobinemia (not true cyanosis) |
| **Peripheral Cyanosis** |
| Reduced cardiac output |
| Cold exposure |
| Redistribution of blood flow from extremities |
| Arterial obstruction |
| Venous obstruction |

- Obtain arterial blood gas to measure systemic $O_2$ saturation. Repeat while pt inhales 100% $O_2$; if saturation fails to increase to >95%, intravascular shunting of blood bypassing the lungs is likely (e.g., right-to-left intracardiac shunts).
- Evaluate for abnormal hemoglobins (e.g., spectroscopy, measurement of methemoglobin level).

For a more detailed discussion, see Loscalzo J: Hypoxia and Cyanosis, Chap. 49, p. 247, in HPIM-19.

# 35 Cough and Hemoptysis

## COUGH

### ETIOLOGY

Acute cough, which is defined as duration <21 days, is usually related to respiratory infection, aspiration, or inhalation of respiratory irritants. Subacute cough (present for 3–8 weeks) is often related to persistent inflammation from a tracheobronchitis

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episode. Chronic cough (>8 weeks in duration) can be caused by many pulmonary and cardiac diseases. Chronic bronchitis related to cigarette smoking is a common cause. If the chest radiograph and physical examination are unremarkable, other common causes of chronic cough include cough-variant asthma, gastroesophageal reflux disease (GERD), postnasal drip related to sinus disease, and medications including ACE inhibitors. Irritation of tympanic membranes and chronic eosinophilic bronchitis also can cause chronic cough with a normal chest radiograph. Ineffective cough can predispose to serious respiratory infections due to difficulty clearing lower respiratory secretions; abnormal airway secretions (e.g., due to bronchiectasis) or tracheomalacia can contribute. Weakness or pain limiting abdominal and intercostal muscle use also can lead to ineffective cough.

### CLINICAL ASSESSMENT

Key issues in the history include triggers for onset of cough, determinants of increased or decreased cough, and sputum production. Symptoms of nasopharyngeal disease should be assessed, including postnasal drip, sneezing, and rhinorrhea. GERD may be suggested by heartburn, hoarseness, and frequent eructation. Cough-variant asthma is suggested by noting the relationship of cough onset to asthmatic triggers. Usage of ACE inhibitors, but not angiotensin receptor blockers, can cause cough long after treatment is initiated.

On physical examination, signs of cardiopulmonary diseases should be assessed, including adventitious lung sounds and digital clubbing. Examination of the nasal passages, posterior pharyngeal wall, auditory canals, and tympanic membranes should be performed.

Laboratory evaluation should include chest radiography. Spirometry with bronchodilator testing can assess for reversible airflow obstruction. With normal spirometry, methacholine challenge testing can be used to assess for asthma. Purulent sputum should be sent for routine bacterial and possibly mycobacterial cultures. Sputum cytology can reveal malignant cells in lung cancer and eosinophils in eosinophilic bronchitis. Esophageal pH probes or radiotransmitter capsules can be used to assess for GERD. Chest CT should be considered in pts with normal chest radiographs who fail to improve with treatment. Evaluation of hemoptysis is discussed below.

### TREATMENT CHRONIC COUGH

In pts with chronic cough and a normal chest x-ray, empiric treatment is directed at the most likely cause based on the history and physical examination. If treatment directed at one empiric cause fails, empiric treatment of an alternative etiology can be considered. Postnasal drip treatment may include antihistamines, nasal corticosteroids, anticholinergics, and/or antibiotics. GERD can be treated with antacids, type 2 histamine blockers, or proton pump inhibitors. Cough-variant asthma is treated with inhaled glucocorticoids and as-needed inhaled β agonists. Pts on ACE inhibitors should be given a 1-month trial of discontinuing this medication. Chronic eosinophilic bronchitis often improves with inhaled glucocorticoid treatment. Symptomatic treatment of cough can include narcotics such as codeine; however, somnolence, constipation, and addiction can result. Dextromethorphan and benzonatate have fewer side effects but reduced efficacy.

## HEMOPTYSIS

### ETIOLOGY

Hemoptysis, expectoration of blood from the respiratory tract, must be differentiated from expectorated blood originating from the nasopharynx or GI tract. Acute

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bronchitis is the most common cause of hemoptysis in the United States; tuberculosis is the leading cause worldwide.

Hemoptysis originating from the alveoli is known as diffuse alveolar hemorrhage (DAH). DAH can be caused by inflammatory diseases including Wegener granulomatosis, systemic lupus erythematosus, and Goodpasture disease. Within the first 100 days after bone marrow transplant, inflammatory DAH can cause severe hypoxemia. Noninflammatory DAH usually results from inhalational injuries from toxic exposures, such as smoke inhalation or cocaine.

Hemoptysis most commonly originates from small- to medium-sized bronchi. Because the bleeding source is usually bronchial arteries, there is potential for rapid blood loss. Airway hemoptysis is often caused by viral or bacterial bronchitis. Pts with bronchiectasis have increased risk of hemoptysis. Pneumonia can cause hemoptysis, especially if cavitation (e.g., tuberculosis) and/or necrotizing pneumonia (e.g., *Klebsiella pneumoniae* and *Staphylococcus aureus*) develop. Paragonimiasis, a helminthic infection common in pts from Southeast Asia and China, can cause hemoptysis and must be differentiated from tuberculosis. Although only 10% of lung cancer pts have hemoptysis at diagnosis, cancers developing in central airways (e.g., squamous cell carcinoma, small-cell carcinoma, and carcinoid tumors) often cause hemoptysis. Cancers that metastasize to the lungs cause hemoptysis less commonly.

Pulmonary vascular sources of hemoptysis include congestive heart failure, which usually causes pink, frothy sputum. Pulmonary embolism with infarction and pulmonary arteriovenous malformations are additional pulmonary vascular etiologies to consider.

## CLINICAL ASSESSMENT

The approaches to assess and treat hemoptysis are shown in Fig. 35-1. History should determine whether the bleeding source is likely the respiratory tract or an alternative source (e.g., nasopharynx, upper GI tract). The quantity of expectorated blood should be estimated, because it influences the urgency of evaluation and treatment. Massive hemoptysis, variably defined as 200–600 mL within 24 h, requires emergent care. The presence of purulent or frothy secretions should be assessed. History of previous hemoptysis episodes and cigarette smoking should be ascertained. Fever and chills should be assessed as potential indicators of acute infection. Recent inhalation of illicit drugs and other toxins should be determined.

Physical examination should include assessment of the nares for epistaxis, and evaluation of the heart and lungs. Pedal edema could indicate congestive heart failure if symmetric, and deep-vein thrombosis with pulmonary embolism if asymmetric. Clubbing could indicate lung cancer or bronchiectasis. Assessment of vital signs and oxygen saturation can provide information about hemodynamic stability and respiratory compromise.

Radiographic evaluation with a chest x-ray should be performed. Chest CT may be helpful to assess for bronchiectasis, pneumonia, lung cancer, and pulmonary embolism. Laboratory studies include a complete blood count and coagulation studies; renal function and urinalysis should be assessed, with additional blood tests including antineutrophil cytoplasmic antibody (ANCA), anti-GBM (glomerular basement membrane), and ANA if DAH is suspected. Sputum should be sent for Gram's stain and routine culture as well as acid-fast bacillus (AFB) smear and culture.

Bronchoscopy is often required to complete the evaluation. In massive hemoptysis, rigid bronchoscopy may be necessary.

## TREATMENT HEMOPTYSIS

As shown in Fig. 35-1, massive hemoptysis may require endotracheal intubation and mechanical ventilation to provide airway stabilization. If the source of bleeding can be identified, isolating the bleeding lung with an endobronchial

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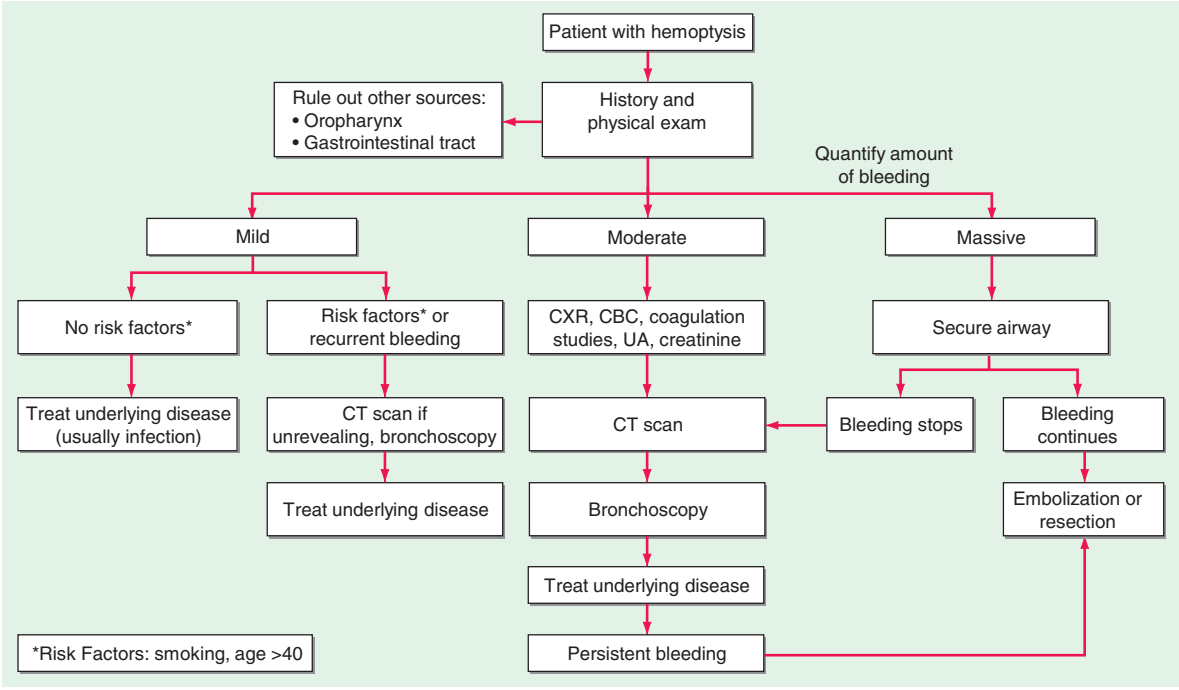


**FIGURE 35-1** An algorithm for the evaluation of hemoptysis. CBC, complete blood count; CXR, chest x-ray; UA, urinalysis. *(From Kritek PA, Fanta CH: HPIM-19.)*

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blocker or double-lumen endotracheal tube is optimal. Pts should be positioned with the bleeding side down. If bleeding persists, bronchial arterial embolization by angiography may be beneficial; however, risk of spinal artery embolization is an important potential adverse event. As a last resort, surgical resection can be considered to stop the bleeding. Cough suppression, typically with narcotics, is desirable.

For a more detailed discussion, see Kritek PA, Fanta CH: Cough and Hemoptysis, Chap. 48, p. 243, in HPIM-19.

# 36 Edema

## DEFINITION

Soft tissue swelling due to abnormal expansion of interstitial fluid volume. Edema fluid is a plasma transudate that accumulates when movement of fluid from vascular to interstitial space is favored. Because detectable generalized edema in the adult reflects a gain of ≥3 L, renal retention of salt and water is necessary for edema to occur. Distribution of edema can be an important guide to cause.

### Localized Edema

Limited to a particular organ or vascular bed; easily distinguished from generalized edema. Unilateral extremity edema is usually due to venous or lymphatic obstruction (e.g., deep venous thrombosis, tumor obstruction, primary lymphedema). Stasis edema of a paralyzed lower extremity also may occur. Allergic reactions ("angioedema") and superior vena caval obstruction are causes of localized facial edema. Bilateral lower-extremity edema may have localized causes, e.g., inferior vena caval obstruction, compression due to ascites, and abdominal mass. Ascites (fluid in peritoneal cavity) and hydrothorax (in pleural space) also may present as isolated localized edema, due to inflammation or neoplasm.

### Generalized Edema

Soft tissue swelling of most or all regions of the body. Bilateral lower-extremity swelling, more pronounced after standing for several hours, and pulmonary edema are usually cardiac in origin. Periorbital edema noted on awakening often results from renal disease and impaired Na excretion. Ascites and edema of lower extremities and scrotum are frequent in cirrhosis, nephrotic syndrome, or CHF.

In *CHF*, diminished cardiac output and arterial underfilling result in both decreased renal perfusion and increased venous pressure with resultant renal Na retention due to renal vasoconstriction, intrarenal blood flow redistribution, direct Na-retentive effects of norepinephrine and angiotensin II, and secondary hyperaldosteronism.

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In *cirrhosis*, arteriovenous shunts and peripheral vasodilation lower renal perfusion, resulting in Na retention. Ascites accumulates when increased intrahepatic vascular resistance produces portal hypertension. As in heart failure, the effects of excess intrarenal and circulating norepinephrine, angiotensin II, and aldosterone lead to renal Na retention and worsening edema. Reduced serum albumin and increased abdominal pressure also promote lower-extremity edema.

In acute or chronic *renal failure*, edema occurs if Na intake exceeds kidneys' ability to excrete Na secondary to marked reductions in glomerular filtration. Severe hypoalbuminemia (<25 g/L [2.5 g/dL]) of any cause (e.g., nephrotic syndrome, nutritional deficiency, chronic liver disease) may lower plasma oncotic pressure, promoting fluid transudation into interstitium; lowering of effective blood volume stimulates renal Na retention and causes edema.

Less common causes of generalized edema: *idiopathic edema*, a syndrome of recurrent rapid weight gain and edema in women of reproductive age; *hypothyroidism*, in which myxedema is typically located in the pretibial region; *drugs* (Table 36-1).

## TREATMENT EDEMA

Primary management is to identify and treat the underlying cause of edema (Fig. 36-1).

Dietary Na restriction (<500 mg/d) may prevent further edema formation. Bed rest enhances response to salt restriction in CHF and cirrhosis. Supportive stockings and elevation of edematous lower extremities help to mobilize interstitial fluid. If severe hyponatremia (<132 mmol/L) is present, water intake also should be reduced (<1500 mL/d). Diuretics (Table 36-2) are indicated for marked peripheral edema, pulmonary edema, CHF, and inadequate dietary salt restriction. Complications are

**TABLE 36-1 DRUGS ASSOCIATED WITH EDEMA FORMATION**

| |
|---|
| Nonsteroidal anti-inflammatory drugs |
| Antihypertensive agents |
| Direct arterial/arteriolar vasodilators |
| Hydralazine |
| Clonidine |
| Methyldopa |
| Guanethidine |
| Minoxidil |
| Calcium channel antagonists |
| α-Adrenergic antagonists |
| Thiazolidinediones |
| Steroid hormones |
| Glucocorticoids |
| Anabolic steroids |
| Estrogens |
| Progestins |
| Cyclosporine |
| Growth hormone |
| Immunotherapies |
| Interleukin 2 |
| OKT3 monoclonal antibody |

***Source:*** From GM Chertow, in E Braunwald, L Goldman (eds): *Primary Cardiology,* 2nd ed. Philadelphia, Saunders, 2003.

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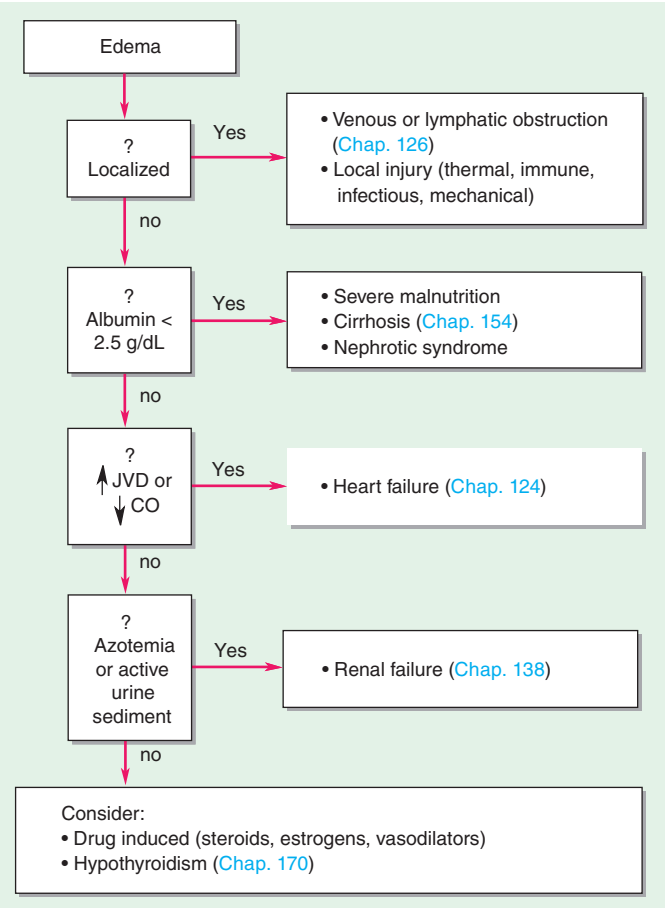


**FIGURE 36-1** Diagnostic approach to edema. CO, cardiac output; JVD, jugular venous distention. *(From Chap. 42: HMOM-18.)*

listed in Table 36-3. Weight loss by diuretics should be limited to 1–1.5 kg/d. Distal ("potassium sparing") diuretics or metolazone may be added to loop diuretics for enhanced effect. Note that intestinal edema may impair absorption of oral diuretics and reduce effectiveness. When desired weight is achieved, diuretic doses should be reduced.

In *CHF* (Chap. 124), avoid overdiuresis because it may bring a fall in cardiac output and prerenal azotemia. Avoid diuretic-induced hypokalemia, which predisposes to digitalis toxicity.

In *cirrhosis* and other hepatic causes of edema, spironolactone is the initial diuretic of choice but may produce acidosis and hyperkalemia. Thiazides or small doses of loop diuretics may also be added. However, renal failure may result from volume depletion. Overdiuresis may result in hyponatremia, hypokalemia, and alkalosis, which may worsen hepatic encephalopathy (Chap. 154).

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**TABLE 36-2 DIURETICS FOR EDEMA**

| Drug | Usual Dose | Comments |
|---|---|---|
| **Loop (May be administered PO or IV)** | | |
| Furosemide | 20–120 mg qd or bid | Short acting; potent; effective with low GFR |
| Bumetanide | 0.5–2 mg qd or bid | Better oral absorption than furosemide, but shorter duration of action |
| Torsemide | 20–200 mg qd | Better oral absorption than furosemide, longer duration of action |
| **Distal, K-Losing** | | |
| Hydrochlorothiazide | 12.5–25 mg qd | Causes hypokalemia; need GFR >25 mL/min |
| Chlorthalidone | 12.5–25 mg qd | Long acting (up to 72 h); hypokalemia |
| Metolazone | 1–5 mg qd | Long acting; hypokalemia; effective with low GFR, especially when combined with a loop diuretic |
| **Distal, K-Sparing** | | |
| Spironolactone | 12.5–100 mg qd | Hyperkalemia; acidosis; blocks aldosterone; gynecomastia, impotence, amenorrhea; onset takes 2–3 days; avoid use in renal failure or in combination with ACE inhibitors or potassium supplement |
| Eplerenone | 25–50 mg qd | Similar side effects to spironolactone, but more specific for mineralocorticoid receptor; lower incidence of gynecomastia and amenorrhea |
| Amiloride | 5–10 mg qd or bid | Hyperkalemia; once daily; less potent than spironolactone |
| Triamterene | 100 mg bid | Hyperkalemia; less potent than spironolactone; renal stones |

***Abbreviations:*** ACE, angiotensin-converting enzyme; GFR, glomerular filtration rate.
***Source:*** From Chap. 42, *HMOM-18*.



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**TABLE 36-3 COMPLICATIONS OF DIURETICS**

| Common | Uncommon |
|---|---|
| Volume depletion | Interstitial nephritis (thiazides, furosemide) |
| Prerenal azotemia | Pancreatitis (thiazides) |
| Potassium depletion | Loss of hearing (loop diuretics) |
| Hyponatremia (thiazides) | Anemia, leukopenia, thrombocytopenia (thiazides) |
| Metabolic alkalosis | |
| Hypercholesterolemia | |
| Hyperglycemia (thiazides) | |
| Hyperkalemia (K-sparing) | |
| Hypomagnesemia | |
| Hyperuricemia | |
| Hypercalcemia (thiazides) | |
| GI complaints | |
| Rash (thiazides) | |

***Abbreviation:*** GI, gastrointestinal.
***Source:*** From Chap. 42, *HMOM-18*.

For a more detailed discussion, see Braunwald E, Loscalzo J: Edema, Chap. 50, p. 250, in HPIM-19.

# 37 Abdominal Pain

Numerous causes, ranging from acute, life-threatening emergencies to chronic functional disease and disorders of several organ systems, can generate abdominal pain. Evaluation of acute pain requires rapid assessment of likely causes and early initiation of appropriate therapy. A more detailed and time-consuming approach to diagnosis may be followed in less acute situations. Table 37-1 lists the common causes of abdominal pain.

## APPROACH TO THE PATIENT: **Abdominal Pain**

*History:* History is of critical diagnostic importance. Physical examination may be unrevealing or misleading, and laboratory and radiologic examinations delayed or unhelpful.

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**TABLE 37-1 SOME IMPORTANT CAUSES OF ABDOMINAL PAIN**

| | |
|---|---|
| **Pain Originating in the Abdomen** | |
| Parietal peritoneal inflammation | Vascular disturbances |
| Bacterial contamination | Embolism or thrombosis |
| Perforated appendix or other perforated viscus | Vascular rupture |
| Pelvic inflammatory disease | Pressure or torsional occlusion |
| Chemical irritation | Sickle cell anemia |
| Perforated ulcer | Abdominal wall |
| Pancreatitis | Distortion or traction of mesentery |
| Mittelschmerz | Trauma or infection of muscles |
| Mechanical obstruction of hollow viscera | Distension of visceral surfaces, e.g., by hemorrhage |
| Obstruction of the small or large intestine | Hepatic or renal capsules |
| Obstruction of the biliary tree | Inflammation |
| Obstruction of the ureter | Appendicitis |
| | Typhoid fever |
| | Neutropenic enterocolitis or "typhlitis" |
| **Pain Referred from Extraabdominal Source** | |
| Cardiothoracic | Pleurodynia |
| Acute myocardial infarction | Pneumothorax |
| Myocarditis, endocarditis, pericarditis | Empyema |
| Congestive heart failure | Esophageal disease, including spasm, rupture, or inflammation |
| Pneumonia (especially lower lobes) | Genitalia |
| Pulmonary embolus | Torsion of the testis |
| **Metabolic Causes** | |
| Diabetes | Acute adrenal insufficiency |
| Uremia | Familial Mediterranean fever |
| Hyperlipidemia | Porphyria |
| Hyperparathyroidism | C1-esterase-inhibitor deficiency (angioneurotic edema) |
| **Neurologic/Psychiatric Causes** | |
| Herpes zoster | Spinal cord or nerve root compression |
| Tabes dorsalis | Functional disorders |
| Causalgia | Psychiatric disorders |
| Radiculitis from infection or arthritis | |
| **Toxic Causes** | |
| Lead poisoning | |
| Insect or animal envenomation | |
| Black widow spider bites | |
| Snake bites | |
| **Uncertain Mechanisms** | |
| Narcotic withdrawal | |
| Heat stroke | |

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### CHARACTERISTIC FEATURES OF ABDOMINAL PAIN

*Duration and pattern:* These provide clues to nature and severity, although acute abdominal crisis may occasionally present insidiously or on a background of chronic pain.

*Type and location* provide a rough guide to nature of disease. *Visceral pain* (due to distention of a hollow viscus) localizes poorly and is often perceived in the midline. Intestinal pain tends to be crampy; when originating proximal to the ileocecal valve, it usually localizes above and around the umbilicus. Pain of colonic origin is perceived in the hypogastrium and lower quadrants. Pain from biliary or ureteral obstruction often causes pts to writhe in discomfort. *Somatic pain* (due to peritoneal inflammation) is usually sharper and more precisely localized to the diseased region (e.g., acute appendicitis; capsular distention of liver, kidney, or spleen), exacerbated by movement, causing pts to remain still. Pattern of radiation may be helpful: right shoulder (hepatobiliary origin), left shoulder (splenic), midback (pancreatic), flank (proximal urinary tract), and groin (genital or distal urinary tract).

*Factors that precipitate or relieve pain:* Ask about its relationship to eating (e.g., upper GI, biliary, pancreatic, ischemic bowel disease), defecation (colorectal), urination (genitourinary or colorectal), respiratory (pleuropulmonary, hepatobiliary), position (pancreatic, gastroesophageal reflux, musculoskeletal), menstrual cycle/menarche (tuboovarian, endometrial, including endometriosis), exertion (coronary/intestinal ischemia, musculoskeletal), medication or specific foods (motility disorders, food intolerance, gastroesophageal reflux, porphyria, adrenal insufficiency, ketoacidosis, toxins), and stress (motility disorders, nonulcer dyspepsia, irritable bowel syndrome).

*Associated symptoms:* Look for fevers/chills (infection, inflammatory disease, infarction), weight loss (tumor, inflammatory disease, malabsorption, ischemia), nausea/vomiting (obstruction, infection, inflammatory disease, metabolic disease), dysphagia/odynophagia (esophageal), early satiety (gastric), hematemesis (esophageal, gastric, duodenal), constipation (colorectal, perianal, genitourinary), jaundice (hepatobiliary, hemolytic), diarrhea (inflammatory disease, infection, malabsorption, secretory tumors, ischemia, genitourinary), dysuria/hematuria/vaginal or penile discharge (genitourinary), hematochezia (colorectal or, rarely, urinary), and skin/joint/eye disorders (inflammatory disease, bacterial or viral infection).

*Predisposing factors:* Inquire about family history (inflammatory disease, tumors, pancreatitis), hypertension and atherosclerotic disease (ischemia), diabetes mellitus (motility disorders, ketoacidosis), connective tissue disease (motility disorders, serositis), depression (motility disorders, tumors), smoking (ischemia), recent smoking cessation (inflammatory disease), and ethanol use (motility disorders, hepatobiliary, pancreatic, gastritis, peptic ulcer disease).

*Physical examination:* Evaluate abdomen for prior trauma or surgery, current trauma; abdominal distention, fluid, or air; direct, rebound, and referred tenderness; liver and spleen size; masses, bruits, altered bowel sounds, hernias, arterial masses. Rectal examination assesses presence and location of tenderness, masses, blood (gross or occult). Pelvic examination in women is essential.

*General examination:* Evaluate for evidence of hemodynamic instability, acid-base disturbances, nutritional deficiency, coagulopathy, arterial occlusive disease, stigmata of liver disease, cardiac dysfunction, lymphadenopathy, and skin lesions.

*Routine laboratory and radiologic studies:* Choices depend on clinical setting (esp. severity of pain, rapidity of onset) and may include complete blood count, serum electrolytes, coagulation parameters, serum glucose, and biochemical tests of liver, kidney, and pancreatic function; chest x-ray to determine the presence of diseases involving heart, lung, mediastinum, and pleura; electrocardiogram

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is helpful to exclude referred pain from cardiac disease; plain abdominal radiographs to evaluate bowel displacement, intestinal distention, fluid and gas pattern, free peritoneal air, liver size, and abdominal calcifications (e.g., gallstones, renal stones, chronic pancreatitis).

*Special studies:* These include abdominal ultrasonography (to visualize biliary ducts, gallbladder, liver, pancreas, and kidneys); CT to identify masses, abscesses, evidence of inflammation (bowel wall thickening, mesenteric "stranding," lymphadenopathy, appendicitis), aortic aneurysm; barium contrast radiographs (barium swallow, upper GI series, small-bowel follow-through, barium enema); upper GI endoscopy, sigmoidoscopy, or colonoscopy; cholangiography (endoscopic, percutaneous, or via MRI), angiography (direct or via CT or MRI), and radionuclide scanning. In selected cases, percutaneous biopsy, laparoscopy, and exploratory laparotomy may be required.

## ACUTE, CATASTROPHIC ABDOMINAL PAIN

Intense abdominal pain of acute onset or pain associated with syncope, hypotension, or toxic appearance necessitates rapid yet orderly evaluation. Consider obstruction, perforation, or rupture of hollow viscus; dissection or rupture of major blood vessels (esp. aortic aneurysm); ulceration; abdominal sepsis; ketoacidosis; and adrenal crisis.

### BRIEF HISTORY AND PHYSICAL EXAMINATION

Historic features of importance include age; time of onset of the pain; activity of the pt when the pain began; location and character of the pain; radiation to other sites; presence of nausea, vomiting, or anorexia; temporal changes; changes in bowel habits; and menstrual history. Physical examination should focus on the pt's overall appearance (writhing in pain [ureteral lithiasis] vs. still [peritonitis, perforation]), position (a pt leaning forward may have pancreatitis or gastric perforation into the lesser sac), presence of fever or hypothermia, hyperventilation, cyanosis, bowel sounds, direct or rebound abdominal tenderness, pulsating abdominal mass, abdominal bruits, ascites, rectal blood, rectal or pelvic tenderness, and evidence of coagulopathy. Useful laboratory studies include hematocrit (may be normal with acute hemorrhage or misleadingly high with dehydration), WBC with differential count, arterial blood gases, serum electrolytes, BUN, creatinine, glucose, lipase or amylase, and UA. Females of reproductive age should have a pregnancy test. Radiologic studies should include supine and upright abdominal films (left lateral decubitus view if upright unobtainable) to evaluate bowel caliber and presence of free peritoneal air, cross-table lateral film to assess aortic diameter; CT (when available) to detect evidence of bowel perforation, inflammation, solid organ infarction, retroperitoneal bleeding, abscess, or tumor. Abdominal paracentesis (or peritoneal lavage in cases of trauma) can detect evidence of bleeding or peritonitis. Abdominal ultrasound (when available) reveals evidence of abscess, cholecystitis, biliary or ureteral obstruction, or hematoma and is used to determine aortic diameter.

### DIAGNOSTIC STRATEGIES

The initial decision point is based on whether the pt is hemodynamically stable. If not, one must suspect a vascular catastrophe such as a leaking abdominal aortic aneurysm. Such pts receive limited resuscitation and move immediately to surgical exploration. If the pt is hemodynamically stable, the next decision point is whether the abdomen is rigid. Rigid abdomens are most often due to perforation or obstruction. The diagnosis can generally be made by a chest and plain abdominal radiograph.

If the abdomen is not rigid, the causes may be grouped based on whether the pain is poorly localized or well localized. In the presence of poorly localized pain, one

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should assess whether an aortic aneurysm is possible. If so, a CT scan can make the diagnosis; if not, early appendicitis, early obstruction, mesenteric ischemia, inflammatory bowel disease, pancreatitis, and metabolic problems are all in the differential diagnosis.

Pain localized to the epigastrium may be of cardiac origin or due to esophageal inflammation or perforation, gastritis, peptic ulcer disease, biliary colic or cholecystitis, or pancreatitis. Pain localized to the right upper quadrant includes those same entities plus pyelonephritis or nephrolithiasis, hepatic abscess, subdiaphragmatic abscess, pulmonary embolus, or pneumonia, or it may be of musculoskeletal origin. Additional considerations with left upper quadrant localization are infarcted or ruptured spleen, splenomegaly, and gastric or peptic ulcer. Right lower quadrant pain may be from appendicitis, Meckel's diverticulum, Crohn's disease, diverticulitis, mesenteric adenitis, rectus sheath hematoma, psoas abscess, ovarian abscess or torsion, ectopic pregnancy, salpingitis, familial fever syndromes, urolithiasis, or herpes zoster. Left lower quadrant pain may be due to diverticulitis, perforated neoplasm, or other entities previously mentioned.

### TREATMENT ACUTE, CATASTROPHIC ABDOMINAL PAIN

IV fluids, correction of life-threatening acid-base disturbances, and assessment of need for emergent surgery are the first priority; careful follow-up with frequent reexamination (when possible, by the same examiner) is essential. Relieve the pain. The use of narcotic analgesia is controversial. Traditionally, narcotic analgesics were withheld pending establishment of diagnosis and therapeutic plan, because masking of diagnostic signs may delay needed intervention. However, evidence that narcotics actually mask a diagnosis is sparse.

For a more detailed discussion, see Jacobs DO, Silen W: Abdominal Pain, Chap. 20, p. 103, in HPIM-19.

# 38 Nausea, Vomiting, and Indigestion

## NAUSEA AND VOMITING

*Nausea* refers to the imminent desire to vomit and often precedes or accompanies vomiting. *Vomiting* refers to the forceful expulsion of gastric contents through the mouth. *Retching* refers to labored rhythmic respiratory activity that precedes emesis. *Regurgitation* refers to the gentle expulsion of gastric contents in the absence of nausea and abdominal diaphragmatic muscular contraction. *Rumination* refers to the regurgitation, rechewing, and reswallowing of food from the stomach.

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## PATHOPHYSIOLOGY

Gastric contents are propelled into the esophagus when there is relaxation of the gastric fundus and gastroesophageal sphincter followed by a rapid increase in intraabdominal pressure produced by contraction of the abdominal and diaphragmatic musculature. Increased intrathoracic pressure results in further movement of the material to the mouth. Reflex elevation of the soft palate and closure of the glottis protect the nasopharynx and trachea and complete the act of vomiting. Vomiting is controlled by two brainstem areas, the vomiting center and chemoreceptor trigger zone. Activation of the chemoreceptor trigger zone results in impulses to the vomiting center, which controls the physical act of vomiting.

## ETIOLOGY

Nausea and vomiting are manifestations of a large number of disorders (Table 38-1).

**TABLE 38-1 CAUSES OF NAUSEA AND VOMITING**

| Intraperitoneal | Extraperitoneal | Medications/ Metabolic Disorders |
|---|---|---|
| Obstructing disorders | Cardiopulmonary disease | Drugs |
| Pyloric obstruction | Cardiomyopathy | Cancer chemotherapy |
| Small-bowel obstruction | Myocardial infarction | Antibiotics |
| Colonic obstruction | Labyrinthine disease | Cardiac antiarrhythmics |
| Superior mesenteric artery syndrome | Motion sickness | Digoxin |
| Enteric infections | Labyrinthitis | Oral hypoglycemics |
| Viral | Malignancy | Oral contraceptives |
| Bacterial | Intracerebral disorders | Endocrine/ metabolic disease |
| Inflammatory diseases | Malignancy | Pregnancy |
| Cholecystitis | Hemorrhage | Uremia |
| Pancreatitis | Abscess | Ketoacidosis |
| Appendicitis | Hydrocephalus | Thyroid and parathyroid disease |
| Hepatitis | Psychiatric illness | Adrenal insufficiency |
| Altered sensorimotor function | Anorexia and bulimia nervosa | Toxins |
| Gastroparesis | Depression | Liver failure |
| Intestinal pseudoobstruction | Postoperative vomiting | Ethanol |
| Gastroesophageal reflux | | |
| Chronic idiopathic nausea | | |
| Functional vomiting | | |
| Cyclic vomiting syndrome | | |
| Cannabinoid hyperemesis syndrome | | |
| Rumination syndrome | | |
| Biliary colic | | |
| Abdominal irradiation | | |

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### EVALUATION

The history, including a careful drug history, and the timing and character of the vomitus can be helpful. For example, vomiting that occurs predominantly in the morning is often seen in pregnancy, uremia, and alcoholic gastritis; feculent emesis implies distal intestinal obstruction or gastrocolic fistula; projectile vomiting suggests increased intracranial pressure; vomiting during or shortly after a meal may be due to psychogenic causes or peptic ulcer disease. Associated symptoms may also be helpful: vertigo and tinnitus in Ménière's disease, relief of abdominal pain with vomiting in peptic ulcer, and early satiety in gastroparesis. Plain radiographs can suggest diagnoses such as intestinal obstruction. The upper GI series assesses motility of the proximal GI tract as well as the mucosa. Other studies may be indicated, such as gastric emptying scans (diabetic gastroparesis) and CT scan of the brain.

### COMPLICATIONS

Rupture of the esophagus (Boerhaave's syndrome), hematemesis from a mucosal tear (Mallory-Weiss syndrome), dehydration, malnutrition, dental caries and erosions, metabolic alkalosis, hypokalemia, and aspiration pneumonitis.

### TREATMENT NAUSEA AND VOMITING

Treatment is aimed at correcting the specific cause. The effectiveness of antiemetic medications depends on etiology of symptoms, pt responsiveness, and side effects. Antihistamines such as meclizine and dimenhydrinate are effective for nausea due to inner ear dysfunction. Anticholinergics such as scopolamine are effective for nausea associated with motion sickness. Haloperidol and phenothiazine derivatives such as prochlorperazine are often effective in controlling mild nausea and vomiting, but sedation, hypotension, and parkinsonian symptoms are common side effects. Selective dopamine antagonists such as metoclopramide may be superior to the phenothiazines in treating severe nausea and vomiting and are particularly useful in treatment of gastroparesis. IV metoclopramide may be effective as prophylaxis against nausea when given before chemotherapy. Ondansetron and granisetron, serotonin receptor blockers, and glucocorticoids are used for treating nausea and vomiting associated with cancer chemotherapy. Aprepitant, a neurokinin receptor blocker, is effective at controlling nausea from highly emetic drugs like cisplatin. Erythromycin is effective in some pts with gastroparesis.

## INDIGESTION

*Indigestion* is a nonspecific term that encompasses a variety of upper abdominal complaints including heartburn, regurgitation, and dyspepsia (upper abdominal discomfort or pain). These symptoms are overwhelmingly due to gastroesophageal reflux disease (GERD).

### PATHOPHYSIOLOGY

GERD occurs as a consequence of acid reflux into the esophagus from the stomach, gastric motor dysfunction, or visceral afferent hypersensitivity. A wide variety of situations promote GERD: increased gastric contents (from a large meal, gastric stasis, or acid hypersecretion), physical factors (lying down, bending over), increased pressure on the stomach (tight clothes, obesity, ascites, pregnancy), and loss (usually intermittent) of lower esophageal sphincter tone (diseases such as scleroderma, smoking, anticholinergics, calcium antagonists). Hiatal hernia also promotes acid flow into the esophagus.

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## NATURAL HISTORY

Heartburn is reported once monthly by 40% of Americans and daily by 7%. Functional dyspepsia is defined as >3 months of dyspepsia without an organic cause. Functional dyspepsia is the cause of symptoms in 60% of pts with dyspeptic symptoms. However, peptic ulcer disease from either *Helicobacter pylori* infection or ingestion of NSAIDs is present in 15% of cases.

In most cases, the esophagus is not damaged, but 5% of pts develop esophageal ulcers and some form strictures; 8–20% develop glandular epithelial cell metaplasia, termed *Barrett's esophagus*, which can progress to adenocarcinoma.

Extraesophageal manifestations include asthma, laryngitis, chronic cough, aspiration pneumonitis, chronic bronchitis, sleep apnea, dental caries, halitosis, and hiccups.

## EVALUATION

The presence of dysphagia, odynophagia, unexplained weight loss, recurrent vomiting leading to dehydration, occult or gross bleeding, or a palpable mass or adenopathy are all "alarm" signals that demand directed radiographic, endoscopic, and surgical evaluation. Pts without alarm features are generally treated empirically. Individuals >45 years can be tested for the presence of *H. pylori*. Pts positive for the infection are treated to eradicate the organism. Pts who fail to respond to *H. pylori* treatment, those >45 years old, and those with alarm factors generally undergo upper GI endoscopy.

## TREATMENT INDIGESTION

Weight reduction; elevation of the head of the bed; and avoidance of large meals, smoking, caffeine, alcohol, chocolate, fatty food, citrus juices, and NSAIDs may prevent GERD. Antacids are widely used. Clinical trials suggest that proton pump inhibitors (omeprazole) are more effective than histamine receptor blockers (ranitidine) in pts with or without esophageal erosions. *H. pylori* eradication regimens are discussed in Chap. 147. Motor stimulants like metoclopramide and erythromycin may be useful in a subset of pts with postprandial distress.

Surgical techniques (Nissen fundoplication, Belsey procedure) work best in young individuals whose symptoms have improved on proton pump inhibitors and who otherwise may require lifelong therapy. They can be used in the rare pts who are refractory to medical management. Clinical trials have not documented the superiority of one over another.

Dietary exclusion of gas-producing foods (i.e., low FODMAP [fermentable oligosaccharide, disaccharide, monosaccharide, and polyol] diets), and therapies to modify gut flora can reduce symptoms but efficacy is unproven.

For a more detailed discussion, see Hasler WL: Nausea, Vomiting, and Indigestion, Chap. 54, p. 258, in HPIM-19.

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# 39 Dysphagia

## DYSPHAGIA

*Dysphagia* is difficulty moving food or liquid through the mouth, pharynx, and esophagus. The pt senses swallowed material sticking along the path. *Odynophagia* is pain on swallowing. *Globus pharyngeus* is the sensation of a lump lodged in the throat, with swallowing unaffected.

### PATHOPHYSIOLOGY

Dysphagia is caused by two main mechanisms: mechanical obstruction or motor dysfunction. Mechanical causes of dysphagia can be luminal (e.g., large food bolus, foreign body), intrinsic to the esophagus (e.g., inflammation, webs and rings, strictures, tumors), or extrinsic to the esophagus (e.g., cervical spondylitis, enlarged thyroid or mediastinal mass, vascular compression). The motor function abnormalities that cause dysphagia may be related to defects in initiating the swallowing reflex (e.g., tongue paralysis, lack of saliva, lesions affecting sensory components of cranial nerves X and XI), disorders of the pharyngeal and esophageal striated muscle (e.g., muscle disorders such as polymyositis and dermatomyositis, neurologic lesions such as myasthenia gravis, polio, or amyotrophic lateral sclerosis), and disorders of the esophageal smooth muscle (e.g., achalasia, scleroderma, myotonic dystrophy).

### APPROACH TO THE PATIENT: **Dysphagia**

History can provide a presumptive diagnosis in about 80% of pts. Difficulty only with solids implies mechanical dysphagia. Difficulty with both solids and liquids may occur late in the course of mechanical dysphagia but is an early sign of motor dysphagia. Pts can sometimes pinpoint the site of food sticking. Weight loss out of proportion to the degree of dysphagia may be a sign of underlying malignancy. Hoarseness may be related to involvement of the larynx in the primary disease process (e.g., neuromuscular disorders), neoplastic disruption of the recurrent laryngeal nerve, or laryngitis from gastroesophageal reflux.

Physical examination may reveal signs of skeletal muscle, neurologic, or oropharyngeal diseases. Neck examination can reveal masses impinging on the esophagus. Skin changes might suggest the systemic nature of the underlying disease (e.g., scleroderma).

Dysphagia is nearly always a symptom of organic disease rather than a functional complaint. If oropharyngeal dysphagia is suspected, video-fluoroscopy of swallowing may be diagnostic. Mechanical dysphagia can be evaluated by barium swallow and esophagogastroscopy with endoscopic biopsy. Barium swallow and esophageal motility studies can show the presence of motor dysphagia. An algorithm outlining an approach to the pt with dysphagia is shown in Fig. 39-1.

### OROPHARYNGEAL DYSPHAGIA

Pt has difficulty initiating the swallow; food sticks at the level of the suprasternal notch; nasopharyngeal regurgitation and aspiration may be present.

Causes include the following: for solids only, carcinoma, aberrant vessel, congenital or acquired web (Plummer-Vinson syndrome in iron deficiency), cervical osteophyte; for solids and liquids, cricopharyngeal bar (e.g., hypertensive or hypotensive

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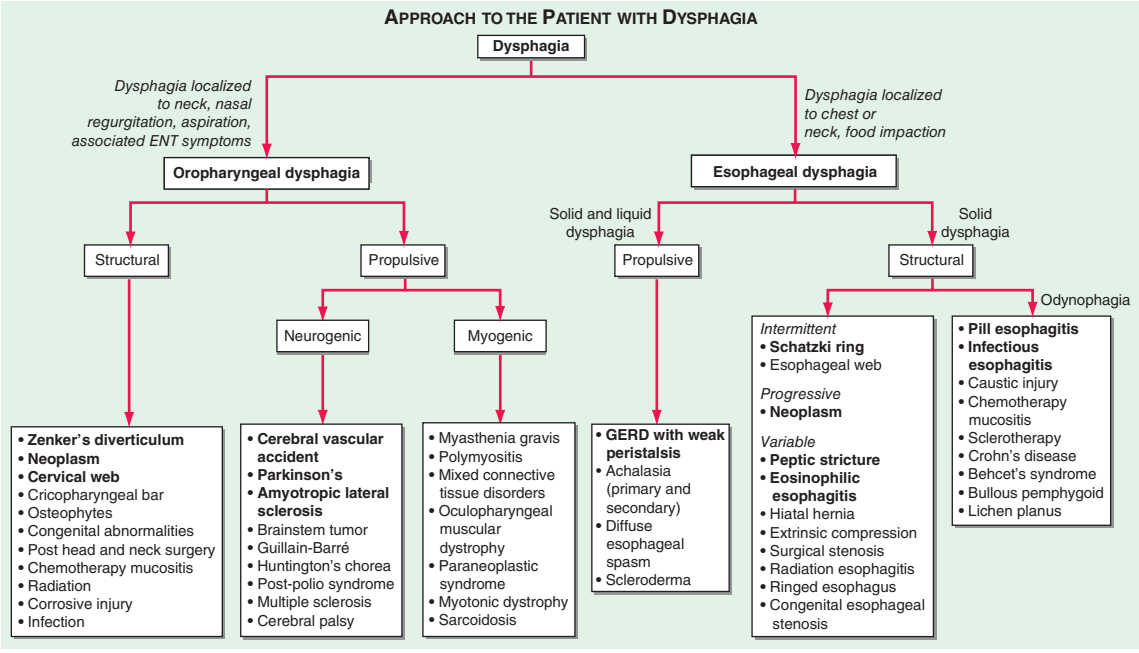


**FIGURE 39-1** Approach to the pt with dysphagia. Etiologies in bold print are the most common. ENT, ear, nose, and throat; GERD, gastroesophageal reflux disease.



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upper esophageal sphincter), Zenker's diverticulum (outpouching in the posterior midline at the intersection of the pharynx and the cricopharyngeus muscle), myasthenia gravis, glucocorticoid myopathy, hyperthyroidism, hypothyroidism, myotonic dystrophy, amyotrophic lateral sclerosis, multiple sclerosis, Parkinson's disease, stroke, bulbar palsy, and pseudobulbar palsy.

### ESOPHAGEAL DYSPHAGIA

Food sticks in the mid or lower sternal area; can be associated with regurgitation, aspiration, odynophagia. Causes include the following: for solids only, lower esophageal ring (Schatzki's ring—symptoms are usually intermittent), peptic stricture (heartburn accompanies this), carcinoma, lye stricture; for solids and liquids, diffuse esophageal spasm (occurs with chest pain and is intermittent), scleroderma (progressive and occurs with heartburn), achalasia (progressive and occurs without heartburn).

## NONCARDIAC CHEST PAIN

Of pts presenting with chest pain, 30% have an esophageal source rather than angina. History and physical examination often cannot distinguish cardiac from noncardiac pain. Exclude cardiac disease first. Causes include the following: gastroesophageal reflux disease, esophageal motility disorders, peptic ulcer disease, gallstones, psychiatric disease (anxiety, panic attacks, depression).

### EVALUATION

Consider a trial of antireflux therapy (omeprazole); if no response, 24-h ambulatory luminal pH monitoring; if negative, esophageal manometry may show motor disorder. Trial of imipramine, 50 mg PO qhs, may be worthwhile. Consider psychiatric evaluation in selected cases.

## ESOPHAGEAL MOTILITY DISORDERS

Pts may have a spectrum of manometric findings ranging from nonspecific abnormalities to defined clinical entities.

### ACHALASIA

Motor obstruction caused by hypertensive lower esophageal sphincter (LES), incomplete relaxation of LES, or loss of peristalsis in smooth-muscle portion of esophagus. Causes include the following: primary (idiopathic) or secondary due to Chagas' disease, lymphoma, carcinoma, chronic idiopathic intestinal pseudoobstruction, ischemia, neurotropic viruses, drugs, toxins, radiation therapy, postvagotomy.

### EVALUATION

Chest x-ray shows absence of gastric air bubble. Barium swallow shows dilated esophagus with distal beaklike narrowing and air-fluid level. Endoscopy is done to rule out cancer, particularly in persons >50 years. Manometry shows normal or elevated LES pressure, decreased LES relaxation, absent peristalsis.

**TREATMENT ACHALASIA**

Pneumatic balloon dilatation is effective in 85%, with 3–5% risk of perforation or bleeding. Injection of botulinum toxin at endoscopy to relax LES is safe and effective in two-thirds of patients, but effects last 6–12 months. Myotomy of LES (Heller procedure) is effective, but 10–30% of pts develop gastroesophageal reflux. Nifedipine, 10–20 mg, or isosorbide dinitrate, 5–10 mg SL ac, may avert need for dilation or surgery. Sildenafil may also augment swallow-induced relaxation of the LES.

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### SPASTIC DISORDERS

Diffuse esophageal spasm involves multiple spontaneous and swallow-induced contractions of the esophageal body that are of simultaneous onset and long duration and are recurrent. Causes include the following: primary (idiopathic) or secondary due to gastroesophageal reflux disease, emotional stress, diabetes, alcoholism, neuropathy, radiation therapy, ischemia, or collagen vascular disease.

An important variant is nutcracker esophagus: high-amplitude (>180 mmHg) peristaltic contractions; particularly associated with chest pain or dysphagia, but correlation between symptoms and manometry is inconsistent. Condition may resolve over time or evolve into diffuse spasm; associated with increased frequency of depression, anxiety, and somatization.

### EVALUATION

Barium swallow shows corkscrew esophagus, pseudodiverticula, and diffuse spasm. Manometry shows spasm with multiple simultaneous esophageal contractions of high amplitude and long duration. In nutcracker esophagus, the contractions are peristaltic and of high amplitude. If heart disease has been ruled out, edrophonium, ergonovine, or bethanechol can be used to provoke spasm.

#### TREATMENT SPASTIC DISORDERS

Anticholinergics are usually of limited value; nitrates (isosorbide dinitrate, 5–10 mg PO ac) and calcium antagonists (nifedipine, 10–20 mg PO ac) are more effective. Those refractory to medical management may benefit from balloon dilation. Rare pts require surgical intervention: longitudinal myotomy of esophageal circular muscle. Treatment of concomitant depression or other psychological disturbance may help.

### SCLERODERMA

Atrophy of the esophageal smooth muscle and fibrosis can make the esophagus aperistaltic and lead to an incompetent LES with attendant reflux esophagitis and stricture. Treatment of gastroesophageal reflux disease is discussed in Chap. 38.

## ESOPHAGEAL INFLAMMATION

### VIRAL ESOPHAGITIS

Herpesviruses I and II, varicella-zoster virus, and CMV can all cause esophagitis; particularly common in immunocompromised pts (e.g., AIDS). Odynophagia, dysphagia, fever, and bleeding are symptoms and signs. Diagnosis is made by endoscopy with biopsy, brush cytology, and culture.

#### TREATMENT VIRAL ESOPHAGITIS

Disease is usually self-limited in the immunocompetent person; viscous lidocaine can relieve pain; in prolonged cases and in immunocompromised hosts, herpes and varicella esophagitis are treated with acyclovir, 400 mg PO five times a day for 14–21 days or valacyclovir 1 g PO tid for 7 days. CMV is treated with ganciclovir, 5 mg/kg IV q12h, until healing occurs, which may take weeks. Oral valganciclovir (900 mg bid) is an effective alternative to parenteral treatment. In nonresponders, foscarnet, 90 mg/kg IV q12h for 21 days, may be effective.

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### *CANDIDA* ESOPHAGITIS

In immunocompromised hosts, or those with malignancy, diabetes, hypoparathyroidism, hemoglobinopathy, systemic lupus erythematosus, corrosive esophageal injury, candidal esophageal infection may present with odynophagia, dysphagia, and oral thrush (50%). Diagnosis is made on endoscopy by identifying yellow-white plaques or nodules on friable red mucosa. Characteristic hyphae are seen on KOH stain. In pts with AIDS, the development of symptoms may prompt an empirical therapeutic trial.

**TREATMENT** *CANDIDA* ESOPHAGITIS

In immunocompromised hosts, fluconazole, 200 mg PO on day 1 followed by 100 mg daily for 2–3 weeks, is treatment of choice; alternatives include itraconazole, 200 mg PO bid, or ketoconazole, 200–400 mg PO daily; long-term maintenance therapy is often required. Poorly responsive pts or those who cannot swallow may respond to caspofungin 50 mg IV qd for 7–21 days.

### PILL-RELATED ESOPHAGITIS

Doxycycline, tetracycline, aspirin, nonsteroidal anti-inflammatory drugs, KCl, quinidine, ferrous sulfate, clindamycin, alprenolol, and alendronate can induce local inflammation in the esophagus. Predisposing factors include recumbency after swallowing pills with small sips of water and anatomic factors impinging on the esophagus and slowing transit.

**TREATMENT** PILL-RELATED ESOPHAGITIS

Withdraw offending drug, use antacids, and dilate any resulting stricture.

### EOSINOPHILIC ESOPHAGITIS

Mucosal inflammation with eosinophils with submucosal fibrosis can be seen especially in pts with food allergies. This diagnosis relies on the presence of symptoms of esophagitis with the appropriate findings on esophageal biopsy. Eotaxin 3, an eosinophil chemokine, has been implicated in its etiology. IL-5 and TARC (thymus and activation-related chemokine) levels may be elevated. Treatment involves a 12-week course of swallowed fluticasone (440 μg bid) using a metered-dose inhaler.

### OTHER CAUSES OF ESOPHAGITIS IN AIDS

*Mycobacteria*, *Cryptosporidium*, *Pneumocystis*, idiopathic esophageal ulcers, and giant ulcers (possible cytopathic effect of HIV) can occur. Ulcers may respond to systemic glucocorticoids.

For a more detailed discussion, see Hirano I, Kahrilas PJ: Dysphagia, Chap. 53, p. 254; and Kahrilas PJ, Hirano I: Diseases of the Esophagus, Chap. 347, p. 1900, in HPIM-19.

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# 40 Diarrhea, Malabsorption, and Constipation

## NORMAL GASTROINTESTINAL FUNCTION

### ABSORPTION OF FLUID AND ELECTROLYTES

Fluid delivery to the GI tract is 8–10 L/d, including 2 L/d ingested; most is absorbed in small bowel. Colonic absorption is normally 0.05–2 L/d, with capacity for 6 L/d if required. Intestinal water absorption passively follows active transport of $Na^+$, $Cl^-$, glucose, and bile salts. Additional transport mechanisms include $Cl^-/HCO_3^-$ exchange, $Na^+/H^+$ exchange, $H^+$, $K^+$, $Cl^-$, and $HCO_3^-$ secretion, $Na^+$-glucose cotransport, and active $Na^+$ transport across the basolateral membrane by $Na^+,K^+$-ATPase.

### NUTRIENT ABSORPTION

1. *Proximal small intestine:* iron, calcium, folate, fats (after hydrolysis of triglycerides to fatty acids by pancreatic lipase and colipase), proteins (after hydrolysis by pancreatic and intestinal peptidases), carbohydrates (after hydrolysis by amylases and disaccharidases); triglycerides absorbed as micelles after solubilization by bile salts; amino acids and dipeptides absorbed via specific carriers; sugars absorbed by active transport
2. *Distal small intestine:* vitamin $B_{12}$, bile salts, water
3. *Colon:* water, electrolytes

### INTESTINAL MOTILITY

Allows propulsion of intestinal contents from stomach to anus and separation of components to facilitate nutrient absorption. Propulsion is controlled by neural, myogenic, and hormonal mechanisms; mediated by migrating motor complex, an organized wave of neuromuscular activity that originates in the distal stomach during fasting and migrates slowly down the small intestine. Colonic motility is mediated by local peristalsis to propel feces. Defecation is effected by relaxation of internal anal sphincter in response to rectal distention, with voluntary control by contraction of external anal sphincter.

## DIARRHEA

### PHYSIOLOGY

Formally defined as fecal output >200 g/d on low-fiber (western) diet; also frequently used to connote loose or watery stools. Mediated by one or more of the following mechanisms:

### OSMOTIC DIARRHEA

Nonabsorbed solutes increase intraluminal oncotic pressure, causing outpouring of water; usually ceases with fasting; stool osmolal gap >40 (see below). Causes include disaccharidase (e.g., lactase) deficiencies, pancreatic insufficiency, bacterial overgrowth, lactulose or sorbitol ingestion, polyvalent laxative abuse, celiac or tropical sprue, and short bowel syndrome. Lactase deficiency can be either primary (more prevalent in blacks and Asians, usually presenting in early adulthood) or

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secondary (from viral, bacterial, or protozoal gastroenteritis, celiac or tropical sprue, or kwashiorkor).

## SECRETORY DIARRHEA

Active ion secretion causes obligatory water loss; diarrhea is usually watery, often profuse, unaffected by fasting; stool $Na^+$ and $K^+$ are elevated with osmolal gap <40. Causes include viral infections (e.g., rotavirus, Norwalk virus), bacterial infections (e.g., cholera, enterotoxigenic *Escherichia coli*, *Staphylococcus aureus*), protozoa (e.g., *Giardia*, *Isospora*, *Cryptosporidium*), AIDS-associated disorders (including mycobacterial and HIV-induced), medications (e.g., theophylline, colchicine, prostaglandins, diuretics), Zollinger-Ellison syndrome (excess gastrin production), vasoactive intestinal peptide (VIP)–producing tumors, carcinoid tumors (histamine and serotonin), medullary thyroid carcinoma (prostaglandins and calcitonin), systemic mastocytosis, basophilic leukemia, distal colonic villous adenomas (direct secretion of potassium-rich fluid), collagenous and microscopic colitis, and choleraic diarrhea (from ileal malabsorption of bile salts).

## EXUDATIVE DIARRHEA

Inflammation, necrosis, and sloughing of colonic mucosa; may include component of secretory diarrhea due to prostaglandin release by inflammatory cells; stools usually contain polymorphonuclear leukocytes as well as occult or gross blood. Causes include bacterial infections (e.g., *Campylobacter*, *Salmonella*, *Shigella*, *Yersinia*, invasive or enterotoxigenic *E. coli*, *Vibrio parahaemolyticus*, *Clostridium difficile* colitis [frequently antibiotic-induced]), colonic parasites (e.g., *Entamoeba histolytica*), Crohn's disease, ulcerative proctocolitis, idiopathic inflammatory bowel disease, radiation enterocolitis, cancer chemotherapeutic agents, and intestinal ischemia.

## ALTERED INTESTINAL MOTILITY

Alteration of coordinated control of intestinal propulsion; diarrhea often intermittent or alternating with constipation. Causes include diabetes mellitus, adrenal insufficiency, hyperthyroidism, collagen-vascular diseases, parasitic infestations, gastrin and VIP hypersecretory states, amyloidosis, laxatives (esp. magnesium-containing agents), antibiotics (esp. erythromycin), cholinergic agents, primary neurologic dysfunction (e.g., Parkinson's disease, traumatic neuropathy), fecal impaction, diverticular disease, and irritable bowel syndrome. Blood in intestinal lumen is cathartic, and major upper GI bleeding leads to diarrhea from increased motility.

## DECREASED ABSORPTIVE SURFACE

Usually arises from surgical manipulation (e.g., extensive bowel resection or rearrangement) that leaves inadequate absorptive surface for fat and carbohydrate digestion and fluid and electrolyte absorption; occurs spontaneously from enteroenteric fistulas (esp. gastrocolic).

## EVALUATION HISTORY

Diarrhea must be distinguished from fecal incontinence, change in stool caliber, rectal bleeding, and small, frequent, but otherwise normal stools. Careful medication history is essential. Alternating diarrhea and constipation suggests fixed colonic obstruction (e.g., from carcinoma) or irritable bowel syndrome. A sudden, acute course, often with nausea, vomiting, and fever, is typical of viral and bacterial infections, diverticulitis, ischemia, radiation enterocolitis, or drug-induced diarrhea and may be the initial presentation of inflammatory bowel disease. More than 90% of acute diarrheal illnesses are infectious in etiology. A longer (>4 weeks), more insidious course suggests malabsorption, inflammatory bowel disease, metabolic or endocrine disturbance, pancreatic insufficiency, laxative abuse, ischemia, neoplasm (hypersecretory state or partial obstruction), or irritable bowel syndrome. Parasitic

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**TABLE 40-1 INFECTIOUS CAUSES OF DIARRHEA IN PTS WITH AIDS**

| Nonopportunistic Pathogens | Opportunistic Pathogens |
|---|---|
| *Shigella* | Protozoa |
| *Salmonella* | *Cryptosporidium* |
| *Campylobacter* | *Isospora belli* |
| *Entamoeba histolytica* | Microsporidia |
| *Chlamydia* | *Blastocystis hominis* |
| *Neisseria gonorrhoeae* | Viruses |
| *Treponema pallidum* and other spirochetes | Cytomegalovirus |
| *Giardia lamblia* | Herpes simplex |
| | Adenovirus |
| | HIV |
| | Bacteria |
| | *Mycobacterium avium* complex |

and certain forms of bacterial enteritis can also produce chronic symptoms. Particularly foul-smelling or oily stool suggests fat malabsorption. Fecal impaction may cause apparent diarrhea because only liquids pass partial obstruction. Several infectious causes of diarrhea are associated with an immunocompromised state (Table 40-1).

## PHYSICAL EXAMINATION

Signs of dehydration are often prominent in severe, acute diarrhea. Fever and abdominal tenderness suggest infection or inflammatory disease but are often absent in viral enteritis. Evidence of malnutrition suggests chronic course. Certain signs are frequently associated with specific deficiency states secondary to malabsorption (e.g., cheilosis with riboflavin or iron deficiency, glossitis with $B_{12}$, folate deficiency). Questions to address in pts with chronic diarrhea are shown in Table 40-2.

## STOOL EXAMINATION

Culture for bacterial pathogens, examination for leukocytes, measurement of *C. difficile* toxin, and examination for ova and parasites are important components of evaluation of pts with severe, protracted, or bloody diarrhea. Presence of blood (fecal occult blood test) or leukocytes (Wright's stain) suggests inflammation (e.g., ulcerative colitis, Crohn's disease, infection, or ischemia). Gram's stain of stool can

**TABLE 40-2 PHYSICAL EXAMINATION IN PTS WITH CHRONIC DIARRHEA**

1. Are there general features to suggest malabsorption or IBD such as anemia, dermatitis herpetiformis, edema, or clubbing?
2. Are there features to suggest underlying autonomic neuropathy or collagen-vascular disease in the pupils, orthostasis, skin, hands, or joints?
3. Is there an abdominal mass or tenderness?
4. Are there any abnormalities of rectal mucosa, rectal defects, or altered anal sphincter functions?
5. Are there any mucocutaneous manifestations of systemic disease such as dermatitis herpetiformis (celiac disease), erythema nodosum (ulcerative colitis), flushing (carcinoid), or oral ulcers for IBD or celiac disease?

***Abbreviation:*** IBD, inflammatory bowel disease.

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be diagnostic of *Staphylococcus*, *Campylobacter*, or *Candida* infection. Steatorrhea (determined with Sudan III stain of stool sample or 72-h quantitative fecal fat analysis) suggests malabsorption or pancreatic insufficiency. Measurement of $Na^+$ and $K^+$ levels in fecal water helps to distinguish osmotic from other types of diarrhea; osmotic diarrhea is implied by stool osmolal gap > 40, where stool osmolal gap = $osmol_{serum}$ $[2 \times (Na^+ + K^+)_{stool}]$.

### LABORATORY STUDIES

Complete blood count may indicate anemia (acute or chronic blood loss or malabsorption of iron, folate, or $B_{12}$), leukocytosis (inflammation), eosinophilia (parasitic, neoplastic, and inflammatory bowel diseases). Serum levels of calcium, albumin, iron, cholesterol, folate, $B_{12}$, vitamin D, and carotene; serum iron-binding capacity; and prothrombin time can provide evidence of intestinal malabsorption or maldigestion.

### OTHER STUDIES

D-Xylose absorption test is a convenient screen for small-bowel absorptive function. Small-bowel biopsy is especially useful for evaluating intestinal malabsorption. Specialized studies include Schilling test ($B_{12}$ malabsorption), lactose $H_2$ breath test (carbohydrate malabsorption), [$^{14}$C]xylose and lactulose $H_2$ breath tests (bacterial overgrowth), glycocholic breath test (ileal malabsorption), triolein breath test (fat malabsorption), and bentiromide and secretin tests (pancreatic insufficiency). Sigmoidoscopy or colonoscopy with biopsy is useful in the diagnosis of colitis (esp. pseudomembranous, ischemic, microscopic); it may not allow distinction between infectious and noninfectious (esp. idiopathic ulcerative) colitis. Barium contrast x-ray studies may suggest malabsorption (thickened bowel folds), inflammatory bowel disease (ileitis or colitis), tuberculosis (ileocecal inflammation), neoplasm, intestinal fistula, or motility disorders.

## TREATMENT DIARRHEA

An approach to the management of acute diarrheal illnesses is shown in Fig. 40-1. Symptomatic therapy includes vigorous rehydration (IV or with oral glucose-electrolyte solutions), electrolyte replacement, binders of osmotically active substances (e.g., kaolin-pectin), and opiates to decrease bowel motility (e.g., loperamide, diphenoxylate); opiates may be contraindicated in infectious or inflammatory causes of diarrhea. An approach to the management of chronic diarrhea is shown in Fig. 40-2.

## MALABSORPTION SYNDROMES

Intestinal malabsorption of ingested nutrients may produce osmotic diarrhea, steatorrhea, or specific deficiencies (e.g., iron; folate; $B_{12}$; vitamins A, D, E, and K). Table 40-3 lists common causes of intestinal malabsorption. Protein-losing enteropathy may result from several causes of malabsorption; it is associated with hypoalbuminemia and can be detected by measuring stool $\alpha_1$-antitrypsin or radiolabeled albumin levels. Therapy is directed at the underlying disease.

## CONSTIPATION

Defined as decrease in frequency of stools to less than one per week or difficulty in defecation; may result in abdominal pain, distention, and fecal impaction, with consequent obstruction or, rarely, perforation. Constipation is a frequent and often

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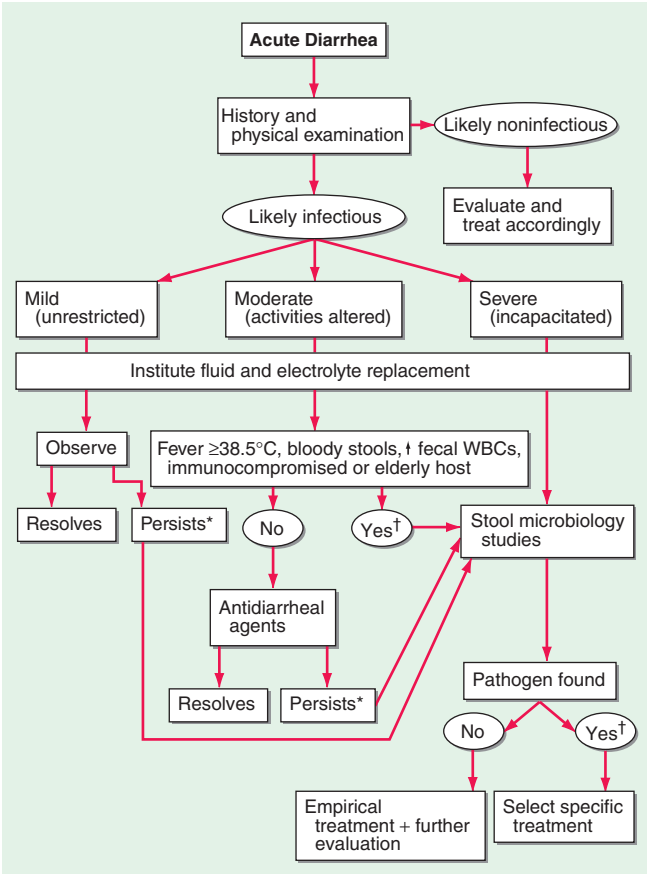


**FIGURE 40-1** Algorithm for the management of acute diarrhea. Consider empirical treatment before evaluation with (*) metronidazole and with (†) quinolone. WBCs, white blood cells.

subjective complaint. Contributory factors may include inactivity, low-fiber diet, and inadequate allotment of time for defecation.

## SPECIFIC CAUSES

Altered colonic motility due to neurologic dysfunction (diabetes mellitus, spinal cord injury, multiple sclerosis, Chagas' disease, Hirschsprung's disease, chronic idiopathic intestinal pseudoobstruction, idiopathic megacolon), scleroderma, drugs (esp. anticholinergic agents, opiates, aluminum- or calcium-based antacids, calcium channel blockers, iron supplements, sucralfate), hypothyroidism, Cushing's syndrome, hypokalemia, hypercalcemia, dehydration, mechanical causes (colorectal tumors, diverticulitis, volvulus, hernias, intussusception), and anorectal pain (from fissures, hemorrhoids, abscesses, or proctitis) leading to retention, constipation, and fecal impaction.

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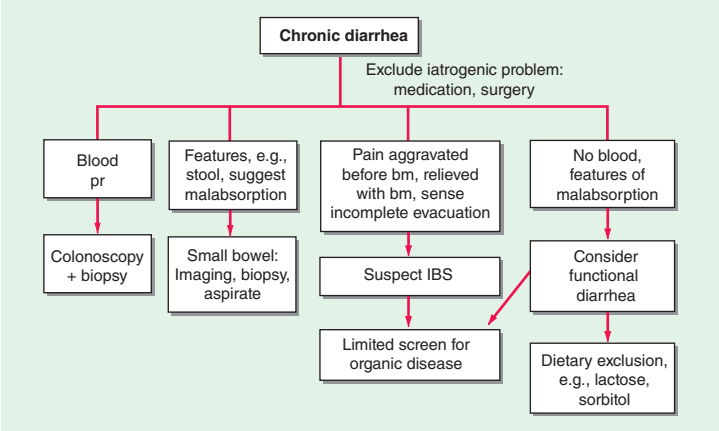
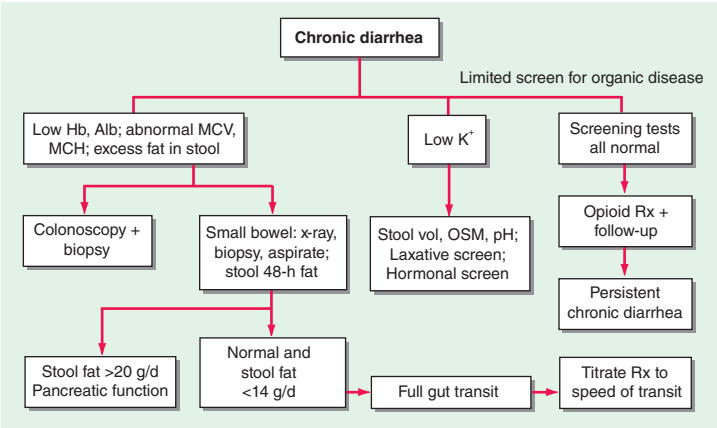



*A*




*B*

**FIGURE 40-2** Chronic diarrhea. **A.** Initial management based on accompanying symptoms or features. **B.** Evaluation based on findings from a limited age-appropriate screen for organic disease. Alb, albumin; bm, bowel movement; Hb, hemoglobin; IBS, irritable bowel syndrome; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; OSM, osmolality; pr, per rectum. *(Reprinted from M Camilleri: Clin Gastroenterol Hepatol 2:198, 2004.)*

## TREATMENT CONSTIPATION

A management approach is shown in Fig. 40-3. In the absence of identifiable cause, constipation may improve with reassurance, exercise, increased dietary fiber, bulking agents (e.g., psyllium), and increased fluid intake. Specific therapies include removal of bowel obstruction (fecalith, tumor), discontinuance of nonessential hypomotility agents (esp. aluminum or calcium-containing antacids, opiates), or substitution of magnesium-based antacids for aluminum-based antacids. For symptomatic relief, magnesium-containing agents or other cathartics are

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**TABLE 40-3 COMMON CAUSES OF MALABSORPTION**

***Maldigestion:*** Chronic pancreatitis, cystic fibrosis, pancreatic carcinoma

***Bile salt deficiency:*** Cirrhosis, cholestasis, bacterial overgrowth (blind loop syndromes, intestinal diverticula, hypomotility disorders), impaired ileal reabsorption (resection, Crohn's disease), bile salt binders (cholestyramine, calcium carbonate, neomycin)

***Inadequate absorptive surface:*** Massive intestinal resection, gastrocolic fistula, jejunoileal bypass

***Lymphatic obstruction:*** Lymphoma, Whipple's disease, intestinal lymphangiectasia

***Vascular disease:*** Constrictive pericarditis, right-sided heart failure, mesenteric arterial or venous insufficiency

***Mucosal disease:*** Infection (esp. ***Giardia***, Whipple's disease, tropical sprue), inflammatory diseases (esp. Crohn's disease), radiation enteritis, eosinophilic enteritis, ulcerative jejunitis, mastocytosis, tropical sprue, infiltrative disorders (amyloidosis, scleroderma, lymphoma, collagenous sprue, microscopic colitis), biochemical abnormalities (gluten-sensitive enteropathy, disaccharidase deficiency, hypogammaglobulinemia, abetalipoproteinemia, amino acid transport deficiencies), endocrine disorders (diabetes mellitus, hypoparathyroidism, adrenal insufficiency, hyperthyroidism, Zollinger-Ellison syndrome, carcinoid syndrome)

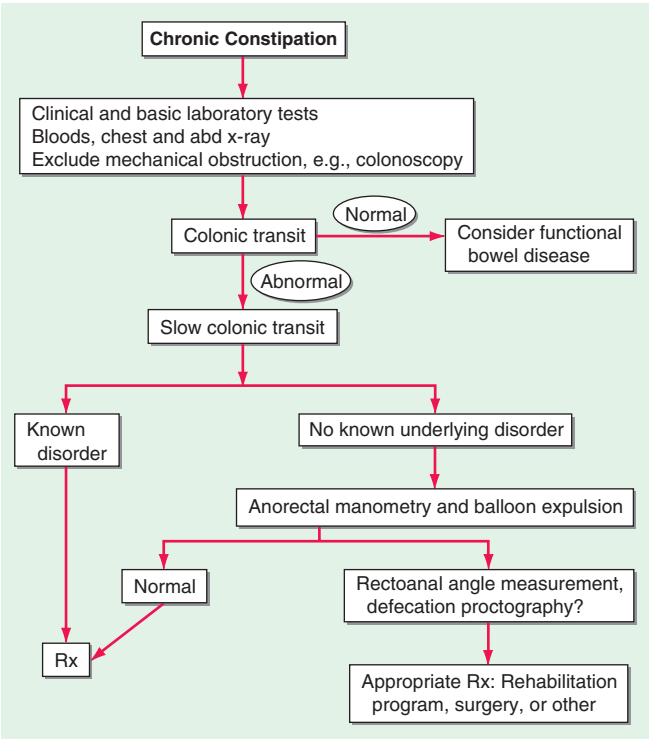


**FIGURE 40-3** Algorithm for the management of constipation. abd, abdominal.

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occasionally needed. With severe hypo- or dysmotility or in the presence of opiates, osmotically active agents (e.g., oral lactulose, intestinal polyethylene glycol–containing lavage solutions) and oral or rectal emollient laxatives (e.g., docusate salts) and mineral oil are most effective.

For a more detailed discussion, see Camilleri M, Murray JA: Diarrhea and Constipation, Chap. 55, p. 264; and Binder HJ: Disorders of Absorption, Chap. 349, p. 1932, in HPIM-19.

# 41 Gastrointestinal Bleeding

## PRESENTATION

1. *Hematemesis:* Vomiting of blood or altered blood ("coffee grounds") indicates bleeding proximal to ligament of Treitz.
2. *Melena:* Altered (black) blood per rectum (>100-mL blood required for one melenic stool) usually indicates bleeding proximal to ligament of Treitz but may be as distal as ascending colon; pseudomelena may be caused by ingestion of iron, bismuth, licorice, beets, blueberries, and charcoal.
3. *Hematochezia:* Bright red or maroon rectal bleeding usually implies bleeding beyond ligament of Treitz but may be due to rapid upper GI bleeding (>1000 mL).
4. *Positive fecal occult blood test with or without iron deficiency.*
5. *Symptoms of blood loss:* e.g., light-headedness or shortness of breath.

### HEMODYNAMIC CHANGES

Orthostatic drop in bp >10 mmHg usually indicates >20% reduction in blood volume (± syncope, light-headedness, nausea, sweating, thirst).

### SHOCK

BP <100 mmHg systolic usually indicates <30% reduction in blood volume (± pallor, cool skin).

### LABORATORY CHANGES

Hematocrit may not reflect extent of blood loss because of delayed equilibration with extravascular fluid. Mild leukocytosis and thrombocytosis. Elevated blood urea nitrogen is common in upper GI bleeding.

### ADVERSE PROGNOSTIC SIGNS

Age >60 years, associated illnesses, coagulopathy, immunosuppression, presentation with shock, rebleeding, onset of bleeding in hospital, variceal bleeding, endoscopic stigmata of recent bleeding (e.g., "visible vessel" in ulcer base [see below]).

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## UPPER GI BLEEDING

### CAUSES

#### Common

Peptic ulcer (accounts for ~50%), gastropathy (alcohol, aspirin, NSAIDs, stress), esophagitis, Mallory-Weiss tear (mucosal tear at gastroesophageal junction due to retching), gastroesophageal varices.

#### Less Common

Swallowed blood (nosebleed); esophageal, gastric, or intestinal neoplasm; anticoagulant and fibrinolytic therapy; hypertrophic gastropathy (Ménétrier's disease); aortic aneurysm; aortoenteric fistula (from aortic graft); arteriovenous malformation; telangiectases (Osler-Weber-Rendu syndrome); Dieulafoy lesion (ectatic submucosal vessel); vasculitis; connective tissue disease (pseudoxanthoma elasticum, Ehlers-Danlos syndrome); blood dyscrasias; neurofibroma; amyloidosis; hemobilia (biliary origin).

### EVALUATION

After hemodynamic resuscitation (see below and Fig. 41-1).

- History and physical examination: Drugs (increased risk of upper and lower GI tract bleeding with aspirin and NSAIDs), prior ulcer, bleeding history, family history, features of cirrhosis or vasculitis, etc. Hyperactive bowel sounds favor upper GI source.
- Nasogastric aspirate for gross blood, if source (upper versus lower) not clear from history; may be falsely negative in up to 16% of pts if bleeding has ceased or duodenum is the source. Testing aspirate for occult blood is meaningless.
- Upper endoscopy: Accuracy >90%; allows visualization of bleeding site and possibility of therapeutic intervention; mandatory for suspected varices, aortoenteric fistulas; permits identification of "visible vessel" (protruding artery in ulcer crater), which connotes high (~50%) risk of rebleeding.
- Upper GI barium radiography: Accuracy ~80% in identifying a lesion, though does not confirm source of bleeding; acceptable alternative to endoscopy in resolved or chronic low-grade bleeding.
- Selective mesenteric arteriography: When brisk bleeding precludes identification of source at endoscopy.
- Radioisotope scanning (e.g., $^{99}$Tc tagged to red blood cells or albumin); used primarily as screening test to confirm bleeding is rapid enough for arteriography to be of value or when bleeding is intermittent and of unclear origin.

## LOWER GI BLEEDING

### CAUSES

Anal lesions (hemorrhoids, fissures), rectal trauma, proctitis, colitis (ulcerative colitis, Crohn's disease, infectious colitis, ischemic colitis, radiation), colonic polyps, colonic carcinoma, angiodysplasia (vascular ectasia), diverticulosis, intussusception, solitary ulcer, blood dyscrasias, vasculitis, connective tissue disease, neurofibroma, amyloidosis, anticoagulation.

### EVALUATION (SEE BELOW AND FIG. 41-2)

- History and physical examination.
- In the presence of hemodynamic changes, perform upper endoscopy followed by colonoscopy. In the absence of hemodynamic changes, perform anoscopy and either flexible sigmoidoscopy or colonoscopy: Exclude hemorrhoids, fissure, ulcer, proctitis, neoplasm.

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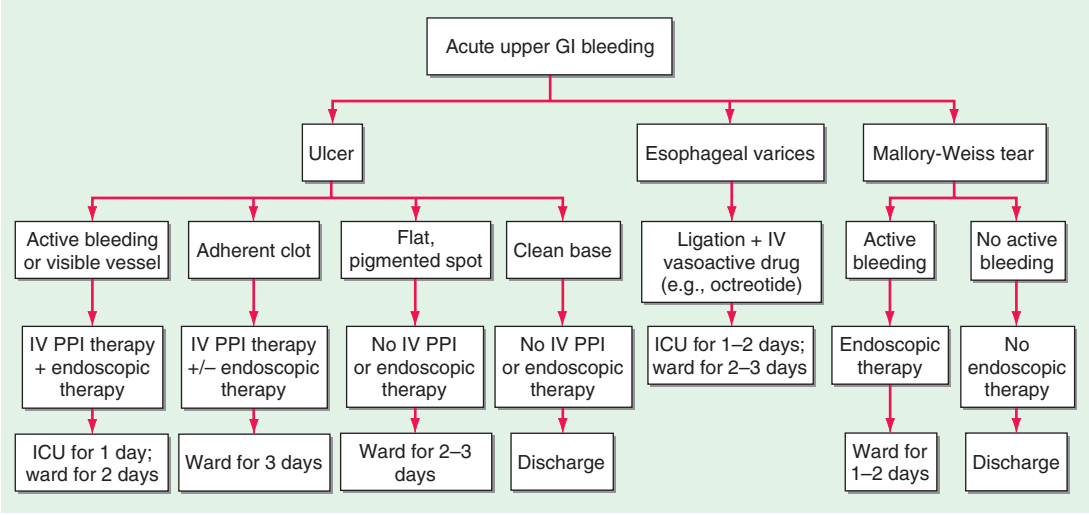


**FIGURE 41-1** Suggested algorithm for pts with acute upper GI bleeding. Recommendations on level of care and time of discharge assume pt is stabilized without further bleeding or other concomitant medical problems. PPI, proton pump inhibitor.

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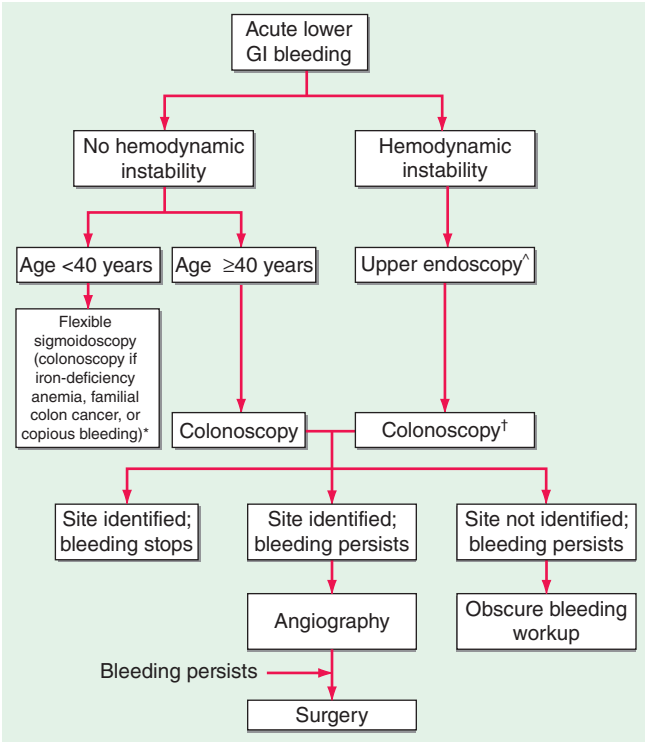


**FIGURE 41-2** Suggested algorithm for pts with acute lower GI bleeding. *Some suggest colonoscopy for any degree of rectal bleeding in pts <40 years as well. ^If upper GI endoscopy reveals definite source, no further evaluation is needed. †If massive bleeding does not allow time for colonic lavage, proceed to angiography.

- Colonoscopy: Often test of choice, but may be impossible if bleeding is massive.
- Barium enema: No role in active bleeding.
- Arteriography: When bleeding is severe (requires bleeding rate >0.5 mL/min; may require prestudy radioisotope bleeding scan as above); defines site of bleeding or abnormal vasculature.
- Surgical exploration (last resort).

## BLEEDING OF OBSCURE ORIGIN

Often small-bowel source. Consider small-bowel enteroclysis x-ray (careful barium radiography via peroral intubation of small bowel), Meckel's scan, enteroscopy (small-bowel endoscopy), or exploratory laparotomy with intraoperative enteroscopy.

## TREATMENT UPPER AND LOWER GI BLEEDING

- Venous access with large-bore IV (14–18 gauge); central venous line for major bleed and pts with cardiac disease; monitor vital signs, urine output, Hct (fall may lag). Gastric lavage of unproven benefit but clears stomach before endoscopy. Iced saline may lyse clots; room-temperature tap water may be preferable. Intubation may be required to protect airway.

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- Type and cross-match blood (six units for major bleed).
- Surgical standby when bleeding is massive.
- Support blood pressure with isotonic fluids (normal saline); albumin and fresh frozen plasma in cirrhotics. Packed red blood cells when available (whole blood if massive bleeding); maintain Hct >25–30. Fresh frozen plasma and vitamin K (10 mg SC or IV) in cirrhotics with coagulopathy.
- IV calcium (e.g., up to 10–20 mL 10% calcium gluconate IV over 10–15 min) if serum calcium falls (due to transfusion of citrated blood). Empirical drug therapy (antacids, $H_2$ receptor blockers, omeprazole) of unproven benefit.
- Specific measures: *Varices:* octreotide (50-µg bolus, 50-µg/h infusion for 2–5 days), Sengstaken-Blakemore tube tamponade, endoscopic sclerosis, or band ligation; propranolol or nadolol in doses sufficient to cause beta blockade reduces risk of recurrent or initial variceal bleeding (do not use in acute bleed) (Chap. 155); *ulcer with visible vessel or active bleeding*: endoscopic bipolar, heater-probe, or laser coagulation or injection of epinephrine; *gastritis*: embolization or vasopressin infusion of left gastric artery; *GI telangiectases*: ethinylestradiol/norethisterone (0.05/1.0 mg PO qd) may prevent recurrent bleeding, particularly in pts with chronic renal failure; *diverticulosis*: mesenteric arteriography with intraarterial vasopressin; *angiodysplasia*: colonoscopic bipolar or laser coagulation, may regress with replacement of stenotic aortic valve.
- Indications for emergency surgery: Uncontrolled or prolonged bleeding, severe rebleeding, aortoenteric fistula. For intractable variceal bleeding, consider transjugular intrahepatic portosystemic shunt (TIPS).

For a more detailed discussion, see Laine L: Gastrointestinal Bleeding, Chap. 57, p. 276, in HPIM-19.

# 42 Jaundice and Evaluation of Liver Function

## JAUNDICE

### Definition

Yellow skin pigmentation caused by elevation in serum bilirubin level (also termed *icterus*); often more easily discernible in sclerae. Scleral icterus becomes clinically evident at a serum bilirubin level of ≥51 µmol/L (≥3 mg/dL); yellow skin discoloration also occurs with elevated serum carotene levels but without pigmentation of the sclerae.

### Bilirubin Metabolism

Bilirubin is the major breakdown product of hemoglobin released from senescent erythrocytes. Initially, it is bound to albumin, transported into the liver, conjugated

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to a water-soluble form (glucuronide) by glucuronosyltransferase, excreted into the bile, and converted to urobilinogen in the colon. Urobilinogen is mostly excreted in the stool; a small portion is reabsorbed and excreted by the kidney. Bilirubin can be filtered by the kidney only in its conjugated form (measured as the "direct" fraction); thus, increased *direct* serum bilirubin level is associated with bilirubinuria. Increased bilirubin production and excretion (even without hyperbilirubinemia, as in hemolysis) produce elevated urinary urobilinogen levels.

## Etiology

Hyperbilirubinemia occurs as a result of (1) overproduction; (2) impaired uptake, conjugation, or excretion of bilirubin; (3) regurgitation of unconjugated or conjugated bilirubin from damaged hepatocytes or bile ducts (Table 42-1).

**TABLE 42-1 CAUSES OF ISOLATED HYPERBILIRUBINEMIA**

- I. Indirect hyperbilirubinemia
  - A. Hemolytic disorders
    - 1. Inherited
      - a. Spherocytosis, elliptocytosis, glucose-6-phosphate dehydrogenase and pyruvate kinase deficiencies
      - b. Sickle cell anemia
    - 2. Acquired
      - a. Microangiopathic hemolytic anemias
      - b. Paroxysmal nocturnal hemoglobinuria
      - c. Spur cell anemia
      - d. Immune hemolysis
      - e. Parasitic infections
        - 1. Malaria
        - 2. Babesiosis
  - B. Ineffective erythropoiesis
    - 1. Cobalamin, folate, and severe iron deficiencies
    - 2. Thalassemia
  - C. Increased bilirubin production
    - 1. Massive blood transfusion
    - 2. Resorption of hematoma
  - D. Drugs
    - 1. Rifampin
    - 2. Probenecid
    - 3. Ribavirin
  - E. Inherited conditions
    - 1. Crigler-Najjar types I and II
    - 2. Gilbert's syndrome
- II. Direct hyperbilirubinemia
  - A. Inherited conditions
    - 1. Dubin-Johnson syndrome
    - 2. Rotor syndrome

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## Evaluation

The initial steps in evaluating the pt with jaundice are to determine whether (1) hyperbilirubinemia is conjugated or unconjugated, and (2) other biochemical liver tests are abnormal (Figs. 42-1 and 42-2, Tables 42-2 and 42-3). Essential clinical examination includes history (especially duration of jaundice, pruritus, associated pain, risk factors for parenterally transmitted diseases, medications, ethanol use, travel history, surgery, pregnancy, presence of any accompanying symptoms), physical examination (hepatomegaly, tenderness over liver, palpable gallbladder, splenomegaly, gynecomastia, testicular atrophy, other stigmata of chronic liver disease), blood liver tests (see below), and complete blood count.

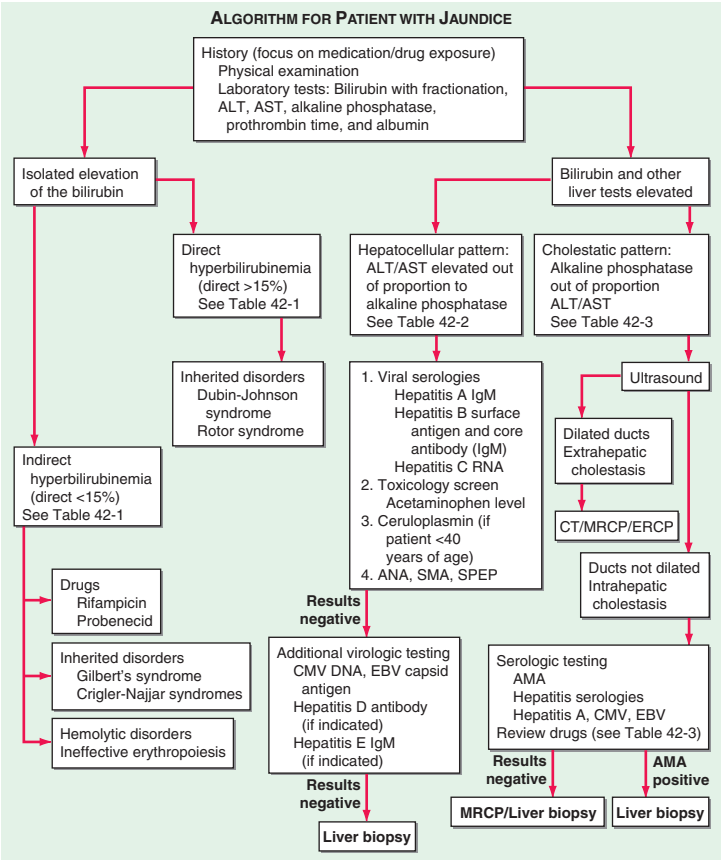


**FIGURE 42-1** Evaluation of the pt with jaundice. ALT, alanine aminotransferase; AMA, antimitochondrial antibody; AST, aspartate aminotransferase; ERCP, endoscopic retrograde cholangiopancreatogram; MRCP, magnetic resonance cholangiopancreatography; SMA, smooth-muscle antibody; SPEP, serum protein electrophoresis.

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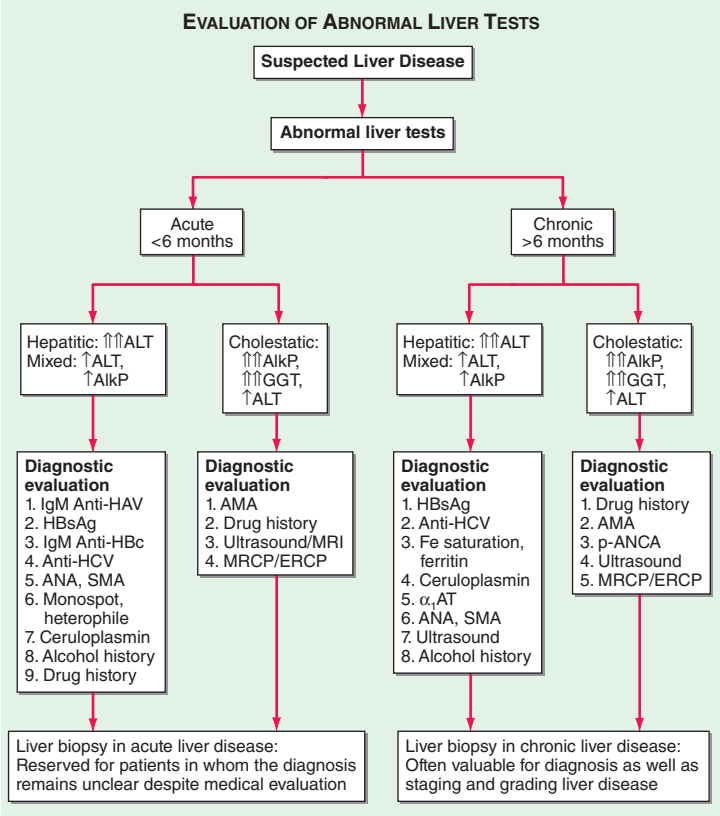


**FIGURE 42-2** Algorithm for evaluation of abnormal liver tests. α AT, α1 antitrypsin; AlkP, alkaline phosphatase; ALT, alanine aminotransferase; AMA, antimitochondrial antibody; ERCP, endoscopic retrograde cholangiopancreatogram; GGT, γ-Glutamyl transpeptidase; HAV, hepatitis A virus; HBc, hepatitis B core; HBsAG, hepatitis B surface antigen; HCV, hepatitis C virus; MRCP, magnetic resonance cholangiopancreatography; p-ANCA, perinuclear antineutrophil cytoplasmic antibody; SMA, smooth-muscle antibody.

## Gilbert Syndrome

Impaired conjugation of bilirubin due to reduced bilirubin UDP glucuronosyltransferase activity. Results in mild unconjugated hyperbilirubinemia, almost always <103 μmol/L (<6 mg/dL). Affects 3–7% of the population; males/females 2–7:1.

## BLOOD TESTS OF LIVER FUNCTION

Used to detect presence of liver disease (Fig. 42-2), discriminate among different types of liver disease (Table 42-4), gauge the extent of known liver damage, and follow response to treatment.

## Bilirubin

Provides indication of hepatic uptake, metabolic (conjugation) and excretory functions; conjugated fraction (direct) distinguished from unconjugated by chemical assay (Table 42-1).

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**TABLE 42-2 HEPATOCELLULAR CONDITIONS THAT MAY PRODUCE JAUNDICE**

| |
|---|
| Viral hepatitis |
| Hepatitis A, B, C, D, and E |
| Epstein-Barr virus |
| Cytomegalovirus |
| Herpes simplex |
| Alcoholic hepatitis |
| Drug toxicity |
| Predictable, dose dependent, (e.g., acetaminophen) |
| Unpredictable, idiosyncratic, (e.g., isoniazid) |
| Environmental toxins |
| Vinyl chloride |
| Jamaica bush tea—pyrrolizidine alkaloids |
| Kava Kava |
| Wild mushrooms—*Amanita phalloides* or *A. verna* |
| Wilson's disease |
| Autoimmune hepatitis |

**TABLE 42-3 CHOLESTATIC CONDITIONS THAT MAY PRODUCE JAUNDICE**

I. Intrahepatic
- A. Viral hepatitis
  1. Fibrosing cholestatic hepatitis—hepatitis B and C
  2. Hepatitis A, Epstein-Barr virus infection, cytomegalovirus infection
- B. Alcoholic hepatitis
- C. Drug toxicity
  1. Pure cholestasis—anabolic and contraceptive steroids
  2. Cholestatic hepatitis—chlorpromazine, erythromycin estolate
  3. Chronic cholestasis—chlorpromazine and prochlorperazine
- D. Primary biliary cirrhosis
- E. Primary sclerosing cholangitis
- F. Vanishing bile duct syndrome
  1. Chronic rejection of liver transplants
  2. Sarcoidosis
  3. Drugs
- G. Congestive hepatopathy and ischemic hepatitis
- H. Inherited conditions
  1. Progressive familial intrahepatic cholestasis
  2. Benign recurrent cholestasis
- I. Cholestasis of pregnancy
- J. Total parenteral nutrition
- K. Nonhepatobiliary sepsis
- L. Benign postoperative cholestasis
- M. Paraneoplastic syndrome

(*Continued*)

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**TABLE 42-3 CHOLESTATIC CONDITIONS THAT MAY PRODUCE JAUNDICE (*CONTINUED*)**

- N. Veno-occlusive disease
- O. Graft-versus-host disease
- P. Infiltrative disease
  1. TB
  2. Lymphoma
  3. Amyloidosis
- Q. Infections
  1. Malaria
  2. Leptospirosis

II. Extrahepatic

- A. Malignant
  1. Cholangiocarcinoma
  2. Pancreatic cancer
  3. Gallbladder cancer
  4. Ampullary cancer
  5. Malignant involvement of the porta hepatis lymph nodes
- B. Benign
  1. Choledocholithiasis
  2. Postoperative biliary strictures
  3. Primary sclerosing cholangitis
  4. Chronic pancreatitis
  5. AIDS cholangiopathy
  6. Mirizzi's syndrome
  7. Parasitic disease (ascariasis)

## Aminotransferases (Transaminases)

Aspartate aminotransferase (AST; SGOT) and alanine aminotransferase (ALT; SGPT); sensitive indicators of liver cell injury; greatest elevations seen in hepatocellular necrosis (e.g., viral hepatitis, toxic or ischemic liver injury, acute hepatic vein obstruction), occasionally with sudden, complete biliary obstruction (e.g., from gallstone); milder abnormalities in cholestatic, cirrhotic, and infiltrative disease; poor correlation between degree of liver cell damage and level of aminotransferases; ALT more specific measure of liver injury, because AST also found in striated muscle and other organs; ethanol-induced liver injury usually produces modest increases with more prominent elevation of AST than ALT.

## Alkaline Phosphatase

Sensitive indicator of cholestasis, biliary obstruction (enzyme increases more quickly than serum bilirubin), and liver infiltration; mild elevations in other forms of liver disease; limited specificity because of wide tissue distribution; elevations also seen in normal childhood, pregnancy, and bone diseases; tissue-specific isoenzymes can be distinguished by fractionation or by differences in heat stability (liver enzyme activity stable under conditions that destroy bone enzyme activity).

## 5′-Nucleotidase (5′-NT)

Pattern of elevation in hepatobiliary disease similar to alkaline phosphatase; has greater specificity for liver disorders; used to determine whether liver is source of

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**TABLE 42-4 LIVER TEST PATTERNS IN HEPATOBILIARY DISORDERS**

| Type of Disorder | Bilirubin | Aminotransferases | Alkaline Phosphatase | Albumin | Prothrombin Time |
|---|---|---|---|---|---|
| Hemolysis/Gilbert's syndrome | Normal to 86 μmol/L (5 mg/dL)<br>85% due to indirect fractions<br>No bilirubinuria | Normal | Normal | Normal | Normal |
| Acute hepatocellular necrosis (viral and drug hepatitis, hepatotoxins, acute heart failure) | Both fractions may be elevated<br>Peak usually follows aminotransferases<br>Bilirubinuria | Elevated, often >500 IU ALT >AST | Normal to <3 times normal elevation | Normal | Usually normal. If >5 × above control and not corrected by parenteral vitamin K, suggests poor prognosis |
| Chronic hepatocellular disorders | Both fractions may be elevated<br>Bilirubinuria | Elevated, but usually <300 IU | Normal to <3 times normal elevation | Often decreased | Often prolonged<br>Fails to correct with parenteral vitamin K |
| Alcoholic hepatitis, cirrhosis | Both fractions may be elevated<br>Bilirubinuria | AST:ALT > 2 suggests alcoholic hepatitis or cirrhosis | Normal to <3 times normal elevation | Often decreased | Often prolonged<br>Fails to correct with parenteral vitamin K |
| Intra- and extra-hepatic cholestasis | Both fractions may be elevated | Normal to moderate elevation | Elevated, often >4 times normal elevation | Normal, unless chronic | Normal<br>If prolonged, will correct with parenteral vitamin K |
| (Obstructive jaundice) | Bilirubinuria | Rarely >500 IU | Elevated, often >4 times normal elevation<br>Fractionate, or confirm liver origin with 5′ nucleotidase or γ-glutamyl transpeptidase | Normal | Normal |
| Infiltrative diseases (tumor, granulomata); partial bile duct obstruction | Usually normal | Normal to slight elevation | | | |

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elevation in serum alkaline phosphatase, esp. in children, pregnant women, pts with possible concomitant bone disease.

### γ-Glutamyl transpeptidase (GGT)

Correlates with serum alkaline phosphatase activity. Elevation is less specific for cholestasis than alkaline phosphatase or 5′-NT.

### Coagulation Factors (See also Chap. 64)

Measure of clotting factor activity; prolongation results from clotting factor deficiency or inactivity; all clotting factors except factor VIII are synthesized in the liver, and deficiency can occur rapidly from widespread liver disease as in hepatitis, toxic injury, or cirrhosis; single best acute measure of hepatic synthetic function; helpful in diagnosis and prognosis of acute liver disease. Clotting factors II, VII, IX, X function only in the presence of the fat-soluble vitamin K; PT prolongation from fat malabsorption distinguished from hepatic disease by rapid and complete response to vitamin K replacement.

### Albumin

Decreased serum levels result from decreased hepatic synthesis (chronic liver disease or prolonged malnutrition) or excessive losses in urine or stool; insensitive indicator of acute hepatic dysfunction, because serum half-life is 2–3 weeks; in pts with chronic liver disease, degree of hypoalbuminemia correlates with severity of liver dysfunction.

### Globulin

Mild polyclonal hyperglobulinemia often seen in chronic liver diseases; marked elevation frequently seen in *autoimmune* chronic active hepatitis.

### Ammonia

Elevated blood levels result from deficiency of hepatic detoxification pathways and portal-systemic shunting, as in fulminant hepatitis, hepatotoxin exposure, and severe portal hypertension (e.g., from cirrhosis); elevation of blood ammonia does not correlate well with hepatic function or the presence or degree of acute encephalopathy.

## HEPATOBILIARY IMAGING PROCEDURES

### Ultrasonography (US)

Rapid, noninvasive examination of abdominal structures; no radiation exposure; relatively low cost, equipment portable; images and interpretation strongly dependent on expertise of examiner; particularly valuable for detecting biliary duct dilation and gallbladder stones (>95%); much less sensitive for intraductal stones (~60%); most sensitive means of detecting ascites; moderately sensitive for detecting hepatic masses but excellent for discriminating solid from cystic structures; useful in directing percutaneous needle biopsies of suspicious lesions; Doppler US useful to determine patency and flow in portal, hepatic veins and portal-systemic shunts; imaging improved by presence of ascites but severely hindered by bowel gas; endoscopic US less affected by bowel gas and is sensitive for determination of depth of tumor invasion through bowel wall.

### CT

Particularly useful for detecting, differentiating, and directing percutaneous needle biopsy of abdominal masses, cysts, and lymphadenopathy; imaging enhanced by intestinal or intravenous contrast dye and unaffected by intestinal gas; somewhat less sensitive than US for detecting stones in gallbladder but more sensitive for choledocholithiasis; may be useful in distinguishing certain forms of diffuse hepatic disease (e.g., fatty infiltration, iron overload).

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## MRI

Most sensitive detection of hepatic masses and cysts; allows easy differentiation of hemangiomas from other hepatic tumors; most accurate noninvasive means of assessing hepatic and portal vein patency, vascular invasion by tumor; useful for monitoring iron, copper deposition in liver (e.g., in hemochromatosis, Wilson's disease). Magnetic resonance cholangiopancreatography (MRCP) can be useful for visualizing the head of the pancreas and the pancreatic and biliary ducts.

## Radionuclide Scanning

Using various radiolabeled compounds, different scanning methods allow sensitive assessment of biliary excretion (HIDA, PIPIDA, DISIDA scans), parenchymal changes (technetium sulfur colloid liver/spleen scan), and selected inflammatory and neoplastic processes (gallium scan); HIDA and related scans particularly useful for assessing biliary patency and excluding acute cholecystitis in situations where US is not diagnostic; CT, MRI, and colloid scans have similar sensitivity for detecting liver tumors and metastases; CT and combination of colloidal liver and lung scans sensitive for detecting right subphrenic (suprahepatic) abscesses.

## Cholangiography

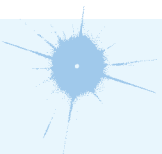
Most sensitive means of detecting biliary ductal calculi, biliary tumors, sclerosing cholangitis, choledochal cysts, fistulas, and bile duct leaks; may be performed via endoscopic (transampullary) or percutaneous (transhepatic) route; allows sampling of bile and ductal epithelium for cytologic analysis and culture; allows placement of biliary drainage catheter and stricture dilation; endoscopic route (endoscopic retrograde cholangiopancreatogram [ERCP]) permits manometric evaluation of sphincter of Oddi, sphincterotomy, and stone extraction.

## Angiography

Most accurate means of determining portal pressures and assessing patency and direction of flow in portal and hepatic veins; highly sensitive for detecting small vascular lesions and hepatic tumors (esp. primary hepatocellular carcinoma); "gold standard" for differentiating hemangiomas from solid tumors; most accurate means of studying vascular anatomy in preparation for complicated hepatobiliary surgery (e.g., portal-systemic shunting, biliary reconstruction) and determining resectability of hepatobiliary and pancreatic tumors. Similar anatomic information (but not intravascular pressures) can often be obtained noninvasively by CT- and MR-based techniques.

## Percutaneous Liver Biopsy

Most accurate in disorders causing diffuse changes throughout the liver; subject to sampling error in focal infiltrative disorders such as metastasis; should not be the initial procedure in the diagnosis of cholestasis. Contraindications to performing a percutaneous liver biopsy include significant ascites and prolonged international normalized ratio (INR). In such settings, the biopsy can be performed via the transjugular approach.



For a more detailed discussion, see John S, Pratt DS: Jaundice, Chap. 58, p. 279; Ghany MG, Hoofnagle JH: Approach to the Patient with Liver Disease, Chap 357, p. 1989; and Pratt DS: Evaluation of Liver Function, Chap. 358, p. 1995, in HPIM-19.

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# 43 Ascites

## DEFINITION

Accumulation of fluid within the peritoneal cavity. Small amounts may be asymptomatic; increasing amounts cause abdominal distention and discomfort, anorexia, nausea, early satiety, heartburn, flank pain, and respiratory distress.

## DETECTION

### Physical Examination

Bulging flanks, fluid wave, shifting dullness, "puddle sign" (dullness over dependent abdomen with pt on hands and knees). May be associated with penile or scrotal edema, umbilical or inguinal herniation, pleural effusion. Evaluation should include rectal and pelvic examination, assessment of liver and spleen. Palmar erythema and spider angiomata seen in cirrhosis. Periumbilical nodule (*Sister Mary Joseph's nodule*) or supraclavicular node (*Virchow's node*) suggests an abdominal malignancy.

### Ultrasonography/CT

Very sensitive; able to distinguish fluid from cystic masses.

## EVALUATION

Diagnostic paracentesis (50–100 mL) essential. Routine evaluation includes gross inspection, protein, albumin, glucose, cell count and differential, Gram's and acid-fast stains, culture, cytology; in selected cases check amylase, LDH, triglycerides, culture for tuberculosis (TB). Rarely, laparoscopy or even exploratory laparotomy may be required. Ascites due to CHF (e.g., pericardial constriction) may require evaluation by right-sided heart catheterization.

### Differential Diagnosis

*Cirrhosis* counts for 84% of cases of ascites. Cardiac ascites, peritoneal carcinomatosis, and "mixed" ascites resulting from cirrhosis and a second disease account for 10–15%.

*Diseases of peritoneum:* Infections (bacterial, tuberculous, fungal, parasitic), neoplasms, connective tissue disease, miscellaneous (Whipple's disease, familial Mediterranean fever, endometriosis, starch peritonitis, etc.).

*Diseases not involving peritoneum:* Cirrhosis, CHF, Budd-Chiari syndrome, hepatic venoocclusive disease, hypoalbuminemia (nephrotic syndrome, protein-losing enteropathy, malnutrition), miscellaneous (myxedema, ovarian diseases, pancreatic disease, chylous ascites).

### Pathophysiologic Classification Using Serum-Ascites Albumin Gradient (SAAG)

Difference in albumin concentrations between serum and ascites as a reflection of imbalances in hydrostatic pressures and can be used to differentiate between potential causes of ascites (Fig. 43-1).

## CIRRHOTIC ASCITES

### Pathogenesis

Contributing factors: (1) portal hypertension, (2) hypoalbuminemia, (3) hepatic lymph, (4) renal sodium retention—secondary to hyperaldosteronism, increased sympathetic nervous system activity (renin-angiotensin production). Initiating event may be peripheral arterial vasodilation triggered by endotoxin and cytokines and mediated by nitric oxide.

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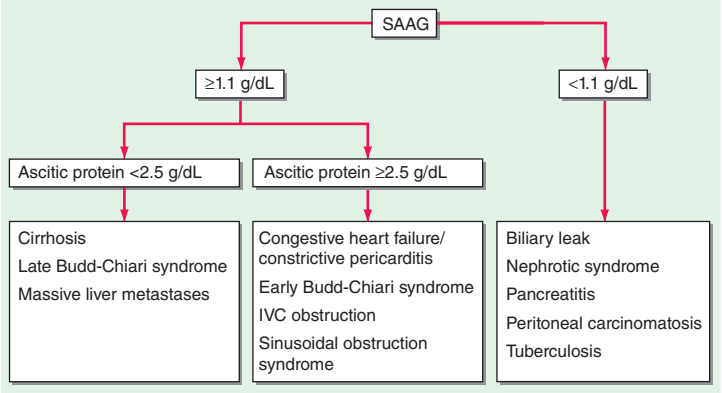


**FIGURE 43-1** Algorithm for the diagnosis of ascites according to the serum-ascites albumin gradient (SAAG).

## TREATMENT CIRRHOTIC ASCITES

1. Rigid salt restriction (<2 g Na/d).
2. For moderate ascites, diuretics usually necessary; spironolactone 100–200 mg/d PO (can be increased to 400 mg/d if low-sodium diet is confirmed and fluid not mobilized); furosemide 40–80 mg/d PO or IV may be added if necessary (greater risk of hepatorenal syndrome [HRS], encephalopathy), can increase to maximum of 120–160 mg/d until effect achieved or complication occurs.
3. Monitor weight, urinary Na and K, serum electrolytes, and creatinine. If ascites is still present with the above measures, this is defined as *refractory ascites*. Treatment modalities include:
   a. Pharmacologic therapy: add midodrine or clonidine to diuretic therapy
   b. Repeated large-volume paracentesis (5 L) with IV infusions of albumin (6–8 g/L ascites removed)
   c. Consider transjugular intrahepatic portosystemic shunt (TIPS). While TIPS manages the ascites, it has not been found to improve survival and is often associated with encephalopathy.

Prognosis for pts with cirrhotic ascites is poor with <50% survival 2 years after onset of ascites. Consider liver transplantation in appropriate candidates with the onset of ascites (Chap. 154).

## COMPLICATIONS

### Spontaneous Bacterial Peritonitis

Suspect in cirrhotic pt with ascites and fever, abdominal pain, worsening ascites, ileus, hypotension, worsening jaundice, or encephalopathy; low ascitic protein concentration (low opsonic activity) is predisposing factor. Diagnosis suggested by ascitic fluid PMN cell count >250/μL; confirmed by positive culture (usually *Escherichia coli* and other gut bacteria; however, gram-positive bacteria including *Streptococcus viridans*, *Staphylococcus aureus*, and *Enterococcus* spp. also can be found). Initial treatment: Cefotaxime 2 g IV q8h. Risk is increased in pts with variceal bleeding, and prophylaxis against spontaneous bacterial peritonitis is recommended when a pt presents with upper GI bleeding.

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### Hepatorenal Syndrome (HRS)

Functional renal failure without renal pathology; occurs in 10% of pts with advanced cirrhosis or acute liver failure. Thought to result from altered renal hemodynamics. Two types: type 1 HRS—decrease in renal function within 1–2 weeks of presentation; type 2 HRS—associated with a rise in serum creatinine but is associated with a better outcome. Often seen in pts with refractory ascites. Treatment: midodrine along with octreotide and IV albumin. For either type 1 or 2 HRS, prognosis is poor in the absence of liver transplantation.

For a more detailed discussion, see Corey KE, Friedman LS: Abdominal Swelling and Ascites, Chap. 59, p. 285; and Bacon BR: Cirrhosis and Its Complications, Chap. 365, p. 2058, in HPIM-19.

# 44 Lymphadenopathy and Splenomegaly

## LYMPHADENOPATHY

Exposure to antigen through a break in the skin or mucosa results in antigen being taken up by an antigen-presenting cell and carried via lymphatic channels to the nearest lymph node. Lymph channels course throughout the body except for the brain and the bones. Lymph enters the node through the afferent vessel and leaves through an efferent vessel. Because antigen-presenting cells pass through lymph nodes, they present antigen to lymphocytes residing there. Lymphocytes in a node are constantly being replaced by antigen-naïve lymphocytes from the blood. They are retained in the node via special homing receptors. B cells populate the lymphoid follicles in the cortex; T cells populate the paracortical regions. When a B cell encounters an antigen to which its surface immunoglobulin can bind, it stays in the follicle for a few days and forms a germinal center where the immunoglobulin gene is mutated in an effort to make an antibody with higher affinity for the antigen. The B cell then migrates to the medullary region, differentiates into a plasma cell, and secretes immunoglobulin into the efferent lymph.

When a T cell in the node encounters an antigen it recognizes, it proliferates and joins the efferent lymph. The efferent lymph laden with antibodies and T cells specific for the inciting antigen passes through several nodes on its way to the thoracic duct, which drains lymph from most of the body. From the thoracic duct, lymph enters the bloodstream at the left subclavian vein. Lymph from the head and neck and the right arm drains into the right subclavian vein. From the bloodstream, the antibody and T cells localize to the site of infection.

Lymphadenopathy may be caused by infections, immunologic diseases, malignancies, lipid storage diseases, or other disorders of uncertain etiology (e.g., sarcoidosis, Castleman's disease; **Table 44-1**). The two major mechanisms of lymphadenopathy are *hyperplasia*, in response to immunologic or infectious stimuli, and *infiltration*, by cancer cells or lipid- or glycoprotein-laden macrophages.

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**TABLE 44-1 DISEASES ASSOCIATED WITH LYMPHADENOPATHY**

1. Infectious diseases
   a. Viral—infectious mononucleosis syndromes (EBV, CMV), infectious hepatitis, herpes simplex, herpesvirus 6, varicella-zoster virus, rubella, measles, adenovirus, HIV, epidemic keratoconjunctivitis, vaccinia, herpesvirus 8
   b. Bacterial—streptococci, staphylococci, cat-scratch disease, brucellosis, tularemia, plague, chancroid, melioidosis, glanders, tuberculosis, atypical mycobacterial infection, primary and secondary syphilis, diphtheria, leprosy
   c. Fungal—histoplasmosis, coccidioidomycosis, paracoccidioidomycosis
   d. Chlamydial—lymphogranuloma venereum, trachoma
   e. Parasitic—toxoplasmosis, leishmaniasis, trypanosomiasis, filariasis
   f. Rickettsial—scrub typhus, rickettsialpox, Q fever
2. Immunologic diseases
   a. Rheumatoid arthritis
   b. Juvenile rheumatoid arthritis
   c. Mixed connective tissue disease
   d. Systemic lupus erythematosus
   e. Dermatomyositis
   f. Sjögren's syndrome
   g. Serum sickness
   h. Drug hypersensitivity—diphenylhydantoin, hydralazine, allopurinol, primidone, gold, carbamazepine, etc.
   i. Angioimmunoblastic lymphadenopathy
   j. Primary biliary cirrhosis
   k. Graft-versus-host disease
   l. Silicone-associated
   m. Autoimmune lymphoproliferative syndrome
3. Malignant diseases
   a. Hematologic—Hodgkin's lymphoma, non-Hodgkin's lymphomas, acute or chronic lymphocytic leukemia, hairy cell leukemia, histiocytic and dendritic cell neoplasms, amyloidosis
   b. Metastatic—from numerous primary sites
4. Lipid storage diseases—Gaucher's, Niemann-Pick, Fabry, Tangier
5. Endocrine diseases—hyperthyroidism
6. Other disorders
   a. Unicentric and multicentric Castleman's disease (giant lymph node hyperplasia)
   b. Sarcoidosis
   c. Dermatopathic lymphadenitis
   d. Lymphomatoid granulomatosis
   e. Histiocytic necrotizing lymphadenitis (Kikuchi's disease)
   f. Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease)
   g. Mucocutaneous lymph node syndrome (Kawasaki's disease)
   h. Familial Mediterranean fever
   i. Severe hypertriglyceridemia
   j. Vascular transformation of sinuses
   k. Inflammatory pseudotumor of lymph node
   l. Congestive heart failure

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## APPROACH TO THE PATIENT: **Lymphadenopathy**

**HISTORY** Age, occupation, animal exposures, sexual orientation, substance abuse history, medication history, and concomitant symptoms influence diagnostic workup. Adenopathy is more commonly malignant in origin in those over age 40 years. Farmers have an increased incidence of brucellosis and lymphoma. Male homosexuals may have AIDS-associated adenopathy. Alcohol and tobacco abuse increase risk of malignancy. Phenytoin may induce adenopathy. The concomitant presence of cervical adenopathy with sore throat or with fever, night sweats, and weight loss suggests particular diagnoses (mononucleosis in the former instance, Hodgkin's disease in the latter).

**PHYSICAL EXAMINATION** Location of adenopathy, size, node texture, and the presence of tenderness are important in differential diagnosis. Generalized adenopathy (three or more anatomic regions) implies systemic infection or lymphoma. Subclavian or scalene adenopathy is always abnormal and should be biopsied. Nodes >4 cm should be biopsied immediately. Rock-hard nodes fixed to surrounding soft tissue are usually a sign of metastatic carcinoma. Tender nodes are most often benign.

**LABORATORY TESTS** Usually laboratory tests are not required in the setting of localized adenopathy. If generalized adenopathy is noted, an excisional node biopsy should be performed for diagnosis, rather than a panoply of laboratory tests.

### TREATMENT LYMPHADENOPATHY

Pts over age 40 years, those with scalene or supraclavicular adenopathy, those with lymph nodes >4 cm in diameter, and those with hard nontender nodes should undergo immediate excisional biopsy. In younger pts with smaller nodes that are rubbery in consistency or tender, a period of observation for 7–14 days is reasonable. Empirical antibiotics are not indicated. If the nodes shrink, no further evaluation is necessary. If they enlarge, excisional biopsy is indicated.

## SPLENOMEGALY

Just as the lymph nodes are specialized to fight pathogens in the tissues, the spleen is the lymphoid organ specialized to fight bloodborne pathogens. It has no afferent lymphatics. The spleen has specialized areas like the lymph node for making antibodies (follicles) and amplifying antigen-specific T cells (periarteriolar lymphatic sheath, or PALS). In addition, it has a well-developed reticuloendothelial system for removing particles and antibody-coated bacteria. The flow of blood through the spleen permits it to filter pathogens from the blood and to maintain quality control over erythrocytes (RBCs)—those that are old and nondeformable are destroyed, and intracellular inclusions (sometimes including pathogens such as *Babesia* and *Plasmodium*) are culled from the cells in a process called *pitting*. Under certain conditions, the spleen can generate hematopoietic cells in place of the marrow.

The normal spleen is about 12 cm in length and 7 cm in width and is not normally palpable. Dullness from the spleen can be percussed between the ninth and eleventh ribs with the pt lying on the right side. Palpation is best performed with the pt supine with knees flexed. The spleen may be felt because it descends when the pt inspires. Physical diagnosis is not sensitive. CT or ultrasound is a superior test.

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Spleen enlargement occurs by three basic mechanisms: (1) hyperplasia or hypertrophy due to an increase in demand for splenic function (e.g., hereditary spherocytosis where demand for removal of defective RBCs is high or immune hyperplasia in response to systemic infection or immune diseases); (2) passive vascular congestion due to portal hypertension; and (3) infiltration with malignant cells, lipid- or glycoprotein-laden macrophages, or amyloid (Table 44-2). Massive enlargement, with spleen palpable >8 cm below the left costal margin, usually signifies a lymphoproliferative or myeloproliferative disorder.

**TABLE 44-2 DISEASES ASSOCIATED WITH SPLENOMEGALY GROUPED BY PATHOGENIC MECHANISM**

| | |
|---|---|
| **Enlargement Due to Increased Demand for Splenic Function** | |
| Reticuloendothelial system hyperplasia (for removal of defective erythrocytes) | Leishmaniasis |
| Spherocytosis | Trypanosomiasis |
| Early sickle cell anemia | Ehrlichiosis |
| Ovalocytosis | Disordered immunoregulation |
| Thalassemia major | Rheumatoid arthritis (Felty's syndrome) |
| Hemoglobinopathies | Systemic lupus erythematosus |
| Paroxysmal nocturnal hemoglobinuria | Collagen vascular diseases |
| Pernicious anemia | Serum sickness |
| Immune hyperplasia | Immune hemolytic anemias |
| Response to infection (viral, bacterial, fungal, parasitic) | Immune thrombocytopenias |
| Infectious mononucleosis | Immune neutropenias |
| AIDS | Drug reactions |
| Viral hepatitis | Angioimmunoblastic lymphadenopathy |
| Cytomegalovirus | Sarcoidosis |
| Subacute bacterial endocarditis | Thyrotoxicosis (benign lymphoid hypertrophy) |
| Bacterial septicemia | Interleukin-2 therapy |
| Congenital syphilis | Extramedullary hematopoiesis |
| Splenic abscess | Myelofibrosis |
| Tuberculosis | Marrow damage by toxins, r adiation, strontium |
| Histoplasmosis | Marrow infiltration by tumors, leukemias, Gaucher's disease |
| Malaria | |
| **Enlargement Due to Abnormal Splenic or Portal Blood Flow** | |
| Cirrhosis | Splenic artery aneurysm |
| Hepatic vein obstruction | Hepatic schistosomiasis |
| Portal vein obstruction, intrahepatic or extrahepatic | Congestive heart failure |
| Cavernous transformation of the portal vein | Hepatic echinococcosis |
| Splenic vein obstruction | Portal hypertension (any cause including the above): "Banti's disease" |

(*Continued*)

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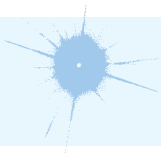
**TABLE 44-2 DISEASES ASSOCIATED WITH SPLENOMEGALY GROUPED BY PATHOGENIC MECHANISM (*CONTINUED*)**

| | |
|---|---|
| **Infiltration of the Spleen** | |
| Intracellular or extracellular depositions | Hodgkin's lymphoma |
| Amyloidosis | Myeloproliferative syndromes (e.g., polycythemia vera, essential thrombocytosis) |
| Gaucher's disease | Angiosarcomas |
| Niemann-Pick disease | Metastatic tumors (melanoma is most common) |
| Tangier disease | Eosinophilic granuloma |
| Hurler's syndrome and other mucopolysaccharidoses | Histiocytic and dendritic cell neoplasms (Histiocytosis X) |
| Hyperlipidemias | Hamartomas |
| Benign and malignant cellular infiltrations | Hemangiomas, fibromas, lymphangiomas |
| Leukemias (acute, chronic, lymphoid, myeloid, monocytic, hairy cell) | Splenic cysts |
| Lymphomas | |
| **Unknown Etiology** | |
| Idiopathic splenomegaly | Iron-deficiency anemia |
| Berylliosis | |

Peripheral blood RBC count, white blood cell count, and platelet count may be normal, decreased, or increased depending on the underlying disorder. Decreases in one or more cell lineages could indicate hypersplenism, increased destruction. In cases with hypersplenism, the spleen is removed and the cytopenia is generally reversed. In the absence of hypersplenism, most causes of splenomegaly are diagnosed on the basis of signs and symptoms and laboratory abnormalities associated with the underlying disorder. Splenectomy is rarely performed for diagnostic purposes.

Individuals who have had splenectomy are at increased risk of sepsis from a variety of organisms including pneumococcus and *Haemophilus influenzae*. Vaccines for these agents should be given before splenectomy is performed. Splenectomy compromises the immune response to T-independent polysaccharide antigens. Newer vaccine formulations are T dependent and are more effective in splenectomized persons.



For a more detailed discussion, see Henry PH, Longo DL: Enlargement of Lymph Nodes and Spleen, Chap. 79, p. 407, in HPIM-19.

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# 45 Anemia and Polycythemia

## ANEMIA

According to World Health Organization criteria, anemia is defined as blood hemoglobin (Hb) concentration <130 g/L (<13 g/dL) or hematocrit (Hct) <39% in adult males; Hb <120 g/L (<12 g/dL) or Hct <37% in adult females.

Signs and symptoms of anemia are varied, depending on the level of anemia and the time course over which it developed. Acute anemia is nearly always due to blood loss or hemolysis. In acute blood loss, hypovolemia dominates the clinical picture; hypotension and decreased organ perfusion are the main issues. Symptoms associated with more chronic onset vary with the age of the pt and the adequacy of blood supply to critical organs. Moderate anemia is associated with fatigue, loss of stamina, breathlessness, and tachycardia. The pt's skin and mucous membranes may appear pale. If the palmar creases are lighter in color than the surrounding skin with the fingers extended, Hb level is often <80 g/L (8 g/dL). In pts with coronary artery disease, anginal episodes may appear or increase in frequency and severity. In pts with carotid artery disease, light-headedness or dizziness may develop.

A physiologic approach to anemia diagnosis is based on the understanding that a decrease in circulating RBCs can be related to either inadequate production of RBCs or increased RBC destruction or loss. Within the category of inadequate production, erythropoiesis can be either ineffective, due to an erythrocyte maturation defect (which usually results in RBCs that are too small or too large), or hypoproliferative (which usually results in RBCs of normal size, but too few of them).

Basic evaluations include (1) reticulocyte index (RI), and (2) review of blood smear and RBC indices (chiefly mean corpuscular volume [MCV]) (Fig. 45-1).

The RI is a measure of RBC production. The reticulocyte count is corrected for the Hct level and for early release of marrow reticulocytes into the circulation, which leads to an increase in the lifespan of the circulating reticulocyte beyond the usual 1 day. Thus, RI = (% reticulocytes × pt Hct/45%) × (1/shift correction factor). The shift correction factor varies with the Hct: 1.5 for Hct = 35%, 2 for Hct = 25%, 2.5 for Hct = 15%. RI <2–2.5% implies inadequate RBC production for the particular level of anemia; RI >2.5% implies excessive RBC destruction or loss.

If the anemia is associated with a low RI, RBC morphology helps distinguish a maturation disorder from hypoproliferative marrow states. Cytoplasmic maturation defects such as iron deficiency or Hb synthesis problems produce smaller RBCs, MCV < 80; nuclear maturation defects such as $B_{12}$ and folate deficiency and drug effects produce larger RBCs, MCV >100. In hypoproliferative marrow states, RBCs are generally normal in morphology but too few are produced. Bone marrow examination is often helpful in the evaluation of anemia but is done most frequently to diagnose hypoproliferative marrow states.

Other laboratory tests indicated to evaluate particular forms of anemia depend on the initial classification based on the pathophysiology of the defect. These are discussed in more detail in Chap. 62.

## POLYCYTHEMIA (ERYTHROCYTOSIS)

Polycythemia is an increase above the normal range of RBCs in the circulation. Concern that the Hb level may be abnormally high should be triggered at a level of 170 g/L (17 g/dL) in men and 150 g/L (15 g/dL) in women. Polycythemia is usually

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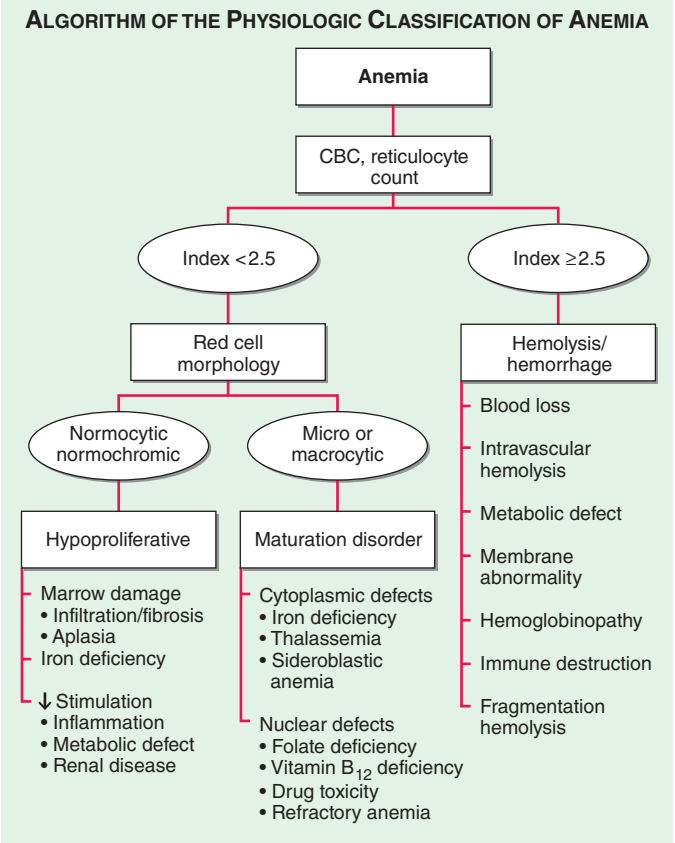


**FIGURE 45-1** The physiologic classification of anemia.

found incidentally at routine blood count. Relative erythrocytosis, due to plasma volume loss (e.g., severe dehydration, burns), does not represent a true increase in total RBC mass. Absolute erythrocytosis is a true increase in total RBC mass.

## CAUSES

Polycythemia vera (a clonal myeloproliferative disorder), erythropoietin-producing neoplasms (e.g., renal cancer, cerebellar hemangioma), chronic hypoxemia (e.g., high altitude, pulmonary disease), carboxyhemoglobin excess (e.g., smokers), high-affinity Hb variants, Cushing's syndrome, androgen excess. Polycythemia vera is distinguished from secondary polycythemia by the presence of splenomegaly, leukocytosis, thrombocytosis, and elevated vitamin $B_{12}$ levels, and by decreased erythropoietin levels and the presence of a mutation in the JAK2 kinase (V617F). An approach to evaluate polycythemic pts is shown in Fig. 45-2.

## COMPLICATIONS

Hyperviscosity (with diminished $O_2$ delivery) with risk of ischemic organ injury and thrombosis (venous or arterial) are most common.

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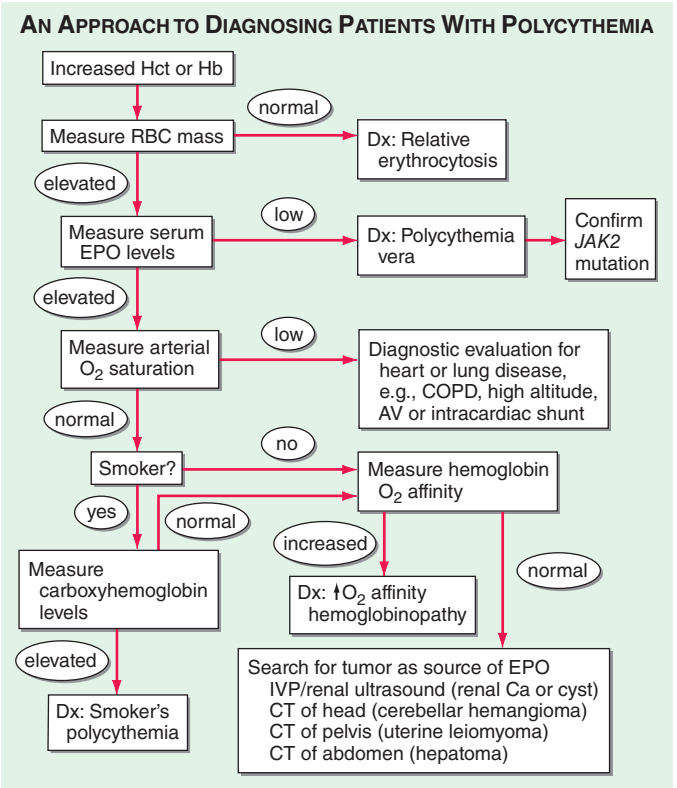
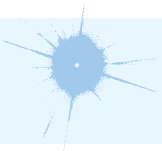



**FIGURE 45-2** An approach to the differential diagnosis of pts with an elevated hemoglobin (possible polycythemia). AV, atrioventricular; COPD, chronic obstructive pulmonary disease; EPO, erythropoietin.

## TREATMENT POLYCYTHEMIA

Phlebotomy recommended for Hct ≥55%, regardless of cause, to low-normal range. Aspirin is routinely given to lower the thrombosis risk.



For a more detailed discussion, see Adamson JW, Longo DL: Anemia and Polycythemia, Chap. 77, p. 392, in HPIM-19.

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# 46 Azotemia and Urinary Abnormalities

## ABNORMALITIES OF RENAL FUNCTION, AZOTEMIA

*Azotemia* is the retention of nitrogenous waste products excreted by the kidney. Increased levels of blood urea nitrogen (BUN) (>10.7 mmol/L [>30 mg/dL]) and creatinine (>133 μmol/L [>1.5 mg/dL]) are ordinarily indicative of impaired renal function. Renal function can be estimated by determining the clearance of creatinine ($CL_{cr}$) (normal >100 mL/min); this can be directly measured from a 24-h urine collection using the following equation:

$$\text{Creatinine clearance (mL/min)} = (\text{uCr} \times \text{uV})/(\text{sCr} \times 1440)$$

1. Where uCr is urine creatinine in mg/dL
2. Where sCr is serum creatinine in mg/dL
3. Where uV is 24-h urine volume in mL
4. Where 1440 represents number of minutes in 24 h

The "adequacy" or "completeness" of the collection is estimated by the urinary volume and creatinine content; creatinine is produced from muscle and excreted at a relatively constant rate. For a 20- to 50-year-old man, creatinine excretion should be 18.5–25.0 mg/kg body weight; for a woman of the same age, it should be 16.5–22.4 mg/kg body weight. For example, an 80-kg man should excrete between ~1500 and 2000 mg of creatinine in an "adequate" collection. Creatinine excretion is also influenced by age and muscle mass. Notably, creatinine is an imperfect measure of glomerular filtration rate (GFR), because it is both filtered by glomeruli and secreted by proximal tubular cells; the relative contribution of tubular secretion increases with advancing renal dysfunction, such that creatinine clearance will provide an overestimate of the "true" GFR in pts with chronic kidney disease. Isotopic markers that are filtered and not secreted (e.g., iothalamate) provide more accurate estimates of GFR.

A formula that allows for an estimate of creatinine clearance in men that accounts for age-related decreases in GFR, body weight, and sex has been derived by Cockcroft-Gault:

$$\text{Creatinine clearance (mL/min)} = (140\text{-age}) \times \text{lean body weight (kg)}/\text{plasma creatinine (mg/dL)} \times 72$$

This value should be multiplied by 0.85 for women.

GFR may also be estimated using serum creatinine–based equations derived from the Modification of Diet in Renal Disease Study. This "eGFR" (estimated glomerular filtration rate) is now reported with serum creatinine by most clinical laboratories in the United States and is the basis for the National Kidney Foundation classification of chronic kidney disease (Table 46-1).

Manifestations of impaired renal function include volume overload, hypertension, electrolyte abnormalities (e.g., hyperkalemia, hypocalcemia, hyperphosphatemia), metabolic acidosis, and hormonal disturbances (e.g., insulin resistance, functional vitamin D deficiency, secondary hyperparathyroidism). When severe, the symptom complex of "uremia" may develop, encompassing one or more of the following symptoms and signs: anorexia, dysgeusia, nausea, vomiting, lethargy, confusion, asterixis, pleuritis, pericarditis, enteritis, pruritus, sleep and taste disturbance, nitrogenous fetor.

An approach to the pt with azotemia is shown in Fig. 46-1.

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**TABLE 46-1 THE CLASSIFICATION OF CHRONIC KIDNEY DISEASE (NATIONAL KIDNEY FOUNDATION GUIDELINES)**

| Kidney Damage Stage | Description | eGFR (mL/min per 1.73 m²) |
|---|---|---|
| 0 | With risk factors for CKD[a] | >90 |
| 1 | With evidence of kidney damage[b] | >90 |
| 2 | Mild decrease in GFR | 60–89 |
| 3 | Moderate decrease in GFR | 30–59 |
| 4 | Severe decrease in GFR | 15–29 |
| 5 | Kidney failure | <15 |

[a]Diabetes, high blood pressure, family history, older age, African ancestry.
[b]Abnormal urinalysis, hematuria, proteinuria, albuminuria.
***Abbreviations:*** CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

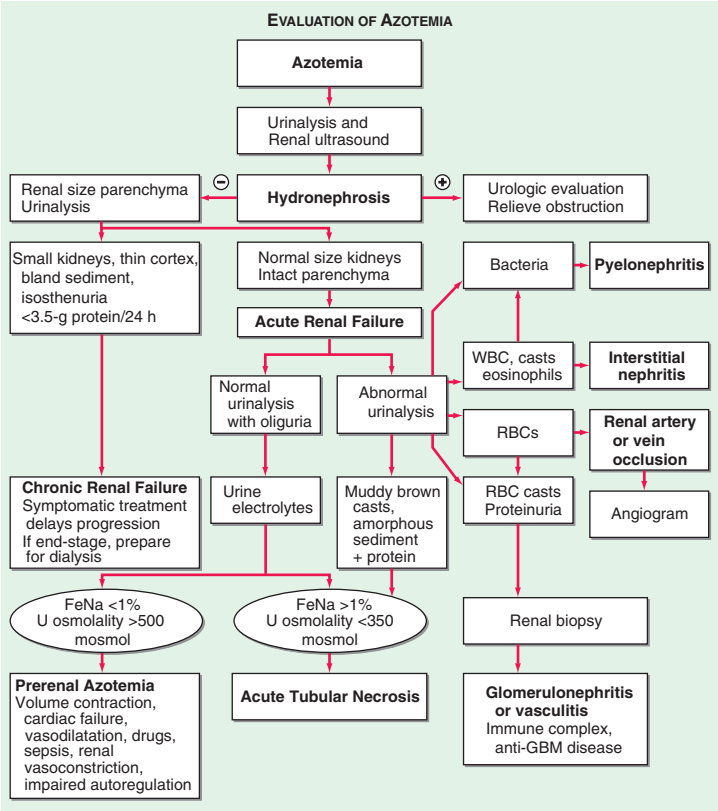


**FIGURE 46-1** Approach to the pt with azotemia. FeNa, fractional excretion of sodium; GBM, glomerular basement membrane. *(From Lin J and Denker BM: Chap. 61, p. 289, HPIM-19.)*

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## ABNORMALITIES OF URINE VOLUME

### Oliguria

This refers to reduced urine output, usually defined as <400 mL/d. *Oligoanuria* refers to a more marked reduction in urine output, i.e., <100 mL/d. *Anuria* indicates the complete absence of urine output. Oliguria most often occurs in the setting of volume depletion and/or renal hypoperfusion, resulting in "prerenal azotemia" and acute renal failure (Chap. 137). Anuria can be caused by complete bilateral urinary tract obstruction; a vascular catastrophe (dissection or arterial occlusion); renal vein thrombosis; renal cortical necrosis; severe acute tubular necrosis; nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme (ACE) inhibitors, and/or angiotensin receptor blockers; and hypovolemic, cardiogenic, or septic shock. Oliguria is never normal, because at least 400 mL of maximally concentrated urine must be produced to excrete the obligate daily osmolar load.

### Polyuria

Polyuria is defined as a urine output >3 L/d. It is often accompanied by nocturia and urinary frequency and must be differentiated from other more common conditions associated with lower urinary tract pathology and urinary urgency or frequency (e.g., cystitis, prostatism). It is often accompanied by hypernatremia (Chap. 1). Polyuria (Table 46-2) can occur as a response to a solute load (e.g., hyperglycemia) or to an abnormality in arginine vasopressin (AVP; also known as antidiuretic hormone [ADH]) action. Diabetes insipidus is termed *central* if due to the insufficient hypothalamic production of AVP and *nephrogenic* if the result of renal insensitivity to the action of AVP. Excess fluid intake can lead to polyuria, but primary polydipsia rarely results in changes in plasma osmolality unless urinary diluting capacity is impaired. Tubulointerstitial diseases, lithium therapy, and resolving acute tubular necrosis or urinary tract obstruction can be associated with nephrogenic diabetes insipidus, which is more rarely caused by mutations in the V2 AVP receptor, the aquaporin-1 water channel in the descending thin limb of the loop of Henle, and the AVP-regulated water channel in principal cells, aquaporin 2.

The approach to the pt with polyuria is shown in Fig. 46-2.

## ABNORMALITIES OF URINE COMPOSITION

### Proteinuria

This is the hallmark of glomerular disease. Levels up to 150 mg/d are considered within normal limits. Typical measurements are semiquantitative, using a

**TABLE 46-2 MAJOR CAUSES OF POLYURIA**

| | |
|---|---|
| Excessive fluid intake | Nephrogenic diabetes insipidus |
| Primary polydipsia | Lithium exposure |
| Iatrogenic (IV fluids) | Urinary tract obstruction |
| Therapeutic | Papillary necrosis |
| Diuretic agents | Reflux nephropathy |
| Osmotic diuresis | Interstitial nephritis |
| Hyperglycemia | Hypercalcemia |
| | Hereditary (V2R, AQP-1/2) |
| Azotemia | Central diabetes insipidus |
| Mannitol | Tumor |
| Radiocontrast | Postoperative |
| | Head trauma |
| | Basilar meningitis |
| | Neurosarcoidosis |

***Abbreviations:*** AQP, aquaporin; V2R, vasopressin type 2 receptor.

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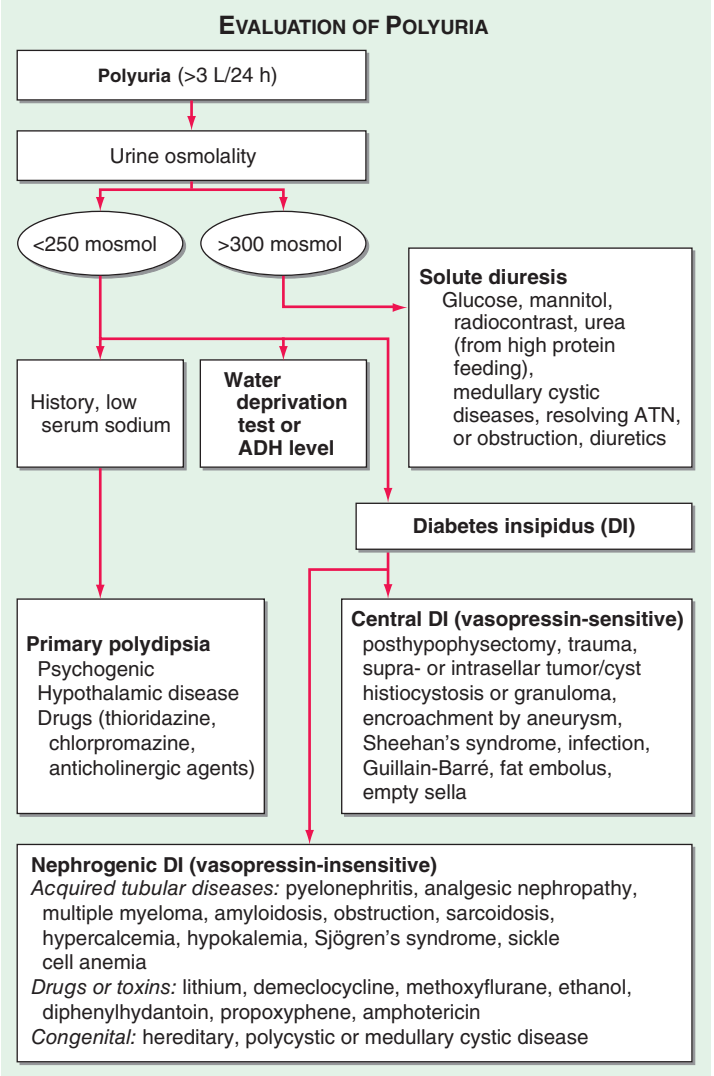


**FIGURE 46-2** Approach to the pt with polyuria. ADH, antidiuretic hormone; ATN, acute tubular necrosis. *(From Lin J and Denker BM: Chap. 61, p. 289, HPIM-19.)*

moderately sensitive dipstick that estimates protein concentration; therefore, the degree of hydration may influence the dipstick protein determination. Most commercially available urine dipsticks detect albumin and do not detect smaller proteins, such as light chains, that require testing with sulfosalicylic acid. More sensitive assays can in turn be used to detect microalbuminuria, an important screening tool for diabetic nephropathy. A urine albumin to creatinine ratio >30 mg/g defines the presence of microalbuminuria.

Formal assessment of urinary protein excretion requires a 24-h urine protein collection (see "Abnormalities of Renal Function, Azotemia," above). The ratio of

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protein to creatinine in a random, "spot" urine can also provide a rough estimate of protein excretion; e.g., a protein/creatinine ratio of 3.0 correlates to ~3.0 g of proteinuria per day.

Urinary protein excretion rates between 500 mg/d and 3 g/d are nonspecific and can be seen in a variety of renal diseases (including hypertensive nephrosclerosis, interstitial nephritis, vascular disease, and other primary renal diseases with little or no glomerular involvement). Transient, lesser degrees of proteinuria (500 mg/d–1.5 g/d) may be seen after vigorous exercise, changes in body position, fever, or congestive heart failure. Protein excretion rates >3 g/d are termed *nephrotic range proteinuria* in that they may be accompanied by hypoalbuminemia, hypercholesterolemia, and edema (the nephrotic syndrome). Nephrotic syndrome can be associated with a variety of extrarenal complications (Chap. 141). Massive degrees of proteinuria (>10 g/d) can be seen with minimal change disease, primary focal segmental glomerulosclerosis (FSGS), membranous nephropathy, diabetic nephropathy, collapsing glomerulopathy (a subtype of primary FSGS), and HIV-associated nephropathy.

Pharmacologic inhibition of ACE or blockade of angiotensin II should be employed to reduce proteinuria; successful reduction of proteinuria decreases the rate of progression to end-stage renal disease in diabetic nephropathy and other glomerulopathies. Specific therapy for a variety of causes of nephrotic syndrome is discussed in Chap. 141.

## Hematuria

Gross hematuria refers to the presence of frank blood in the urine and is more characteristic of lower urinary tract disease and/or bleeding diatheses than intrinsic renal disease (Table 46-3). Cyst rupture in polycystic kidney disease and postpharyngitic flares of IgA nephropathy are exceptions. Microscopic hematuria (>1–2 red blood cells [RBCs] per high-powered field), accompanied by proteinuria, hypertension, and an active urinary sediment (the "nephritic syndrome") is most likely related to an inflammatory glomerulonephritis, classically poststreptococcal glomerulonephritis (Chap. 141).

**TABLE 46-3 MAJOR CAUSES OF HEMATURIA**

| |
|---|
| **Lower Urinary Tract** |
| Bacterial cystitis |
| Interstitial cystitis |
| Urethritis (infectious or inflammatory) |
| Passed or passing kidney stone |
| Transitional cell carcinoma of bladder or structures proximal to it |
| Squamous cell carcinoma of bladder (e.g., following schistosomiasis) |
| **Upper Urinary Tract** |
| Renal cell carcinoma |
| Age-related renal cysts |
| Other neoplasms (e.g., oncocytoma, hamartoma) |
| Acquired renal cystic disease |
| Congenital cystic disease, including autosomal dominant form |
| Glomerular diseases |
| Interstitial renal diseases, including interstitial nephritis |
| Nephrolithiasis |
| Pyelonephritis |
| Renal infarction |
| Hypercalciuria |
| Hyperuricosuria |

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Free hemoglobin and myoglobin are detected by dipstick; a negative urinary sediment with strongly heme-positive dipstick is characteristic of either hemolysis or rhabdomyolysis, which can be differentiated by clinical history and laboratory testing. RBC casts are not a sensitive finding but when seen are highly specific for glomerulonephritis. Specificity of urinalysis can be enhanced by examining urine with a phase contrast microscope capable of detecting dysmorphic red cells ("acanthocytes") associated with glomerular disease.

The approach to the pt with hematuria is shown in Fig. 46-3.

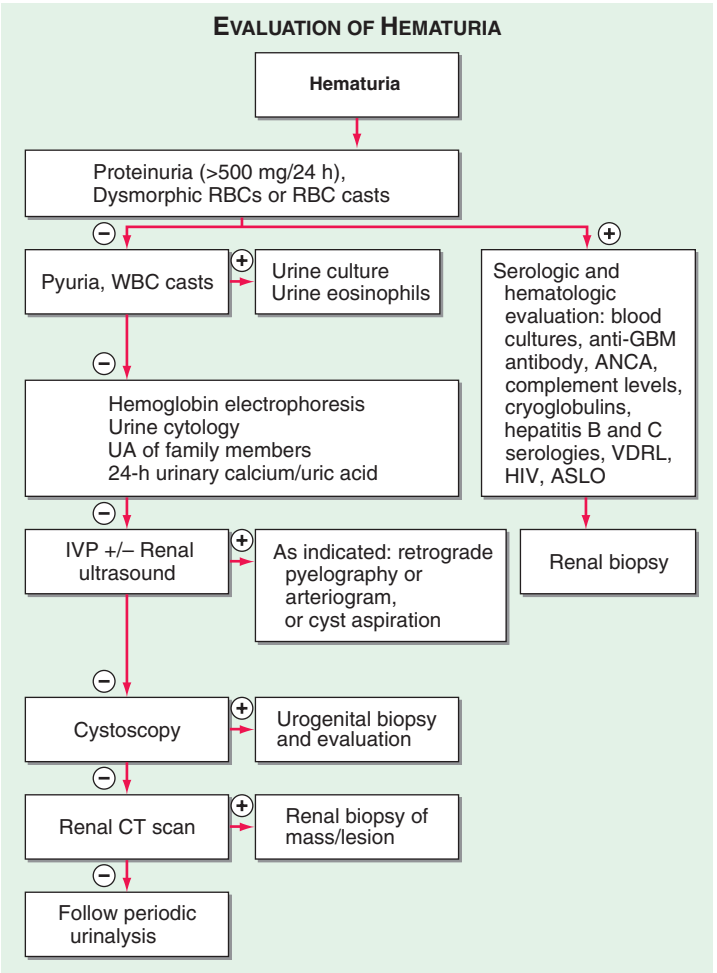


**FIGURE 46-3** Approach to the pt with hematuria. ANCA, antineutrophil cytoplasmic antibody; ASLO, antistreptolysin O; GBM, glomerular basement membrane; VDRL, Venereal Disease Research Laboratory. *(From Lin J and Denker BM: Chap. 61, p. 289, HPIM-19.)*

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## PYURIA

This may accompany hematuria in inflammatory glomerular diseases. Isolated pyuria is most commonly observed in association with an infection of the upper or lower urinary tract. Pyuria may also occur with allergic interstitial nephritis (often with a preponderance of eosinophils), transplant rejection, and noninfectious, nonallergic tubulointerstitial diseases, including atheroembolic renal disease. The finding of "sterile" pyuria (i.e., urinary white blood cells without bacteria) in the appropriate clinical setting should raise suspicion of renal tuberculosis.

For a more detailed discussion, see Lin J, Denker BM: Azotemia and Urinary Abnormalities, Chap. 61, p. 289, in HPIM-19.

# 47 Pain and Swelling of Joints

Musculoskeletal complaints are extremely common in outpatient medical practice and are among the leading cause of disability and absenteeism from work. Pain in the joints must be evaluated in a uniform, thorough, and logical fashion to ensure the best chance of accurate diagnosis and to plan appropriate follow-up testing and therapy. Joint pain and swelling may be manifestations of disorders affecting primarily the musculoskeletal system or may reflect systemic disease.

## INITIAL ASSESSMENT OF A MUSCULOSKELETAL COMPLAINT (FIG. 47-1)

1. *Articular versus nonarticular:* Is the pain located in a joint or in a periarticular structure such as soft tissue or muscle?
2. *Inflammatory versus noninflammatory:* Inflammatory disease is suggested by local signs of inflammation (erythema, warmth, swelling); systemic features (morning stiffness, fatigue, fever, weight loss); or laboratory evidence of inflammation (thrombocytosis, elevated ESR or C-reactive protein).
3. *Acute (≤6 weeks) versus chronic.*
4. *Localized versus systemic.*

## HISTORIC FEATURES

- Age, sex, race, and family history
- Symptom onset (abrupt or gradual), evolution (chronic constant, intermittent, migratory, additive), and duration (acute versus chronic)
- Number and distribution of involved structures: monarticular (one joint), oligoarticular (two to three joints), polyarticular (more than three joints); symmetry
- Other articular features: morning stiffness, effect of movement, features that improve/worsen Sx

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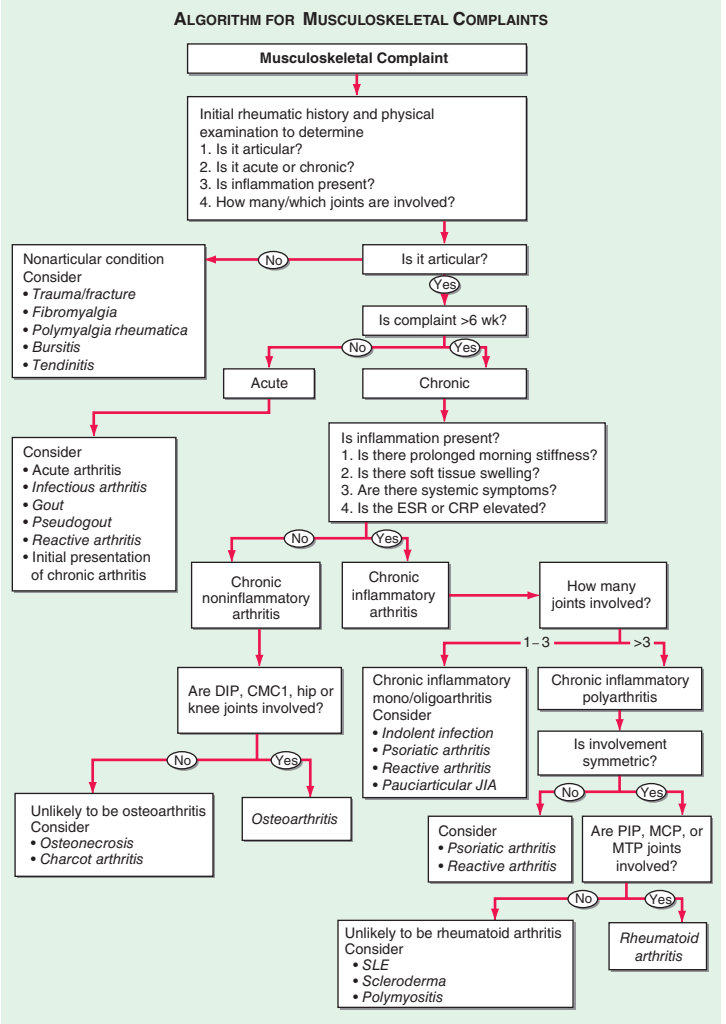


**FIGURE 47-1** Algorithm for the diagnosis of musculoskeletal complaints. An approach to formulating a differential diagnosis (shown in italics). CMC, carpometacarpal; CRP, C-reactive protein; DIP, distal interphalangeal; ESR, erythrocyte sedimentation rate; JIA, juvenile idiopathic arthritis; MCP, metacarpophalangeal; MTP, metatarsophalangeal; PIP, proximal interphalangeal.

- Extraarticular Sx: e.g., fever, rash, weight loss, visual change, dyspnea, diarrhea, dysuria, numbness, weakness
- Recent events: e.g., trauma, drug administration, travel, other illnesses

## PHYSICAL EXAMINATION

Complete examination is essential: particular attention to skin, mucous membranes, nails (may reveal characteristic pitting in psoriasis), eyes. Careful and thorough

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examination of involved and uninvolved joints and periarticular structures; this should proceed in an organized fashion from head to foot or from extremities inward toward axial skeleton; special attention should be paid to identifying the presence or absence of:

- Warmth and/or erythema
- Swelling
- Synovial thickening
- Subluxation, dislocation, joint deformity
- Joint instability
- Limitations to active and passive range of motion
- Crepitus
- Periarticular changes
- Muscular changes including weakness, atrophy

## LABORATORY INVESTIGATIONS

Additional evaluation usually indicated for monarticular, traumatic, inflammatory, or chronic conditions or for conditions accompanied by neurologic changes or systemic manifestations.

- For all evaluations: include CBC, ESR, or C-reactive protein
- Where there are suggestive clinical features, include: rheumatoid factor, antibodies to cyclic citrullinated peptides (anti-CCPs), ANA, antineutrophil cytoplasmic antibodies (ANCA), antistreptolysin O titer, Lyme antibodies
- Where systemic disease is present or suspected: renal/hepatic function tests, UA
- Uric acid: useful only when gout diagnosed and therapy contemplated
- CPK, aldolase: consider with muscle pain, weakness
- Synovial fluid aspiration and analysis: always indicated for acute monarthritis or when infectious or crystal-induced arthropathy is suspected. Should be examined for (1) appearance, viscosity; (2) cell count and differential (suspect septic joint if WBC count >50,000/μL); (3) crystals using polarizing microscope; (4) Gram's stain, cultures (Fig. 47-2).

## DIAGNOSTIC IMAGING

Conventional radiography using plain x-rays is a valuable tool in the diagnosis and staging of articular disorders (Table 47-1).

Additional imaging procedures, including ultrasound, radionuclide scintigraphy, CT, and MRI, may be helpful in selected clinical settings.

## SPECIAL CONSIDERATIONS IN THE ELDERLY PATIENT

The evaluation of joint and musculoskeletal disorders in the elderly pt presents a special challenge given the frequently insidious onset and chronicity of disease in this age group, the confounding effect of other medical conditions, and the increased variability of many diagnostic tests in the geriatric population. Although virtually all

**TABLE 47-1 APPLICATIONS FOR CONVENTIONAL RADIOGRAPHY IN ARTICULAR DISEASE**

| |
|---|
| Trauma |
| Suspected chronic joint or bone infection |
| Progressive joint disability |
| Monarticular involvement |
| Baseline assessment of a chronic articular process |
| When therapeutic alterations are considered (such as for rheumatoid arthritis) |

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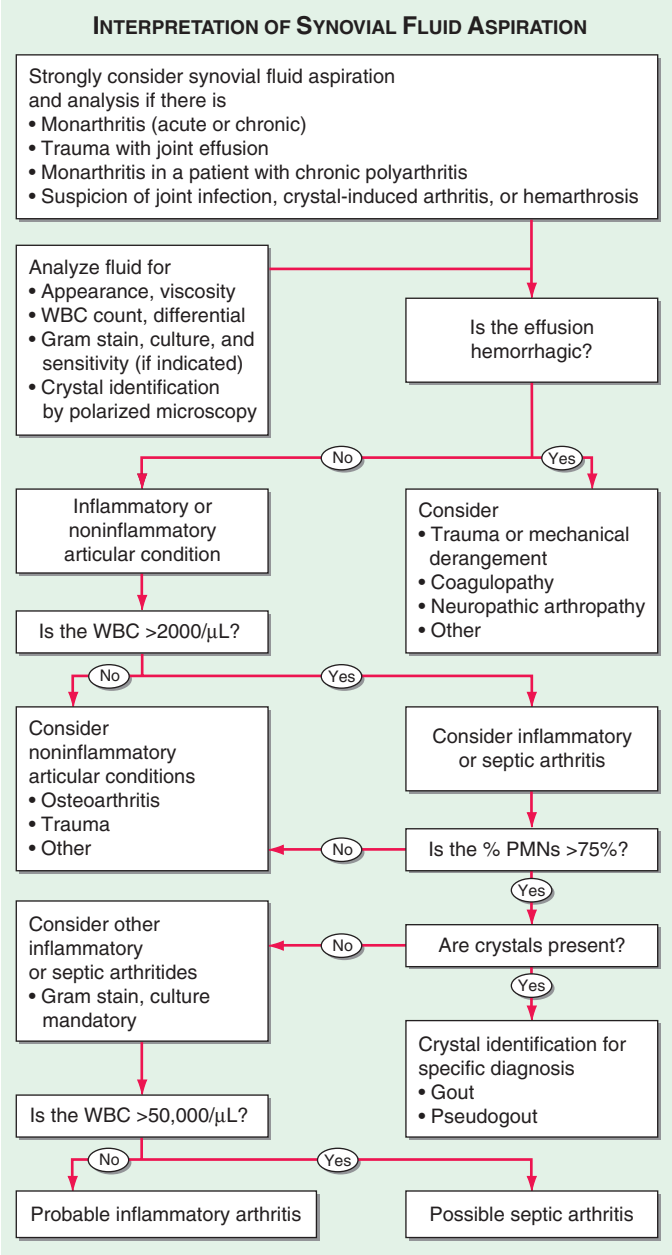


**FIGURE 47-2** Algorithmic approach to the use and interpretation of synovial fluid aspiration and analysis. PMNs, polymorphonuclear leukocytes.

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musculoskeletal conditions may afflict the elderly, certain disorders are especially frequent. Special attention should be paid to identifying the potential rheumatic consequences of intercurrent medical conditions and therapies when evaluating the geriatric pt with musculoskeletal complaints.

For a more detailed discussion, see Cush JJ: Approach to Articular and Musculoskeletal Disorders, Chap. 393, p. 2216, in HPIM-19.

# 48 Back and Neck Pain

## LOW BACK PAIN

Cost of low back pain (LBP) in the United States is ~$100 billion annually. Back symptoms are most common cause of disability in those <45 years; LBP is the second most common cause of visiting a physician in the United States; 70% of people will have LBP at some point in their lives.

### TYPES OF LOW BACK PAIN

- *Local pain*: caused by injury to pain-sensitive structures that compress or irritate sensory nerve endings; pain located near the affected part of the back.
- *Pain referred to the back*: abdominal or pelvic origin; back pain unaffected by posture.
- *Pain of spine origin*: restricted to the back or referred to lower limbs or buttock. Diseases of upper lumbar spine refer pain to upper lumbar region, groin, or anterior thighs. Diseases of lower lumbar spine refer pain to buttocks, posterior thighs, calves, or feet.
- *Radicular back pain*: radiates from spine to leg in specific nerve root territory. Coughing, sneezing, lifting heavy objects, or straining may elicit pain.
- *Pain associated with muscle spasm*: diverse causes; accompanied by tense paraspinal muscles, dull or aching pain in the paraspinal region, and abnormal posture.

### EXAMINATION

Include abdomen and rectum to search for visceral sources of pain. Inspection may reveal scoliosis or muscle spasm. Palpation may elicit pain over a diseased spine segment. Pain from hip may be confused with spine pain; manual internal/external rotation of leg at hip (with knee and hip in flexion) reproduces the hip pain.

Straight leg raising (SLR) sign—elicited by passive flexion of leg at the hip with pt in supine position; maneuver stretches L5/S1 nerve roots and sciatic nerve passing posterior to the hip; SLR sign is positive if maneuver reproduces the pain. Crossed SLR sign—positive when SLR on one leg reproduces symptoms in opposite leg or buttocks; nerve/nerve root lesion is on the painful side. Reverse SLR sign—passive

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**TABLE 48-1 LUMBOSACRAL RADICULOPATHY: NEUROLOGIC FEATURES**

| Lumbosacral Nerve Roots | Examination Findings | | | Pain Distribution |
|---|---|---|---|---|
| | Reflex | Sensory | Motor | |
| L2[a] | — | Upper anterior thigh | Psoas (hip flexors) | Anterior thigh |
| L3[a] | — | Lower anterior thigh<br>Anterior knee | Psoas (hip flexors)<br>Quadriceps (knee extensors)<br>Thigh adductors | Anterior thigh, knee |
| L4[a] | Quadriceps (knee) | Medial calf | Quadriceps (knee extensors)[b]<br>Thigh adductors | Knee, medial calf<br>Anterolateral thigh |
| L5[c] | — | Dorsal surface—foot<br>Lateral calf | Peronei (foot evertors)[b]<br>Tibialis anterior (foot dorsiflexors)<br>Gluteus medius (hip abductors)<br>Toe dorsiflexors | Lateral calf, dorsal foot, posterolateral thigh, buttocks |
| S1[c] | Gastrocnemius/soleus (ankle) | Plantar surface—foot<br>Lateral aspect—foot | Gastrocnemius/soleus (foot plantar flexors)[b]<br>Abductor hallucis (toe flexors)[b]<br>Gluteus maximus (hip extensors) | Bottom foot, posterior calf, posterior thigh, buttocks |

[a]Reverse straight leg–raising sign present—see "Examination of the Back."
[b]These muscles receive the majority of innervation from this root.
[c]Straight leg–raising sign present—see "Examination of the Back" in Engstrom JW, Deyo RA: Back and Neck Pain, Chap. 22, p. 111, in *HPIM-19*.

extension of leg backward with pt standing; maneuver stretches L2–L4 nerve roots, lumbosacral plexus, and femoral nerve passing anterior to the hip.

Neurologic examination—search for focal atrophy, weakness, reflex loss, diminished sensation in a dermatomal distribution. Findings with radiculopathy are summarized in Table 48-1.

## LABORATORY EVALUATION

"Routine" laboratory studies and lumbar spine x-rays are rarely needed for nonspecific acute LBP (<3 months) but indicated when risk factors for serious underlying disease are present (Table 48-2). MRI and CT-myelography are tests of choice for

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**TABLE 48-2 ACUTE LOW BACK PAIN: RISK FACTORS FOR AN IMPORTANT STRUCTURAL CAUSE**

| |
|---|
| **History** |
| Pain worse at rest or at night |
| Prior history of cancer |
| History of chronic infection (especially lung, urinary tract, skin) |
| History of trauma |
| Incontinence |
| Age >70 years |
| Intravenous drug use |
| Glucocorticoid use |
| History of a rapidly progressive neurologic deficit |
| **Examination** |
| Unexplained fever |
| Unexplained weight loss |
| Percussion tenderness over the spine |
| Abdominal, rectal, or pelvic mass |
| Internal/external rotation of the leg at the hip; heel percussion sign |
| Straight leg– or reverse straight leg–raising signs |
| Progressive focal neurologic deficit |

anatomic definition of spine disease. Electromyography (EMG) and nerve conduction studies useful for functional assessment of peripheral nervous system.

## ETIOLOGY

### Lumbar Disk Disease

Common cause of low back and leg pain; usually at L4–L5 or L5–S1 levels. Dermatomal sensory loss, reduction or loss of deep tendon reflexes, or myotomal pattern of weakness more informative than pain pattern for localization. Usually unilateral; can be bilateral with large central disk herniations compressing multiple nerve roots and causing cauda equina syndrome (Chap. 188).

Indications for lumbar disk surgery:

- Progressive motor weakness on examination or progressive nerve root injury is demonstrated on EMG.
- Cauda equina syndrome or spinal cord compression is usually indicated by abnormal bowel or bladder function.
- Incapacitating nerve root pain despite conservative treatment for at least 6–8 weeks: Trials indicate surgery leads to more rapid pain relief but no difference at 1–2 years compared with nonsurgical treatment.

### Spinal Stenosis

A narrowed spinal canal producing neurogenic claudication, i.e., back, buttock, and/or leg pain induced by walking or standing and relieved by sitting. Symptoms are usually bilateral. Unlike vascular claudication, symptoms are provoked by standing without walking. Unlike lumbar disk disease, symptoms are relieved by sitting. Focal neurologic deficits common; severe neurologic deficits (paralysis, incontinence) rare. Stenosis results from acquired (75%), congenital, or mixed acquired/congenital factors.

- Symptomatic treatment adequate for mild disease
- Surgery indicated when medical therapy does not allow for activities of daily living

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or if focal neurologic signs are present. Most pts treated surgically experience relief of back and leg pain; 25% develop recurrent stenosis within 7–10 years.

## Trauma

*Low back strain* or *sprain* used to describe minor, self-limited injuries associated with LBP. *Vertebral fractures* from trauma result in anterior wedging or compression of vertebral bodies; burst fractures involving vertebral body and posterior spine elements can occur. Neurologic impairment common with vertebral fractures; early surgical intervention indicated. CT scans used to screen for spine disease in moderate to severe trauma; superior to routine x-rays for bony disease. Most common cause of *nontraumatic fracture* is osteoporosis; others include osteomalacia, hyperparathyroidism, hyperthyroidism, multiple myeloma, or metastatic carcinoma.

## Spondylolisthesis

Slippage of anterior spine forward, leaving posterior elements behind; L4–L5 > L5–S1 levels; can produce LBP or radiculopathy/cauda equina syndrome (Chap. 188).

## Osteoarthritis (Spondylosis)

Back pain induced by spine movement and associated with stiffness. Increases with age; radiologic findings do not correlate with severity of pain. Osteophytes or combined disc-osteophytes may cause or contribute to central spinal canal stenosis, lateral recess stenosis, or neural foraminal narrowing.

## Vertebral Metastases (Chap. 20)

Back pain most common neurologic symptom in pts with systemic cancer and may be presenting complaint (20%); pain typically not relieved by rest and worse at night. MRI or CT-myelography demonstrates vertebral body metastasis; disk space is spared.

## Vertebral Osteomyelitis

Back pain unrelieved by rest; focal spine tenderness, elevated ESR. Primary source of infection usually urinary tract, skin, or lung; IV drug abuse a risk factor. Destruction of the vertebral bodies and disk space common. Lumbar spinal epidural abscess presents as back pain and fever; examination may be normal or show radicular findings, spinal cord involvement, or cauda equina syndrome. Extent of abscess best defined by MRI.

## Lumbar Adhesive Arachnoiditis

May follow inflammation within subarachnoid space; fibrosis results in clumping of nerve roots, best seen by MRI; treatment is unsatisfactory.

## Immune Disorders

Ankylosing spondylitis, rheumatoid arthritis, reactive arthritis, psoriatic arthritis, and inflammatory bowel disease.

## Osteoporosis

Loss of bone substance resulting from immobilization, hyperparathyroidism, chronic glucocorticoid use, other medical disorders, or increasing age (particularly in females). Sole manifestation may be back pain exacerbated by movement. Can also occur in the upper back.

## Visceral Diseases

Pelvis refers pain to sacral region, lower abdomen to mid-lumbar region, upper abdomen to lower thoracic or upper lumbar region. Local signs are absent; normal movements of the spine are painless. Rupture of an abdominal aortic aneurysm may produce isolated back pain.

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## Other

Chronic LBP with no clear cause; psychiatric disorders, substance abuse may be associated.

## TREATMENT LOW BACK PAIN

### ACUTE LOW BACK PAIN (ALBP)

- Pain of <3 months duration.
- Spine infections, fractures, tumors, or rapidly progressive neurologic deficits require urgent diagnostic evaluation.
- If "risk factors" (Table 48-2) are absent, initial treatment is symptomatic and no diagnostic tests necessary.
- When leg pain absent, prognosis is excellent; full recovery in 85%.
- Clinical trials do not show benefit from bed rest >2 days. Possible benefits of early activity—cardiovascular conditioning, disk and cartilage nutrition, bone and muscle strength, increased endorphin levels.
- Spinal manipulation appears to be equivalent to conventional medical therapies and may be a useful alternative for some patients.
- Proof lacking to support physical therapy, massage, acupuncture, ultrasound, laser therapy, corsets, or traction.
- Self-application of ice or heat or use of shoe insoles is optional given low cost and risk.
- Drug treatment of ALBP includes NSAIDs and acetaminophen (Chap. 5).
- Muscle relaxants (cyclobenzaprine) may be useful but sedation is a common side effect.
- Opioids are not clearly superior to NSAIDs or acetaminophen for ALBP.
- No evidence to support oral or injected epidural glucocorticoids.

### CHRONIC LOW BACK PAIN (CLBP)

- Pain lasting >12 weeks; differential diagnosis includes most conditions described above.
- Cause can be clarified by neuroimaging and EMG/nerve conduction studies; diagnosis of radiculopathy secure when results concordant with findings on neurologic examination. Treatment should not be based on neuroimaging alone: up to one-third of asymptomatic young adults have a herniated lumbar disk by CT or MRI.
- Management based on identification of underlying cause; when specific cause not found, conservative management necessary.
- Treatment measures include acetaminophen, NSAIDs, and tricyclic antidepressants.
- Evidence supports the use of exercise therapy; effective in returning some pts to work, diminishing pain, and improving walking distances.
- Cognitive-behavioral therapy may have some use; long-term results unclear.
- Alternative therapies including spinal manipulation, acupuncture, and massage are frequently tried; trials are mixed as to their effectiveness.
- Epidural glucocorticoids and facet joint injections are not effective in the absence of radiculopathy.
- Surgical intervention for chronic LBP without radiculopathy is controversial, and clinical trials do not support its use.

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## NECK AND SHOULDER PAIN

Usually arises from diseases of the cervical spine and soft tissues of the neck; typically precipitated by movement and may be accompanied by focal tenderness and limitation of motion.

### ETIOLOGY

#### Trauma to the Cervical Spine

Trauma to the cervical spine (fractures, subluxation) places spine at risk for compression; immediate immobilization of the neck is essential to minimize movement of unstable cervical spine segments.

*Whiplash injury* is due to trauma (usually automobile accidents) causing cervical musculoligamentous injury due to hyperflexion or hyperextension. This diagnosis is not applied to pts with fractures, disk herniation, head injury, focal neurologic findings, or altered consciousness.

#### Cervical Disk Disease

Herniation of a lower cervical disk is a common cause of neck, shoulder, arm, or hand pain or tingling. Neck pain (worse with movement), stiffness, and limited range of motion are common. With nerve root compression, pain may radiate into shoulder or arm. Extension and lateral rotation of the neck narrows the intervertebral foramen and may reproduce radicular symptoms (Spurling's sign). In young individuals, acute radiculopathy from a ruptured disk is often traumatic. *Subacute radiculopathy* is less likely to be related to a specific traumatic incident and may involve both disk disease and spondylosis. Clinical features of cervical nerve root lesions are summarized in Table 48-3.

#### Cervical Spondylosis

Osteoarthritis of the cervical spine may produce neck pain that radiates into the back of the head, shoulders, or arms; can also be source of headaches in the posterior occipital region. A combined radiculopathy and myelopathy may occur. An electrical sensation elicited by neck flexion and radiating down the spine from the neck (Lhermitte's symptom) usually indicates spinal cord involvement. MRI or CT-myelography can define the anatomic abnormalities, and EMG and nerve conduction studies can quantify the severity and localize the levels of nerve root injury.

#### Other Causes of Neck Pain

Includes *rheumatoid arthritis* of the cervical facet joints, ankylosing spondylitis, *herpes zoster* (shingles), *neoplasms* metastatic to the spine, *infections* (osteomyelitis and epidural abscess), and *metabolic bone diseases*. Neck pain may also be referred from the heart with coronary artery ischemia (cervical angina syndrome).

#### Thoracic Outlet

An anatomic region containing the first rib, subclavian artery and vein, brachial plexus, clavicle, and lung apex. Injury may result in posture- or movement-induced pain around the shoulder and supraclavicular region. *True neurogenic thoracic outlet syndrome* is uncommon and results from compression of the lower trunk of the brachial plexus by an anomalous band of tissue; treatment is surgical division of the band. *Arterial thoracic outlet syndrome* results from compression of the subclavian artery by a cervical rib; treatment is thrombolysis or anticoagulation, plus surgical excision of the cervical rib. *Venous thoracic outlet syndrome* is due to subclavian vein thrombosis producing swelling of the arm and pain. The vein may be compressed by a cervical rib or anomalous scalene muscle. *Disputed thoracic outlet syndrome* includes a large number of pts with chronic arm and shoulder pain of unclear cause; surgery is controversial and treatment is often unsuccessful.

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**TABLE 48-3 CERVICAL RADICULOPATHY: NEUROLOGIC FEATURES**

| Cervical Nerve Roots | Examination Findings | | | Pain Distribution |
|---|---|---|---|---|
| | Reflex | Sensory | Motor | |
| C5 | Biceps | Lateral deltoid | Rhomboids[a] (elbow extends backward with hand on hip)<br>Infraspinatus[a] (arm rotates externally with elbow flexed at the side)<br>Deltoid[a] (arm raised laterally 30–45° from the side) | Lateral arm, medial scapula |
| C6 | Biceps | Thumb/index finger<br>Dorsal hand/lateral forearm | Biceps[a] (arm flexed at the elbow in supination)<br>Pronator teres (forearm pronated) | Lateral forearm, thumb/index fingers |
| C7 | Triceps | Middle fingers<br>Dorsal forearm | Triceps[a] (forearm extension, flexed at elbow)<br>Wrist/finger extensors[a] | Posterior arm, dorsal forearm, dorsal hand |
| C8 | Finger flexors | Palmar surface of little finger<br>Medial hand and forearm | Abductor pollicis brevis (abduction of thumb)<br>First dorsal interosseous (abduction of index finger)<br>Abductor digiti minimi (abduction of little finger) | Fourth and fifth fingers, medial hand and forearm |
| T1 | Finger flexors | Axilla and medial arm | Abductor pollicis brevis (abduction of thumb)<br>First dorsal interosseous (abduction of index finger)<br>Abductor digiti minimi (abduction of little finger) | Medial arm, axilla |

[a]These muscles receive the majority of innervation from this root.

## Brachial Plexus and Nerves

Pain from injury to the brachial plexus or peripheral nerves can mimic pain of cervical spine origin. *Neoplastic infiltration* can produce this syndrome, as can *postradiation fibrosis* (pain less often present). *Acute brachial neuritis* consists of acute onset of severe shoulder or scapular pain followed over days by weakness of proximal arm

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and shoulder girdle muscles innervated by the upper brachial plexus; onset often preceded by an infection or immunization.

## Shoulder

If signs of radiculopathy are absent, differential diagnosis includes mechanical shoulder pain (tendinitis, bursitis, rotator cuff tear, dislocation, adhesive capsulitis, and cuff impingement under the acromion) and referred pain (subdiaphragmatic irritation, angina, Pancoast [apical lung] tumor). Mechanical pain is often worse at night, associated with shoulder tenderness, and aggravated by abduction, internal rotation, or extension of the arm.

## TREATMENT NECK AND SHOULDER PAIN

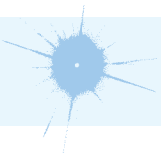
- Indications for cervical disk surgery are similar to those for lumbar disk; however, with cervical disease, an aggressive approach is indicated if spinal cord injury is threatened.

### NECK PAIN WITHOUT RADICULOPATHY

- Spontaneous improvement is expected for most acute neck pain.
- Symptomatic treatment includes analgesic medications.
- If not related to trauma, supervised exercise appears to be effective.
- No valid clinical evidence to support cervical fusion or cervical disk arthroplasty.
- Low-level laser therapy may be effective but additional trials are needed.
- No evidence to support radiofrequency neurotomy or cervical facet injections.

### NECK PAIN WITH RADICULOPATHY

- Natural history is favorable and many will improve without specific therapy.
- NSAIDs, acetaminophen, or both with or without muscle relaxants is appropriate initial therapy.
- Soft cervical collars are modestly helpful in limiting movements that exacerbate pain.
- Indications for surgery include a progressive radicular motor deficit, pain that limits function and fails to respond to conservative management, or spinal cord compression.
- *Cervical spondylosis* with bony, compressive cervical radiculopathy is generally treated with surgical decompression to interrupt the progression of neurologic signs although it is unclear if long-term outcomes are improved over medical therapy.
- Surgical options for *cervical herniated disks* consist of anterior cervical diskectomy alone, laminectomy with diskectomy, or diskectomy with fusion. The cumulative risk of subsequent radiculopathy or myelopathy at cervical segments adjacent to the fusion is ~3% per year and 26% per decade.



For more detailed discussion, see Engstrom JW, Deyo RA: Back and Neck Pain, Chap. 22, p. 111, in HPIM-19.

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# 49 Headache

## APPROACH TO THE PATIENT: Headache

Among the most common reasons that pts seek medical attention; can be either primary or secondary (Table 49-1). First step—distinguish serious from benign etiologies. Symptoms that raise suspicion for a serious cause are listed in Table 49-2. Intensity of head pain rarely has diagnostic value; most pts who present with worst headache of their lives have migraine. Headache location can suggest involvement of local structures (temporal pain in giant cell arteritis, facial pain in sinusitis). Ruptured aneurysm (instant onset), cluster headache (peak over 3–5 min), and migraine (pain increases over minutes to hours) differ in time to peak intensity. Provocation by environmental factors suggests a benign cause.

Complete neurologic examination is important in evaluation of headache. If examination is abnormal or if serious underlying cause is suspected, an imaging study (CT or MRI) is indicated as a first step. Lumbar puncture (LP) is required when meningitis (stiff neck, fever) or subarachnoid hemorrhage (following negative imaging) is a possibility. The psychological state of the pt should also be evaluated because a relationship exists between pain and depression.

## MIGRAINE

A benign, episodic syndrome of headache associated with other symptoms of neurologic dysfunction in varying admixtures. Second to tension-type as most common cause of headache; afflicts ~15% of women and 6% of men annually. Diagnostic criteria are listed in Table 49-3. Onset usually in childhood, adolescence, or early adulthood; however, initial attack may occur at any age. Family history is often present. Women may have increased sensitivity to attacks during menstrual cycle. Classic triad: premonitory visual (scotoma or scintillations), sensory, or motor symptoms; unilateral throbbing headache; and nausea and vomiting. Most pts do not have visual aura or other premonitory symptoms. Photo- and phonophobia common. Vertigo may occur. Focal neurologic disturbances without headache or vomiting (migraine equivalents) may also occur. An attack lasting 4–72 h is typical, as is relief after sleep. Attacks may be triggered by glare, bright lights, sounds, hunger, stress, physical exertion, hormonal fluctuations, lack of sleep, alcohol, or other chemical stimulation.

**TABLE 49-1 COMMON CAUSES OF HEADACHE**

| Primary Headache | | Secondary Headache | |
|---|---|---|---|
| **Type** | **%** | **Type** | **%** |
| Tension-type | 69 | Systemic infection | 63 |
| Migraine | 16 | Head injury | 4 |
| Idiopathic stabbing | 2 | Vascular disorders | 1 |
| Exertional | 1 | Subarachnoid hemorrhage | <1 |
| Cluster | 0.1 | Brain tumor | 0.1 |

***Source:*** After J Olesen et al: *The Headaches*. Philadelphia, Lippincott Williams & Wilkins, 2005.

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**TABLE 49-2 HEADACHE SYMPTOMS THAT SUGGEST A SERIOUS UNDERLYING DISORDER**

| |
|---|
| Sudden-onset headache |
| First severe headache |
| "Worst" headache ever |
| Vomiting that precedes headache |
| Subacute worsening over days or weeks |
| Pain induced by bending, lifting, cough |
| Pain that disturbs sleep or presents immediately upon awakening |
| Known systemic illness |
| Onset after age 55 years |
| Fever or unexplained systemic signs |
| Abnormal neurologic examination |
| Pain associated with local tenderness, e.g., region of temporal artery |

## TREATMENT MIGRAINE

- Three approaches to migraine treatment: nonpharmacologic (such as the avoidance of pt-specific triggers; information for pts is available at *www.achenet.org*); drug treatment of acute attacks (Tables 49-4 and 49-5); and prophylaxis (Table 49-6).
- Drug treatment necessary for most migraine pts, but avoidance or management of environmental triggers alone is sufficient for some.
- General principles of pharmacologic treatment:
  - Response rates vary from 50% to 70%.
  - Initial drug choice is empirical and individualized—influenced by age, coexisting illnesses, and side effect profile.
  - Efficacy of prophylactic treatment may take several months to assess with each drug.
  - When an acute attack requires additional medication 60 min after the first dose, then the initial drug dose should be increased for subsequent attacks or another class of drug tried.
- Mild to moderate acute migraine attacks often respond to over-the-counter (OTC) NSAIDs when taken early.
- Triptans are widely used and have many formulations.

**TABLE 49-3 SIMPLIFIED DIAGNOSTIC CRITERIA FOR MIGRAINE**

| **Repeated attacks of headache lasting 4–72 h in patients with a normal physical examination, no other reasonable cause for the headache, and:** | |
|---|---|
| **At Least Two of the Following Features:** | **Plus at Least One of the Following Features:** |
| Unilateral pain | Nausea/vomiting |
| Throbbing pain | Photophobia and phonophobia |
| Aggravation by movement | |
| Moderate or severe intensity | |

***Source:*** Adapted from the International Headache Society Classification (Headache Classification Committee of the International Headache Society, 2013).

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**TABLE 49-4 TREATMENT OF ACUTE MIGRAINE**

| Drug | Trade Name | Dosage |
|---|---|---|
| **Simple Analgesics** | | |
| Acetaminophen, aspirin, caffeine | Excedrin Migraine | Two tablets or caplets q6h (max eight per day) |
| **NSAIDs** | | |
| Naproxen | Aleve, Anaprox, generic | 220–550 mg PO bid |
| Ibuprofen | Advil, Motrin, Nuprin, generic | 400 mg PO q3–4h |
| Tolfenamic acid | Clotam Rapid | 200 mg PO; may repeat ×1 after 1–2 h |
| Diclofenac K | Cambia | 50 mg PO with water |
| **5-HT$_1$ Receptor Agonists** | | |
| **Oral** | | |
| Ergotamine 1 mg, caffeine 100 mg | Cafergot | One or two tablets at onset, then one tablet q½h (max 6 per day, 10 per week) |
| Naratriptan | Amerge | 2.5-mg tablet at onset; may repeat once after 4 h |
| Rizatriptan | Maxalt<br>Maxalt-MLT | 5- to 10-mg tablet at onset; may repeat after 2 h (max 30 mg/d) |
| Sumatriptan | Imitrex | 50- to 100-mg tablet at onset; may repeat after 2 h (max 200 mg/d) |
| Frovatriptan | Frova | 2.5-mg tablet at onset, may repeat after 2 h (max 5 mg/d) |
| Almotriptan | Axert | 12.5-mg tablet at onset, may repeat after 2 h (max 25 mg/d) |
| Eletriptan | Relpax | 40 or 80 mg |
| Zolmitriptan | Zomig<br>Zomig Rapimelt | 2.5-mg tablet at onset; may repeat after 2 h (max 10 mg/d) |
| **Nasal** | | |
| Dihydroergotamine | Migranal Nasal Spray | Prior to nasal spray, the pump must be primed four times; one spray (0.5 mg) is administered, followed in 15 min by a second spray |
| Sumatriptan | Imitrex Nasal Spray | 5- to 20-mg intranasal spray as four sprays of 5 mg or a single 20-mg spray (may repeat once after 2 h, not to exceed a dose of 40 mg/d) |
| Zolmitriptan | Zomig | 5-mg intranasal spray as one spray (may repeat once after 2 h, not to exceed a dose of 10 mg/d) |
| **Parenteral** | | |
| Dihydroergotamine | DHE-45 | 1 mg IV, IM, or SC at onset and q1h (max 3 mg/d, 6 mg per week) |
| Sumatriptan | Imitrex Injection<br>Alsuma<br>Sumavel DosePro | 6 mg SC at onset (may repeat once after 1 h for max of two doses in 24 h) |

(*Continued*)

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**TABLE 49-4 TREATMENT OF ACUTE MIGRAINE (*CONTINUED*)**

| Drug | Trade Name | Dosage |
|---|---|---|
| **Dopamine Receptor Antagonists** | | |
| **Oral** | | |
| Metoclopramide | Reglan,[a] generic[a] | 5–10 mg/d |
| Prochlorperazine | Compazine,[a] generic[a] | 1–25 mg/d |
| **Parenteral** | | |
| Chlorpromazine | Generic[a] | 0.1 mg/kg IV at 2 mg/min; max 35 mg/d |
| Metoclopramide | Reglan,[a] generic | 10 mg IV |
| Prochlorperazine | Compazine,[a] generic[a] | 10 mg IV |
| **Other** | | |
| **Oral** | | |
| Acetaminophen, 325 mg, *plus* dichloralphenazone, 100 mg, *plus* isometheptene, 65 mg | Midrin, generic | Two capsules at onset followed by one capsule q1h (max five capsules) |
| **Nasal** | | |
| Butorphanol | Generic | 1 mg (one spray in one nostril), may repeat if necessary in 1–2 h |
| **Parenteral** | | |
| Opioids | Generic[a] | Multiple preparations and dosages; see Table 5-2 |

[a]Not all drugs are specifically indicated by the FDA for migraine. Local regulations and guidelines should be consulted.
***Note:*** Antiemetics (e.g., domperidone 10 mg or ondansetron 4 or 8 mg) or prokinetics (e.g., metoclopramide 10 mg) are sometimes useful adjuncts.
***Abbreviations:*** 5-HT, 5-hydroxytryptamine.

- There is likely less frequent headache recurrence when using ergots, but more frequent nausea.
- For prophylaxis, tricyclic antidepressants are a good first choice for young people with difficulty falling asleep; verapamil is often a first choice for prophylaxis in the elderly.

## Tension-Type Headache

Common in all age groups. Pain is described as bilateral tight, bandlike discomfort. May persist for hours or days; usually builds slowly.

- Pain can be managed generally with simple analgesics such as acetaminophen, aspirin, or NSAIDs.
- Often related to stress; responds to behavioral approaches including relaxation.
- Amitriptyline may be helpful for chronic (>15 days per month) tension-type headache prophylaxis.

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**TABLE 49-5 CLINICAL STRATIFICATION OF ACUTE SPECIFIC MIGRAINE TREATMENTS**

| Clinical Situation | Treatment Options |
|---|---|
| Failed NSAIDs/analgesics | **First tier**<br>Sumatriptan 50 or 100 mg PO<br>Almotriptan 12.5 mg PO<br>Rizatriptan 10 mg PO<br>Eletriptan 40 mg PO<br>Zolmitriptan 2.5 mg PO<br>**Slower effect/better tolerability**<br>Naratriptan 2.5 mg PO<br>Frovatriptan 2.5 mg PO<br>**Infrequent headache**<br>Ergotamine/caffeine 1–2/100 mg PO<br>Dihydroergotamine nasal spray 2 mg |
| Early nausea or difficulties taking tablets | Zolmitriptan 5-mg nasal spray<br>Sumatriptan 20-mg nasal spray<br>Rizatriptan 10-mg MLT wafer |
| Headache recurrence | Ergotamine 2 mg (most effective PR/usually with caffeine)<br>Naratriptan 2.5 mg PO<br>Almotriptan 12.5 mg PO<br>Eletriptan 40 mg |
| Tolerating acute treatments poorly | Naratriptan 2.5 mg<br>Almotriptan 12.5 mg |
| Early vomiting | Zolmitriptan 5-mg nasal spray<br>Sumatriptan 25 mg PR<br>Sumatriptan 6 mg SC |
| Menses-related headache | **Prevention**<br>Ergotamine PO at night<br>Estrogen patches<br>**Treatment**<br>Triptans<br>Dihydroergotamine nasal spray |
| Very rapidly developing symptoms | Zolmitriptan 5-mg nasal spray<br>Sumatriptan 6 mg SC<br>Dihydroergotamine 1 mg IM |

## Cluster Headache

Rare form of primary headache; population frequency 0.1%. Characterized by episodes of recurrent, deep, unilateral, retroorbital searing pain. Unilateral lacrimation and nasal and conjunctival congestion may be present. Visual complaints, nausea, or vomiting is rare. Unlike migraine, pts with cluster tend to move about during attacks. A core feature is periodicity. Typically, daily bouts of one to two attacks of relatively short-duration unilateral pain for 8–10 weeks a year; usually followed by a pain-free interval that averages a little less than a year. Alcohol may provoke attacks.

- Prophylaxis with verapamil (40–80 mg twice daily to start), lithium (400–800 mg/d), or prednisone (60 mg/d for 7 days followed by a taper over 21 days).
- High-flow oxygen (10–12 L/min for 15–20 min) or sumatriptan (6 mg SC or 20-mg nasal spray) is useful for the acute attack.

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**TABLE 49-6 PREVENTIVE TREATMENTS IN MIGRAINE[a]**

| Drug | Dose | Selected Side Effects |
|---|---|---|
| Pizotifen[b] | 0.5–2 mg qd | Weight gain<br>Drowsiness |
| β Blocker | | |
| Propranolol | 40–120 mg bid | Reduced energy |
| Metoprolol | 25–100 mg bid | Tiredness<br>Postural symptoms<br>Contraindicated in asthma |
| Antidepressants | | |
| Amitriptyline | 10–75 mg at night | Drowsiness |
| Dosulepin | 25–75 mg at night | |
| Nortriptyline | 25–75 mg at night | ***Note:*** Some patients may only need a total dose of 10 mg, although generally 1–1.5 mg/kg body weight is required |
| Venlafaxine | 75–150 mg/d | |
| Anticonvulsants | | |
| Topiramate | 25–200 mg/d | Paresthesias<br>Cognitive symptoms<br>Weight loss<br>Glaucoma<br>Caution with nephrolithiasis |
| Valproate | 400–600 mg bid | Drowsiness<br>Weight gain<br>Tremor<br>Hair loss<br>Fetal abnormalities<br>Hematologic or liver abnormalities |
| Serotonergic drugs | | |
| Methysergide[c] | 1–4 mg qd | Drowsiness<br>Leg cramps<br>Hair loss<br>Retroperitoneal fibrosis (1-month drug holiday is required every 6 months) |
| Other classes | | |
| Flunarizine[b] | 5–15 mg qd | Drowsiness<br>Weight gain<br>Depression<br>Parkinsonism |
| Candesartan | 16 mg daily | Dizziness |
| Chronic migraine | | |
| Onabotulinum toxin type A | 155 U | Loss of brow furrow |
| No convincing evidence from controlled trials | | |
| Verapamil | | |

(*Continued*)

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**TABLE 49-6 PREVENTIVE TREATMENTS IN MIGRAINE[a] (*CONTINUED*)**

| Drug | Dose | Selected Side Effects |
|---|---|---|
| Controlled trials demonstrate *no effect* | | |
| Nimodipine | | |
| Clonidine | | |
| Selective serotonin reuptake inhibitors: fluoxetine | | |

[a]Commonly used preventives are listed with typical doses and common side effects. Not all listed medicines are approved by the U.S. Food and Drug Administration; local regulations and guidelines should be consulted.
[b]Not available in the United States.
[c]Not currently available worldwide.

- Deep-brain stimulation of the posterior hypothalamic gray matter is successful for refractory cases as is the less-invasive approach of occipital nerve stimulation.

## Post-Concussion Headache

Common following motor vehicle collisions, other head trauma; severe injury, or loss of consciousness often not present. Symptoms of headache, dizziness, vertigo, impaired memory, poor concentration, irritability; typically remits after several weeks to months. Neurologic examination and neuroimaging studies normal. Not a functional disorder; cause unknown and treatment usually not satisfactory.

## Lumbar Puncture Headache

Typical onset within 48 h after LP; follows 10–30% of LPs. Positional: onset when pt sits or stands, relief by lying flat. Most cases remit spontaneously in ≤1 week. Oral or IV caffeine (500 mg IV over 2 h) successful in many; epidural blood patch effective immediately in refractory cases.

## Indomethacin-Responsive Headaches

A diverse set of disorders that respond often exquisitely to indomethacin (25 mg two to three times daily). Includes:

- *Paroxysmal hemicrania:* Frequent unilateral, severe, short-lasting episodes of headache that are often retroorbital and associated with autonomic phenomena such as lacrimation and nasal congestion.
- *Hemicrania continua:* Moderate and continuous unilateral pain associated with fluctuations of severe pain that may be associated with autonomic features.
- *Primary stabbing headache:* Stabbing pain confined to the head or rarely the face lasting from 1 to many seconds or minutes.
- *Primary cough headache:* Transient severe head pain with coughing, bending, lifting, sneezing, or stooping; lasts for several minutes. Usually benign, but posterior fossa mass lesion in some pts; therefore consider brain MRI.
- *Primary exertional headache:* Features similar to cough headache and migraine, but precipitated by any form of exercise.

## FACIAL PAIN

Most common cause of facial pain is dental; triggered by hot, cold, or sweet foods. Exposure to cold repeatedly induces dental pain. Trigeminal neuralgia consists of paroxysmal, electric shock—like episodes of pain in the distribution of trigeminal nerve; occipital neuralgia presents as lancinating occipital pain. These disorders are discussed in Chap. 187.

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For a more detailed discussion, see Goadsby PJ, Raskin NH: Headache, Chap. 21, p. 107; and Goadsby PJ, Raskin NH: Migraine and Other Primary Headache Disorders, Chap. 447, p. 2586, in HPIM-19.

# 50 Syncope

*Syncope* is a transient, self-limited loss of consciousness due to acute global impairment of cerebral blood flow. It may occur suddenly, without warning, or may be preceded by presyncopal symptoms such as light-headedness or faintness, weakness, fatigue, nausea, dimming vision, ringing in ears, or sweating. The syncopal pt appears pale and has a faint, rapid, or irregular pulse. Breathing may be almost imperceptible; transient myoclonic or clonic movements may occur. Recovery of consciousness is prompt and complete if pt is maintained in a horizontal position and cerebral perfusion is restored.

## APPROACH TO THE PATIENT: Syncope

The cause may be apparent only at the time of the event, leaving few, if any, clues when the pt is seen by the physician. Other disorders must be distinguished from syncope, including seizures, vertebrobasilar ischemia, hypoxemia, and hypoglycemia (see below). First consider serious underlying etiologies; among these are massive internal hemorrhage, myocardial infarction (can be painless), and cardiac arrhythmias. In elderly pts, a sudden faint without obvious cause should raise the question of complete heart block or a tachyarrhythmia. Loss of consciousness in particular situations, such as during venipuncture or micturition, suggests a benign abnormality of vascular tone. The position of the pt at the time of the syncopal episode is important; syncope in the supine position is unlikely to be vasovagal and suggests arrhythmia or seizure. Medications must be considered, including nonprescription drugs or health store supplements, with particular attention to recent changes. Symptoms of impotence, bowel and bladder difficulties, disturbed sweating, or an abnormal neurologic examination suggest a primary neurogenic cause. An algorithmic approach is presented in Fig. 50-1.

## ETIOLOGY

Syncope is usually due to a neurally mediated disorder, orthostatic hypotension, or an underlying cardiac condition (Table 50-1). Not infrequently the cause is multifactorial.

### Neurocardiogenic (Vasovagal and Vasodepressor) Syncope

The common faint, experienced by normal persons, accounts for approximately half of all episodes of syncope. It is frequently recurrent and may be provoked by hot or

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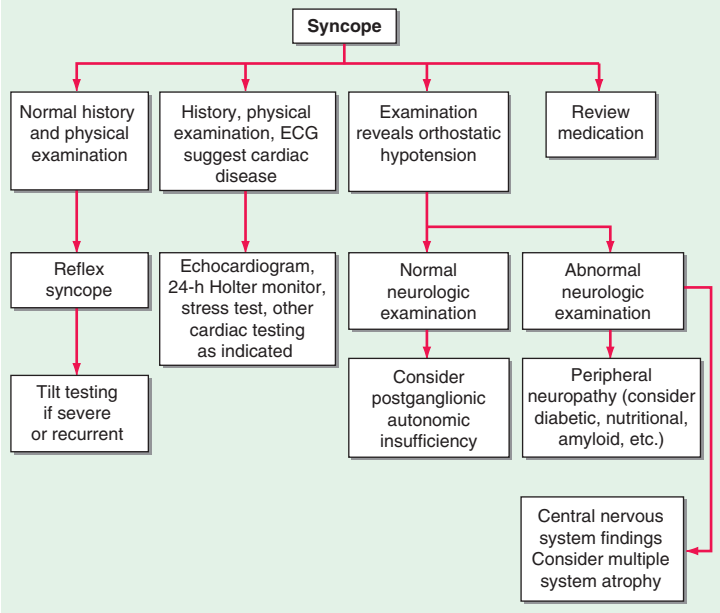


**FIGURE 50-1** Approach to the pt with syncope.

**TABLE 50-1 CAUSES OF SYNCOPE**

| |
|---|
| **A. Neurally Mediated Syncope** |
| Vasovagal syncope |
| Provoked fear, pain, anxiety, intense emotion, sight of blood, unpleasant sights and odors, orthostatic stress |
| Situational reflex syncope |
| Pulmonary |
| Cough syncope, wind instrument player's syncope, weightlifter's syncope, "mess trick"[a] and "fainting lark,"[b] sneeze syncope, airway instrumentation |
| Urogenital |
| Postmicturition syncope, urogenital tract instrumentation, prostatic massage |
| Gastrointestinal |
| Swallow syncope, glossopharyngeal neuralgia, esophageal stimulation, gastrointestinal tract instrumentation, rectal examination, defecation syncope |
| Cardiac |
| Bezold-Jarisch reflex, cardiac outflow obstruction |
| Carotid sinus |
| Carotid sinus sensitivity, carotid sinus massage |
| Ocular |
| Ocular pressure, ocular examination, ocular surgery |

(*Continued*)

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**TABLE 50-1 CAUSES OF SYNCOPE (*CONTINUED*)**

| |
|---|
| **B. Orthostatic Hypotension** |
| Primary autonomic failure due to idiopathic central and peripheral neurodegenerative diseases—the "synucleinopathies" |
| Lewy body diseases |
| Parkinson's disease |
| Lewy body dementia |
| Pure autonomic failure |
| Multiple system atrophy (the Shy-Drager syndrome) |
| Secondary autonomic failure due to autonomic peripheral neuropathies |
| Diabetes |
| Hereditary amyloidosis (familial amyloid polyneuropathy) |
| Primary amyloidosis (AL amyloidosis; immunoglobulin light chain associated) |
| HSAN (especially type III—familial dysautonomia) |
| Idiopathic immune-mediated autonomic neuropathy |
| Autoimmune autonomic ganglionopathy |
| Sjögren's syndrome |
| Paraneoplastic autonomic neuropathy |
| HIV neuropathy |
| Postprandial hypotension |
| Iatrogenic (drug-induced) |
| Volume depletion |
| **C. Cardiac Syncope** |
| Arrhythmias |
| Sinus node dysfunction |
| Atrioventricular dysfunction |
| Supraventricular tachycardias |
| Ventricular tachycardias |
| Inherited channelopathies |
| Cardiac structural disease |
| Valvular disease |
| Myocardial ischemia |
| Obstructive and other cardiomyopathies |
| Atrial myxoma |
| Pericardial effusions and tamponade |

[a]Hyperventilation for ~1 min, followed by sudden chest compression.
[b]Hyperventilation (~20 breaths) in a squatting position, rapid rise to standing, then Valsalva.
***Abbreviation:*** HSAN, Hereditary sensory and autonomic neuropathies.

crowded environment, alcohol, fatigue, pain, hunger, prolonged standing, or stressful situations.

## Postural (Orthostatic) Hypotension

Sudden rising from a recumbent position or standing quietly is a precipitating circumstance. Cause of syncope in many elderly and incidence rises with age; polypharmacy with antihypertensive or antidepressant drugs often a contributor; physical deconditioning may also play a role. Also occurs with autonomic nervous system disorders, either peripheral (diabetes, nutritional, or amyloid polyneuropathy) or central (multiple system atrophy, Parkinson's disease). Some cases are idiopathic.

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## DIFFERENTIAL DIAGNOSIS

### Seizures

The differential diagnosis is often between syncope and a generalized seizure. Syncope is more likely if the event was provoked by acute pain or emotion or occurred immediately after arising from a lying or sitting position; seizures are typically not related to posture. Pts with syncope often describe a stereotyped transition from consciousness to unconsciousness that develops over a few seconds. Seizures either occur very abruptly without a transition or are preceded by premonitory symptoms such as an epigastric rising sensation, perception of odd odors, or racing thoughts. Pallor is seen during syncope; cyanosis is usually seen during a seizure. The duration of unconsciousness is usually very brief (i.e., seconds) in syncope and more prolonged (i.e., >5 min) in a seizure. Injury from falling and incontinence are common in seizure, rare in syncope. Whereas tonic-clonic movements are the hallmark of a generalized seizure, myoclonic and other movements also occur in up to 90% of syncopal episodes and eyewitnesses will often have a difficult time distinguishing between the two etiologies.

### Hypoglycemia

Severe hypoglycemia is usually due to a serious disease or insulin use. Hunger is a premonitory feature that is not typical in syncope. The glucose level at the time of a spell is diagnostic.

### Cataplexy

Abrupt partial or complete loss of muscular tone triggered by strong emotions; occurs in 60–75% of narcolepsy pts. Unlike syncope, consciousness is maintained throughout the attacks that typically last between 30 s and 2 min. No premonitory symptoms.

### Psychiatric Disorders

Apparent loss of consciousness can be present in generalized anxiety, panic disorders, major depression, and somatization disorder. Frequently resembles presyncope, although the symptoms are not accompanied by prodromal symptoms and are not relieved by recumbency. Attacks can often be reproduced by hyperventilation and have associated symptoms of panic attacks such as a feeling of impending doom, air hunger, palpitations, and tingling of the fingers and perioral region. Such pts are rarely injured despite numerous falls. There are no clinically significant hemodynamic changes.

## TREATMENT SYNCOPE

Therapy is determined by the underlying cause.

- Pts with neurally mediated syncope should be reassured and instructed to avoid situations or stimuli that provoke attacks. Plasma volume expansion should occur with fluid and salt.
- Drug therapy may be necessary for resistant neurally medicated syncope. Fludrocortisone, vasoconstricting agents, and β-adrenergic antagonists are widely used although there is no consistent evidence from randomized trials.
- Pts with orthostatic hypotension should first be treated with removal of vasoactive medications. Then consider nonpharmacologic (pt education regarding moves from supine to upright, increasing fluids and salt in diet) and finally pharmacologic methods such as fludrocortisone and vasoconstricting agents such as midodrine, L-dihydroxyphenylserine, and pseudoephedrine.
- Management of cardiac causes depends in the underlying disorder. Cardiac pacing or cardioverter-defibrillator implantation is sometimes necessary.
- Management of refractory orthostatic hypotension is discussed in Chap. 186.

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For a more detailed discussion, see Freeman R: Syncope, Chap. 27, p. 142, in HPIM-19.

# 51 Dizziness and Vertigo

## APPROACH TO THE PATIENT: Dizziness or Vertigo

The term *dizziness* is used by pts to describe a variety of sensations or gait unsteadiness. With a careful history, distinguishing between *faintness* (presyncope; Chap. 50) and *vertigo* (a sense of movement of the body or the environment, most often a feeling of spinning) is usually possible.

When the meaning of *dizziness* is uncertain, provocative tests to reproduce the symptoms may be helpful. Valsalva maneuver, hyperventilation, or postural changes leading to orthostasis may reproduce faintness. Rapid rotation in a swivel chair is a simple provocative test to reproduce vertigo.

Benign positional vertigo is identified by the Dix-Hallpike maneuver to elicit vertigo and the characteristic nystagmus; the pt begins in a sitting position with head turned 45°; holding the back of the head, examiner gently lowers pt to supine position with head extended backward 20° and observes for nystagmus; after 30 s the pt is raised to sitting position and after 1 min rest the maneuver is repeated on other side.

If a central cause for the vertigo is suspected (e.g., no signs of peripheral vertigo, no hearing loss, no ear sensations, or the presence of other neurologic abnormalities indicating central nervous system [CNS] disease), then prompt evaluation for central pathology is required. The initial test is usually an MRI scan of the posterior fossa. Distinguishing between central and peripheral etiologies can be accomplished with vestibular function tests, including videonystagmography and simple bedside examinations including the *head impulse test* (rapid, small amplitude head rotations while pt instructed to fixate on the examiner's face; if peripheral, a catch-up saccade is seen at the end of the rotation) and *dynamic visual acuity* (measure acuity at rest and with head rotated back and forth by examiner; a drop in acuity of more than one line on a near card or Snellen chart indicates vestibular dysfunction).

### FAINTNESS

Faintness is usually described as light-headedness followed by visual blurring and postural swaying along with a feeling of warmth, diaphoresis, and nausea. It is a symptom of insufficient blood, oxygen, or, rarely, glucose supply to the brain. It can occur prior to a syncopal event of any etiology (Chap. 50) and with hyperventilation

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**TABLE 51-1 FEATURES OF PERIPHERAL AND CENTRAL VERTIGO**

- Nystagmus from an acute peripheral lesion is unidirectional, with fast phases beating away from the ear with the lesion. Nystagmus that changes direction with gaze is due to a central lesion.
- Transient mixed vertical-torsional nystagmus occurs in BPPV, but pure vertical or pure torsional nystagmus is a central sign.
- Nystagmus from a peripheral lesion may be inhibited by visual fixation, whereas central nystagmus is not suppressed.
- Absence of a head impulse sign in a pt with acute prolonged vertigo should suggest a central cause.
- Unilateral hearing loss suggests peripheral vertigo. Findings such as diplopia, dysarthria, and limb ataxia suggest a central disorder.

***Abbreviation:*** BPPV, benign paroxysmal positional vertigo.

or hypoglycemia. Light-headedness can rarely occur during an aura before a seizure. Chronic light-headedness is a common somatic complaint with depression.

## VERTIGO

Usually due to a disturbance in the vestibular system; abnormalities in the visual or somatosensory systems may also contribute to vertigo. Frequently accompanied by nausea, postural unsteadiness, and gait ataxia; may be provoked or worsened by head movement.

*Physiologic vertigo* results from unfamiliar head movement (seasickness) or a mismatch between visual-proprioceptive-vestibular system inputs (height vertigo, visual vertigo during motion picture chase scenes). *Pathologic vertigo* may be caused by a peripheral (labyrinth or eighth nerve) or central CNS lesion. Distinguishing between these causes is the essential first step in diagnosis (Table 51-1) as only central lesions require urgent imaging, usually with MRI.

### Peripheral Vertigo

Usually severe, accompanied by nausea and emesis. Tinnitus, a feeling of ear fullness, or hearing loss may occur. A characteristic jerk nystagmus is almost always present. The nystagmus does not change direction with a change in direction of gaze; it is usually horizontal with a torsional component and has its fast phase away from the side of the lesion. It is inhibited by visual fixation. The pt senses spinning motion away from the lesion and tends to have difficulty walking, with falls toward the side of the lesion, particularly in the darkness or with eyes closed. No other neurologic abnormalities are present.

Acute prolonged vertigo may be caused by infection, trauma, or ischemia. Often no specific etiology is found, and the term *acute labyrinthitis* (or *vestibular neuritis*) is used to describe the event. Acute bilateral labyrinthine dysfunction is usually due to drugs (aminoglycoside antibiotics), alcohol, or a neurodegenerative disorder. Recurrent labyrinthine dysfunction with signs and symptoms of cochlear disease is usually due to *Ménière's disease* (recurrent vertigo accompanied by tinnitus and deafness). Positional vertigo is usually precipitated by a recumbent head position; *benign paroxysmal positional vertigo* (BPPV) of the posterior semicircular canal is particularly common; the pattern of nystagmus is distinctive. BPPV may follow trauma but is usually idiopathic; it generally abates spontaneously after weeks or months. *Vestibular schwannomas* of the eighth cranial nerve (acoustic neuroma) usually present with hearing loss and tinnitus, sometimes accompanied by facial weakness and sensory loss due to involvement of cranial nerves VII and V. *Psychogenic vertigo* should be suspected in pts with chronic incapacitating vertigo who also have agoraphobia, panic attacks, a normal neurologic examination, and no nystagmus.

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## Central Vertigo

Identified by associated brainstem or cerebellar signs such as dysarthria, diplopia, dysphagia, hiccups, other cranial nerve abnormalities, weakness, or limb ataxia; depending on the cause, headache may be present. The nystagmus can take almost any form (i.e., vertical or multidirectional) but is often purely horizontal without a torsional component and changes direction with different directions of gaze. Central nystagmus is not inhibited by fixation. Central vertigo may be chronic, mild, and is usually not accompanied by tinnitus or hearing loss. It may be due to vascular, demyelinating, neurodegenerative, or neoplastic disease. Vertigo may be a manifestation of migraine or, rarely, of temporal lobe epilepsy.

### TREATMENT VERTIGO

- Treatment of acute vertigo consists of vestibular suppressant drugs for short-term relief (Table 51-2). They may hinder central compensation, prolonging the duration of symptoms, and therefore should be used sparingly.

**TABLE 51-2 TREATMENT OF VERTIGO**

| Agent[a] | Dose[b] |
|---|---|
| Antihistamines | |
| Meclizine | 25–50 mg three times daily |
| Dimenhydrinate | 50 mg one to two times daily |
| Promethazine | 25 mg two to three times daily (also can be given rectally and IM) |
| Benzodiazepines | |
| Diazepam | 2.5 mg one to three times daily |
| Clonazepam | 0.25 mg one to three times daily |
| Anticholinergic | |
| Scopolamine transdermal[c] | Patch |
| Physical therapy | |
| Repositioning maneuvers[d] | |
| Vestibular rehabilitation | |
| Other | |
| Diuretics and/or low-sodium (1000 mg/d) diet[e] | |
| Antimigrainous drugs[f] | |
| Methylprednisolone[g] | 100 mg daily days 1–3; 80 mg daily days 4–6; 60 mg daily days 7–9; 40 mg daily days 10–12; 20 mg daily days 13–15; 10 mg daily days 16–18, 20, 22 |
| Selective serotonin reuptake inhibitors[h] | |

[a]All listed drugs are approved by the U.S. Food and Drug Administration, but most are not approved for the treatment of vertigo.
[b]Usual oral (unless otherwise stated) starting dose in adults; a higher maintenance dose can be reached by a gradual increase.
[c]For motion sickness only.
[d]For benign paroxysmal positional vertigo.
[e]For Ménière's disease.
[f]For vestibular migraine.
[g]For acute vestibular neuritis (started within 3 days of onset).
[h]For psychosomatic vertigo.

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- Vestibular rehabilitation promotes central adaptation processes and may habituate motion sensitivity and other symptoms of psychosomatic dizziness.
- BPPV may respond dramatically to repositioning exercises such as the Epley maneuver designed to empty particulate debris from the posterior semicircular canal (*www.dizziness-and-balance.com/disorders/bppv/bppv.html*).
- For vestibular neuritis, antiviral medications are of no proven benefit unless herpes zoster oticus is present. Some data suggest that glucocorticoids improve the likelihood of recovery in vestibular neuritis if given within 3 days of symptom onset.
- Ménière's disease may respond to a low-salt diet (1 g/d) or to a diuretic. Otolaryngology referral is recommended.
- Recurrent episodes of migraine-associated vertigo should be treated with antimigraine therapy (**Chap. 49**).

For a more detailed discussion, see Walker MF, Daroff RB: Dizziness, and Vertigo, Chap. 28, p. 148, in HPIM-19.

# 52 Acute Visual Loss and Double Vision

## APPROACH TO THE PATIENT: Acute Visual Loss or Double Vision

Accurate measurement of visual acuity in each eye (with glasses or contact lenses) is of primary importance. Additional assessments include testing of pupils, eye movements, ocular alignment, and visual fields. Slit-lamp examination can exclude corneal infection, trauma, glaucoma, uveitis, and cataract. Ophthalmoscopic examination to inspect the optic disc and retina often requires pupillary dilation using 1% tropicamide and 2.5% phenylephrine; risk of provoking an attack of narrow-angle glaucoma is remote.

Visual field mapping by finger confrontation localizes lesions in the visual pathway (**Fig. 52-1**); formal testing using a perimeter may be necessary. The goal is to determine whether the lesion is anterior to, at, or posterior to the optic chiasm. A scotoma confined to one eye is caused by an anterior lesion affecting the optic nerve or globe; swinging flashlight test may reveal an afferent pupil defect. History and ocular examination are usually sufficient for diagnosis. If a bitemporal hemianopia is present, lesion is located at optic chiasm (e.g., pituitary adenoma, meningioma). Homonymous visual field loss signals a retrochiasmal lesion affecting the optic tract, lateral geniculate body, optic radiations, or visual cortex (e.g., stroke, tumor, abscess). Neuroimaging is recommended for any pt with a bitemporal or homonymous hemianopia.

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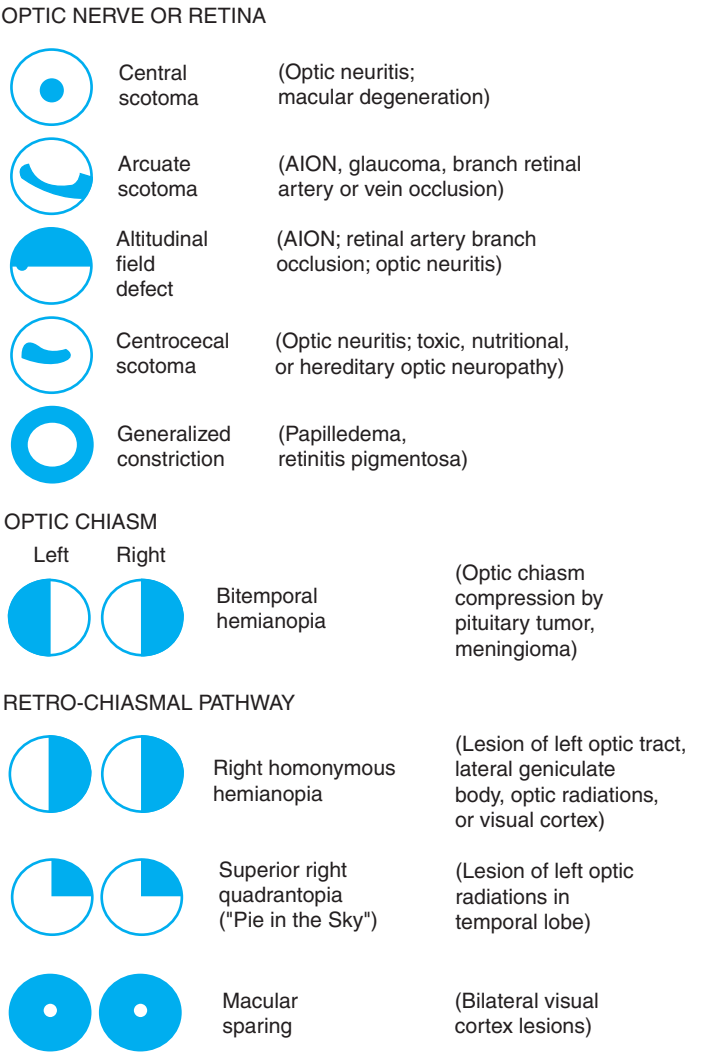


**FIGURE 52-1** Deficits in visual fields caused by lesions affecting visual pathways.

## TRANSIENT OR SUDDEN VISUAL LOSS

*Amaurosis fugax* (*transient monocular blindness*; a TIA of the retina) usually occurs from a retinal embolus often arising from ipsilateral carotid stenosis or the heart. Prolonged occlusion of the central retinal artery results in classic fundus appearance of a milky, infarcted retina with cherry red fovea. Any pt with compromise of the retinal circulation should be evaluated promptly for stroke risk factors (e.g., carotid atheroma, heart disease, atrial fibrillation). *Occipital cortex lesions* can be confused with amaurosis fugax because many pts mistakenly ascribe symptoms to their left or right eye, when in fact they are occurring in the left or right hemifield of both eyes. Interruption of blood flow to the visual cortex causes sudden graying of vision, occasionally with flashing

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lights or other symptoms that mimic *migraine*. The history may be the only guide to the correct diagnosis. Pts should be questioned about the precise pattern and duration of visual loss and other neurologic symptoms, especially those of posterior circulation dysfunction such as diplopia, vertigo, numbness, or weakness.

Marked *systemic hypertension* can cause visual loss from exudates, hemorrhages, cotton-wool spots (focal nerve fiber layer infarcts), and optic disc edema.

In central or branch *retinal vein occlusion*, the fundus examination reveals engorged, phlebitic veins with extensive retinal hemorrhages.

In age-related *macular degeneration*, characterized by extensive drusen and scarring of the pigment epithelium, leakage of blood or fluid from subretinal neovascular membranes can produce sudden central visual loss.

Flashing lights and floaters may indicate a fresh *vitreous detachment*. Separation of the vitreous from the retina is a frequent involutional event in the elderly. It is not harmful unless it creates sufficient traction to produce a *retinal detachment*. *Vitreous hemorrhage* may occur in diabetic pts from retinal neovascularization.

*Papilledema* refers to optic disc edema from raised intracranial pressure. Transient visual obscurations are common, but visual acuity is not affected unless the papilledema is severe, long-standing, or accompanied by macular exudates or hemorrhage. Enlarged blind spots and peripheral constriction are typical. Neuroimaging should be obtained to exclude an intracranial mass. If negative, a LP is required to confirm elevation of the intracranial pressure. *Pseudotumor cerebri* (idiopathic intracranial hypertension) is a diagnosis of exclusion. Most pts are young, female, and obese; some are found to have occult cerebral venous sinus thrombosis. Treatment is with acetazolamide, repeated LPs, and weight loss (via bariatric surgery if necessary); some pts require lumboperitoneal shunting to prevent blindness.

*Optic neuritis* is a common cause of monocular optic disc swelling and visual loss. If site of inflammation is retrobulbar, fundus will appear normal on initial examination. The typical pt is female, age 15–45, with pain provoked by eye movements. Glucocorticoids, typically IV methylprednisolone (1 g daily for 3 days) followed by oral prednisone (1 mg/kg daily for 11 days), may hasten recovery in severely affected pts but make no difference in final acuity (measured 6 months after the attack). If an MRI shows multiple demyelinating lesions, treatment for multiple sclerosis (Chap. 190) should be considered. Optic neuritis involving both eyes simultaneously or sequentially suggests neuromyelitis optica.

*Anterior ischemic optic neuropathy* (AION) is an infarction of the optic nerve head due to inadequate perfusion via the posterior ciliary arteries. Pts have sudden visual loss, often noted on awakening, and painless swelling of the optic disc. It is important to differentiate between nonarteritic (idiopathic) AION and arteritic AION. There is no treatment for nonarteritic AION. In contrast, arteritic AION is caused by *giant cell (temporal) arteritis* and requires immediate glucocorticoid therapy to prevent blindness; temporal artery biopsy establishes the diagnosis. The ESR and C-reactive protein should be checked in any elderly pt with acute optic disc swelling or symptoms suggestive of polymyalgia rheumatica (associated with arteritic AION).

## DOUBLE VISION (DIPLOPIA)

First step: clarify whether diplopia persists in either eye after covering the opposite eye; if it does the diagnosis is monocular diplopia usually caused by disease intrinsic to the eye with no dire implications for the pt. Occasionally it is a symptom of malingering or psychiatric disease.

If pt has diplopia while being examined, motility testing will usually reveal an abnormality in ocular excursions. However, if the degree of angular separation between the double images is small, the limitation of eye movements may be subtle and difficult to detect. In this situation, the cover test is useful. While the pt is fixating upon a distant target, one eye is covered while observing the other eye for a movement of redress as it takes up fixation. If none is seen, the procedure is repeated with the other eye. With genuine diplopia, this test should reveal ocular malalignment,

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**TABLE 52-1 COMMON CAUSES OF DIPLOPIA**

| |
|---|
| Brainstem stroke (skew deviation, nuclear or fascicular palsy) |
| Microvascular infarction (III, IV, VI nerve palsy) |
| Tumor (brainstem, cavernous sinus, superior orbital fissure, orbit) |
| Multiple sclerosis (internuclear ophthalmoplegia, ocular motor nerve palsy) |
| Aneurysm (III nerve) |
| Raised intracranial pressure (VI nerve) |
| Postviral inflammation |
| Meningitis (bacterial, fungal, granulomatosis, neoplastic) |
| Carotid-cavernous fistula or thrombosis |
| Herpes zoster |
| Tolosa-Hunt syndrome |
| Wernicke-Korsakoff syndrome |
| Botulism |
| Myasthenia gravis |
| Guillain-Barré or Fisher syndrome |
| Graves' disease |
| Orbital pseudotumor |
| Orbital myositis |
| Trauma |
| Orbital cellulitis |

especially if the head is turned or tilted in the position that gives rise to the worst symptoms.

Common causes of diplopia are summarized in Table 52-1. The physical findings in isolated ocular motor nerve palsies are:

- CN III: Ptosis and deviation of the eye down and outwards, causing vertical and horizontal diplopia. A dilated pupil suggests direct compression of the third nerve; if present, the possibility of an aneurysm of the posterior communicating artery must be considered urgently. If pupil is spared, a microvascular infarction is likely the cause, especially in pts with diabetes or hypertension.
- CN IV: Vertical diplopia with cyclotorsion; the affected eye is slightly elevated, and limitation of depression is seen when the eye is held in adduction. The pt may assume a head tilt to the opposite side (e.g., left head tilt in right fourth nerve paresis).
- CN VI: Horizontal diplopia worse on gaze to the side of the lesion; the affected eye cannot abduct.

The development of multiple ocular motor nerve palsies, or diffuse ophthalmoplegia, raises the possibility of myasthenia gravis. In this disease, the pupils are always normal. Systemic weakness may be absent. Multiple ocular motor nerve palsies should be investigated with neuroimaging focusing on the cavernous sinus, superior orbital fissure, and orbital apex where all three nerves are in close proximity. Diplopia that cannot be explained by a single ocular motor nerve palsy may also be caused by carcinomatous or fungal meningitis, Graves' disease, Guillain-Barré syndrome (especially the Miller Fisher variant), or Tolosa-Hunt syndrome (painful granulomatous inflammation of the cavernous sinus).

For a more detailed discussion, see Horton JC: Disorders of the Eye, Chap. 39, p. 195, in HPIM-19.

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# 53 Weakness and Paralysis

## APPROACH TO THE PATIENT: Weakness or Paralysis

*Weakness* is a reduction of power in one or more muscles. *Paralysis* indicates weakness that is so severe that the muscle cannot be contracted at all, whereas *paresis* refers to less severe weakness. The prefix *hemi-* refers to one half of the body, *para-* to both legs, and *quadri-* to all four limbs. The suffix *-plegia* signifies severe weakness or paralysis.

Increased *fatigability* or limitation in function due to pain or articular stiffness is often confused with weakness by pts. Increased time is sometimes required for full power to be exerted, and this *bradykinesia* may be misinterpreted as weakness. Severe proprioceptive sensory loss may also lead to complaints of weakness because adequate feedback information about the direction and power of movements is lacking. Finally, *apraxia*, a disorder of planning and initiating a skilled or learned movement, is sometimes mistaken for weakness.

The history should focus on the tempo of development of weakness, presence of sensory and other neurologic symptoms, medication history, predisposing medical conditions, and family history.

Weakness or paralysis is typically accompanied by other neurologic abnormalities that help to indicate the site of the responsible lesion (Table 53-1). It is important to distinguish weakness arising from disorders of upper motor neurons (i.e., motor neurons in the cerebral cortex and their axons that descend through the subcortical white matter, internal capsule, brainstem, and spinal cord) from disorders of the motor unit (i.e., lower motor neurons in the ventral horn of the spinal cord and their axons in the spinal roots and peripheral nerves, neuromuscular junction, and skeletal muscle).

Table 53-2 lists common causes of weakness by the primary site of pathology. Table 53-3 summarizes patterns with lesions of different parts of the nervous system.

An algorithm for the initial workup of weakness is shown in Fig. 53-1.

**TABLE 53-1 SIGNS THAT DISTINGUISH THE ORIGIN OF WEAKNESS**

| Sign | Upper Motor Neuron | Lower Motor Neuron | Myopathic | Psychogenic |
|---|---|---|---|---|
| Atrophy | None | Severe | Mild | None |
| Fasciculations | None | Common | None | None |
| Tone | Spastic | Decreased | Normal/ decreased | Variable/ paratonia |
| Distribution of weakness | Pyramidal/ regional | Distal/ segmental | Proximal | Variable/ inconsistent with daily activities |
| Muscle stretch reflexes | Hyperactive | Hypoactive/ absent | Normal/ hypoactive | Normal |
| Babinski sign | Present | Absent | Absent | Absent |

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**TABLE 53-2 COMMON CAUSES OF WEAKNESS**

| Upper Motor Neuron |
|---|
| ***Cortex:*** Ischemia; hemorrhage; intrinsic mass lesion (primary or metastatic cancer, abscess); extrinsic mass lesion (subdural hematoma); degenerative (amyotrophic lateral sclerosis) |
| ***Subcortical white matter/internal capsule:*** Ischemia; hemorrhage; intrinsic mass lesion (primary or metastatic cancer, abscess); immunologic (multiple sclerosis); infectious (progressive multifocal leukoencephalopathy) |
| ***Brainstem:*** Ischemia, immunologic (multiple sclerosis) |
| ***Spinal cord:*** Extrinsic compression (cervical spondylosis, metastatic cancer, epidural abscess); immunologic (multiple sclerosis, transverse myelitis); infectious (AIDS-associated myelopathy, HTLV-I–associated myelopathy, tabes dorsalis); nutritional deficiency (subacute combined degeneration) |
| **Motor Unit** |
| ***Spinal motor neuron:*** Degenerative (amyotrophic lateral sclerosis), infectious (poliomyelitis) |
| ***Spinal root:*** Compressive (degenerative disk disease); immunologic (Guillain-Barré syndrome); infectious (AIDS-associated polyradiculopathy, Lyme disease) |
| ***Peripheral nerve:*** Metabolic (diabetes mellitus, uremia, porphyria); toxic (ethanol, heavy metals, many drugs, diphtheria); nutritional ($B_{12}$ deficiency); inflammatory (polyarteritis nodosa); hereditary (Charcot-Marie-Tooth); immunologic (paraneoplastic, paraproteinemia); infectious (AIDS-associated polyneuropathies and mononeuritis multiplex); compressive (entrapment) |
| ***Neuromuscular junction:*** Immunologic (myasthenia gravis); toxic (botulism, aminoglycosides) |
| ***Muscle:*** Inflammatory (polymyositis, inclusion body myositis); degenerative (muscular dystrophy); toxic (glucocorticoids, ethanol, AZT); infectious (trichinosis); metabolic (hypothyroid, periodic paralyses); congenital (central core disease) |

***Abbreviation:*** AZT, azidothymidine.

**TABLE 53-3 CLINICAL DIFFERENTIATION OF WEAKNESS ARISING FROM DIFFERENT AREAS OF THE NERVOUS SYSTEM**

| Location of Lesion | Pattern of Weakness | Associated Signs |
|---|---|---|
| **Upper motor neuron** | | |
| Cerebral cortex | Hemiparesis (face and arm predominantly, or leg predominantly) | Hemisensory loss, seizures, homonymous hemianopia or quadrantanopia, aphasia, apraxias, gaze preference |
| Internal capsule | Hemiparesis (face, arm, leg may be equally affected) | Hemisensory deficit; homonymous hemianopia or quadrantanopia |
| Brainstem | Hemiparesis (arm and leg; face may not be involved at all) | Vertigo, nausea and vomiting, ataxia and dysarthria, eye movement abnormalities, cranial nerve dysfunction, altered level of consciousness, Horner's syndrome |
| Spinal cord | Quadriparesis if midcervical or above<br>Paraparesis if low cervical or thoracic | Sensory level; bowel and bladder dysfunction |

(*Continued*)

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**TABLE 53-3 CLINICAL DIFFERENTIATION OF WEAKNESS ARISING FROM DIFFERENT AREAS OF THE NERVOUS SYSTEM (*CONTINUED*)**

| Location of Lesion | Pattern of Weakness | Associated Signs |
|---|---|---|
| | Hemiparesis below level of lesion (Brown-Séquard) | Contralateral pain/temperature loss below level of lesion |
| **Motor unit** | | |
| Spinal motor neuron | Diffuse weakness, may involve control of speech and swallowing | Muscle fasciculations and atrophy; no sensory loss |
| Spinal root | Radicular pattern of weakness | Dermatomal sensory loss; radicular pain common with compressive lesions |
| Peripheral nerve | | |
| Polyneuropathy | Distal weakness, usually feet more than hands; usually symmetric | Distal sensory loss, usually feet more than hands |
| Mononeuropathy | Weakness in distribution of single nerve | Sensory loss in distribution of single nerve |
| Neuromuscular junction | Fatigable weakness, usually with ocular involvement producing diplopia and ptosis | No sensory loss; no reflex changes |
| Muscle | Proximal weakness | No sensory loss; diminished reflexes only when severe; may have muscle tenderness |

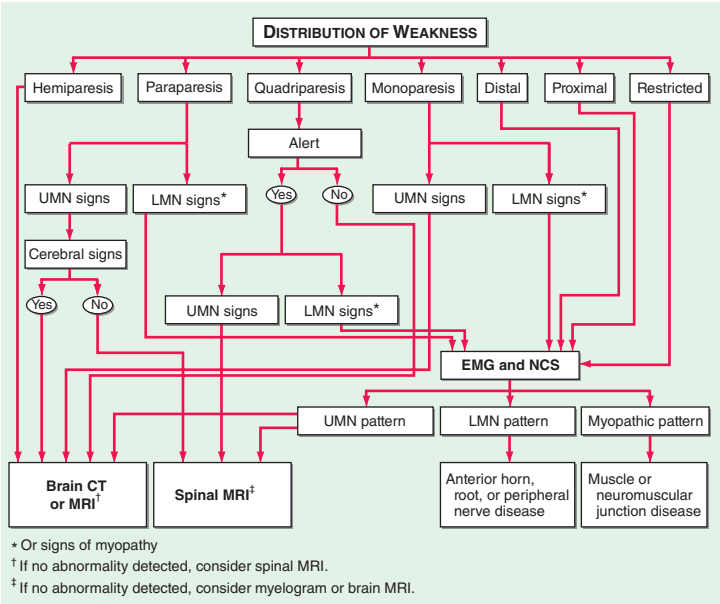


**FIGURE 53-1** An algorithm for the initial workup of a pt with weakness. EMG, electromyography; LMN, lower motor neuron; NCS, nerve conduction studies; UMN, upper motor neuron.

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For a more detailed discussion, see Aminoff MJ: Neurologic Causes of Weakness and Paralysis, Chap. 30, p. 154, in HPIM-19.

# 54 Tremor and Movement Disorders

## APPROACH TO THE PATIENT: Movement Disorders

Divided into akinetic rigid forms, with muscle rigidity and slowness of movement, and hyperkinetic forms, with involuntary movements. In both types, preservation of strength is the rule. Most movement disorders arise from disruption of basal ganglia circuits; common causes are degenerative diseases (hereditary and idiopathic), drug induced, organ system failure, CNS infection, and ischemia. Clinical features of the various movement disorders are summarized below.

### BRADYKINESIA

Inability to initiate changes in activity or perform ordinary volitional movements rapidly and easily. There is a slowness of movement and a paucity of automatic motions such as eye blinking and arm swinging while walking. Usually due to Parkinson's disease or other causes of parkinsonism (Chap. 182).

### TREMOR

Rhythmic oscillation of a part of the body due to intermittent muscle contractions, usually involving the distal limbs and less commonly the head, tongue, or jaw. A coarse tremor at rest, 4–5 beats/s, is usually due to Parkinson's disease. A fine postural tremor of 8–10 beats/s may be an exaggeration of normal physiologic tremor or indicate familial essential tremor (ET). An intention tremor, most pronounced during voluntary movement toward a target, is found with cerebellar pathway disease.

### ESSENTIAL TREMOR (ET)

This is the most common movement disorder. The tremor of ET must be distinguished from early Parkinson's disease (Table 54-1). The pathophysiology of ET is unknown. Approximately 50% of cases have a positive family history with autosomal dominant inheritance; linkage studies have implicated several loci, and recently a mutation in the fused in sarcoma (*FUS*) gene, previously implicated in familial ALS, was identified in one ET family. The oligodendrocyte gene *LINGO1* has been suggested in association studies, especially in early onset familial cases. Many pts with ET have mild symptoms and require no treatment.

- When activities of daily living such as eating and writing are impaired, therapy with propranolol (20–120 mg/d) or primidone (12.5–750 mg/d) leads to benefit in 50% of pts.
- Surgical therapies targeting the thalamus may be effective in refractory cases.

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**TABLE 54-1 ADVANCED EXAMINATION PEARLS: DIFFERENTIATING ESSENTIAL TREMOR FROM PARKINSONIAN TREMOR**

| | Essential Tremor | Parkinsonian Tremor |
|---|---|---|
| Speed | 5–10 Hz | 4–6 Hz |
| Symmetry | Bilateral | Usually asymmetric |
| Most common component | Postural | Rest |
| Other parkinsonian symptoms | Absent | Present |
| Helped with alcohol | Usually | Rarely |
| Family history | Present often | Usually absent |

## DYSTONIA

Consists of sustained or repetitive involuntary muscle contractions, frequently causing twisting movements and abnormal posture. May be generalized or focal; >300,000 cases in the United States.

Focal dystonias are common and include blepharospasm of the eyelids; spasmodic dysphonia involving the vocal cords; oromandibular dystonia of the face, lips, tongue, and jaw; cervical dystonia of the neck musculature (torticollis); and limb dystonias that are often task specific such as writer's cramp, playing a musical instrument (musician's cramp), or putting in golf (yips).

More than 16 causative genes have been identified. Idiopathic torsional dystonia is a predominantly childhood-onset form of generalized dystonia with an autosomal dominant pattern of inheritance that mainly affects Ashkenazi Jewish families; most are linked to a mutation in the *DYT1* gene on chromosome 9. Other generalized dystonias occur as a consequence of drugs such as antiemetics, neuroleptics, and treatments for Parkinson's disease.

- Therapy for focal dystonias usually involves botulinum toxin injections into the affected musculature.
- All forms of dystonia may respond to anticholinergic medications (e.g., trihexyphenidyl 20–120 mg/d), baclofen (20–120 mg/d), or tetrabenazine (initial dose 12.5 mg/d, usual maintenance 25–75 mg/d).
- Surgical therapies, including deep brain stimulation (DBS), may be effective in refractory cases.

## CHOREOATHETOSIS

A combination of chorea (rapid, graceful, dance-like movements) and athetosis (slow, distal, writhing movements). The two usually exist together, though one may be more prominent. Choreic movements predominate in rheumatic (Sydenham's) chorea and Huntington's disease (HD). Systemic lupus erythematosus is the most common systemic disorder that causes chorea, but it can also be seen with hyperthyroidism, various autoimmune disorders, infections including HIV, metabolic alterations, and with a variety of medications. Hemiballismus is a violent form of chorea that comprises wild, flinging movements on one side of the body; the most common cause is a lesion (often infarct or hemorrhage) of the subthalamic nucleus. Athetosis is prominent in some forms of cerebral palsy. Chronic neuroleptic use may lead to tardive dyskinesia, in which choreoathetotic movements are usually restricted to the buccal, lingual, and mandibular areas.

## HUNTINGTON'S DISEASE (HD)

A progressive, fatal, autosomal dominant disorder characterized by motor, behavioral, and cognitive dysfunction. Onset is typically between 25 and 45 years. Rapid, nonpatterned, semipurposeful, involuntary choreiform movements are the hallmark

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feature; dysarthria, gait disturbance, and oculomotor abnormalities also occur. In late stages, chorea becomes less prominent, and the picture is dominated by dystonia, rigidity, bradykinesia, myoclonus, and spasticity. Eventually, behavioral and cognitive disturbances can be a major source of disability. HD is caused by an expansion in the number of polyglutamine (cytosine-adenine-guanine [CAG]) repeats in coding sequence of the *HTT* gene encoding the protein huntingtin.

- Treatment involves a multidisciplinary approach with medical, neuropsychiatric, social, and genetic counseling for pts and families.
- Dopamine-blocking agents may control the chorea; tetrabenazine may also treat chorea but can cause secondary parkinsonism.
- Depression and anxiety should be treated with appropriate antidepressant and antianxiety drugs.
- Psychosis can be treated with atypical neuroleptic agents.
- No disease-modifying agents currently exist.

## TICS

Brief, rapid, recurrent, and seemingly purposeless stereotyped muscle contractions. Gilles de la Tourette syndrome (TS) is a neurobehavioral, multiple tic disorder that may involve motor tics (especially twitches of the face, neck, and shoulders) and phonic tics (grunts, words, coprolalia, echolalia). Pts may experience an irresistible urge to express tics but characteristically can voluntarily suppress them for short periods of time. Onset is usually between 2 and 15 years of age, and tics often lessen or even disappear in adulthood.

- Drug treatment is only indicated when tics are disabling and interfere with quality of life.
- Therapy is generally initiated with clonidine, starting at low dose, or guanfacine (0.5–2 mg/d). If these agents are not effective, neuroleptics may be used.

## MYOCLONUS

Rapid (<100 ms), brief, shock-like, jerky, movements, usually multifocal. Like asterixis, often occurs in a diffuse encephalopathy. Following cardiac arrest, diffuse cerebral hypoxia may produce multifocal myoclonus. Spinal cord injury can also cause myoclonus. Myoclonus occurs in normal individuals when waking up or falling asleep.

- Treatment, indicated only when function is impaired, consists of treating the underlying condition or removing an offending agent.
- Drug therapies include valproic acid (800–3000 mg/d), piracetam (8–20 g/d), clonazepam (2–15 mg/d), levetiracetam (1000–3000 mg/d), or primidone (500–1000 mg/d).

## ASTERIXIS

Brief, arrhythmic interruptions of sustained voluntary muscle contraction, usually observed as a brief lapse of posture of wrists in dorsiflexion with arms outstretched, "negative myoclonus." This "liver flap" may be seen in any encephalopathy related to drug intoxication, organ system failure, or CNS infection. Therapy is correction of the underlying disorder.

For a more detailed discussion, see Olanow CW, Schapira AHV, Obeso JA: Parkinson's Disease and Other Movement Disorders, Chap. 449, p. 2609, in HPIM-19.

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# 55 Aphasia

Aphasias are disturbances in the comprehension or production of spoken or written language. Clinical examination should assess spontaneous speech (fluency), comprehension, repetition, naming, reading, and writing. A classification scheme is presented in Table 55-1. In nearly all right-handed individuals and many left-handed pts, language localization is in the left hemisphere.

## CLINICAL FEATURES

### Wernicke's Aphasia

Although speech sounds grammatical, melodic, and effortless (fluent), it is virtually incomprehensible due to errors in word usage, structure, and tense and the presence of paraphasic errors and neologisms ("jargon"). Comprehension of written and spoken material is severely impaired, as are reading, writing, and repetition. The pt usually seems unaware of the deficit and is not frustrated. Associated symptoms can include parietal lobe sensory deficits and homonymous hemianopia. Motor disturbances are rare.

Lesion is located in posterior perisylvian region. Most common cause is embolism to the inferior division of dominant middle cerebral artery (MCA); less commonly intracerebral hemorrhage, severe head trauma, or tumor is responsible.

**TABLE 55-1 CLINICAL FEATURES OF APHASIAS AND RELATED CONDITIONS COMMONLY SEEN IN CEREBROVASCULAR ACCIDENTS**

| | Comprehension | Repetition of Spoken Language | Naming | Fluency |
|---|---|---|---|---|
| Wernicke's | Impaired | Impaired | Impaired | Preserved or increased |
| Broca's | Preserved (except grammar) | Impaired | Impaired | Decreased |
| Global | Impaired | Impaired | Impaired | Decreased |
| Conduction | Preserved | Impaired | Impaired | Preserved |
| Nonfluent (anterior) transcortical | Preserved | Preserved | Impaired | Impaired |
| Fluent (posterior) transcortical | Impaired | Preserved | Impaired | Preserved |
| Isolation | Impaired | Echolalia | Impaired | No purposeful speech |
| Anomic | Preserved | Preserved | Impaired | Preserved except for word-finding pauses |
| Pure word deafness | Impaired only for spoken language | Impaired | Preserved | Preserved |
| Pure alexia | Impaired only for reading | Preserved | Preserved | Preserved |

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## Broca's Aphasia

Speech output is sparse (nonfluent), slow, labored, interrupted by many word-finding pauses, and usually dysarthric; output may be reduced to a grunt or single word. Naming and repetition also impaired. Most pts have severe writing impairment. Comprehension of written and spoken language is relatively preserved. The pt is often aware of and visibly frustrated by deficit. With large lesions, a dense hemiparesis may occur, and eyes may deviate toward side of lesion. More commonly, lesser degrees of contralateral face and arm weakness are present. Sensory loss is rarely found, and visual fields are intact.

Lesion involves dominant inferior frontal gyrus (Broca's area), although cortical and subcortical areas along superior sylvian fissure and insula are often involved. Commonly caused by vascular lesions involving the superior division of the MCA; less commonly due to tumor, intracerebral hemorrhage, or abscess.

## Global Aphasia

All aspects of speech and language are impaired. Pt cannot read, write, or repeat and has poor auditory comprehension. Speech output is minimal and nonfluent. Hemiplegia, hemisensory loss, and homonymous hemianopia are usually present. Syndrome represents the combined dysfunction of Wernicke's and Broca's areas, usually resulting from proximal occlusion of MCA supplying dominant hemisphere (less commonly hemorrhage, trauma, or tumor).

## Conduction Aphasia

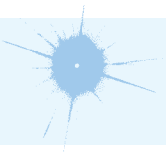
Speech output is fluent but paraphasic, comprehension of spoken language is intact, and repetition is severely impaired, as are naming and writing. Lesion spares, but functionally disconnects, Wernicke's and Broca's areas. Most cases are embolic, involving supramarginal gyrus of dominant parietal lobe, dominant superior temporal lobe, or arcuate fasciculus.

### LABORATORY EVALUATION

CT scan or MRI usually identifies the location and nature of the causative lesion.

### TREATMENT APHASIA

- Speech therapy may be helpful in treatment of certain types of aphasia; more effective in Broca's aphasia than in Wernicke's.
- When the lesion is caused by a stroke, recovery of language function generally peaks within 2–6 months, after which time further progress is limited.



For a more detailed discussion, see Mesulam M-M: Aphasia, Memory Loss, and Other Focal Cerebral Disorders, Chap. 36, p. 176 in HPIM-19.

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# 56 Sleep Disorders

Disorders of sleep are among the most common problems seen by clinicians. More than one-half of adults experience at least intermittent sleep disturbances, and 50–70 million Americans suffer from a chronic sleep disturbance which can adversely affect daytime functioning as well as physical and mental health.

## APPROACH TO THE PATIENT: Sleep Disorders

Pts may complain of (1) difficulty in initiating and maintaining sleep at night (insomnia); (2) excessive daytime sleepiness or tiredness; (3) unusual behaviors during sleep (parasomnias); or (4) circadian rhythm disorders associated with jet lag, shift work, and delayed sleep phase syndrome. Careful history of sleep habits and reports from the sleep partner (e.g., heavy snoring, falling asleep while driving) are a cornerstone of diagnosis. Pts with excessive sleepiness should be advised to avoid driving until effective therapy achieved. Completion of a day-by-day sleep-work-drug log for 1–2 weeks is often helpful. Work and sleep times (including daytime naps and nocturnal awakenings) as well as drug and alcohol use, including caffeine and hypnotics, should be noted each day. The physical examination may show a small airway, large tonsils, or a neurologic or medical disorder that contributes to the complaint. Objective sleep laboratory recording is necessary to evaluate specific disorders such as sleep apnea, periodic limb movements, and narcolepsy.

## INSOMNIA

Insomnia is the complaint of poor sleep and usually presents as difficulty initiating or maintaining sleep. People with insomnia are dissatisfied with their sleep and feel it impairs their ability to function well. Affected individuals often experience fatigue, decreased mood, irritability, malaise, and cognitive impairment. *Chronic insomnia*, lasting >3 months, occurs in about 10% of adults. *Acute or short-term insomnia* affects over 30% of adults and is often precipitated by stressful life events. Most insomnia begins in adulthood, but many patients may be predisposed and report easily disturbed sleep predating the insomnia, suggesting that their sleep is lighter than usual.

All insomnias can be exacerbated and perpetuated by behaviors that are not conducive to initiating or maintaining sleep. *Inadequate sleep hygiene* is characterized by a behavior pattern prior to sleep, and/or a bedroom environment, that is not conducive to sleep. In preference to hypnotic medications, the pt should attempt to avoid stressful activities before bed, reserve the bedroom environment for sleeping, and maintain regular rising times.

### Psychophysiologic Insomnia

These pts are preoccupied with a perceived inability to sleep adequately at night. Rigorous attention should be paid to sleep hygiene and correction of counterproductive, arousing behaviors before bedtime. Behavioral therapies are the treatment of choice.

### Drugs and Medications

Caffeine is the most common pharmacologic cause of insomnia although a wide range of psychoactive drugs can interfere with sleep, including alcohol and nicotine.

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Numerous medications, including antidepressants, stimulants, and glucocorticoids, can produce insomnia. Severe rebound insomnia can result from the acute withdrawal of hypnotics, especially following the use of short-acting benzodiazepines.

## Movement Disorders

Pts with *restless legs syndrome* (RLS) complain of creeping dysesthesias deep within the calves or feet associated with an irresistible urge to move the affected limbs; symptoms are typically worse at night. Iron deficiency and renal failure can cause secondary RLS. One-third of pts have multiple affected family members. Treatment is with dopaminergic drugs (pramipexole 0.25–0.5 mg daily at 7 PM or ropinirole 0.5–4.0 mg daily at 7 PM). *Periodic limb movements of sleep* (PLMS) consist of stereotyped extensions of the great toe and dorsiflexion of the foot recurring every 20–40 s during non-REM sleep. Treatment options include dopaminergic medications.

## Other Neurologic Disorders

A variety of neurologic disorders produce sleep disruption through both indirect, nonspecific mechanisms (e.g., neck or back pain) or by impairment of central neural structures involved in the generation and control of sleep itself. Common disorders to consider include *dementia* from any cause, *epilepsy*, *Parkinson's disease*, and *migraine*.

## Psychiatric Disorders

Approximately 80% of pts with mental disorders complain of impaired sleep. The underlying diagnosis may be depression, mania, an anxiety disorder, or schizophrenia.

## Medical Disorders

In *asthma*, daily variation in airway resistance results in marked increases in asthmatic symptoms at night, especially during sleep. Treatment of asthma with theophylline-based compounds, adrenergic agonists, or glucocorticoids can independently disrupt sleep. Inhaled glucocorticoids that do not disrupt sleep may provide a useful alternative to oral drugs. *Chronic obstructive pulmonary disease*, pain from rheumatologic disorders or neuropathy, *cystic fibrosis*, *hyperthyroidism*, *menopause*, and *gastroesophageal reflux* are other causes.

## TREATMENT INSOMNIA

Primary insomnia is a diagnosis of exclusion.

- Treatment of a medical or psychiatric disease that may be contributing should be addressed first.
- Attention should be paid to improving sleep hygiene and avoiding counterproductive behaviors before bedtime (Table 56-1).
- Cognitive behavioral therapy emphasizes understanding the nature of normal sleep, the circadian rhythm, the use of light therapy, and visual imagery to block unwanted thought intrusions.
- Pharmacotherapy reserved for instances when insomnia persists after treatment of contributing factors. Antihistamines are the primary active ingredient in most over-the-counter sleep aids. Benzodiazepine receptor agonists are effective and well tolerated; options include zaleplon (5–20 mg), zolpidem (5–10 mg), triazolam (0.125–0.25 mg), eszopiclone (1–3 mg), and temazepam (15–30 mg). Heterocyclic antidepressants such as trazodone (25–100 mg) are often used due to their lack of abuse potential and lower cost. Limit use to a short period of time for acute insomnia or intermittent use for chronic insomnia.

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**TABLE 56-1 METHODS TO IMPROVE SLEEP HYGIENE IN INSOMNIA PATIENTS**

| Helpful Behaviors | Behaviors to Avoid |
|---|---|
| Use the bed only for sleep and sex<br>• If you cannot sleep within 20 min, get out of bed and read or do other relaxing activities in dim light before returning to bed | Avoid behaviors that interfere with sleep physiology, including:<br>• Napping, especially after 3:00 PM<br>• Attempting to sleep too early<br>• Caffeine after lunchtime |
| Make quality sleep a priority<br>• Go to bed and get up at the same time each day<br>• Ensure a restful environment (comfortable bed, bedroom quiet and dark) | In the 2–3 h before bedtime, avoid:<br>• Heavy eating<br>• Smoking or alcohol<br>• Vigorous exercise |
| Develop a consistent bedtime routine. For example:<br>• Prepare for sleep with 20–30 min of relaxation (e.g., soft music, meditation, yoga, pleasant reading)<br>• Take a warm bath | When trying to fall asleep, avoid:<br>• Solving problems<br>• Thinking about life issues<br>• Reviewing events of the day |

## DISORDERS OF EXCESSIVE DAYTIME SLEEPINESS

Differentiation of sleepiness from subjective complaints of fatigue may be difficult. Quantification of daytime sleepiness can be performed in a sleep laboratory using a multiple sleep latency test (MSLT), the repeated daytime measurement of sleep latency under standardized conditions. An approach to the evaluation is summarized in Table 56-2.

### Sleep Apnea Syndromes

Respiratory dysfunction during sleep is a common cause of excessive daytime sleepiness and/or disturbed nocturnal sleep, affecting an estimated 24% of middle-aged men and 9% of middle-aged women. Episodes may be due to occlusion of the airway (*obstructive sleep apnea*), absence of respiratory effort (*central sleep apnea*), or a combination of these factors (*mixed sleep apnea*). Obstruction is exacerbated by obesity, supine posture, sedatives (especially alcohol), nasal obstruction, and hypothyroidism. Sleep apnea is particularly prevalent in overweight men and in the elderly and is undiagnosed in most affected individuals. Treatment consists of correction of the above factors, positive airway pressure devices, oral appliances, and sometimes surgery (Chap. 137).

### Narcolepsy

A disorder of excessive daytime sleepiness and intrusion of REM-related sleep phenomena into wakefulness (cataplexy, hypnagogic hallucinations, and sleep paralysis). *Cataplexy*, the abrupt loss of muscle tone in arms, legs, or face, is precipitated by emotional stimuli such as laughter or sadness. Symptoms of narcolepsy typically begin in the second decade. The prevalence is 1 in 2000. Narcolepsy has a genetic basis; almost all narcoleptics with cataplexy are positive for HLA DQB1*0602. Hypothalamic neurons containing the neuropeptide hypocretin (orexin) regulate the sleep/wake cycle and loss of these cells, possibly due to autoimmunity, has been implicated in narcolepsy. Diagnosis is made with sleep studies confirming a short daytime sleep latency and a rapid transition to REM sleep.

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**TABLE 56-2 EVALUATION OF THE PATIENT WITH EXCESSIVE DAYTIME SLEEPINESS**

| Findings on History and Physical Examination | Diagnostic Evaluation | Diagnosis | Therapy |
|---|---|---|---|
| Difficulty waking in the morning, rebound sleep on weekends, and vacations with improvement in sleepiness | Sleep log | Insufficient sleep | Sleep education and behavioral modification to increase amount of sleep |
| Obesity, snoring, hypertension | Polysomnogram | Obstructive sleep apnea (Chap. 137) | Continuous positive airway pressure; upper airway surgery (e.g., uvulopalatopharyngoplasty); dental appliance; weight loss |
| Cataplexy, hypnogogic hallucinations, sleep paralysis | Polysomnogram and multiple sleep latency test | Narcolepsy | Stimulants (e.g., modafinil, methylphenidate); REM sleep-suppressing antidepressants (e.g., venlafaxine); sodium oxybate |
| Restless legs, kicking movements during sleep | Assessment for predisposing medical conditions (e.g., iron deficiency or renal failure) | Restless legs syndrome with or without periodic limb movements | Treatment of predisposing condition if possible; dopamine agonists (e.g., pramipexole, ropinirole) |
| Sedating medications, stimulant withdrawal, head trauma, systemic inflammation, Parkinson's disease, and other neurodegenerative disorders, hypothyroidism, encephalopathy | Thorough medical history and examination including detailed neurologic examination | Sleepiness due to a drug or medical condition | Change medications, treat underlying condition, consider stimulants |

## TREATMENT NARCOLEPSY

- Somnolence is treated with modafinil (200–400 mg/d given as a single dose each morning).
- Older stimulants such as methylphenidate (10–20 mg bid) or dextroamphetamine (10 mg bid) are alternatives, particularly in refractory pts.
- Cataplexy, hypnagogic hallucinations, and sleep paralysis respond to the tricyclic antidepressants protriptyline (10–40 mg/d) and clomipramine (25–50 mg/d)

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and to fluoxetine (10–20 mg each morning) and venlafaxine (37.5–150 mg each morning). Alternatively, sodium oxybate given at bedtime, and 3–4 h later, is effective in reducing daytime cataplectic episodes.

- Adequate nocturnal sleep time and the use of short naps are other useful preventative measures.

## CIRCADIAN RHYTHM SLEEP DISORDERS

Insomnia or hypersomnia may occur in disorders of sleep timing rather than sleep generation. Such conditions may be (1) organic—due to a defect in the circadian pacemaker or its input from entraining stimuli, or (2) environmental—due to a disruption of exposure to entraining stimuli (light/dark cycle). Examples of the latter include jet-lag disorder and shift work. Shift work sleepiness can be treated with modafinil (200 mg) or armodafinil (150 mg) taken 30–60 min before the start of each night shift as well as properly timed exposure to bright light. Safety programs should promote education about sleep and increase awareness of hazards associated with night work.

*Delayed sleep-wake phase syndrome* is characterized by late sleep onset and awakening with otherwise normal sleep architecture. Bright-light phototherapy in the morning hours or melatonin therapy during the evening hours may be effective.

*Advanced sleep-wake phase syndrome* moves sleep onset to the early evening hours with early morning awakening. These pts may benefit from bright-light phototherapy during the evening hours. Some autosomal dominant cases result from mutations in a gene (*PER2*) involved in regulation of the circadian clock.

For a more detailed discussion, see Czeisler CA, Scammell TE, Saper CB: Sleep Disorders, Chap. 38, p. 184, in HPIM-19.

# 57 Dysuria and Bladder Pain

## DYSURIA

*Dysuria*, or pain that occurs during urination, is commonly perceived as burning or stinging in the urethra and is a symptom of several syndromes that can be distinguished by the presence or absence of other symptoms.

### Epidemiology

Approximately 50% of women experience dysuria at some time in their lives; ~20% report having had dysuria within the past year. Dysuria is less common among men.

### Clinical manifestations

The underlying syndromes that cause dysuria differ somewhat between men and women.

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- In women, most dysuria syndromes can be categorized as either bacterial cystitis or lower genital tract infections (e.g., vaginitis, urethritis, sexually transmitted infections [STIs]) (see Chaps. 83 and 144). The presence of urinary frequency, urinary urgency, suprapubic pain, and/or hematuria is more typical of bacterial cystitis than of STIs.
- In men, dysuria is often due to STIs or involvement of the prostate (e.g., acute or chronic bacterial prostatitis) (see Chaps. 83 and 144). In addition, dysuria and other symptoms of cystitis can occur in the setting of significant benign prostatic hyperplasia that leads to urinary stasis with an accompanying bacterial infection.
- In both sexes, dysuria can result from noninfectious disorders. Noninfectious causes of acute dysuria include lower urinary tract stones, trauma, and urethral exposure to topical chemicals. Chronic dysuria may be attributable to lower urinary tract cancers, certain medications, Behçet's syndrome, or interstitial cystitis/bladder pain syndrome (see Chap. 144).

## Diagnosis

Among women presenting with dysuria, the probability of bacterial cystitis is ~50%. This figure rises to >90% if four criteria are fulfilled: (1) dysuria and (2) frequency without either (3) vaginal discharge or (4) irritation.

- Healthy, nonpregnant women who meet the above criteria can be diagnosed with uncomplicated bacterial cystitis; other women with dysuria should be further evaluated by urine dipstick, urine culture, and a pelvic examination.
- Men should be evaluated with urinalysis, urine culture, and prostate examination.

## Treatment

Once the underlying cause of dysuria is identified, it should be treated appropriately, as outlined in other chapters.

### BLADDER PAIN

Pts perceive pain as coming from the urinary bladder if it is suprapubic in location, alters with bladder filling or emptying, and/or is associated with urinary symptoms such as urgency and frequency.

- Bladder pain occurring acutely (i.e., lasting ≤2 days) is helpful in distinguishing bacterial cystitis from lower genital tract infections.

Chronic or recurrent bladder pain may accompany lower urinary tract stones, pelvic cancers, urethral diverticulum, cystitis induced by radiation or certain medications, tuberculous cystitis, bladder neck obstruction, neurogenic bladder, urogenital prolapse, or benign prostatic hyperplasia. The diagnosis of interstitial cystitis/bladder pain syndrome should be considered in pts who do not have one of these conditions (see Chap. 144).

For a more detailed discussion, see Warren JW: Dysuria, Bladder Pain, and the Interstitial Cystitis/Bladder Pain Syndrome, Chap. 60e; and Gupta K, Trautner BW: Urinary Tract Infections, Pyelonephritis, and Prostatitis, Chap. 162, p. 861, in HPIM-19.

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# 58 Sore Throat, Earache, and Upper Respiratory Symptoms

- URIs are among the leading causes of lost time from work or school.
- Distinguishing pts with primary viral URI from those with primary bacterial URI is difficult since the signs and symptoms are the same.
- URIs are often treated with antibiotics even though bacteria cause only 25% of cases. Inappropriate prescribing of antibiotics for URIs is a leading cause of antibiotic resistance in common community-acquired pathogens such as *Streptococcus pneumoniae*.

## NONSPECIFIC URIs

- **Definition:** Nonspecific URIs (the "common cold") have no prominent localizing features.
- **Etiology:** A wide variety of viruses (e.g., rhinoviruses, coronaviruses, parainfluenza viruses, influenza viruses, adenoviruses) can cause nonspecific URIs.
- **Clinical manifestations:** an acute, mild, self-limited catarrhal syndrome, typically characterized by rhinorrhea, nasal congestion, cough, and sore throat
  - Hoarseness, malaise, sneezing, and fever are more variable.
  - The median duration of symptoms is ~1 week (range, 2–10 days).
  - Secondary bacterial infections complicate 0.5–2% of colds and are associated with a prolonged course and/or increased severity of illness, often with localization of signs and symptoms. Purulent nasal and throat secretions are poor predictors of bacterial infection.
- **Treatment:** Symptom-based treatment (e.g., with decongestants, NSAIDs) is typically all that is required. Antibiotics are not indicated.

## SINUS INFECTIONS

- Rhinosinusitis is an inflammatory condition most commonly involving the maxillary sinus; next, in order of frequency, are the ethmoid, frontal, and sphenoid sinuses.
- Sinusitis accounts for millions of visits to primary care physicians each year and is the fifth most common diagnosis for which antibiotics are prescribed.

### ACUTE SINUSITIS

- **Definition:** sinusitis of <4 weeks' duration
- **Etiology:** Infectious and noninfectious causes lead to sinus ostial obstruction and retention of mucus.
  - Infectious causes include viruses (e.g., rhinovirus, parainfluenza virus, influenza virus) and bacteria (e.g., *S. pneumoniae*, nontypable *Haemophilus influenzae*, and [in children] *Moraxella catarrhalis*).
    - In immunocompromised pts, fungi (e.g., *Rhizopus*, *Mucor*, and occasionally *Aspergillus*) can be involved.



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  - Nosocomial cases are often polymicrobial and involve *Staphylococcus aureus* and gram-negative bacilli.
  - Noninfectious causes include allergic rhinitis, barotrauma, and exposure to chemical irritants.
- **Clinical manifestations:** Common manifestations include nasal drainage and congestion, facial pain or pressure, and headache.
  - Tooth pain and halitosis can be associated with bacterial sinusitis.
  - Pain localizes to the involved sinus and is often worse when the pt bends over or is supine.
  - Advanced frontal sinusitis can present as "Pott's puffy tumor": swelling and pitting edema over the frontal bone from a communicating subperiosteal abscess.
  - Life-threatening complications include meningitis, epidural abscess, and brain abscess.
- **Diagnosis:** It is difficult to distinguish viral from bacterial sinusitis clinically, although viral cases greatly outnumber bacterial cases.
  - Only 40–50% of pts with symptoms of >10 days' duration, purulent nasal drainage, nasal obstruction, and facial pain have bacterial sinusitis.
  - If fungal sinusitis is a consideration, involved areas should be biopsied.
  - Except in nosocomial cases, sinus CT or radiography is not recommended for acute sinusitis. Nosocomial sinusitis should be confirmed by sinus CT, with sinus aspirates sent for culture and susceptibility testing (ideally before antimicrobial treatment is initiated).

## TREATMENT ACUTE SINUSITIS

- Most pts improve without antibiotic treatment.
- For pts with mild to moderate symptoms, treatment should focus on symptom relief and facilitation of sinus drainage (e.g., oral and topical decongestants, nasal saline lavage).
- Antibiotics should be given to pts with severe disease at presentation and considered for pts without improvement after 10 days.
  - See Table 58-1 for recommended regimens for adults.
  - For pts who do not respond to initial antimicrobial treatment, consultation with an otolaryngologist about possible sinus aspiration and/or lavage should be considered.
- Surgery should be considered for pts with severe disease, intracranial complications, or invasive fungal sinusitis.

## CHRONIC SINUSITIS

- **Definition:** sinusitis of >12 weeks' duration
- **Etiology:** commonly associated with bacterial or fungal infection
- **Chronic bacterial sinusitis:** Impaired mucociliary clearance leads to repeated infections as opposed to one persistent infection.
  - Pts have constant nasal congestion and sinus pressure, with periods of increased severity.
  - Sinus CT can define the extent of disease, detect an underlying anatomic defect or obstructing process, and assess response to treatment.
  - Endoscopy-derived tissue samples for histology and culture should be obtained to guide treatment.
  - Repeated antibiotic courses are required, often for 3–4 weeks at a time. Adjunctive measures include intranasal administration of glucocorticoids, sinus irrigation, and surgical evaluation.

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**TABLE 58-1 GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF ACUTE SINUSITIS IN ADULTS**

| Diagnostic Criteria | Treatment Recommendations[a] |
|---|---|
| Moderate symptoms (e.g., nasal purulence/congestion or cough) for >10 d *or*<br>Severe symptoms of any duration, including unilateral/focal facial swelling or tooth pain | *Initial therapy:*<br>Amoxicillin, 500 mg PO tid; *or*<br>Amoxicillin/clavulanate, 500/125 mg PO tid or 875/125 mg PO bid[b]<br>*Penicillin allergy:*<br>Doxycycline, 100 mg PO bid; *or*<br>Clindamycin, 300 mg PO tid<br>*Exposure to antibiotics within 30 d or >30% prevalence of penicillin-resistant Streptococcus pneumoniae:*<br>Amoxicillin/clavulanate (extended release), 2000/125 mg PO bid; *or*<br>An antipneumococcal fluoroquinolone (e.g., moxifloxacin, 400 mg PO daily)<br>*Recent treatment failure:*<br>Amoxicillin/clavulanate (extended release), 2000 mg PO bid; *or*<br>An antipneumococcal fluoroquinolone (e.g., moxifloxacin, 400 mg PO daily) |

[a]The duration of therapy is generally 7–10 days (with consideration of a 5-day course), with appropriate follow-up. Severe disease may warrant IV antibiotics and consideration of hospital admission.
[b]Although the evidence is not as strong, amoxicillin/clavulanate may be considered for initial use, particularly if local rates of penicillin resistance or β-lactamase production are high.

- **Chronic fungal sinusitis:** a noninvasive disease in immunocompetent hosts, typically due to *Aspergillus* and dematiaceous molds. Recurrence is common.
  - Mild, indolent disease is usually cured with endoscopic surgery and without antifungal agents.
  - Unilateral disease with a mycetoma (fungus ball) in the sinus is treated with surgery and—if bony erosion has occurred—antifungal agents.
  - Allergic fungal sinusitis, seen in pts with nasal polyps and asthma, presents as pansinusitis and thick, eosinophil-laden mucus with the consistency of peanut butter.

## INFECTIONS OF THE EAR AND MASTOID

### EXTERNAL EAR INFECTIONS

In the absence of local or regional adenopathy, consider noninfectious causes of inflammation, among which trauma, insect bites, and environmental exposures are more commonly implicated than are autoimmune diseases (e.g., lupus) or vasculitides (e.g., granulomatosis with polyangiitis).

- *Auricular cellulitis*: Tenderness, erythema, swelling, and warmth of the external ear, particularly the lobule, follow minor trauma. Treat with warm compresses and antibiotics active against *S. aureus* and streptococci (e.g., cephalexin, dicloxacillin).

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- *Perichondritis*: Infection of the perichondrium of the auricular cartilage follows local trauma (e.g., ear piercing). The infection may closely resemble auricular cellulitis, although the lobule is less often involved in perichondritis.
  - Treatment requires systemic antibiotics active against the most common etiologic agents, *Pseudomonas aeruginosa* and *S. aureus*, and typically consists of an antipseudomonal penicillin (e.g., piperacillin) or a penicillinase-resistant penicillin (e.g., nafcillin) plus an antipseudomonal quinolone (e.g., ciprofloxacin). Surgical drainage may be needed; resolution can take weeks.
  - If perichondritis fails to respond to adequate treatment, consider noninfectious inflammatory etiologies (e.g., relapsing polychondritis).
- *Otitis externa*: a collection of diseases involving primarily the auditory meatus and resulting from a combination of heat and retained moisture, with desquamation and maceration of the epithelium of the outer ear canal. All forms are predominantly bacterial in origin; *P. aeruginosa* and *S. aureus* are the most common pathogens.
  - *Acute localized otitis externa*: furunculosis in the outer third of the ear canal, usually due to *S. aureus*. Treatment consists of an oral antistaphylococcal penicillin (e.g., dicloxacillin, cephalexin), with surgical drainage in cases of abscess formation.
  - *Acute diffuse otitis externa* (swimmer's ear): infection in macerated, irritated canals that is typically due to *P. aeruginosa* and is characterized by severe pain, erythema, and swelling of the canal and white clumpy discharge from the ear. Treatment includes cleansing of the canal to remove debris and use of topical agents (e.g., hypertonic saline, mixtures of alcohol and acetic acid, antibiotic preparations combining neomycin and polymyxin), with or without glucocorticoids to reduce inflammation.
  - *Chronic otitis externa:* erythematous, scaling, pruritic dermatitis that usually arises from persistent drainage from a chronic middle-ear infection, other causes of repeated irritation, or rare chronic infections such as tuberculosis or leprosy. Treatment consists of identifying and eliminating the offending process; successful resolution is frequently difficult.
  - *Malignant or necrotizing otitis externa*: a slowly progressive infection characterized by purulent otorrhea, an erythematous swollen ear and external canal, and severe otalgia out of proportion to exam findings, with granulation tissue present in the posteroinferior wall of the canal, near the junction of bone and cartilage
    - This potentially life-threatening disease, which occurs primarily in elderly diabetic or immunocompromised pts, can involve the base of the skull, meninges, cranial nerves, and brain.
    - *P. aeruginosa* is the most common etiologic agent, but other gram-negative bacilli, *S. aureus*, *Staphylococcus epidermidis*, *Actinomyces,* and *Aspergillus* have been reported.
    - A biopsy specimen of granulation tissue (or deeper tissues) should be obtained for culture.
    - Treatment involves systemic antibiotics for 6–8 weeks and consists of antipseudomonal agents (e.g., piperacillin, ceftazidime) with an aminoglycoside or a fluoroquinolone; antibiotic drops active against *Pseudomonas*, combined with glucocorticoids, are used as adjunctive treatment.
    - Recurs in up to 20% of cases. Aggressive glycemic control in diabetic pts helps with treatment and prevention of recurrence.

## MIDDLE-EAR INFECTIONS

Eustachian tube dysfunction, often in association with URIs, causes inflammation with a sterile transudate. Viral or bacterial superinfection often occurs.

- ***Acute otitis media:*** typically follows a viral URI, which can directly cause viral otitis media or, more commonly, predispose to bacterial otitis media

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- **Etiology:** *S. pneumoniae* is isolated in up to 35% of cases; nontypable *H. influenzae* and *M. catarrhalis* are other common causes of bacterial otitis media. Concern is increasing about community-acquired methicillin-resistant *S. aureus* (MRSA) as an emerging etiologic agent. Viruses (e.g., RSV, influenza virus, rhinovirus, enterovirus) have been recovered either alone or with bacteria in up to 40% of cases.
- **Clinical manifestations:** The tympanic membrane is immobile, erythematous, bulging, or retracted and can perforate spontaneously.
  - Other findings may include otalgia, otorrhea, decreased hearing, and fever.
  - In isolation, erythema of the tympanic membrane is nonspecific as it is common in association with inflammation of the upper respiratory mucosa.
- **Treatment:** Indications for antibiotic treatment and regimens are listed in Table 58-2; antibiotic prophylaxis and surgical interventions offer little benefit in recurrent acute otitis media.

- ***Serous otitis media*:** Also known as otitis media with effusion, this condition can persist for weeks (e.g., acute effusions) or months (e.g., after an episode of acute otitis media) without signs of infection and is associated with significant hearing loss in the affected ear.
  - The majority of cases resolve spontaneously within 3 months without antibiotic treatment.
  - Antibiotic treatment or myringotomy with tympanostomy tubes is reserved for pts with bilateral effusions that have persisted for at least 3 months and are associated with significant bilateral hearing loss.
- ***Chronic otitis media*:** persistent or recurrent purulent otorrhea with tympanic membrane perforation, usually associated with conductive hearing loss
  - Inactive disease, characterized by a central perforation of the tympanic membrane, is treated with repeated courses of topical antibiotic drops during periods of drainage.
  - Active disease involves formation of a cholesteatoma that may enlarge and ultimately lead to erosion of bone, meningitis, and brain abscess; surgical treatment is required.
- ***Mastoiditis*:** accumulation of purulent exudate in the mastoid air cells that erodes surrounding bones and causes abscess-like cavities
  - Pts have pain, erythema, and mastoid process swelling causing displacement of the pinna along with the signs and symptoms of otitis media.
  - Rare complications include subperiosteal abscess, deep neck abscess, and septic thrombosis of the lateral sinus.
  - Broad-spectrum empirical IV antibiotic regimens targeting *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* can be narrowed once culture results are available; mastoidectomy is reserved for complicated cases or pts in whom medical management fails.

## INFECTIONS OF THE PHARYNX AND ORAL CAVITY

Sore throat is the most common presenting symptom and one of the most common reasons for ambulatory care visits by adults and children.

### ACUTE PHARYNGITIS

- **Etiology:** Respiratory viruses are the most common identifiable cause, although ~30% of cases have no etiology identified.
  - Viruses: Rhinoviruses and coronaviruses cause ~20% and ~5% of cases, respectively; influenza and parainfluenza viruses are seasonal causes; HSV, coxsackievirus, CMV, EBV, and HIV are other important viral causes.
  - Bacteria: Group A *Streptococcus* (GAS) accounts for 5–15% of adult cases. *Fusobacterium necrophorum*, which can cause Lemierre's disease, is increasingly identified as a cause of pharyngitis in adolescents and is isolated nearly as often as

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**TABLE 58-2 GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF ACUTE OTITIS MEDIA**

| Illness Severity | Diagnostic Criteria | Treatment Recommendations |
|---|---|---|
| Mild to moderate | >2 yrs *or* 6 mo to 2 yrs without middle-ear effusion | *Observation alone* (deferring antibiotic therapy for 48–72 h and limiting management to symptom relief) |
| | <6 mo; *or*<br>6 mo to 2 yrs with middle-ear effusion (fluid in the middle ear, evidenced by decreased TM mobility, air/fluid level behind TM, bulging TM, purulent otorrhea) *and* acute onset of signs and symptoms of middle-ear inflammation, including fever, otalgia, decreased hearing, tinnitus, vertigo, erythematous TM; *or*<br>>2 yrs with bilateral disease, TM perforation, high fever, immunocompromise, emesis | *Initial therapy*[a]<br>Amoxicillin, 80–90 mg/kg qd (up to 2 g) PO in divided doses (bid or tid); *or*<br>Cefdinir, 14 mg/kg qd PO in 1 dose or divided doses (bid); *or*<br>Cefuroxime, 30 mg/kg qd PO in divided doses (bid); *or*<br>Azithromycin, 10 mg/kg qd PO on day 1 followed by 5 mg/kg qd PO for 4 d<br>*Exposure to antibiotics within 30 d or recent treatment failure*[a,b]*:*<br>Amoxicillin, 90 mg/kg qd (up to 2 g) PO in divided doses (bid), plus clavulanate, 6.4 mg/kg qd PO in divided doses (bid); *or*<br>Ceftriaxone, 50 mg/kg IV/IM qd for 3 d; *or*<br>Clindamycin, 30–40 mg/kg qd PO in divided doses (tid) |
| Severe | As above, with temperature ≥39.0°C (102°F); *or*<br>Moderate to severe otalgia | *Initial therapy*[a]<br>Amoxicillin, 90 mg/kg qd (up to 2 g) PO in divided doses (bid), plus clavulanate, 6.4 mg/kg qd PO in divided doses (bid); *or*<br>Ceftriaxone, 50 mg/kg IV/IM qd for 3 d<br>*Exposure to antibiotics within 30 d or recent treatment failure*[a,b]<br>Ceftriaxone, 50 mg/kg IV/IM qd for 3 d; *or*<br>Clindamycin, 30–40 mg/kg qd PO in divided doses (tid); *or*<br>Consider tympanocentesis with culture |

[a]Duration (unless otherwise specified): 10 days for pts <6 years old and pts with severe disease; 5–7 days (with consideration of observation only in previously healthy individuals with mild disease) for pts ≥6 years old.
[b]Failure to improve and/or clinical worsening after 48–72 h of observation or treatment.
***Abbreviation:*** TM, tympanic membrane.
***Source:*** American Academy of Pediatrics Subcommittee on Management of Acute Otitis Media, 2004.

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GAS. Rare bacterial causes that should be considered in appropriate exposure groups include *Neisseria gonorrhoeae*, *Corynebacterium diphtheriae*, *Yersinia enterocolitica*, and *Treponema pallidum*.

- **Clinical manifestations:** Specific signs and symptoms sometimes suggest that one etiology is more likely than another.
  - Respiratory viruses: Symptoms usually are not severe and are associated with coryza without fever, tender cervical lymphadenopathy, or pharyngeal exudates.
  - Influenza virus and adenovirus: evidenced by severe exudative pharyngitis with fever, myalgias, and—for adenovirus—conjunctivitis
  - HSV: presents as pharyngeal inflammation and exudates with vesicles and ulcers on the palate
  - Coxsackievirus (herpangina): characterized by small vesicles on the soft palate and uvula that rupture to form shallow white ulcers
  - EBV and CMV: present as exudative pharyngitis in association with other signs of infectious mononucleosis
  - HIV: associated with fever, acute pharyngitis, myalgias, malaise, and sometimes a maculopapular rash
  - Streptococci: Presentation ranges from mild disease to profound pharyngeal pain, fever, chills, abdominal pain, and a hyperemic pharyngeal membrane with tonsillar hypertrophy and exudates; coryzal symptoms are absent.
  - Other bacteria: often present as exudative pharyngitis without other specific findings
- **Diagnosis:** The primary goal of diagnostic testing is to identify cases of GAS pharyngitis.
  - Rapid antigen-detection tests for GAS offer good specificity (>90%) but variable sensitivity (65–90%); throat cultures are recommended for children, but not adults, in the setting of negative rapid testing.
  - Samples for specific cultures for other bacterial and viral causes should be obtained if these diagnoses are suspected.
  - If HIV is being considered, testing for HIV RNA should be performed.
- **Treatment:** Antibiotic treatment for GAS infection (penicillin VK, 500 mg PO tid × 10 days; or benzathine penicillin G, 1.2 million units IM × 1 dose) is recommended for pts with a positive rapid antigen detection test or throat swab culture; treatment modestly reduces symptom duration and prevents the development of rheumatic fever.
  - Long-term penicillin prophylaxis (benzathine penicillin G, 1.2 million units IM every 3–4 weeks; or penicillin VK, 250 mg PO bid) is indicated for pts at risk of recurrent rheumatic fever.
  - Symptom-based treatment of viral pharyngitis is generally sufficient.
  - Specific antiviral treatment (e.g., oseltamivir, acyclovir) may be helpful in selected cases of influenza and HSV infection.

### ORAL INFECTIONS

Oral-labial herpesvirus infections and oropharyngeal candidiasis are discussed in Chaps. 99 and 106, respectively.

## INFECTIONS OF THE LARYNX AND EPIGLOTTIS

- *Laryngitis*: Acute laryngitis is a common syndrome caused by nearly all the major respiratory viruses and by some bacteria (e.g., GAS, *C. diphtheriae*, and *M. catarrhalis*). Chronic cases of infectious laryngitis are much less common in developed countries than in low-income countries and are caused by *Mycobacterium tuberculosis*, endemic fungi (e.g., *Histoplasma*, *Blastomyces*, *Coccidioides*), and *Cryptococcus*.
  - Pts are hoarse, exhibit reduced vocal pitch or aphonia, and have coryzal symptoms.

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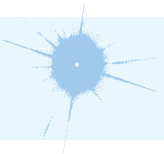
  - Treatment of acute laryngitis consists of humidification, voice rest, and—if GAS is cultured—antibiotic administration. Treatment of chronic laryngitis depends on the pathogen, whose identification usually requires biopsy with culture.
- *Epiglottitis*: acute, rapidly progressive cellulitis of the epiglottis and adjacent structures that can result in complete—and sometimes fatal—airway obstruction
  - Epiglottitis is caused by GAS, *S. pneumoniae*, *Haemophilus parainfluenzae*, and *S. aureus*; pediatric cases due to *H. influenzae* type b are now rare because of vaccination.
  - Symptoms include fever, severe sore throat, and systemic toxicity, and pts often drool while sitting forward. Examination may reveal respiratory distress, inspiratory stridor, and chest wall retractions.
  - Direct visualization in the examination room (i.e., with a tongue blade) should not be performed, given the risk of complete airway obstruction. Direct fiberoptic laryngoscopy in a controlled environment (e.g., an operating room) may be performed for diagnosis, procurement of specimens for culture, and placement of an endotracheal tube.
  - Treatment focuses on airway protection. After blood and epiglottis samples are obtained for cultures, IV antibiotics active against *H. influenzae* (e.g., ampicillin/sulbactam or a second- or third-generation cephalosporin) should be given for 7–10 days.

## INFECTIONS OF DEEP NECK STRUCTURES

These infections, which include Ludwig's angina, Lemierre's syndrome, and retropharyngeal abscess, are discussed in Chap. 92.



For a more detailed discussion, see Rubin MA, Ford LC, Gonzales R: Sore Throat, Earache, and Upper Respiratory Symptoms, Chap. 44, p. 225, in HPIM-19.

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# 59 General Examination of the Skin

As dermatologic evaluation relies heavily on the objective cutaneous appearance, physical examination is often performed prior to taking a complete history in pts presenting with a skin problem. A differential diagnosis can usually be generated on the basis of a thorough examination with precise descriptions of the skin lesion(s) and narrowed with pertinent facts from the history. Laboratory or diagnostic procedures are then used, when appropriate, to clarify the diagnosis.

## PHYSICAL EXAMINATION

Examination of skin should take place in a well-illuminated room with pt completely disrobed. Helpful ancillary equipment includes a hand lens and a pocket flashlight to provide peripheral illumination of lesions. An ideal examination includes evaluation of the skin, hair, nails, and mucous membranes. The examination often begins with an assessment of the entire skin viewed at a distance, which is then narrowed down to focus on the individual lesions.

### DISTRIBUTION

As illustrated in Fig. 59-1, the distribution of skin lesions can provide valuable clues to the identification of the disorder: generalized (systemic diseases); sun-exposed (SLE, photoallergic, phototoxic, polymorphous light eruption, porphyria cutanea tarda); dermatomal (herpes zoster); extensor surfaces (elbows and knees in psoriasis); flexural surfaces (antecubital and popliteal fossae in atopic dermatitis).

### ARRANGEMENT AND SHAPE

Can describe individual or multiple lesions: *Linear* (contact dermatitis such as poison ivy); *annular*—"ring-shaped" lesion (erythema chronicum migrans, erythema annulare centrificum, tinea corporis); *iris* or *target lesion*—two or three concentric circles of differing hue (erythema multiforme); *nummular*—"coin-shaped" (nummular eczema); *morbilliform*—"measles-like" with small confluent papules coalescing into unusual shapes (measles, drug eruption); *herpetiform*—grouped vesicles, papules, or erosions (herpes simplex).

### PRIMARY LESIONS

Cutaneous changes caused directly by disease process (Table 59-1).

### SECONDARY LESIONS

Changes in area of primary pathology often due to secondary events, e.g., scratching, secondary infection, bleeding (Table 59-2).

### OTHER DESCRIPTIVE TERMS

Color, e.g., violaceous, erythematous; physical characteristics, e.g., warm, tender; sharpness of edge, surface contour—flat-topped, pedunculated (on a stalk), verrucous (wartlike), umbilicated (containing a central depression).



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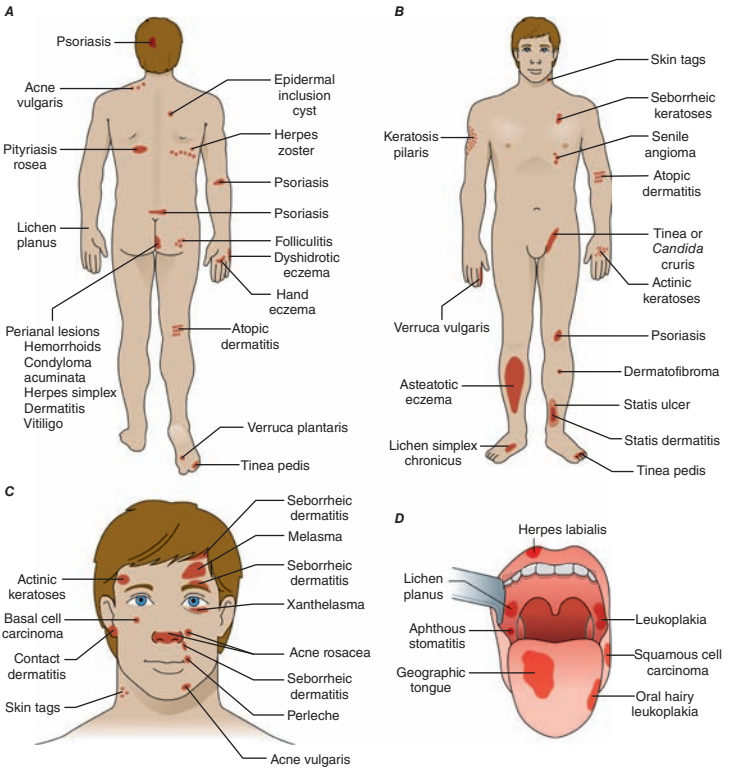


**FIGURE 59-1** The distribution of some common dermatologic diseases and lesions.

## HISTORY

A complete history should be obtained, with special attention being paid to the following points:

1. Evolution of the lesion—site of onset, manner in which eruption progressed or spread, duration, periods of resolution or improvement in chronic eruptions
2. Symptoms associated with the eruption—itching, burning, pain, numbness; what has relieved symptoms; time of day when symptoms are most severe
3. Current or recent medications—both prescription and over-the-counter
4. Associated systemic symptoms (e.g., malaise, fatigue, arthralgias)
5. Ongoing or previous illnesses
6. History of allergies
7. Presence of photosensitivity
8. Review of systems
9. Family history
10. Social, sexual, or travel history

## ADDITIONAL DIAGNOSTIC PROCEDURES

### SKIN BIOPSY

Minor surgical procedure. Choice of site very important.

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**TABLE 59-1 DESCRIPTION OF PRIMARY SKIN LESIONS**

**Macule:** A flat, colored lesion, <2 cm in diameter, not raised above the surface of the surrounding skin. A "freckle," or ephelid, is a prototype pigmented macule.

**Patch:** A large (>2 cm) flat lesion with a color different from the surrounding skin. This differs from a macule only in size.

**Papule:** A small, solid lesion, <0.5 cm in diameter, raised above the surface of the surrounding skin and hence palpable (e.g., a closed comedone, or whitehead, in acne).

**Nodule:** A larger (0.5–5.0 cm), firm lesion raised above the surface of the surrounding skin. This differs from a papule only in size (e.g., a dermal nevomelanocytic nevus).

**Tumor:** A solid, raised growth >5 cm in diameter.

**Plaque:** A large (>1 cm), flat-topped, raised lesion; edges may either be distinct (e.g., in psoriasis) or gradually blend with surrounding skin (e.g., in eczematous dermatitis).

**Vesicle:** A small, fluid-filled lesion, <0.5 cm in diameter, raised above the plane of surrounding skin. Fluid is often visible, and the lesions are translucent [e.g., vesicles in allergic contact dermatitis caused by *Toxicodendron* (poison ivy)].

**Pustule:** A vesicle filled with leukocytes. ***Note:*** The presence of pustules does not necessarily signify the existence of an infection.

**Bulla:** A fluid-filled, raised, often translucent lesion >0.5 cm in diameter.

**Wheal:** A raised, erythematous, edematous papule or plaque, usually representing short-lived vasodilatation and vasopermeability.

**Telangiectasia:** A dilated, superficial blood vessel.

## POTASSIUM HYDROXIDE PREPARATION

Useful for detection of dermatophyte or yeast. Scale is collected from advancing edge of a scaling lesion by gently scraping with side of a microscope slide or a scalpel blade. Nail lesions are best sampled by trimming back nail and scraping subungual debris. A drop of 10–20% potassium hydroxide is added to slide, and coverslip is applied. The slide may be gently heated and examined under microscope.

**TABLE 59-2 DESCRIPTION OF SECONDARY SKIN LESIONS**

**Lichenification:** A distinctive thickening of the skin that is characterized by accentuated skin-fold markings.

**Scale:** Excessive accumulation of stratum corneum.

**Crust:** Dried exudate of body fluids that may be either yellow (i.e., serous crust) or red (i.e., hemorrhagic crust).

**Erosion:** Loss of epidermis without an associated loss of dermis.

**Ulcer:** Loss of epidermis and at least a portion of the underlying dermis.

**Excoriation:** Linear, angular erosions that may be covered by crust and are caused by scratching.

**Atrophy:** An acquired loss of substance. In the skin, this may appear as a depression with intact epidermis (i.e., loss of dermal or subcutaneous tissue) or as sites of shiny, delicate, wrinkled lesions (i.e., epidermal atrophy).

**Scar:** A change in the skin secondary to trauma or inflammation. Sites may be erythematous, hypopigmented, or hyperpigmented depending on their age or character. Sites on hair-bearing areas may be characterized by destruction of hair follicles.

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This technique can be utilized to identify hyphae in dermatophyte infections, pseudohyphae and budding yeast in *Candida* infections, and "spaghetti and meatballs" yeast forms in tinea versicolor.

### TZANCK PREPARATION

Useful for determining presence of herpes viruses (herpes simplex virus or herpes zoster virus). Optimal lesion to sample is an early vesicle. Lesion is gently unroofed with no. 15 scalpel blade, and base of vesicle is gently scraped with belly of blade (keep blade perpendicular to skin surface to prevent laceration). Scrapings are transferred to slide and stained with Wright's or Giemsa stain. A positive preparation has multinucleated giant cells. Culture or immunofluorescence testing must be performed to identify the specific virus.

### DIASCOPY

Assesses whether a lesion blanches with pressure. Done by pressing a magnifying lens or microscope slide on lesion and observing changes in vascularity. For example, hemangiomas will usually blanch; purpuric lesions will not.

### WOOD'S LIGHT EXAMINATION

Useful for detecting bacterial or fungal infection or accentuating features of some skin lesions.

### PATCH TESTS

To document cutaneous sensitivity to specific antigen.

For a more detailed discussion, see Lawley TJ, Yancey KB: Approach to the Patient with a Skin Disorder, Chap. 70, p. 339, in HPIM-19.

# 60 Common Skin Conditions

## PAPULOSQUAMOUS DISORDERS

Disorders exhibiting papules and scale.

### PSORIASIS

A chronic, recurrent disorder. Classic lesion is a well-marginated, erythematous plaque with silvery-white surface scale. Distribution includes extensor surfaces (i.e., knees, elbows, and buttocks); may also involve palms and scalp (particularly anterior scalp margin). Associated findings include psoriatic arthritis (Chap. 161) and nail changes (onycholysis, pitting or thickening of nail plate with accumulation of subungual debris).

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**TREATMENT** PSORIASIS

Maintain cutaneous hydration; topical glucocorticoids; topical vitamin D analogue (calcipotriol) and retinoid (tazarotene); UV light (PUVA, when UV used in combination with psoralens); for severe disease methotrexate or cyclosporine; acitretin can also be used but is teratogenic. Ustekinumab (human monoclonal antibody that blocks IL-12 and IL-23) or apremilast (phosphodiesterase 4 inhibitor) can be considered for chronic, moderate to severe plaque psoriasis. Etanercept (dimeric fusion protein: TNF receptor/Fc human IgG1), infliximab, and adalimumab (monoclonal antibodies directed against TNF) are approved for psoriasis and psoriatic arthritis.

### PITYRIASIS ROSEA

A self-limited condition lasting 3–8 weeks. Initially, there is a single 2- to 6-cm annular salmon-colored patch (herald patch) with a peripheral rim of scale, followed in days to weeks by a generalized eruption involving the trunk and proximal extremities. Individual lesions are similar to but smaller than the herald patch and are arranged in symmetric fashion with long axis of each individual lesion along skin lines of cleavage. Appearance may be similar to that of secondary syphilis.

**TREATMENT** PITYRIASIS ROSEA

Disorder is self-limited, so treatment is directed at symptoms; oral antihistamines for pruritus; topical glucocorticoids; UV-B phototherapy in some cases.

### LICHEN PLANUS

Disorder of unknown cause; can follow administration of certain drugs, chronic graft-versus-host disease, hepatitis C; lesions are pruritic, polygonal, flat-topped, and violaceous. Course is variable, but most pts have spontaneous remissions 6–24 months after onset of disease.

**TREATMENT** LICHEN PLANUS

Topical glucocorticoids.

## ECZEMATOUS DISORDERS

### ECZEMA

Eczema, or dermatitis, is a reaction pattern that presents with variable clinical and histologic findings; it is the final common expression for a number of disorders.

### ATOPIC DERMATITIS

One aspect of atopic triad of hayfever, asthma, and eczema. Usually an intermittent, chronic, severely pruritic, eczematous dermatitis with scaly erythematous patches, vesiculation, crusting, and fissuring. Lesions are most commonly on flexures, with prominent involvement of antecubital and popliteal fossae; generalized erythroderma in severe cases.

**TREATMENT** ECZEMA AND ATOPIC DERMATITIS

Avoidance of irritants; cutaneous hydration; topical glucocorticoids; treatment of infected lesions [often with *Staphylococcus aureus* (SA)—consider

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community-acquired methicillin-resistant strains (CA-MRSA)]. Systemic glucocorticoids only for severe exacerbations unresponsive to topical conservative therapy. Topical calcineurin inhibitors have been used for severe disease but may carry toxicity.

### ALLERGIC CONTACT DERMATITIS

A delayed hypersensitivity reaction that occurs after cutaneous exposure to an antigenic substance. Lesions occur at site of contact and are vesicular, weeping, crusting; linear arrangement of vesicles is common. Most frequent allergens are resin from plants of the genus *Toxicodendron* (poison ivy, oak, sumac), nickel, rubber, and cosmetics.

**TREATMENT ALLERGIC CONTACT DERMATITIS**

Avoidance of sensitizing agent; topical glucocorticoids; consideration of systemic glucocorticoids over 2–3 weeks for widespread disease.

### IRRITANT CONTACT DERMATITIS

Inflammation of the skin due to direct injury by an exogenous agent. The most common area of involvement is the hands, where dermatitis is initiated or aggravated by chronic exposure to water and detergents. Features may include skin dryness, cracking, erythema, and edema.

**TREATMENT IRRITANT CONTACT DERMATITIS**

Avoidance of irritants; barriers (use of protective gloves); topical glucocorticoids; treatment of secondary bacterial or dermatophyte infection.

### SEBORRHEIC DERMATITIS

A chronic noninfectious process characterized by erythematous patches with greasy yellowish scale. Lesions are generally on scalp, eyebrows, nasolabial folds, axillae, central chest, and posterior auricular area.

**TREATMENT SEBORRHEIC DERMATITIS**

Nonfluorinated topical glucocorticoids; shampoos containing coal tar, salicylic acid, or selenium sulfide.

## INFECTIONS

### IMPETIGO

A superficial infection of skin secondary to either *S. aureus* or group A β-hemolytic streptococci. The primary lesion is a superficial pustule that ruptures and forms a "honey-colored" crust. Tense bullae are associated with *S. aureus* infections (bullous impetigo). Lesions may occur anywhere but commonly involve the face. Impetigo and *furunculosis* (painful erythematous nodule, or boil) have gained prominence because of increasing incidence of CA-MRSA.

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**TREATMENT** IMPETIGO

Gentle debridement of adherent crusts with soaks and topical antibiotics; appropriate oral antibiotics depending on organism.

## ERYSIPELAS

Superficial cellulitis, most commonly on face, characterized by a bright red, sharply demarcated, intensely painful, warm plaque. Because of superficial location of infection and associated edema, surface of plaque may exhibit a *peau d'orange* (orange peel) appearance. Most commonly due to infection with group A β-hemolytic streptococci, occurring at sites of trauma or other breaks in skin.

**TREATMENT** ERYSIPELAS

Appropriate antibiotics depending on organism.

## HERPES SIMPLEX (SEE ALSO CHAP. 99)

Recurrent eruption characterized by grouped vesicles on an erythematous base that progress to erosions; often secondarily infected with staphylococci or streptococci. Infections frequently involve mucocutaneous surfaces around the oral cavity, genitals, or anus. Can also cause severe visceral disease including esophagitis, pneumonitis, encephalitis, and disseminated herpes simplex virus infection. Tzanck preparation of an unroofed early vesicle reveals multinucleated giant cells. Confirmed by detection of virus, viral antigen, or viral DNA in scrapings from lesions.

**TREATMENT** HERPES SIMPLEX

Will differ based on disease manifestations and level of immune competence (Chap. 99); appropriate antibiotics for secondary infections, depending on organism.

## HERPES ZOSTER (SEE ALSO CHAP. 99)

Eruption of grouped vesicles on an erythematous base usually limited to a single dermatome ("shingles"); disseminated lesions can also occur, especially in immunocompromised pts. Tzanck preparation reveals multinucleated giant cells; indistinguishable from herpes simplex except by culture. Detection of varicella zoster virus DNA by PCR is confirmatory but of limited availability. Postherpetic neuralgia, lasting months to years, may occur, especially in the elderly.

**TREATMENT** HERPES ZOSTER

Will differ based on disease manifestations and level of immune competence (Chap. 99).

## DERMATOPHYTE INFECTION

Skin fungus, may involve any area of body; due to infection of stratum corneum, nail plate, or hair. Appearance may vary from mild scaliness to florid inflammatory dermatitis. Common sites of infection include the foot (tinea pedis), nails (tinea unguium), groin (tinea cruris), or scalp (tinea capitis). Classic lesion of tinea corporis ("ringworm") is an erythematous papulosquamous patch, often with central clearing

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and scale along peripheral advancing border. Hyphae are often seen on KOH preparation, although tinea capitis and tinea corporis may require culture or biopsy.

**TREATMENT DERMATOPHYTE INFECTION**

Depends on affected site and type of infection. Topical imidazoles, triazoles, and allylamines may be effective. Haloprogin, undecylenic acid, ciclopirox olamine, and tolnaftate are also effective, but nystatin is not active against dermatophytes. Griseofulvin, 500 mg/d, if systemic therapy required. Itraconazole or terbinafine may be effective for nail infections.

### CANDIDIASIS

Fungal infection caused by a related group of yeasts. Manifestations may be localized to the skin or rarely systemic and life-threatening. Predisposing factors include diabetes mellitus, cellular immune deficiencies, and HIV (Chap. 105). Frequent sites include the oral cavity, chronically wet macerated areas, around nails, intertriginous areas. Diagnosed by clinical pattern and demonstration of yeast on KOH preparation or culture.

**TREATMENT CANDIDIASIS**

(See also Chap. 106) Removal of predisposing factors; topical nystatin or azoles; systemic therapy reserved for immunosuppressed pts, unresponsive chronic or recurrent disease; vulvovaginal candidiasis may respond to a single dose of fluconazole, 150 mg.

### WARTS

Cutaneous neoplasms caused by human papilloma viruses (HPVs). Typically dome-shaped lesions with irregular, filamentous surface. Propensity for the face, arms, and legs; often spread by shaving. HPVs are also associated with genital or perianal lesions and play a role in the development of cancer of the uterine cervix and anogenital skin (Chap. 83).

**TREATMENT WARTS**

Cryotherapy with liquid nitrogen, keratinolytic agents (salicylic acid). For genital warts, application of podophyllin solution is effective but can be associated with marked local reactions; topical imiquimod also has been used. HPV vaccine reduces the incidence of anogenital and cervical carcinoma.

## ACNE

### ACNE VULGARIS

Usually a self-limited disorder of teenagers and young adults. Comedones (small cysts formed in hair follicles) are clinical hallmark; often accompanied by inflammatory lesions of papules, pustules, or nodules; may scar in severe cases.

**TREATMENT ACNE VULGARIS**

Careful cleaning and removal of oils; oral tetracycline or erythromycin; topical antibacterials (e.g., benzoyl peroxide), topical retinoic acid. Systemic isotretinoin

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only for unresponsive severe nodulocystic acne (risk of severe adverse events including teratogenicity and possible association with depression).

### ACNE ROSACEA

Inflammatory disorder affecting predominantly the central face, rarely affecting pts <30 years of age. Tendency toward exaggerated flushing, with eventual superimposition of papules, pustules, and telangiectasias; may lead to rhinophyma and ocular problems.

**TREATMENT ACNE ROSACEA**

Oral tetracycline, 250–500 mg bid; doxycycline 100 mg bid, minocycline 50-100 mg bid, topical metronidazole and topical nonfluorinated glucocorticoids may be useful.

## VASCULAR DISORDERS

### ERYTHEMA NODOSUM

Septal panniculitis characterized by erythematous, warm, tender subcutaneous nodular lesions typically over anterior tibia. Lesions are usually flush with skin surface but are indurated and have appearance of an erythematous/violaceous bruise. Lesions usually resolve spontaneously in 3–6 weeks without scarring. Commonly seen in sarcoidosis, administration of certain drugs (esp. sulfonamides, oral contraceptives, and estrogens), and a wide range of infections including streptococcal and tubercular; may be idiopathic.

**TREATMENT ERYTHEMA NODOSUM**

Identification and treatment/removal of underlying cause. NSAIDs for severe or recurrent lesions; systemic glucocorticoids are effective but dangerous if underlying infection is not appreciated.

### ERYTHEMA MULTIFORME

A reaction pattern of skin consisting of a variety of lesions but most commonly erythematous papules and bullae. "Target" or "iris" lesion is characteristic and consists of concentric circles of erythema and normal flesh-colored skin, often with a central vesicle or bulla.

Distribution of lesions classically acral, esp. palms and soles. Three most common causes are drug reaction (particularly penicillins and sulfonamides) or concurrent herpetic or *Mycoplasma* infection. Can rarely affect mucosal surfaces and internal organs (erythema multiforme major or Stevens-Johnson syndrome).

**TREATMENT ERYTHEMA MULTIFORME**

Provocative agent should be sought and eliminated if drug-related. In mild cases limited to skin, only symptomatic treatment is needed (antihistamines, NSAID). For Stevens-Johnson syndrome, systemic glucocorticoids have been used but are controversial; prevention of secondary infection and maintenance of nutrition and fluid/electrolyte balance are critical.

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### URTICARIA

A common disorder, either acute or chronic, characterized by evanescent (individual lesions lasting <24 h), pruritic, edematous, pink to erythematous plaques with a whitish halo around margin of individual lesions. Lesions range in size from papules to giant coalescent lesions (10–20 cm in diameter). Often due to drugs, systemic infection, or foods (esp. shellfish). If individual lesions last >24 h, consider diagnosis of urticarial vasculitis.

#### TREATMENT URTICARIA

See Chap. 156.

### VASCULITIS

Palpable purpura (nonblanching, elevated lesions) is the cutaneous hallmark of vasculitis. Other lesions include petechiae (esp. early lesions), necrosis with ulceration, bullae, and urticarial lesions (urticarial vasculitis). Lesions usually most prominent on lower extremities. Associations include infections, autoimmune diseases, primary systemic vasculitides, malignancy, hepatitis B and C, drugs (esp. thiazides), and inflammatory bowel disease. May occur as an idiopathic, predominantly cutaneous vasculitis.

#### TREATMENT VASCULITIS

Will differ based on cause. Pursue identification and treatment/elimination of an exogenous cause or underlying disease. If part of a systemic vasculitis, treat based on major organ-threatening features (Chap. 159). Immunosuppressive therapy should be avoided in idiopathic, predominantly cutaneous vasculitis as disease frequently does not respond and rarely causes irreversible organ system dysfunction.

## CUTANEOUS DRUG REACTIONS

Cutaneous reactions are among the most frequent medication toxicities. These can have a wide range of severity and manifestations including urticaria, photosensitivity, erythema multiforme, fixed drug reactions, erythema nodosum, vasculitis, lichenoid reactions, bullous drug reactions, Stevens-Johnson syndrome, and toxic epidermal necrolysis (TEN). Diagnosis is usually made by appearance and careful medication history.

#### TREATMENT CUTANEOUS DRUG REACTIONS

Withdrawal of the medication. Treatment based on nature and severity of cutaneous pathology.

For a more detailed discussion, see Lawley LP, McCall CO, Lawley TJ: Eczema, Psoriasis, Cutaneous Infections, Acne, and Other Common Skin Disorders, Chap. 71, p. 344; Shinkai K, Stern RS, Wintroub BU: Cutaneous Drug Reactions, Chap. 74, p. 377; and Bolognia JL, Braverman IM: Skin Manifestations of Internal Disease, Chap. 72, p. 353, in HPIM-19.

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# 61 Examination of Blood Smears and Bone Marrow

## BLOOD SMEARS

### ERYTHROCYTE (RBC) MORPHOLOGY

- Normal: 7.5 μm diameter. Roughly the size of the nucleus of a small lymphocyte.
- *Reticulocytes* (Wright's stain): large, grayish-blue, admixed with pink (polychromasia).
- *Anisocytosis*: variation in RBC size; large cells imply delay in erythroid precursor DNA synthesis caused by folate or $B_{12}$ deficiency or drug effect; small cells imply a defect in hemoglobin synthesis caused by iron deficiency or abnormal hemoglobin genes. The automated red cell distribution width (RDW) is a measure of anisocytosis.
- *Poikilocytosis*: abnormal RBC shapes; the following are examples:
  1. *Acanthocytes* (spur cells): irregularly spiculated; abetalipoproteinemia, severe liver disease, rarely anorexia nervosa.
  2. *Echinocytes* (burr cells): regularly shaped, uniformly distributed spiny projections; uremia, RBC volume loss.
  3. *Elliptocytes*: elliptical; hereditary elliptocytosis.
  4. *Schistocytes* (schizocytes): fragmented cells of varying sizes and shapes; microangiopathic or macroangiopathic hemolytic anemia.
  5. *Sickled cells*: elongated, crescentic; sickle cell anemias.
  6. *Spherocytes*: small hyperchromic cells lacking normal central pallor; hereditary spherocytosis, extravascular hemolysis as in autoimmune hemolytic anemia, G6PD deficiency.
  7. *Target cells*: central and outer rim staining with intervening ring of pallor; liver disease, thalassemia, hemoglobin C, and sickle C diseases.
  8. *Teardrop cells*: myelofibrosis, other infiltrative processes of marrow (e.g., carcinoma).
  9. *Rouleaux formation*: alignment of RBCs in stacks; may be artifactual or due to paraproteinemia (e.g., multiple myeloma, macroglobulinemia).

### RBC INCLUSIONS

- *Howell-Jolly bodies*: 1-μm-diameter basophilic cytoplasmic inclusion that represents a residual nuclear fragment, usually single; asplenic pts.
- *Basophilic stippling*: multiple, punctate basophilic cytoplasmic inclusions composed of precipitated mitochondria and ribosomes; lead poisoning, thalassemia, myelofibrosis.
- *Pappenheimer (iron) bodies*: iron-containing granules usually composed of mitochondria and ribosomes resemble basophilic stippling but also stain with Prussian blue; lead poisoning, other sideroblastic anemias.
- *Heinz bodies*: spherical inclusions of precipitated hemoglobin seen only with supravital stains, such as crystal violet; G6PD deficiency (after oxidant stress such as infection, certain drugs), unstable hemoglobin variants.
- *Parasites*: characteristic intracytoplasmic inclusions; malaria, babesiosis.



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### LEUKOCYTE INCLUSIONS AND NUCLEAR CONTOUR ABNORMALITIES

- *Toxic granulations*: dark cytoplasmic granules; bacterial infection.
- *Döhle bodies*: 1- to 2-μm blue, oval cytoplasmic inclusions; bacterial infection, Chédiak-Higashi anomaly.
- *Auer rods*: eosinophilic, rodlike cytoplasmic inclusions; acute myeloid leukemia (some cases).
- *Hypersegmentation*: neutrophil nuclei contain more than the usual 2–4 lobes; usually >5% have ≥5 lobes or a single cell with 7 lobes is adequate to make the diagnosis; folate or $B_{12}$ deficiency, drug effects.
- *Hyposegmentation*: neutrophil nuclei contain fewer lobes than normal, either one or two: Pelger-Hüet anomaly, pseudo–Pelger-Hüet or acquired Pelger-Hüet anomaly in acute leukemia.

### PLATELET ABNORMALITIES

- *Platelet clumping*: an in vitro artifact—is often readily detectable on smear; can lead to falsely low platelet count by automated cell counters.
- *Giant platelets*: can be a sign of a very young platelet or increased platelet production or abnormal karyocyte maturation; if the platelets are >5–6 μm in diameter, they may not be counted as platelets by electronic counters.

## BONE MARROW

*Aspiration* assesses cell morphology. *Biopsy* assesses overall marrow architecture, including degree of cellularity. Biopsy should precede aspiration to avoid aspiration artifact (mainly hemorrhage) in the specimen.

### INDICATIONS

#### Aspiration

Hypoproliferative or unexplained anemia, leukopenia, or thrombocytopenia, suspected leukemia or myeloma or marrow defect, evaluation of iron stores, workup of some cases of fever of unknown origin.

#### Special Tests

Histochemical staining (leukemias), cytogenetic studies (leukemias, lymphomas), microbiology (bacterial, mycobacterial, fungal cultures), Prussian blue (iron) stain (assessment of iron stores, diagnosis of sideroblastic anemias).

#### Biopsy

Performed in addition to aspiration for pancytopenia (aplastic anemia), metastatic tumor, granulomatous infection (e.g., mycobacteria, brucellosis, histoplasmosis), myelofibrosis, lipid storage disease (e.g., Gaucher's, Niemann-Pick), any case with "dry tap" on aspiration; evaluation of marrow cellularity. When biopsy and aspirate are both planned, the biopsy should be performed first because of the risk of bleeding artifact from biopsy of an aspiration site.

#### Special Tests

Histochemical staining (e.g., acid phosphatase for metastatic prostate carcinoma), immunoperoxidase staining (e.g., immunoglobulin or cell surface marker detection in multiple myeloma, leukemia, or lymphoma; lysozyme detection in monocytic leukemia), reticulin staining (increased in myelofibrosis), microbiologic staining (e.g., acid-fast staining for mycobacteria).

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## INTERPRETATION

### Cellularity

Defined as percentage of space occupied by hematopoietic cells. The space that is not hematopoietic tissue is usually fat. Cellularity decreases with age after age 65 years from about 50% to 25–30% with a corresponding increase in fat.

### Erythroid:Granulocytic (E:G) Ratio

Normally about 1:2, the E:G ratio is decreased in acute and chronic infection, leukemoid reactions (e.g., chronic inflammation, metastatic tumor), acute and chronic myeloid leukemia, myelodysplastic disorders ("preleukemia"), and pure red cell aplasia; increased in agranulocytosis, anemias with erythroid hyperplasia (megaloblastic, iron-deficiency, thalassemia, hemorrhage, hemolysis, sideroblastic), and erythrocytosis (excessive RBC production); normal in aplastic anemia (though marrow hypocellular), myelofibrosis (marrow hypocellular), multiple myeloma, lymphoma, anemia of chronic disease. Some centers use the term M:E (myeloid to erythroid) ratio; normal value is 2:1 and increases with diseases that promote myeloid activity or inhibit erythroid activity and decreases with diseases that inhibit myeloid activity or promote erythroid activity.

For a more detailed discussion, see Adamson JW, Longo DL: Anemia and Polycythemia, Chap. 77, p. 392; Holland SM, Gallin JI: Disorders of Granulocytes and Monocytes, Chap. 80, p. 413; and Longo DL: Atlas of Hematology and Analysis of Peripheral Blood Smears, Chap. 81e in HPIM-19.

# 62 Red Blood Cell Disorders

Anemia is a common clinical problem in medicine. A physiologic approach (outlined in Chap. 45) provides the most efficient path to diagnosis and management. Anemias arise either because red blood cell (RBC) production is inadequate or because RBC lifespan (normally 120 days) is shortened through loss from the circulation or destruction.

## HYPOPROLIFERATIVE ANEMIAS

These are the most common anemias. Usually the RBC morphology is normal and the reticulocyte index (RI) is low. Marrow damage, early iron deficiency, and decreased erythropoietin production or action may produce anemia of this type.

Marrow damage may be caused by infiltration of the marrow with tumor or fibrosis that crowds out normal erythroid precursors or by the absence of erythroid precursors (aplastic anemia) as a consequence of exposure to drugs, radiation, chemicals, viruses (e.g., hepatitis), autoimmune mechanisms, or genetic factors,

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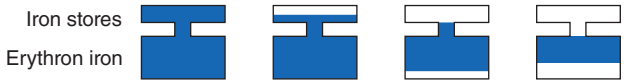


| | Normal | Negative iron balance | Iron-deficient erythropoiesis | Iron-deficiency anemia |
|---|---|---|---|---|
| Marrow iron stores | 1–3+ | 0–1+ | 0 | 0 |
| Serum ferritin (μg/L) | 50–200 | <20 | <15 | <15 |
| TIBC (μg/dL) | 300–360 | >360 | >380 | >400 |
| SI (μg/dL) | 50–150 | NL | <50 | <30 |
| Saturation (%) | 30–50 | NL | <20 | <10 |
| Marrow sideroblasts (%) | 40–60 | NL | <10 | <10 |
| RBC protoporphyrin (μg/dL) | 30–50 | NL | >100 | >200 |
| RBC morphology | NL | NL | NL | Microcytic/ hypochromic |

**FIGURE 62-1** Measurements of marrow iron stores, serum ferritin, and total iron-binding capacity (TIBC) are sensitive to early iron-store depletion. Iron-deficient erythropoiesis is recognized from additional abnormalities in the serum iron (SI), percent transferrin saturation, the pattern of marrow sideroblasts, and the red cell protoporphyrin level. Pts with iron-deficiency anemia demonstrate all the same abnormalities plus hypochromic microcytic anemia. (*From RS Hillman, CA Finch: Red Cell Manual, 7th. ed, Philadelphia, Davis, 1996, with permission.*)

either hereditary (e.g., Fanconi's anemia) or acquired (e.g., paroxysmal nocturnal hemoglobinuria). Most cases of aplasia are idiopathic. The tumor or fibrosis that infiltrates the marrow may originate in the marrow (as in leukemia or myelofibrosis) or be secondary to processes originating outside the marrow (as in metastatic cancer or myelophthisis).

Early iron-deficiency anemia (or iron-deficient erythropoiesis) is associated with a decrease in serum ferritin levels (<15 μg/L), moderately elevated total iron-binding capacity (TIBC) (>380 μg/dL), serum iron (SI) level <50 μg/dL, and an iron saturation of <30% but >10% (Fig. 62-1). RBC morphology is generally normal until iron deficiency is severe (see below).

Decreased stimulation of erythropoiesis can be a consequence of inadequate erythropoietin production [e.g., renal disease destroying the renal tubular cells that produce it or hypometabolic states (endocrine deficiency or protein starvation)] in which insufficient erythropoietin is produced or of inadequate erythropoietin action. In older people, erythropoietin levels normally increase to maintain normal hemoglobin levels. If this increase does not happen, anemia may develop. About 11% of community-dwelling adults over age 65 and up to 45% of nursing home residents have this aging-related anemia. It is a relative erythropoietin deficiency without renal disease. The anemia of chronic disease is a common entity. It is multifactorial in pathogenesis: inhibition of erythropoietin production, inhibition of iron

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reutilization (which blocks the response to erythropoietin), and inhibition of erythroid colony proliferation by inflammatory cytokines (e.g., tumor necrosis factor, interferon γ). Hepcidin, a small iron-binding molecule produced by the liver during an acute-phase inflammatory response, may bind iron and prevent its reutilization in hemoglobin synthesis. The laboratory tests shown in Table 62-1 may assist in the differential diagnosis of hypoproliferative anemias. Measurement of hepcidin in the urine is not yet practical or widely available.

## MATURATION DISORDERS

These result from either defective hemoglobin synthesis, leading to cytoplasmic maturation defects and small relatively empty red cells, or abnormally slow DNA replication, leading to nuclear maturation defects and large full red cells. Defects in hemoglobin synthesis usually result from insufficient iron supply (iron deficiency) or decreased globin production (thalassemia) or are idiopathic (sideroblastic anemia). Defects in DNA synthesis are usually due to nutritional problems (vitamin $B_{12}$ and folate deficiency), toxic (methotrexate or other cancer chemotherapeutic agent) exposure, or intrinsic marrow maturation defects (refractory anemia, myelodysplasia).

Laboratory tests useful in the differential diagnosis of the microcytic anemias are shown in Table 62-2. Mean corpuscular volume (MCV) is generally 60–80 fL. Increased lactate dehydrogenase (LDH) and indirect bilirubin levels suggest an increase in RBC destruction and favor a cause other than iron deficiency. Iron status is best assessed by measuring SI, TIBC, and ferritin levels. Macrocytic MCVs are >94 fL. Folate status is best assessed by measuring red blood cell folate levels. Vitamin $B_{12}$ status is best assessed by measuring serum $B_{12}$, homocysteine, and methylmalonic acid levels. Homocysteine and methylmalonic acid levels are elevated in the setting of $B_{12}$ deficiency.

## ANEMIA DUE TO RBC DESTRUCTION OR ACUTE BLOOD LOSS

### BLOOD LOSS

Trauma, GI hemorrhage (may be occult) are common causes; less common are genitourinary sources (menorrhagia, gross hematuria), internal bleeding such as intraperitoneal from spleen or organ rupture, retroperitoneal, iliopsoas hemorrhage (e.g., in hip fractures). Acute bleeding is associated with manifestations of hypovolemia, reticulocytosis, macrocytosis; chronic bleeding is associated with iron deficiency, hypochromia, microcytosis.

### HEMOLYSIS

Causes are listed in Table 62-3.

1. *Intracellular RBC abnormalities*: most are inherited enzyme defects [glucose-6-phosphate dehydrogenase (G6PD) deficiency > pyruvate kinase deficiency], hemoglobinopathies, sickle cell anemia and variants, thalassemia, unstable hemoglobin variants.
2. *G6PD deficiency*: leads to episodes of hemolysis precipitated by ingestion of drugs that induce oxidant stress on RBCs. These include antimalarials (chloroquine), sulfonamides, analgesics (phenacetin), and other miscellaneous drugs (Table 62-4).
3. *Sickle cell anemia*: characterized by a single-amino-acid change in β globin (valine for glutamic acid in the 6th residue) that produces a molecule of decreased solubility, especially in the absence of $O_2$. Although anemia and chronic hemolysis are present, the major disease manifestations relate to vasoocclusion from misshapen sickled RBCs. Infarcts in lung, bone, spleen, retina, brain, and other organs lead to symptoms and dysfunction (Fig. 62-2).

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**TABLE 62-1 DIAGNOSIS OF HYPOPROLIFERATIVE ANEMIAS**

| Tests | Iron Deficiency | Inflammation | Renal Disease | Hypometabolic States | Anemia of Aging |
|---|---|---|---|---|---|
| Anemia | Mild to severe | Mild | Mild to severe | Mild | Mild |
| MCV (fL) | 60–90 | 80–90 | 90 | 90 | 80–90 |
| Morphology | Normomicrocytic | Normocytic | Normocytic | Normocytic | Normocytic |
| SI | <30 | <50 | Normal | Normal | Normal |
| TIBC | >360 | <300 | Normal | Normal | Normal |
| Saturation (%) | <10 | 10–20 | Normal | Normal | Normal |
| Serum ferritin (μg/L) | <15 | 30–200 | 115–150 | Normal | Normal |
| Iron stores | 0 | 2–4+ | 1–4+ | Normal | Normal |
| Erythropoietin levels | High | Normal or High | Low | Normal or Low | Normal |

***Abbreviations:*** MCV, mean corpuscular volume; SI, serum iron; TIBC, total iron-binding capacity.

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**TABLE 62-2 DIAGNOSIS OF MICROCYTIC ANEMIA**

| Tests | Iron Deficiency | Inflammation | Thalassemia | Sideroblastic Anemia |
|---|---|---|---|---|
| Smear | Micro/hypo | Normal micro/hypo | Micro/hypo with targeting | Variable |
| SI | <30 | <50 | Normal to high | Normal to high |
| TIBC | >360 | <300 | Normal | Normal |
| Percent saturation | <10 | 10–20 | 30–80 | 30–80 |
| Ferritin (μg/L) | <15 | 30–200 | 50–300 | 50–300 |
| Hemoglobin pattern on electrophoresis | Normal | Normal | Abnormal with β thalassemia; can be normal with α thalassemia | Normal |

***Abbreviations:*** SI, serum iron; TIBC, total iron-binding capacity.

4. *Membrane abnormalities* (rare): spur cell anemia (cirrhosis, anorexia nervosa), paroxysmal nocturnal hemoglobinuria, hereditary spherocytosis (increased RBC osmotic fragility, spherocytes), hereditary elliptocytosis (causes mild hemolytic anemia).
5. *Immunohemolytic anemia* (positive Coombs' test, spherocytes). Two types: (a) *warm antibody* (usually IgG): idiopathic, lymphoma, chronic lymphocytic leukemia, systemic lupus erythematosus, drugs (e.g., methyldopa, penicillins, quinine, quinidine, isoniazid, sulfonamides); and (b) *cold antibody*—cold agglutinin disease (IgM) due to *Mycoplasma* infection, infectious mononucleosis, lymphoma, idiopathic; paroxysmal cold hemoglobinuria (IgG) due to syphilis, viral infections.

**TABLE 62-3 CLASSIFICATION OF HEMOLYTIC ANEMIAS[a]**

| | Intracorpuscular Defects | Extracorpuscular Factors |
|---|---|---|
| Hereditary | Hemoglobinopathies<br>Enzymopathies<br>Membrane-cytoskeletal defects | Familial (atypical) hemolytic uremic syndrome |
| Acquired | Paroxysmal nocturnal hemoglobinuria (PNH) | Mechanical destruction (microangiopathic)<br>Toxic agents<br>Drugs<br>Infectious<br>Autoimmune |

[a]Hereditary causes correlate with intracorpuscular defects because these defects are due to inherited mutations. The one exception is PNH because the defect is due to an acquired somatic mutation. Similarly, acquired causes correlate with extracorpuscular factors because mostly these factors are exogenous. The one exception is familial hemolytic uremic syndrome (HUS; often referred to as atypical HUS) because here an inherited abnormality allows complement activation to be excessive, with bouts of production of membrane attack complex capable of destroying normal red cells.

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**TABLE 62-4 DRUGS THAT CARRY RISK OF CLINICAL HEMOLYSIS IN PERSONS WITH G6PD DEFICIENCY**

| | Definite Risk | Possible Risk | Doubtful Risk |
|---|---|---|---|
| Antimalarials | Primaquine<br>Dapsone/ chlorproguanil[a] | Chloroquine | Quinine |
| Sulphonamides/ sulphones | Sulfamethoxazole<br>Others<br>Dapsone | Sulfasalazine<br>Sulfadimidine | Sulfisoxazole<br>Sulfadiazine |
| Antibacterial/ antibiotics | Cotrimoxazole<br>Nalidixic acid<br>Nitrofurantoin<br>Niridazole | Ciprofloxacin<br>Norfloxacin | Chloramphenicol<br>*p*-Aminosalicylic acid |
| Antipyretic/ analgesics | Acetanilide<br>Phenazopyridine | Acetylsalicylic acid high dose (>3 g/d) | Acetylsalicylic acid (<3 g/d)<br>Acetaminophen<br>Phenacetin |
| Other | Naphthalene<br>Methylene blue | Vitamin K analogues<br>Ascorbic acid >1 g<br>Rasburicase | Doxorubicin<br>Probenecid |

[a]Marketed as Lapdap from 2003 to 2008.

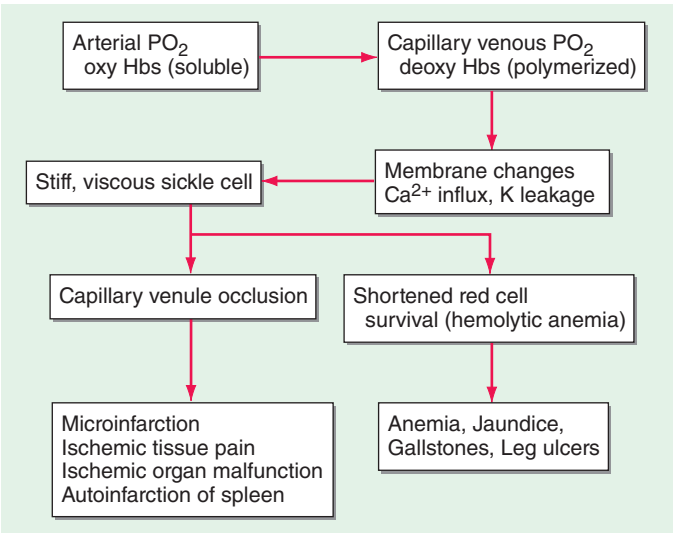


**FIGURE 62-2** Pathophysiology of sickle cell crisis.

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6. *Mechanical trauma* (macro- and microangiopathic hemolytic anemias; schistocytes): prosthetic heart valves, vasculitis, malignant hypertension, eclampsia, renal graft rejection, giant hemangioma, scleroderma, thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome, disseminated intravascular coagulation, march hemoglobinuria (e.g., marathon runners, bongo drummers).
7. *Direct toxic effect*: infections (e.g., malaria, *Clostridium perfringens* toxin, toxoplasmosis).
8. *Hypersplenism* (pancytopenia may be present).

## LABORATORY ABNORMALITIES

Elevated RI, polychromasia and nucleated RBCs on smear; also spherocytes, elliptocytes, schistocytes, or target, spur, or sickle cells may be present depending on disorder; elevated unconjugated serum bilirubin and LDH, elevated plasma hemoglobin, low or absent haptoglobin; urine hemosiderin present in intravascular but not extravascular hemolysis, Coombs' test (immunohemolytic anemias), osmotic fragility test (hereditary spherocytosis), hemoglobin electrophoresis (sickle cell anemia, thalassemia), G6PD assay (best performed after resolution of hemolytic episode to prevent false-negative result).

# TREATMENT ANEMIA

**GENERAL APPROACHES** The acuteness and severity of the anemia determine whether transfusion therapy with packed RBCs is indicated. Rapid occurrence of severe anemia (e.g., after acute GI hemorrhage resulting in Hct <25%, following volume repletion) or development of angina or other symptoms is an indication for transfusion. Hct should increase 3–4% [Hb by 10 g/L (1 g/dL)] with each unit of packed RBCs, assuming no ongoing losses. Chronic anemia (e.g., vitamin $B_{12}$ deficiency), even when severe, may not require transfusion therapy if the pt is compensated and specific therapy (e.g., vitamin $B_{12}$) is instituted.

## SPECIFIC DISORDERS

1. *Iron deficiency*: find and treat cause of blood loss, oral iron (e.g., $FeSO_4$ 300 mg tid).
2. *Folate deficiency*: common in malnourished, alcoholics; less common now than before folate food supplementation; folic acid 1 mg PO qd (5 mg qd for pts with malabsorption).
3. *Vitamin $B_{12}$ deficiency*: can be managed either with parenteral vitamin $B_{12}$ 100 μg IM qd for 7 d, then 100–1000 μg IM per month or with 2 mg oral crystalline vitamin $B_{12}$ per day. An inhaled formulation is also available.
4. *Anemia of chronic disease*: treat underlying disease; in uremia use recombinant human erythropoietin, 50–150 U/kg three times a week; role of erythropoietin in other forms of anemia of chronic disease is less clear; response more likely if serum erythropoietin levels are low. Target Hb 9–10 g/dL. Iron administration is not useful.
5. *Sickle cell anemia*: hydroxyurea 10–30 mg/kg per day PO increases level of Hemoglobin F (HbF) and prevents sickling, treat infections early, supplemental folic acid; painful crises treated with oxygen, analgesics (opioids), hydration, and hypertransfusion; consider allogeneic bone marrow transplantation in pts with increasing frequency of crises.
6. *Thalassemia*: transfusion to maintain Hb >90 g/L (>9 g/dL), folic acid, prevention of Fe overload with deferoxamine (parenteral) or deferasirox (oral) chelation; consider splenectomy and allogeneic bone marrow transplantation.

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7. *Aplastic anemia*: antithymocyte globulin and cyclosporine leads to improvement in 70%, bone marrow transplantation in young pts with a matched donor.
8. *Autoimmune hemolysis*: glucocorticoids, sometimes immunosuppressive agents, danazol, plasmapheresis, rituximab.
9. *G6PD deficiency*: avoid agents known to precipitate hemolysis.

For a more detailed discussion, see Adamson JW: Iron Deficiency and Other Hypoproliferative Anemias, Chap. 126, p. 625; Benz EJ: Disorders of Hemoglobin, Chap. 127, p. 631; Hoffbrand AV: Megaloblastic Anemias, Chap. 128, p. 640; Luzzato L: Hemolytic Anemias and Anemia Due to Acute Blood Loss, Chap. 129, p. 649; and Young NS: Bone Marrow Failure Syndromes Including Aplastic Anemia and Myelodysplasia, Chap. 130; p. 662 in HPIM-19.

# 63 Leukocytosis and Leukopenia

## LEUKOCYTOSIS

### APPROACH TO THE PATIENT: Leukocytosis

Review smear (are abnormal cells present?) and obtain differential count. The normal values for concentration of blood leukocytes are shown in Table 63-1.

### NEUTROPHILIA

Absolute neutrophil count (polys and bands) >10,000/μL. The pathophysiology of neutrophilia involves increased production, increased marrow mobilization, or decreased margination (adherence to vessel walls).

#### Causes

(1) *Exercise*, *stress*; (2) *infections*—esp. bacterial; smear shows increased numbers of immature neutrophils ("left shift"), toxic granulations, Döhle bodies; (3) *burns*;

**TABLE 63-1 NORMAL VALUES FOR LEUKOCYTE CONCENTRATION IN BLOOD**

| Cell Type | Mean, cells/μL | 95% Confidence Intervals, cells/μL | Total WBC, % |
|---|---|---|---|
| Neutrophil | 3650 | 1830–7250 | 30–60% |
| Lymphocyte | 2500 | 1500–4000 | 20–50% |
| Monocyte | 430 | 200–950 | 2–10% |
| Eosinophil | 150 | 0–700 | 0.3–5% |
| Basophil | 30 | 0–150 | 0.6–1.8% |

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(4) *tissue necrosis* (e.g., myocardial, pulmonary, renal infarction); (5) *chronic inflammatory disorders* (e.g., gout, vasculitis); (6) *drugs* (e.g., glucocorticoids, epinephrine, lithium); (7) *cytokines* [e.g., granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF)]; (8) *myeloproliferative disorders* (Chap. 65); (9) *metabolic* (e.g., ketoacidosis, uremia); (10) *other*—malignant neoplasms, acute hemorrhage or hemolysis, after splenectomy.

## LEUKEMOID REACTION

Extreme elevation of leukocyte count (>50,000/μL) composed of mature and/or immature neutrophils.

### Causes

(1) *Infection* (severe, chronic, e.g., tuberculosis), esp. in children; (2) *hemolysis* (severe); (3) *malignant neoplasms* (esp. carcinoma of the breast, lung, kidney); (4) *cytokines* (e.g., G-CSF, GM-CSF). May be distinguished from chronic myeloid leukemia (CML) by measurement of the leukocyte alkaline phosphatase (LAP) level: elevated in leukemoid reactions, depressed in CML.

## LEUKOERYTHROBLASTIC REACTION

Similar to leukemoid reaction with addition of nucleated red blood cells (RBCs) and schistocytes on blood smear.

### Causes

(1) *Myelophthisis*—invasion of the bone marrow by tumor, fibrosis, granulomatous processes; smear shows "teardrop" RBCs; (2) *myelofibrosis*—same pathophysiology as myelophthisis, but the fibrosis is a primary marrow disorder; (3) *hemorrhage* or *hemolysis* (rarely, in severe cases).

## LYMPHOCYTOSIS

Absolute lymphocyte count >5000/μL.

### Causes

(1) *Infection*—infectious mononucleosis, hepatitis, cytomegalovirus, rubella, pertussis, tuberculosis, brucellosis, syphilis; (2) *endocrine disorders*—thyrotoxicosis, adrenal insufficiency; (3) *neoplasms*—chronic lymphocytic leukemia (CLL), most common cause of lymphocyte count >10,000/μL.

## MONOCYTOSIS

Absolute monocyte count >800/μL.

### Causes

(1) *Infection*—subacute bacterial endocarditis, tuberculosis, brucellosis, rickettsial diseases (e.g., Rocky Mountain spotted fever), malaria, leishmaniasis; (2) *granulomatous diseases*—sarcoidosis, Crohn's disease; (3) *collagen vascular diseases*—rheumatoid arthritis, systemic lupus erythematosus (SLE), polyarteritis nodosa, polymyositis, temporal arteritis; (4) *hematologic diseases*—leukemias, lymphoma, myeloproliferative and myelodysplastic syndromes, hemolytic anemia, chronic idiopathic neutropenia; (5) *malignant neoplasms*.

## EOSINOPHILIA

Absolute eosinophil count >500/μL.

### Causes

(1) *Drugs*, (2) *parasitic infections*, (3) *allergic diseases*, (4) *collagen vascular diseases*, (5) *malignant neoplasms*, (6) *hypereosinophilic syndromes*.

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### BASOPHILIA

Absolute basophil count >100/μL.

#### Causes

(1) *Allergic diseases*, (2) *myeloproliferative disorders* (esp. CML), (3) *chronic inflammatory disorders* (rarely).

## LEUKOPENIA

Total leukocyte count <4300/μL.

### NEUTROPENIA

Absolute neutrophil count <2000/μL (increased risk of bacterial infection with count <1000/μL). The pathophysiology of neutropenia involves decreased production or increased peripheral destruction.

#### Causes

(1) *Drugs*—cancer chemotherapeutic agents are most common cause, also phenytoin, carbamazepine, indomethacin, chloramphenicol, penicillins, sulfonamides, cephalosporins, propylthiouracil, phenothiazines, captopril, methyldopa, procainamide, chlorpropamide, thiazides, cimetidine, allopurinol, colchicine, ethanol, penicillamine, and immunosuppressive agents; (2) *infections*—viral (e.g., influenza, hepatitis, infectious mononucleosis, HIV), bacterial (e.g., typhoid fever, miliary tuberculosis, fulminant sepsis), malaria; (3) *nutritional*—$B_{12}$, folate deficiencies; (4) *benign*—benign ethnic neutropenia (BEN) seen in up to 25% of blacks, no associated risk of infection; (5) *hematologic diseases*—cyclic neutropenia (q21d, with recurrent infections common), leukemia, myelodysplasia (preleukemia), aplastic anemia, bone marrow infiltration (uncommon cause), Chédiak-Higashi syndrome; (6) *hypersplenism*—e.g., Felty's syndrome, congestive splenomegaly, Gaucher's disease; (7) *autoimmune diseases*—idiopathic, SLE, lymphoma (may see positive antineutrophil antibodies); (8) *genetics*—inheritance of an allele of the Duffy antigen receptor for cytokines (DARC) can be associated with constitutive neutropenia that is not associated with predilection to infection; more common in African Americans.

**TREATMENT THROMBOTIC DISORDERS**

In addition to usual sources of infection, consider paranasal sinuses, oral cavity (including teeth and gums), anorectal region; empirical therapy with broad-spectrum antibiotics (e.g., ceftazidime) is indicated after blood and other appropriate cultures are obtained. Prolonged febrile neutropenia (>7 days) leads to increased risk of disseminated fungal infections; requires addition of antifungal chemotherapy (e.g., amphotericin B). The duration of chemotherapy-induced neutropenia may be shortened by a few days by treatment with the cytokines GM-CSF or G-CSF.

### LYMPHOPENIA

Absolute lymphocyte count <1000/μL.

#### Causes

(1) *Acute stressful illness*—e.g., myocardial infarction, pneumonia, sepsis; (2) *glucocorticoid therapy*; (3) *lymphoma* (esp. Hodgkin's lymphoma); (4) *immunodeficiency syndromes*—ataxia telangiectasia and Wiskott-Aldrich and DiGeorge syndromes; (5) *immunosuppressive therapy*—e.g., antilymphocyte globulin, cyclophosphamide; (6) *large-field radiation therapy* (esp. for lymphoma); (7) *intestinal lymphangiectasia*

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(increased lymphocyte loss); (8) *chronic illness*—e.g., congestive heart failure, uremia, SLE, disseminated malignancies; (9) *bone marrow failure/replacement*—e.g., aplastic anemia, miliary tuberculosis.

### MONOCYTOPENIA

Absolute monocyte count <100/μL.

#### Causes

(1) *Acute stressful illness*, (2) *glucocorticoid therapy*, (3) *aplastic anemia*, (4) *leukemia* (certain types, e.g., hairy cell leukemia), (5) *chemotherapeutic and immunosuppressive agents*.

### EOSINOPENIA

Absolute eosinophil count <50/μL.

#### Causes

(1) *Acute stressful illness*, (2) *glucocorticoid therapy*.

For a more detailed discussion, see Holland SM, Gallin JI: Disorders of Granulocytes and Monocytes, Chap. 80, p. 413; in HPIM-19.

# 64 Bleeding and Thrombotic Disorders

## BLEEDING DISORDERS

Bleeding may result from abnormalities of (1) platelets, (2) blood vessel walls, or (3) coagulation. Platelet disorders characteristically produce petechial and purpuric skin lesions and bleeding from mucosal surfaces. Defective coagulation results in ecchymoses, hematomas, and mucosal and, in some disorders, recurrent joint bleeding (hemarthroses).

### PLATELET DISORDERS

#### Thrombocytopenia

Normal platelet count is 150,000–350,000/μL. Thrombocytopenia is defined as a platelet count <100,000/μL. Bleeding time, a measurement of platelet function, is abnormally increased if platelet count <100,000/μL; injury or surgery may provoke excess bleeding. Spontaneous bleeding is unusual unless count <20,000/μL; platelet count <10,000/μL is often associated with serious hemorrhage. Bone marrow examination shows increased number of megakaryocytes in disorders associated with accelerated platelet destruction; decreased number in disorders of platelet production. Evaluation of thrombocytopenia is shown in Fig. 64-1.

#### Causes

(1) Production defects such as marrow injury (e.g., drugs, irradiation), marrow failure (e.g., aplastic anemia), marrow invasion (e.g., carcinoma, leukemia, fibrosis); (2) sequestration due to splenomegaly; (3) accelerated destruction—causes include:

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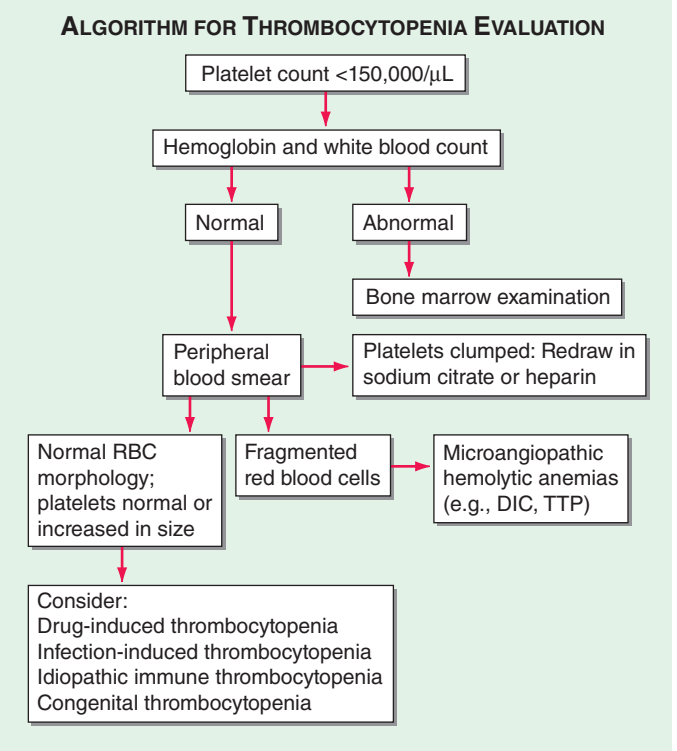


**FIGURE 64-1** Algorithm for evaluating the thrombocytopenic pt. DIC, disseminated intravascular coagulation; TTP, thrombotic thrombocytopenic purpura.

- *Drugs* such as chemotherapeutic agents, thiazides, ethanol, estrogens, sulfonamides, quinidine, quinine, methyldopa.
- *Heparin-induced thrombocytopenia* (HIT) is seen in 5% of pts receiving >5 days of therapy and is due to in vivo platelet aggregation often from anti–platelet factor 4 antibodies. Arterial and occasionally venous thromboses may result. Despite the low platelets, HIT is a hypercoagulable state.
- *Autoimmune destruction* by an antibody mechanism; may be idiopathic or associated with systemic lupus erythematosus (SLE), lymphoma, HIV.
- *Idiopathic thrombocytopenic purpura* (ITP) has two forms: an acute, self-limited disorder of childhood requiring no specific therapy, and a chronic disorder of adults (esp. women 20–40 years). Chronic ITP may be due to autoantibodies to glycoprotein IIb/IIIa or glycoprotein Ib-IX complexes.
- *Disseminated intravascular coagulation* (DIC): platelet consumption with coagulation factor depletion [prolonged prothrombin time (PT), partial thromboplastin time (PTT)] and stimulation of fibrinolysis [generation of fibrin split products (FSPs)]. Blood smear shows microangiopathic hemolysis (schistocytes). Causes include infection (esp. meningococcal, pneumococcal, gram-negative bacteremias), extensive burns, trauma, or thrombosis; giant hemangioma, retained dead fetus, heat stroke, mismatched blood transfusion, metastatic carcinoma, acute promyelocytic leukemia.

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- *Thrombotic thrombocytopenic purpura* (TTP): rare disorder characterized by microangiopathic hemolytic anemia, fever, thrombocytopenia, renal dysfunction (and/or hematuria), and neurologic dysfunction caused by failure to cleave von Willebrand factor (vWF) normally.
- *Hemorrhage with extensive transfusion*.

## Pseudothrombocytopenia

Platelet clumping usually secondary to collection of blood in EDTA (0.3% of pts). Examination of blood smear establishes diagnosis.

## Thrombocytosis

Platelet count >350,000/μL. Either primary (essential thrombocytosis; Chap. 65) or secondary (reactive); latter secondary to severe hemorrhage, iron deficiency, surgery, after splenectomy (transient), malignant neoplasms (esp. Hodgkin's lymphoma, polycythemia vera), chronic inflammatory diseases (e.g., inflammatory bowel disease), recovery from acute infection, vitamin $B_{12}$ deficiency, drugs (e.g., vincristine, epinephrine). Rebound thrombocytosis may occur after marrow recovery from cytotoxic agents, alcohol, vitamin $B_{12}$ replenishment. Primary thrombocytosis may be complicated by bleeding and/or thrombosis; secondary rarely causes hemostatic problems.

## Disorders of Platelet Function

Suggested by the finding of prolonged bleeding time with normal platelet count. Defect is in platelet adhesion, aggregation, or granule release. Causes include (1) drugs—aspirin, other nonsteroidal anti-inflammatory drugs, dipyridamole, clopidogrel or prasugrel, heparin, penicillins, esp. carbenicillin, ticarcillin; (2) uremia; (3) cirrhosis; (4) dysproteinemias; (5) myeloproliferative and myelodysplastic disorders; (6) von Willebrand disease (vWD; see below); (7) cardiopulmonary bypass.

### HEMOSTATIC DISORDERS DUE TO BLOOD VESSEL WALL DEFECTS

Causes include (1) aging; (2) drugs—e.g., glucocorticoids (chronic therapy), penicillins, sulfonamides; (3) vitamin C deficiency; (4) TTP; (5) hemolytic uremic syndrome; (6) Henoch-Schönlein purpura; (7) paraproteinemias; (8) hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease).

### DISORDERS OF BLOOD COAGULATION

## Congenital Disorders

1. *Hemophilia A*: incidence 1:5000; sex-linked recessive deficiency of factor VIII (low plasma factor VIII coagulant activity, but normal amount of factor VIII–related antigen—vWF). Laboratory features: elevated PTT, normal PT.
2. *Hemophilia B* (Christmas disease): incidence 1:30,000, sex-linked recessive, due to factor IX deficiency. Clinical and laboratory features similar to hemophilia A.
3. *von Willebrand disease:* most common inherited coagulation disorder (1:800–1000), usually autosomal dominant; primary defect is reduced synthesis or chemically abnormal factor VIII–related antigen produced by platelets and endothelium, resulting in abnormal platelet function.

## Acquired Disorders

1. *Vitamin K deficiency*: impairs production of factors II (prothrombin), VII, IX, and X; vitamin K is a cofactor in the carboxylation of glutamate residues on prothrombin complex proteins; major source of vitamin K is dietary (esp. green vegetables), with minor production by gut bacteria. Laboratory features: elevated PT and PTT.
2. *Liver disease*: results in deficiencies of all clotting factors except VIII. Laboratory features: elevated PT, normal or elevated PTT.

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3. *Other disorders*: DIC, fibrinogen deficiency (liver disease, L-asparaginase therapy, rattlesnake bites), other factor deficiencies, circulating anticoagulants (lymphoma, SLE, idiopathic), massive transfusion (dilutional coagulopathy).

## TREATMENT BLEEDING DISORDERS

### THROMBOCYTOPENIA CAUSED BY DRUGS

Discontinue use of possible offending agents; expect recovery in 7–10 days. Platelet transfusions may be needed if platelet count <10,000/μL.

### HIT

Discontinue heparin promptly. A direct thrombin inhibitor such as lepirudin (0.4-mg/kg bolus, 0.15-mg/kg per hour infusion; PTT target 1.5–2.5 × baseline) or argatroban (2-μg/kg per min infusion; PTT target 1.5–3 × baseline) should be used for treatment of thromboses. Do not use low-molecular-weight heparin (LMWH), as antibodies often cross-react. Fondaparinux is also effective.

### CHRONIC ITP

Prednisone, initially 1–2 mg/kg per day, then slow taper to keep the platelet count >60,000/μL. Dexamethasone 40 mg/d for 4 days, q2–4 weeks may be even more effective. intravenous immunoglobulin (IVIg) (2 g/kg in divided doses over 2–5 days) to block phagocytic destruction may be useful. Rituximab is effective in pts refractory to glucocorticoids. Eltrombopag (50 mg PO qd) boosts platelet production and allows delay or avoidance of splenectomy. Splenectomy, danazol (androgen), or other agents (e.g., vincristine, cyclophosphamide, fludarabine) are indicated for refractory pts or those requiring >5–10 mg prednisone daily.

### DIC

Control of underlying disease most important; platelets, fresh-frozen plasma (FFP) to correct clotting parameters. Heparin may be beneficial in pts with acute promyelocytic leukemia.

### TTP

Plasmapheresis and FFP infusions (plasma exchange), possibly IV IgG; recovery in two-thirds of cases. Plasmapheresis removes inhibitors of the vWF cleavage enzyme (ADAMTS13), and FFP replaces the enzyme.

### DISORDERS OF PLATELET FUNCTION

Remove or reverse underlying cause. Dialysis and/or cryoprecipitate infusions (10 bags/24 h) may be helpful for platelet dysfunction associated with uremia.

### HEMOSTATIC DISORDERS

Withdraw offending drugs, replace vitamin C, plasmapheresis, and plasma infusion for TTP.

### HEMOPHILIA A

Factor VIII replacement for bleeding or before surgical procedure; degree and duration of replacement depends on severity of bleeding. Give factor VIII (e.g., Recombinate) to obtain a 15% (for mild bleeding) to 50% (for severe bleeding) factor VIII level. The duration should range from a single dose of factor VIII to therapy bid for up to 2 weeks. Dose is calculated as follows:

$$\text{Factor VIII dose} = (\text{Target level - baseline level}) \times \text{weight (kg)} \times 0.5 \text{ unit/kg}$$

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Up to 30% of pts may develop anti–factor VIII antibodies; activated factor VII or factor eight inhibitor bypass agent (FEIBA) may stop or prevent bleeding in these pts.

### HEMOPHILIA B

Recombinant factor IX (e.g., Benefix), FFP or factor IX concentrates (e.g., Proplex, Konyne). Because of the longer half-life, once-daily treatment is sufficient. Dose is calculated as follows:

$$\text{Factor IX dose} = (\text{Target level - baseline level}) \times \text{weight (kg)} \times 1 \text{ unit/kg}$$

### VON WILLEBRAND DISEASE

Desmopressin (1-deamino-8-D-arginine vasopressin) increases release of vWF from endothelial stores in type 1 vWD. It is given IV (0.3 μg/kg) or by nasal spray (2 squirts of 1.5-mg/mL fluid in each nostril). For types 2A, 2M, and 3, cryoprecipitate (plasma product rich in factor VIII) or factor VIII concentrate (Humate-P, Koate HS) is used: up to 10 bags bid for 48–72 h, depending on the severity of bleeding.

### VITAMIN K DEFICIENCY

Vitamin K, 10 mg SC or slow IV.

### LIVER DISEASE

Fresh-frozen plasma.

## THROMBOTIC DISORDERS

### HYPERCOAGULABLE STATE

Consider in pts with recurrent episodes of venous thrombosis [i.e., deep-vein thrombosis (DVT), pulmonary embolism (PE)]. Causes include (1) venous stasis (e.g., pregnancy, immobilization); (2) vasculitis; (3) cancer and myeloproliferative disorders; (4) oral contraceptives; (5) lupus anticoagulant—antibody to platelet phospholipid, stimulates coagulation; (6) HIT; (7) deficiencies of endogenous anticoagulant factors—antithrombin III, protein C, protein S; (8) factor V Leiden—mutation in factor V (Arg → Glu at position 506) confers resistance to inactivation by protein C, accounts for 25% of cases of recurrent thrombosis; (9) prothrombin gene mutation—Glu → Arg at position 20210 results in increased prothrombin levels; accounts for about 6% of thromboses; (10) other—paroxysmal nocturnal hemoglobinuria, dysfibrinogenemias (abnormal fibrinogen).

The approach to the diagnosis of the pt with DVT and/or PE is discussed in Chap. 133.

## TREATMENT THROMBOTIC DISORDERS

Correct underlying disorder whenever possible; long-term warfarin therapy is otherwise indicated.

### ANTICOAGULANT AGENTS

1. *Heparin:* enhances activity of antithrombin III; parenteral agent of choice. LMWH is the preparation of choice (enoxaparin or dalteparin). It can be administered SC, monitoring of the PTT is unnecessary, and it is less likely to induce antibodies and thrombocytopenia. The usual dose is 100 U/kg SC bid. Unfractionated heparin should be given only if LMWH is unavailable. In adults, the dose of unfractionated heparin is 25,000–40,000 U continuous IV infusion over 24 h following initial IV bolus of 5000 U; monitor by following PTT; should be maintained between 1.5 and 2 times upper normal limit. Prophylactic

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anticoagulation to lower risk of venous thrombosis recommended in some pts (e.g., postoperative, immobilized). Prophylactic doses of unfractionated heparin are 5000 U SC bid or tid. Major complication of unfractionated heparin therapy is hemorrhage—manage by discontinuing heparin; for severe bleeding, administer protamine (1 mg/100 U heparin); results in rapid neutralization.

2. *Warfarin* (Coumadin): vitamin K antagonist, decreases levels of factors II, VII, IX, X, and anticoagulant proteins C and S. Administered over 2–3 days; initial load of 5–10 mg PO qd followed by titration of daily dose to keep PT 1.5–2 times control PT or 2–3 times if the International Normalized Ratio (INR) method is used. Complications include hemorrhage, warfarin-induced skin necrosis (rare, occurs in persons deficient in protein C), teratogenic effects. Warfarin effect reversed by administration of vitamin K; FFP infused if urgent reversal necessary. Numerous drugs potentiate or antagonize warfarin effect. Potentiating agents include chlorpromazine, chloral hydrate, sulfonamides, chloramphenicol, other broad-spectrum antibiotics, allopurinol, cimetidine, tricyclic antidepressants, disulfiram, laxatives, high-dose salicylates, thyroxine, clofibrate. Some pts who are sensitive to warfarin effects have genetic defects metabolizing the drug. Antagonizing agents include vitamin K, barbiturates, rifampin, cholestyramine, oral contraceptives, thiazides.
3. *Fondaparinux:* a pentapeptide that directly inhibits factor Xa. It is given at a dose of 2.5 mg SC daily for prophylaxis and 7.5 mg SC daily for treatment of thrombosis and does not require monitoring. Unlike the heparins, it does not bind to platelet factor 4 and does not elicit the antibodies that produce HIT. *Apixaban* and *rivaroxaban* are oral factor Xa inhibitors. Apixaban (5 mg PO bid) as effective as warfarin in DVT and more effective in stroke prevention in atrial fibrillation (AF).
4. *Argatroban and lepirudin:* direct thrombin inhibitors. These agents are being compared to LMWH and are commonly used in pts with HIT. Both are monitored with the activated PTT. *Dabigatran* (150 mg PO bid) is an oral thrombin inhibitor and is non-inferior to warfarin in both DVT and stroke prevention in AF.

In-hospital anticoagulation is usually initiated with heparin for 4–10 days, with subsequent maintenance on warfarin after an overlap of 3 days. Duration of therapy depends on underlying condition; calf DVT with clear precipitating cause, 3 months; proximal or idiopathic DVT or PE, 6–12 months; recurrent idiopathic DVT, 12 months minimum; embolic disease with ongoing risk factor, long term, indefinite. The new oral Xa and thrombin inhibitors are easier to use than warfarin but much more expensive. They are at least comparably effective, have lower bleeding rates, and do not require laboratory monitoring. Reversal agents are in development.

## FIBRINOLYTIC AGENTS

Tissue plasminogen activators (tPAs) mediate clot lysis by activating plasmin, which degrades fibrin. Currently available versions include streptokinase, urokinase, anistreplase (acylated plasminogen streptokinase activator complex), and three modestly distinct forms of recombinant tPA: alteplase, tenecteplase, and reteplase. Indications include treatment of DVT, with lower incidence of postphlebitic syndrome (chronic venous stasis, skin ulceration) than with heparin therapy; massive PE, arterial embolic occlusion of an extremity, treatment of acute myocardial infarction (MI), unstable angina pectoris. Dosages for fibrinolytic agents: (1) tPA—for acute MI and massive PE (adult >65 kg), 10-mg IV bolus over 1–2 min, then 50 mg IV over 1 h, and 40 mg IV over next 2 h (total dose = 100 mg). tPA is slightly more effective but more expensive than streptokinase for treatment of acute MI. (2) Streptokinase—for acute MI, 1.5 million IU IV over 60 min; or 20,000 IU as a bolus intracoronary (IC) infusion, followed by 2000 IU/min for 60 min IC. For PE or arterial or DVT, 250,000 IU over 30 min, then 100,000 IU/h for 24 h (PE) or

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72 h (arterial or DVT). (3) Urokinase—for PE, 4400 IU/kg IV over 10 min, then 4400 (IU/kg)/h IV for 12 h.

Fibrinolytic therapy is usually followed by a period of anticoagulant therapy with heparin. Fibrinolytic agents are contraindicated in pts with (1) active internal bleeding; (2) recent (<2–3 months) cerebrovascular accident; (3) intracranial neoplasm, aneurysm, or recent head trauma.

## ANTIPLATELET AGENTS

Aspirin inhibits platelet function by blocking the ability of cyclooxygenase (COX-1) to synthesize thromboxane A2. The thienopyridines (ticlopidine and clopidogrel) inhibit ADP-induced platelet aggregation by blocking its receptor ($P2Y_{12}$). Dipyridamole acts by inhibiting phosphodiesterase, which permits cAMP levels to increase and block activation. Glycoprotein IIb/IIIa (GPIIb/IIIa) antagonists block the integrin receptors on the platelet and prevent platelet aggregation. Three such agents are now in use: abciximab, an Fab antibody fragment that binds to the activated form of GPIIb/IIIa; eptifibatide, a cyclic heptapeptide that includes the KGD tripeptide motif that the GPIIb/IIIa receptor recognizes; and tirofiban, a tyrosine derivative that mimics the KGD motif.

Aspirin (160–325 mg/d) plus clopidogrel (400-mg loading dose then 75 mg/d) may be beneficial in lowering incidence of arterial thrombotic events (stroke, MI) in high-risk pts. Antiplatelet agents are useful in preventing strokes, complications from percutaneous coronary interventions, and progression of unstable angina.

For a more detailed discussion, see Konkle BA: Bleeding and Thrombosis, Chap. 78, p. 400; Konkle BA: Disorders of Platelets and Vessel Wall, Chap. 140, p. 725; Arruda VR, High KA: Coagulation Disorders, Chap. 141, p. 732; Freedman JE, Loscalzo J: Arterial and Venous Thrombosis, Chap. 142, p. 740; and Weitz JI: Antiplatelet, Anticoagulant, and Fibrinolytic Drugs, Chap. 143, p. 745, in HPIM-19.

# 65 Myeloid Leukemias, Myelodysplasia, and Myeloproliferative Syndromes

## ACUTE MYELOID LEUKEMIA (AML)

AML is a clonal malignancy of myeloid bone marrow precursors in which poorly differentiated cells accumulate in the bone marrow and circulation.

Signs and symptoms occur because of the absence of mature cells normally produced by the bone marrow, including granulocytes (susceptibility to infection) and platelets (susceptibility to bleeding). In addition, if large numbers of immature malignant myeloblasts circulate, they may invade organs and rarely produce dysfunction. There are distinct morphologic subtypes (Table 65-1) that have largely

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**TABLE 65-1 AML CLASSIFICATION SYSTEMS**

| |
|---|
| **World Health Organization Classification**[a] |
| **AML with recurrent genetic abnormalities** |
| AML with t(8;21)(q22;q22); *RUNX1-RUNX1T1*[b] |
| AML with inv(16)(p13.1;1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*[b] |
| Acute promyelocytic leukemia with t(15;17)(q22;q12); *PML-RARA*[b] |
| AML with t(9;11)(p22;q23); *MLLT3-MLL* |
| AML with t(6;9)(p23;q34); *DEK-NUP214* |
| AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1* |
| AML (megakaryoblastic) with t(1;22)(p13;q13); *RBM15-MKL1* |
| *Provisional entity: AML with mutated NPM1* |
| *Provisional entity: AML with mutated CEBPA* |
| **AML with myelodysplasia-related changes** |
| **Therapy-related myeloid neoplasms** |
| **AML not otherwise specified** |
| AML with minimal differentiation |
| AML without maturation |
| AML with maturation |
| Acute myelomonocytic leukemia |
| Acute monoblastic and monocytic leukemia |
| Acute erythroid leukemia |
| Acute megakaryoblastic leukemia |
| Acute basophilic leukemia |
| Acute panmyelosis with myelofibrosis |
| **Myeloid sarcoma** |
| **Myeloid proliferations related to Down syndrome** |
| Transient abnormal myelopoiesis |
| Myeloid leukemia associated with Down syndrome |
| **Blastic plasmacytoid dendritic cell neoplasm** |
| **Acute leukemia of ambiguous lineage** |
| Acute undifferentiated leukemia |
| Mixed phenotype acute leukemia with t(9;22)(q34;q11,20); *BCR-ABL11* |
| Mixed phenotype acute leukemia with t(v;11q23); *MLL* rearranged |
| Mixed phenotype acute leukemia, B/myeloid, NOS |
| Mixed phenotype acute leukemia, T/myeloid, NOS |
| *Provisional entity: Natural killer (NK)-cell lymphoblastic leukemia/lymphoma* |
| **French-American-British (FAB) Classification**[c] |
| MO: Minimally differentiated leukemia |
| Ml: Myeloblastic leukemia without maturation |
| M2: Myeloblastic leukemia with maturation |
| M3: Hypergranular promyelocytic leukemia |
| M4: Myelomonocytic leukemia |
| M4Eo: Variant: Increase in abnormal marrow eosinophils |
| M5: Monocytic leukemia |
| M6: Erythroleukemia (DiGuglielmo's disease) |
| M7: Megakaryoblastic leukemia |

[a]From SH Swerdlow et al (eds): *World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues.* Lyon, IARC Press, 2008.
[b]Diagnosis is AML regardless of blast count.
[c]From JM Bennett et al: *Ann Intern Med* 103:620, 1985.
***Abbreviation:*** AML, acute myeloid leukemia.

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overlapping clinical features. Of note is the propensity of pts with acute promyelocytic leukemia (APL) (FAB M3) to develop bleeding and disseminated intravascular coagulation, especially during induction chemotherapy, because of the release of procoagulants from their cytoplasmic granules.

## Incidence and Etiology

In the United States about 20,830 cases occurred in 2015. AML accounts for about 80% of acute leukemias in adults. Etiology is unknown for the vast majority. As we age, mutations may occur in normal stem cells that convey a proliferative advantage and establish so-called clonal hematopoiesis. In the setting of clonal hematopoiesis, the relative risk for developing acute leukemia increases but the absolute risk is still very small. Three environmental exposures increase the risk: chronic benzene exposure, radiation exposure, and prior treatment with alkylating agents (especially in addition to radiation therapy) and topoisomerase II inhibitors (e.g., doxorubicin and etoposide). Chronic myeloid leukemia (CML), myelodysplasia, and myeloproliferative syndromes may all evolve into AML. Certain genetic abnormalities are associated with particular morphologic variants: t(15;17) with APL, inv(16) with eosinophilic leukemia; others occur in a number of types. Chromosome 11q23 abnormalities are often seen in leukemias developing after exposure to topoisomerase II inhibitors. Chromosome 5 or 7 deletions are seen in leukemias following radiation plus chemotherapy. The particular genetic abnormality has a strong influence on treatment outcome. Expression of MDR1 (multidrug resistance efflux pump) is common in older pts and adversely affects prognosis.

## Clinical and Laboratory Features

Initial symptoms of acute leukemia have usually been present for <3 months; a preleukemic syndrome may be present in some 25% of pts with AML. Signs of anemia, pallor, fatigue, weakness, palpitations, and dyspnea on exertion are most common. White blood cell count (WBC) may be low, normal, or markedly elevated; circulating blast cells may or may not be present; with WBC $>100 \times 10^9$ blasts per liter, leukostasis in lungs and brain may occur. Minor pyogenic infections of the skin are common. Thrombocytopenia leads to spontaneous bleeding, epistaxis, petechiae, conjunctival hemorrhage, gingival bleeding, and bruising, especially with platelet count <20,000/μL. Anorexia and weight loss are common; fever may be present.

Bacterial and fungal infection are common; risk is heightened with total neutrophil count <5000/μL, and breakdown of mucosal and cutaneous barriers aggravates susceptibility; infections may be clinically occult in presence of severe leukopenia, and prompt recognition requires a high degree of clinical suspicion.

Hepatosplenomegaly occurs in about one-third of pts; leukemic meningitis may present with headache, nausea, seizures, papilledema, cranial nerve palsies.

Metabolic abnormalities may include hyponatremia, hypokalemia, elevated serum lactate dehydrogenase (LDH), hyperuricemia, and (rarely) lactic acidosis. With very high blast cell count in the blood, spurious hyperkalemia and hypoglycemia may occur (potassium released from and glucose consumed by tumor cells after the blood was drawn).

# TREATMENT ACUTE MYELOID LEUKEMIA

Leukemic cell mass at time of presentation may be $10^{11}$–$10^{12}$ cells; when total leukemic cell numbers fall below ~$10^9$, they are no longer detectable in blood or bone marrow and pt appears to be in complete remission (CR). Thus, aggressive therapy must continue past the point when initial cell bulk is reduced if leukemia is to be eradicated. Typical phases of chemotherapy include remission induction and postremission therapy, with treatment lasting about 1 year. Figure 65-1 outlines a treatment algorithm.

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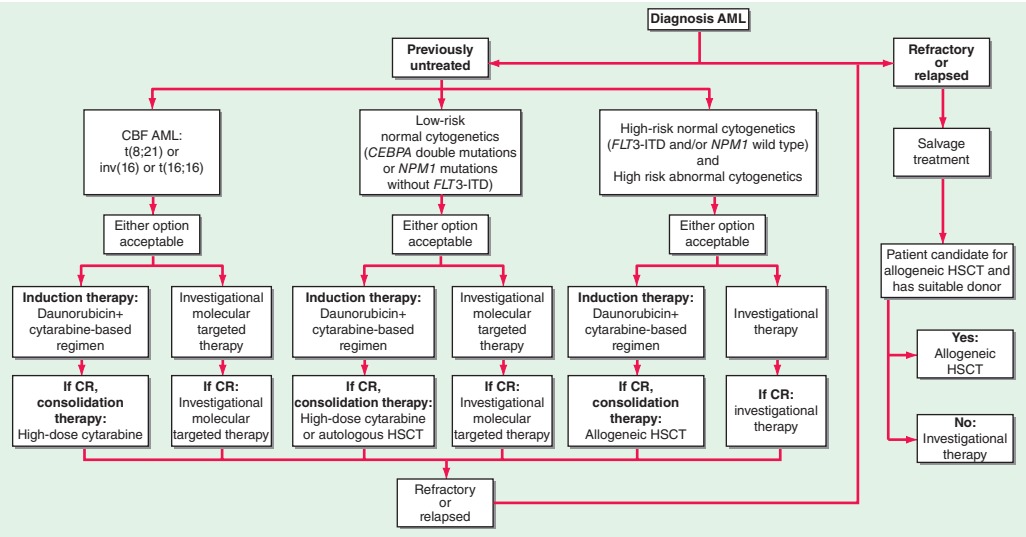


**FIGURE 65-1** Flow chart for the therapy of newly diagnosed acute myeloid leukemia (AML). For all forms of AML except acute promyelocytic leukemia (APL), standard therapy includes a regimen based on a 7-day continuous infusion of cytarabine (100–200 mg/m2 per day) and a 3-day course of daunorubicin (60–90 mg/m2 per day) with or without additional drugs. Idarubicin (12–13 mg/m2 per day) could be used in place of daunorubicin (not shown). Patients who achieve complete remission (CR) undergo postremission consolidation therapy, including sequential courses of high-dose cytarabine, autologous hematopoietic stem cell transplantation (HSCT), allogeneic HSCT, or novel therapies, based on their predicted risk of relapse (i.e., risk-stratified therapy). Patients with APL (see text for treatment) usually receive tretinoin and arsenic trioxide–based regimens with or without anthracycline-based chemotherapy and possibly maintenance with tretinoin. CBF, core binding factor; ITD, internal tandem duplication.

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Supportive care with transfusions of red cells and platelets [from cytomegalovirus (CMV)-seronegative donors, if pt is a candidate for bone marrow transplantation] is very important, as are aggressive prevention, diagnosis, and treatment of infections. Colony-stimulating factors offer little or no benefit; some recommend their use in older pts and those with active infections. Febrile neutropenia should be treated with broad-spectrum antibiotics (e.g., ceftazidime 1 g q8h); if febrile neutropenia persists beyond 7 days, amphotericin B should be added.

About 60–80% of pts will achieve initial remission when treated with cytarabine 100–200 (mg/m$^2$)/d by continuous infusion for 7 days, and daunorubicin [45 (mg/m$^2$)/d] or idarubicin [12–13 (mg/m$^2$)/d] for 3 days. Addition of etoposide may improve CR duration. Half of treated pts enter CR with the first cycle of therapy, and another 25% require two cycles. About 10–30% of pts achieve 5-year disease-free survival and probable cure. Pts achieving a CR who have low risk of relapse [cells contain t(8;21) or inv(16)] receive 3–4 cycles of cytarabine. Those at high risk of relapse may be considered for allogeneic bone marrow transplantation.

Response to treatment after relapse is short, and prognosis for pts who have relapsed is poor. In APL, arsenic trioxide plus *trans*-retinoic acid (tretinoin) induces differentiation of the leukemic cells and molecular complete remissions. A fraction of patients may develop pulmonary symptoms from the sludging of differentiated neoplastic granulocytes in the lung. Glucocorticoids may speed recovery from this syndrome.

Bone marrow transplantation from identical twin or human leukocyte antigen (HLA)-identical sibling is effective treatment for AML. Typical protocol uses high-dose chemotherapy ± total-body irradiation to ablate host marrow, followed by infusion of marrow from donor. Risks are substantial (unless marrow is from identical twin). Complications include graft-versus-host disease, interstitial pneumonitis, opportunistic infections (especially CMV). Comparison between transplantation and high-dose cytarabine as postremission therapy has not produced a clear advantage for either approach. Up to 30% of otherwise end-stage pts with refractory leukemia achieve probable cure from transplantation; results are better when transplant is performed during remission. Results are best for children and young adults.

## CHRONIC MYELOID LEUKEMIA (CML)

CML is a clonal malignancy usually characterized by splenomegaly and production of increased numbers of granulocytes; course is initially indolent but eventuates in leukemic phase (blast crisis) that has a poorer prognosis than de novo AML; rate of progression to blast crisis is variable; overall survival averages 4 years from diagnosis.

### Incidence and Etiology

In the United States about 14,620 cases have occurred in 2015. More than 90% of cases have a reciprocal translocation between chromosomes 9 and 22, creating the Philadelphia (Ph) chromosome and a fusion gene product called *BCR-ABL*. (BCR is from 9, ABL from 22.) The chromosome abnormality appears in all bone marrow–derived cells except T cells. The protein made by the chimeric gene is 210 kDa in chronic phase and 190 kDa in acute blast transformation. In some pts, the chronic phase is clinically silent and pts present with acute leukemia with the Ph chromosome.

### Clinical and Laboratory Features

Symptoms develop gradually; easy fatigability, malaise, anorexia, abdominal discomfort and early satiety from the large spleen, excessive sweating. Occasional pts are found incidentally based on elevated leukocyte count. WBC is usually >25,000/μL

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with the increase accounted for by granulocytes and their precursors back to the myelocyte stage; bands and mature forms predominate. Basophils may account for 10–15% of the cells in the blood. Platelet count is normal or increased. Anemia is often present. Neutrophil alkaline phosphatase score is low. Marrow is hypercellular with granulocytic hyperplasia. Marrow blast cell count is normal or slightly elevated. Serum levels of vitamin $B_{12}$, $B_{12}$-binding proteins, and LDH are elevated in proportion to the WBC. With high blood counts, spurious hyperkalemia and hypoglycemia may be seen.

## Natural History

Chronic phase lasts for 2–4 years. Accelerated phase is marked by anemia disproportionate to the disease activity or treatment. Platelet counts fall. Additional cytogenetic abnormalities appear. Blast cell counts increase. Usually within 6–8 months, overt blast crisis develops in which maturation ceases and blasts predominate. The clinical picture is that of acute leukemia. Half of the cases become AML, one-third have morphologic features of acute lymphoid leukemia, 10% are erythroleukemia, and the rest are undifferentiated. Survival in blast crisis is often <4 months.

## TREATMENT CHRONIC MYELOID LEUKEMIA

Criteria for response are provided in Table 65-2. Allogeneic bone marrow transplantation has the potential to cure the disease in chronic phase. However, the first treatment is imatinib, a molecule that inhibits the chimeric gene product's tyrosine kinase activity. A daily oral dose of 400 mg produces complete hematologic remission of >90% and cytogenetic remission in 76%. If a matched donor is available, it is best to transplant pts in complete remission. Several mechanisms of resistance to imatinib have emerged, and it is unlikely that it leads to permanent remissions when used alone; however, follow-up is not sufficient to draw firm conclusions.

Pts who no longer respond to imatinib may respond to other tyrosine kinase inhibitors such as dasatinib (100 mg PO qd) or nilotinib (400 mg PO bid). The T315I mutation in the *BCR/ABL* gene conveys resistance to all three kinase inhibitors.

**TABLE 65-2 RESPONSE CRITERIA IN CHRONIC MYELOID LEUKEMIA**

| | |
|---|---|
| Hematologic | |
| Complete response[a] | White blood cell count <10,000/μL, normalmorphology<br>Normal hemoglobin and platelet counts |
| Incomplete response | White blood cell count ≥10,000/μl |
| Cytogenetic | Percentage of bone marrow metaphases with t(9;22) |
| Complete response | 0 |
| Partial response | ≤35 |
| Minor response | 36–85[b] |
| No response | 85–100 |
| Molecular | Presence of *BCR/ABL* transcript by RT-PCR |
| Complete response | None (<0.1%) |
| Incomplete response | Any |

[a]Complete hematologic response requires the disappearance of splenomegaly.
[b]Up to 15% normal metaphases are occasionally seen at diagnosis (when 30 metaphases are analyzed).
***Abbreviation:*** RT-PCR, reverse transcriptase polymerase chain reaction.

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Ponatinib (45 mg/d) is effective in patients with the T315I mutation, but concerns have been raised about vascular toxicity. Allopurinol, 300 mg/d, prevents urate nephropathy. The only curative therapy for the disease is HLA-matched allogeneic bone marrow transplantation. The optimal timing of transplantation is unclear, but transplantation in chronic phase is more effective than transplantation in accelerated phase or blast crisis. Transplantation appears most effective in pts treated within a year of diagnosis. Long-term disease-free survival may be obtained in 50–60% of transplanted pts. Infusion of donor lymphocytes can restore remission in relapsing pts. In pts without a matched donor, autologous transplantation may be helpful using peripheral blood stem cells. Treatment of pts in blast crisis with imatinib can obtain responses, but they are not durable.

## MYELODYSPLASTIC SYNDROMES (MDS)

These are clonal abnormalities of marrow cells characterized by varying degrees of cytopenias affecting one or more cell lines. The World Health Organization (WHO) classification of myelodysplastic syndromes is shown in Table 65-3. Other terms that have been used to describe one or more of the entities include *preleukemia* and *oligoblastic leukemia*.

### Incidence and Etiology

About 3000 cases occur each year, mainly in persons >50 years old (median age, 68). As in AML, exposure to benzene, radiation, and chemotherapeutic agents may lead to MDS. Chromosome abnormalities occur in up to 80% of cases, including deletion of part or all of chromosomes 5, 7, and 9 (20 or 21 less commonly) and addition of part or all of chromosome 8. Mutations in genes involved in RNA splicing such as *SF3B1* have a more favorable outcome; mutations in genes often involve in AML such as *RUNX* and *ASXL1* have poorer prognosis.

### Clinical and Laboratory Features

Symptoms depend on the affected lineages, 85% of pts are anemic, 50% have neutropenia, and about one-third have thrombocytopenia. The pathologic features of MDS are a cellular marrow with varying degrees of cytologic atypia including delayed nuclear maturation, abnormal cytoplasmic maturation, accumulation of ringed sideroblasts (iron-laden mitochondria surrounding the nucleus), uni- or bilobed megakaryocytes, micromegakaryocytes, and increased myeloblasts. Table 65-3 lists features used to identify distinct entities. Prognosis is defined by marrow blast %, karyotype, and lineages affected. The International Prognostic Scoring System is shown in Table 65-4.

### TREATMENT MYELODYSPLASTIC SYNDROMES

Allogeneic bone marrow transplantation is the only curative therapy and may cure 60% of those so treated. However, the majority of pts with MDS are too old to receive transplantation. 5-Azacytidine (75 mg/m$^2$ daily × 7, q 4 weeks) can delay transformation to AML by 8–10 months. Decitabine (15 mg/m$^2$ by continuous IV infusion, q8h daily × 3, q 6 weeks) may induce responses lasting a median of 1 year in 20% of pts. Lenalidomide (10 mg/d), a thalidomide analogue with fewer central nervous system effects, causes a substantial fraction of pts with the 5q– syndrome to become transfusion-independent. Pts with low erythropoietin levels may respond to erythropoietin, and a minority of pts with neutropenia respond to granulocyte colony-stimulating factor. Supportive care is the cornerstone of treatment.

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**TABLE 65-3 WORLD HEALTH ORGANIZATION (WHO) CLASSIFICATION OF MYELODYSPLASTIC SYNDROMES/NEOPLASMS**

| Name | WHO Estimated Proportion of Patients with MDS | Peripheral Blood: Key Features | Bone Marrow: Key Features |
|---|---|---|---|
| *Refractory cytopenias with unilineage dysplasia (RCUD):* | | | |
| Refractory anemia (RA) | 10–20% | Anemia <1% of blasts | Unilineage erythroid dysplasia (in ≥10% of cells) <5% blasts |
| Refractory neutropenia (RN) | <1% | Neutropenia <1% blasts | Unilineage granulocytic dysplasia <5% blasts |
| Refractory thrombocytopenia (RT) | <1% | Thrombocytopenia <1% blasts | Unilineage megakaryocytic dysplasia <5% blasts |
| Refractory anemia with ring sideroblasts (RARS) | 3–11% | Anemia<br>No blasts | Unilineage erythroid dysplasia ≥15% of erythroid precursors are ring sideroblasts <5% blasts |
| Refractory cytopenias with multilineage dysplasia (RCMD) | 30% | Cytopenia(s) <1% blasts<br>No Auer rods | Multilineage dysplasia ± ring sideroblasts <5% blasts<br>No Auer rods |
| Refractory anemia with excess blasts, type 1 (RAEB-1) | 40% | Cytopenia(s) <5% blasts<br>No Auer rods | Unilineage or multilineage dysplasia |
| Refractory anemia with excess blasts, type 2 (RAEB-2) | | Cytopenia(s) 5–19% blasts<br>± Auer rods | Unilineage or multilineage dysplasia 10–19% blasts<br>± Auer rods |
| MDS associated with isolated del(5q) | Uncommon | Anemia<br>Normal or high platelet count<br><1% blasts | Isolated 5q31 chromosome deletion<br>Anemia; hypolobated megakaryocytes<br><5% blasts |

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| | | | |
|---|---|---|---|
| Childhood MDS, including refractory cytopenia of childhood (*provisional*) (RCC) | 1 % | Pancytopenia | <5% marrow blasts for RCC<br>Marrow usually hypocellular |
| MDS, unclassifiable (MDS-U) | ? | Cytopenia<br>≤1% blasts | Does not fit other categories<br>Dysplasia<br><5% blasts<br>If no dysplasia, MDS-associated karyotype |

***Note:*** If peripheral blood blasts are 2–4%, the diagnosis is RAEB-1 even if marrow blasts are <5%. If Auer rods are present, the WHO considers the diagnosis RAEB-2 if the blast proportion is <20% (even if <10%), AML if at least 20% blasts. For all subtypes, peripheral blood monocytes are $<1 \times 10^9$/L. Bicytopenia may be observed in RCUD subtypes, but pancytopenia with unilineage marrow dysplasia should be classified as MDS-U. Therapy-related MDS (t-MDS), whether due to alkylating agents, topoisomerase II (t-MDS/t-AML) in the WHO classification of AML and precursor lesions. The listing in this table excludes MDS/myeloproliferative neoplasm overlap categories, such as chronic myelomonocytic leukemia, juvenile myelomonocytic leukemia, and the provisional entity RARS with thrombocytosis.

***Abbreviation:*** MDS, myelodysplastic syndrome.



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**TABLE 65-4 INTERNATIONAL PROGNOSTIC SCORING SYSTEM (IPSS)**

| | Score Value | | | | |
|---|---|---|---|---|---|
| **Prognostic Variable** | **0** | **0.5** | **1** | **1.5** | **2** |
| Bone marrow blasts (%) | <5% | 5–10% | | 11–20% | 21–30% |
| Karyotype[a] | Good | Intermediate | Poor | | |
| Cytopenia[b] (lineages affected) | 0 or 1 | 2 or 3 | | | |
| **Risk Group Scores** | **Score** | | | | |
| Low | 0 | | | | |
| Intermediate-1 | 0.5–1 | | | | |
| Intermediate-2 | 1.5–2 | | | | |
| High | ≥2.5 | | | | |

[a]Good, normal, -Y, del(5q), del(20q); poor, complex (≥3 abnormalities) or chromosome 7 abnormalities; intermediate, all other abnormalities.
[b]Cytopenias defined as Hb <100 g/L, platelet count <100,000/μL, absolute neutrophil count <1500/μL.

## MYELOPROLIFERATIVE SYNDROMES

The three major myeloproliferative syndromes are polycythemia vera, idiopathic myelofibrosis, and essential thrombocytosis. All are clonal disorders of hematopoietic stem cells and all are associated with a mutation in the *JAK2* kinase (V617F) that results in activation of the kinase. The mutation is seen in 90% of pts with polycythemia vera and ~45% of pts with idiopathic myelofibrosis and essential thrombocytosis.

### POLYCYTHEMIA VERA

The most common myeloproliferative syndrome, this is characterized by an increase in red blood cell (RBC) mass, massive splenomegaly, and clinical manifestations related to increased blood viscosity, including neurologic symptoms (vertigo, tinnitus, headache, visual disturbances) and thromboses (myocardial infarction, stroke, peripheral vascular disease; uncommonly, mesenteric and hepatic). It must be distinguished from other causes of increased RBC mass (Chap. 45). This is most readily done by assaying serum erythropoietin levels. Polycythemia vera is associated with very low erythropoietin levels; in other causes of erythrocytosis, erythropoietin levels are high. Assays for the *JAK2*(V617F) mutation are now widely available. Pts are effectively managed with phlebotomy. Some pts require splenectomy to control symptoms, and those with severe pruritus may benefit from psoralens and UV light. 20% develop myelofibrosis, <5% acute leukemia. An inhibitor of JAK1 and *JAK2*, ruxolitinib, is being tested.

### IDIOPATHIC MYELOFIBROSIS

This rare entity is characterized by marrow fibrosis, myeloid metaplasia with extramedullary hematopoiesis, and splenomegaly. Evaluation of a blood smear reveals teardrop-shaped RBC, nucleated RBC, and some early granulocytic forms, including promyelocytes. However, many entities may lead to marrow fibrosis and extramedullary hematopoiesis, and the diagnosis of primary idiopathic myelofibrosis is made only when the many other potential causes are ruled out. The following diseases are in the differential diagnosis: CML, polycythemia vera, Hodgkin's disease, cancer metastatic to the marrow (especially from breast and prostate), infection (particularly granulomatous infections), and hairy cell leukemia. Supportive therapy

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is generally used; novel inhibitors of *JAK2* and telomerase have shown activity in reducing splenomegaly and marrow fibrosis in some cases; however, no study has yet shown a particular drug therapy to improve survival. Cases that do not have *JAK2* mutations often have mutations in *CALR*.

### ESSENTIAL THROMBOCYTOSIS

This is usually noted incidentally upon routine platelet count done in an asymptomatic person. Like myelofibrosis, many conditions can produce elevated platelet counts; thus, the diagnosis is one of exclusion. Platelet count must be >500,000/μL, and known causes of thrombocytosis must be ruled out including CML, iron deficiency, splenectomy, malignancy, infection, hemorrhage, polycythemia vera, myelodysplasia, and recovery from vitamin $B_{12}$ deficiency. Although usually asymptomatic, pts should be treated if they develop migraine headache, transient ischemic attack, or other bleeding or thrombotic disease manifestations. Interferon α is effective therapy, as are anagrelide and hydroxyurea. Treatment should not be given just because the absolute platelet count is high in the absence of other symptoms. *JAK2* and *CALR* mutations account for about 80% of cases; *MPL* mutations, about 10%.

For a more detailed discussion, see Young NS: Aplastic Anemia, Myelodysplasia, and Related Bone Marrow Failure Syndromes, Chap. 130, p. 662; Spivak JL: Polycythemia Vera and Other Myeloproliferative Diseases, Chap. 131, p. 672; and Marcucci G, Bloomfield CD: Acute Myeloid Leukemia, Chap. 132, p. 678; Kantarjian H, Cortes J: Chronic Myeloid Leukemia, Chap. 133, p. 687, in HPIM-19.

# 66 Lymphoid Malignancies

### DEFINITION

Neoplasms of lymphocytes usually represent malignant counterparts of cells at discrete stages of normal lymphocyte differentiation. When bone marrow and peripheral blood involvement dominate the clinical picture, the disease is classified as a *lymphoid leukemia*. When lymph nodes and/or other extranodal sites of disease are the dominant site(s) of involvement, the tumor is called a *lymphoma*. The distinction between lymphoma and leukemia is sometimes blurred; e.g., small lymphocytic lymphoma and chronic lymphoid leukemia are tumors of the same cell type and are distinguished arbitrarily on the basis of the absolute number of peripheral blood lymphocytes ($>5 \times 10^9$/L defines leukemia).

### CLASSIFICATION

Historically, lymphoid tumors have had separate pathologic classifications based on the clinical syndrome—lymphomas according to the Rappaport, Kiel, or Working Formulation systems; acute leukemias according to the French-American-British (FAB) system; Hodgkin's disease (HD) according to the Rye classification. Myelomas

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have generally not been subclassified by pathologic features of the neoplastic cells. The World Health Organization (WHO) has proposed a unifying classification system that brings together all lymphoid neoplasms into a single framework. Although the new system bases the definitions of disease entities on histology, genetic abnormalities, immunophenotype, and clinical features, its organization is based on cell of origin (B cell vs. T cell) and maturation stage (precursor vs. mature) of the tumor, features that are of limited value to the clinician. Table 66-1 lists the disease entities according to a more clinically useful schema based on the clinical manifestations and natural history of the diseases.

## INCIDENCE

Lymphoid tumors are increasing in incidence. Nearly 127,000 cases were diagnosed in 2015 in the United States (Fig. 66-1).

## ETIOLOGY

The cause(s) for the vast majority of lymphoid neoplasms is unknown. The malignant cells are monoclonal and often contain numerous genetic abnormalities. Some genetic alterations are characteristic of particular histologic entities: t(8;14) in Burkitt's lymphoma, t(14;18) in follicular lymphoma, t(11;14) in mantle cell lymphoma, t(2;5) in anaplastic large cell lymphoma, translocations or mutations involving *bcl*-6 on 3q27 in diffuse large cell lymphoma, and others. In most cases, translocations involve insertion of a distant chromosome segment into the antigen receptor genes (either immunoglobulin or T cell receptor) during the rearrangement of the gene segments that form the receptors.

Three viruses—Epstein-Barr virus (EBV), human herpesvirus 8 (HHV-8) (both herpes family viruses), and human T-lymphotropic virus type I (HTLV-I, a retrovirus)—may cause some lymphoid tumors. EBV has been strongly associated with African Burkitt's lymphoma and the lymphomas that complicate immunodeficiencies (disease-related or iatrogenic). EBV has an uncertain relationship to mixed cellularity HD and angiocentric lymphoma. HHV-8 causes a rare entity, body cavity lymphoma, mainly in pts with AIDS. HTLV-I is associated with adult T cell leukemia/lymphoma (ATL). Both the virus and the disease are endemic to southwestern Japan and the Caribbean.

Gastric *Helicobacter pylori* infection is associated with gastric mucosa-associated lymphoid tissue (MALT) lymphoma and perhaps gastric large-cell lymphoma. Eradication of the infection produces durable remissions in about half of pts with gastric MALT lymphoma. MALT lymphomas of other sites are associated with either infection (ocular adnexae, *Chlamydia psittaci*; small intestine, *Campylobacter jejuni*; skin, *Borrelia*) or autoimmunity (salivary gland, Sjögren's syndrome; thyroid gland, Hashimoto's thyroiditis).

Inherited or acquired immunodeficiencies and autoimmune disorders predispose individuals to lymphoma. Lymphoma is 17 times more common in HIV-infected than in HIV-noninfected people. Lymphoma occurs with increased incidence in farmers and meat workers; HD is increased in wood workers.

## DIAGNOSIS AND STAGING

Excisional biopsy is the standard diagnostic procedure; adequate tissue must be obtained. Tissue undergoes three kinds of studies: (1) light microscopy to discern the pattern of growth and the morphologic features of the malignant cells, (2) flow cytometry for assessment of immunophenotype, and (3) genetic studies (cytogenetics, DNA sequencing). Needle aspirates of nodal or extranodal masses are not adequate diagnostic procedures. Leukemia diagnosis and lymphoma staging include generous bilateral iliac crest bone marrow biopsies. Differential diagnosis of adenopathy is reviewed in Chap. 44.

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**TABLE 66-1 CLINICAL SCHEMA OF LYMPHOID NEOPLASMS**

| |
|---|
| **Chronic lymphoid leukemias/lymphomas** |
| Chronic lymphocytic leukemia/small lymphocytic lymphoma (99% B cell, 1% T cell) |
| Prolymphocytic leukemia (90% B cell, 10% T cell) |
| Large granular lymphocyte leukemia (80% NK cell, 20% T cell) |
| Hairy cell leukemia (99–100% B cell) |
| **Indolent lymphoma** |
| Follicular center cell lymphoma, grades I and II (100% B cell) |
| Lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia (100% B cell) |
| Marginal zone lymphoma (100% B cell) |
| Extranodal (MALT lymphoma) |
| Nodal (monocytoid B cell lymphoma) |
| Splenic marginal zone lymphoma |
| Cutaneous T cell lymphoma (mycosis fungoides) (100% T cell) |
| **Aggressive lymphoma** |
| Diffuse large cell lymphoma (85% B cell, 15% T cell) includes immunoblastic |
| Follicular center cell lymphoma, grade III (100% B cell) |
| Mantle cell lymphoma (100% B cell) |
| Primary mediastinal (thymic) large B cell lymphoma (100% B cell) |
| Burkitt-like lymphoma (100% B cell) |
| Peripheral T cell lymphoma (100% T cell) |
| Angioimmunoblastic lymphoma (100% T cell) |
| Angiocentric lymphoma (80% T cell, 20% NK cell) |
| Intestinal T cell lymphoma (100% T cell) |
| Anaplastic large cell lymphoma (70% T cell, 30% null cell) |
| **Acute lymphoid leukemias/lymphomas** |
| Precursor lymphoblastic leukemia/lymphoma (80% T cell, 20% B cell) |
| Burkitt's leukemia/lymphoma (100% B cell) |
| Adult T cell leukemia/lymphoma (100% T cell) |
| **Plasma cell disorders** (100% B cell) |
| Monoclonal gammopathy of uncertain significance |
| Solitary plasmacytoma |
| Extramedullary plasmacytoma |
| Multiple myeloma |
| Plasma cell leukemia |
| **Hodgkin's lymphoma** (cell of origin mainly B cell) |
| Lymphocyte predominant |
| Nodular sclerosis |
| Mixed cellularity |
| Lymphocyte depleted |

***Abbreviations:*** MALT, mucosa-associated lymphatic tissue; NK, natural killer.

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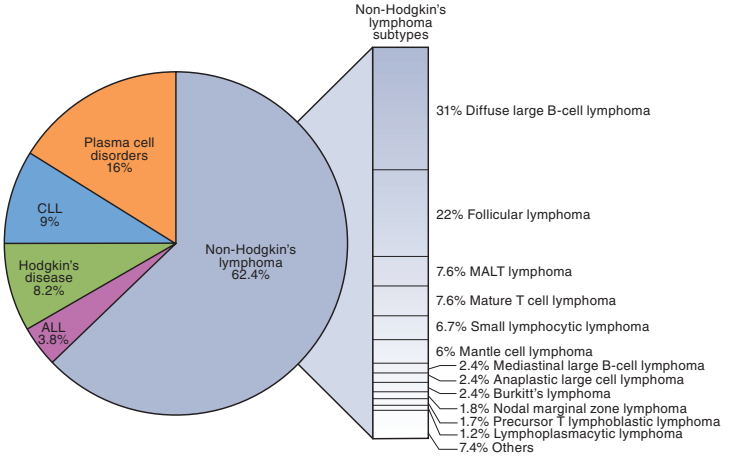


**FIGURE 66-1** Relative frequency of lymphoid malignancies. ALL, acute lymphoid leukemia; CLL, chronic lymphoid leukemia; MALT, mucosa-associated lymphoid tissue.

Staging varies with the diagnosis. In acute leukemia, peripheral blood blast counts are most significant in assessing prognosis. In chronic leukemia, peripheral blood red blood cell (RBC) and platelet counts are most significant in assessing prognosis. Non-Hodgkin's lymphomas have five clinical prognostic factors; indolent and aggressive lymphomas share three of these, advanced stage, high lactate dehydrogenase (LDH) levels, and age >60 years. In follicular lymphoma, the last two factors are Hb <120 g/L (<12 g/dL) and more than four nodal sites of involvement. In aggressive lymphoma, more than one extranodal site and performance status predict outcome. In myeloma, serum levels of paraprotein, creatinine, and $\beta_2$-microglobulin levels predict survival.

## CHRONIC LYMPHOID LEUKEMIAS/LYMPHOMAS

Most of these entities have a natural history measured in years. (Prolymphocytic leukemia is very rare and can be very aggressive.) Chronic lymphocytic leukemia (CLL) is the most common entity in this group (~15,000 cases/year in the United States) and the most common leukemia in the Western world.

### CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

Usually presents as asymptomatic lymphocytosis in pts >60 years. The malignant cell is a CD5+ B cell that looks like a normal small lymphocyte. Trisomy 12 is the most common genetic abnormality. Prognosis is related to stage; stage is determined mainly by the degree to which the tumor cells crowd out normal hematopoietic elements from the marrow (Table 66-2). Cells may infiltrate nodes and spleen as well as marrow. Nodal involvement may be related to the expression of an adhesion molecule that allows the cells to remain in the node rather than recirculate. Pts often have hypogammaglobulinemia. Up to 20% have autoimmune antibodies that may produce autoimmune hemolytic anemia, thrombocytopenia, or red cell aplasia. Death is from infection, marrow failure, or intercurrent illnesses. In 5%, the disease evolves to aggressive lymphoma (Richter's syndrome) that is refractory to treatment.

Subsets of CLL may exist based on whether the immunoglobulin expressed by the tumor cell contains mutations (more indolent course, good prognosis) or retains the

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**TABLE 66-2 STAGING OF B-CELL CLL AND RELATION TO SURVIVAL**

| Stage | Clinical Features | Median Survival, Years |
|---|---|---|
| **RAI** | | |
| 0 | Lymphocytosis | 12 |
| I | Lymphocytosis + adenopathy | 9 |
| II | Lymphocytosis + splenomegaly | 7 |
| III | Anemia | 1–2 |
| IV | Thrombocytopenia | 1–2 |
| **BINET** | | |
| A | No anemia/thrombocytopenia, <3 involved sites | >10 |
| B | No anemia/thrombocytopenia, >3 involved sites | 5 |
| C | Anemia and/or thrombocytopenia | 2 |

germ-line sequence (more aggressive course, poor response to therapy). Methods to distinguish the two subsets clinically are not well defined; CD38+ tumors may have poorer prognosis. The expression of ZAP-70, an intracellular tyrosine kinase normally present in T cells and aberrantly expressed in about 45% of CLL cases, may be a better way to define prognostic subsets. ZAP-70-positive cases usually need treatment within about 3–4 years from diagnosis; ZAP-70-negative cases usually don't require treatment for 8–11 years.

## TREATMENT CHRONIC LYMPHOCYTIC LEUKEMIA

Supportive care is generally given until anemia or thrombocytopenia develops. At that time, tests are indicated to assess the cause of the anemia or thrombocytopenia. Decreased RBC and/or platelet counts related to peripheral destruction may be treated with splenectomy or glucocorticoids without cytotoxic therapy in many cases. If marrow replacement is the mechanism, therapy is indicated. Fludarabine, 25 (mg/m$^2$)/d IV × 5 days every 4 weeks, induces responses in about 75% of pts, complete responses in half. Rituximab (375–500 mg/m$^2$ day 1), fludarabine (25 mg/m$^2$ days 2–4 on cycle 1 and 1–3 in subsequent cycles), plus cyclophosphamide (250 mg/m$^2$ with fludarabine) induce complete responses in nearly 70% of pts but the regimen is associated with significant myelotoxicity. Glucocorticoids increase the risk of infection without adding a substantial antitumor benefit. Monthly IV immunoglobulin (IVIg) significantly reduces risk of serious infection but is expensive and usually reserved for pts who have had a serious infection. Alkylating agents are also active against the tumor. Ibrutinib, an inhibitor of Bruton's tyrosine kinase, is highly active in CLL and some use it as primary therapy. Therapeutic intent is palliative in most pts. Young pts may be candidates for high-dose therapy and autologous or allogeneic hematopoietic cell transplantation; long-term disease-free survival has been noted. Minitransplant, in which the preparative regimen is immunosuppressive but not myeloablative, may be less toxic and as active or more active in disease treatment than high-dose therapy. Monoclonal antibodies alemtuzumab (anti-CD52) and rituximab, obinutuzumab, and ofatumumab (all anti-CD20s) also are active as single agents or combined with chlorambucil.

See Chaps. 134 and 135e in HPIM-19 for discussion of the rarer entities.

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## INDOLENT LYMPHOMAS

These entities have a natural history measured in years. Median survival is about 14 years. Follicular lymphoma is the most common indolent lymphoma, accounting for about one-third of all lymphoid malignancies.

### FOLLICULAR LYMPHOMA

Usually presents with painless peripheral lymphadenopathy, often involving several nodal regions. "B symptoms" (fever, sweats, weight loss) occur in 10%, less common than with Hodgkin's lymphoma. In about 25%, nodes wax and wane before the pt seeks medical attention. Median age is 55 years. Disease is widespread at diagnosis in 85%. Liver and bone marrow are commonly involved extranodal sites.

The tumor has a follicular or nodular growth pattern reflecting the follicular center origin of the malignant cell. The t(14;18) is present in 85% of cases, resulting in the overexpression of bcl-2, a protein involved in prevention of programmed cell death. The normal follicular center B cell is undergoing active mutation of the immunoglobulin variable regions in an effort to generate antibody of higher affinity for the selecting antigen. Follicular lymphoma cells also have a high rate of mutation that leads to the accumulation of genetic damage. Over time, follicular lymphomas acquire sufficient genetic damage (e.g., mutated p53) to accelerate their growth and evolve into diffuse large B-cell lymphomas that are often refractory to treatment. The majority of pts dying from follicular lymphoma have undergone histologic transformation. This transformation occurs at a rate of about 7% per year and is an attribute of the disease, not the treatment. The rate of histologic progression has decreased as treatment has improved.

### TREATMENT FOLLICULAR LYMPHOMA

Only 15% of pts have localized disease, but the majority of these pts are curable with radiation therapy. Although many forms of treatment induce tumor regression in advanced-stage pts, disease cure has been elusive. No therapy, single-agent alkylators, nucleoside analogues (fludarabine, cladribine), combination chemotherapy, radiation therapy, and biologic agents [interferon (IFN) α, monoclonal antibodies such as rituximab (anti-CD20)] are all considered appropriate. More than 90% of pts are responsive to treatment; complete responses are seen in about 50–75% of pts treated aggressively. The median duration of remission of pts treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) + rituximab exceeds 6 years. Bendamustine + rituximab is an active combination. Younger pts are being treated experimentally with high-dose therapy and autologous hematopoietic stem cells or minitransplant. It is not yet clear whether this is curative. Radioimmunotherapy with isotopes guided by anti-CD20 antibody (ibritumomab tiuxetan, In-111; tositumomab, I-131) may produce durable responses. Combination chemotherapy with or without IFN maintenance may prolong survival and delay or prevent histologic progression, especially in pts with poor prognostic features. Remissions appear to last longer with chemotherapy plus rituximab; some data suggest that the longer remissions are leading to improved survival.

See Chaps. 134 and 135e in HPIM-19 for discussion of the other indolent lymphomas.

## AGGRESSIVE LYMPHOMAS

A large number of pathologic entities share an aggressive natural history; median survival untreated is 6 months, and nearly all untreated pts are dead within 1 year. Pts may present with asymptomatic adenopathy or symptoms referable to involvement

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of practically any nodal or extranodal site: Mediastinal involvement may produce superior vena cava syndrome or pericardial tamponade; retroperitoneal nodes may obstruct ureters; abdominal masses may produce pain, ascites, or GI obstruction or perforation; CNS involvement may produce confusion, cranial nerve signs, headache, seizures, and/or spinal cord compression; bone involvement may produce pain or pathologic fracture. About 45% of pts have B symptoms.

Diffuse large B-cell lymphoma is the most common histologic diagnosis among the aggressive lymphomas, accounting for 35–45% of all lymphomas. Aggressive lymphomas together account for ~60% of all lymphoid tumors. About 85% of aggressive lymphomas are of mature B-cell origin; 15% are derived from peripheral (postthymic) T cells.

## APPROACH TO THE PATIENT: **Aggressive Lymphoma**

Early diagnostic biopsy is critical. Pt workup is directed by symptoms and known patterns of disease. Pts with Waldeyer's ring involvement should undergo careful evaluation of the GI tract. Pts with bone or bone marrow involvement should have a lumbar puncture to evaluate meningeal CNS involvement.

## TREATMENT AGGRESSIVE LYMPHOMAS

Localized aggressive lymphomas are usually treated with four cycles of CHOP combination chemotherapy ± involved-field radiation therapy. About 85% of these pts are cured. CHOP + rituximab appears to be even more effective than CHOP + radiation therapy. The specific therapy used for pts with more advanced disease is controversial. Six cycles of CHOP + rituximab is the treatment of choice for advanced-stage disease. Outcome is influenced by tumor bulk (usually measured by LDH levels, stage, and number of extranodal sites) and physiologic reserve (usually measured by age and Karnofsky status) (Table 66-3). CHOP + rituximab cures about two-thirds of pts. The use of a sequential high-dose chemotherapy regimen in pts with high-intermediate and high-risk disease has yielded long-term survival in about 75% of pts in some institutions. Other studies fail to confirm a role for high-dose therapy.

About 30–45% of pts not cured with initial standard combination chemotherapy may be salvaged with high-dose therapy and autologous hematopoietic stem cell transplantation.

Specialized approaches are required for lymphomas involving certain sites (e.g., CNS, stomach) or under certain complicating clinical circumstances (e.g., concurrent illness, AIDS). Lymphomas occurring in iatrogenically immunosuppressed pts may regress when immunosuppressive medication is withheld. Lymphomas occurring post–allogeneic marrow transplant may regress with infusions of donor leukocytes.

Pts with rapidly growing bulky aggressive lymphoma may experience tumor lysis syndrome when treated (Chap. 25); prophylactic measures (hydration, urine alkalinization, allopurinol, rasburicase) may be lifesaving.

# ACUTE LYMPHOID LEUKEMIAS/LYMPHOMAS

## ACUTE LYMPHOBLASTIC LEUKEMIA AND LYMPHOBLASTIC LYMPHOMA

These are more common in children than adults (~6000 total cases/year). The majority of cases have tumor cells that appear to be of thymic origin, and pts may have mediastinal masses. Pts usually present with recent onset of signs of marrow failure

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**TABLE 66-3 INTERNATIONAL PROGNOSTIC INDEX FOR NHL**

| | |
|---|---|
| Five clinical risk factors: | |
| Age ≥60 years | |
| Serum lactate dehydrogenase levels elevated | |
| Performance status ≥2 (ECOG) or ≤70 (Karnofsky) | |
| Ann Arbor stage III or IV | |
| >1 site of extranodal involvement | |
| Pts are assigned a number for each risk factor they have. | |
| Pts are grouped differently based on the type of lymphoma. | |
| For diffuse large B-cell lymphoma: | |
| 0, 1 factor = low risk: | 35% of cases; 5-year survival, 73% |
| 2 factors = low-intermediate risk: | 27% of cases; 5-year survival, 51% |
| 3 factors = high-intermediate risk: | 22% of cases; 5-year survival, 43% |
| 4, 5 factors = high risk: | 16% of cases; 5-year survival, 26% |
| For diffuse large B-cell lymphoma treated with R-CHOP: | |
| 0 factor = very good: | 10% of cases; 5-year survival, 94% |
| 1, 2 factors = good: | 45% of cases; 5-year survival, 79% |
| 3, 4, 5 factors = poor: | 45% of cases; 5-year survival, 55% |

***Abbreviations:*** ECOG, Eastern Cooperative Oncology Group; NHL, non-Hodgkin's lymphoma; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone.

(pallor, fatigue, bleeding, fever, infection). Hepatosplenomegaly and adenopathy are common. Males may have testicular enlargement reflecting leukemic involvement. Meningeal involvement may be present at diagnosis or develop later. Elevated LDH, hyponatremia, and hypokalemia may be present, in addition to anemia, thrombocytopenia, and high peripheral blood blast counts. The leukemic cells are more often FAB type L2 in adults than in children, where L1 predominates. Leukemia diagnosis requires at least 20% lymphoblasts in the marrow. Prognosis is adversely affected by high presenting white count, age >35 years, and the presence of t(9;22), t(1;19), and t(4;11) translocations. HOX11 expression identifies a more favorable subset of T cell acute lymphoblastic leukemia.

## TREATMENT ACUTE LYMPHOBLASTIC LEUKEMIA AND LYMPHOBLASTIC LYMPHOMA

Successful treatment requires intensive induction phase, CNS prophylaxis, and maintenance chemotherapy that extend for about 2 years. Vincristine, L-asparaginase, cytarabine, daunorubicin, and prednisone are particularly effective agents. Intrathecal or high-dose systemic methotrexate is effective CNS prophylaxis. Long-term survival of 60–65% of pts may be achieved. The role and timing of bone marrow transplantation in primary therapy are debated, but up to 30% of relapsed pts may be cured with salvage transplantation.

## BURKITT'S LYMPHOMA/LEUKEMIA

This is also more common in children. It is associated with translocations involving the c-*myc* gene on chromosome 8 rearranging with immunoglobulin heavy or light chain genes. Pts often have disseminated disease with large abdominal masses, hepatomegaly, and adenopathy. If a leukemic picture predominates, it is classified as FAB L3.

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### TREATMENT BURKITT'S LYMPHOMA/LEUKEMIA

Resection of large abdominal masses improves treatment outcome. Aggressive leukemia regimens that include vincristine, cyclophosphamide, 6-mercaptopurine, doxorubicin, and prednisone are active. CODOX-M and the BFM regimen are the most effective regimens. Cure may be achieved in 50–60%. The need for maintenance therapy is unclear. Prophylaxis against tumor lysis syndrome is important (Chap. 25).

### ADULT T CELL LEUKEMIA/LYMPHOMA (ATL)

This is very rare; only a small fraction (~2%) of persons infected with HTLV-I go on to develop the disease. Some HTLV-I-infected pts develop spastic paraplegia from spinal cord involvement without developing cancer. The characteristic clinical syndrome of ATL includes high white count without severe anemia or thrombocytopenia, skin infiltration, hepatomegaly, pulmonary infiltrates, meningeal involvement, and opportunistic infections. The tumor cells are CD4+ T cells with cloven hoof- or flower-shaped nuclei. Hypercalcemia occurs in nearly all pts and is related to cytokines produced by the tumor cells.

### TREATMENT ADULT T CELL LEUKEMIA/LYMPHOMA

Aggressive therapy is associated with serious toxicity related to the underlying immunodeficiency. Glucocorticoids relieve hypercalcemia. The tumor is responsive to therapy, but responses are generally short lived. Zidovudine and IFN may be palliative in some pts.

## PLASMA CELL DISORDERS

The hallmark of plasma cell disorders is the production of immunoglobulin molecules or fragments from abnormal plasma cells. The intact immunoglobulin molecule, or the heavy chain or light chain produced by the abnormal plasma cell clone, is detectable in the serum and/or urine and is called the M (for monoclonal) component. The amount of the M component in any given pt reflects the tumor burden in that pt. In some, the presence of a clonal light chain in the urine (Bence Jones protein) is the only tumor product that is detectable. M components may be seen in pts with other lymphoid tumors, nonlymphoid cancers, and noncancerous conditions such as cirrhosis, sarcoidosis, parasitic infestations, and autoimmune diseases.

### MULTIPLE MYELOMA

A malignant proliferation of plasma cells in the bone marrow (notably not in lymph nodes). Nearly 27,000 new cases are diagnosed each year. Disease manifestations result from tumor expansion, local and remote actions of tumor products, and the host response to the tumor. About 70% of pts have bone pain, usually involving the back and ribs, precipitated by movement. Bone lesions are multiple, lytic, and rarely accompanied by an osteoblastic response. Thus, bone scans are less useful than radiographs. The production of osteoclast-activating cytokines by tumor cells leads to substantial calcium mobilization, hypercalcemia, and symptoms related to it. Decreased synthesis and increased catabolism of normal immunoglobulins lead to hypogammaglobulinemia, and a poorly defined tumor product inhibits granulocyte migration. These changes create a susceptibility to bacterial infections, especially the pneumococcus, *Klebsiella pneumoniae*, and *Staphylococcus aureus* affecting the lung and *Escherichia coli* and other gram-negative pathogens affecting the urinary tract. Infections affect at least 75% of pts at some time in their course. Renal failure may affect 25% of pts; its pathogenesis is multifactorial—hypercalcemia, infection, toxic

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effects of light chains, urate nephropathy, and dehydration. Neurologic symptoms may result from hyperviscosity, cryoglobulins, and rarely amyloid deposition in nerves. Anemia occurs in 80% related to myelophthisis and inhibition of erythropoiesis by tumor products. Clotting abnormalities may produce bleeding.

## Diagnosis

Marrow plasmacytosis >10%, lytic bone lesions, and a serum and/or urine M component are the classic triad. Monoclonal gammopathy of uncertain significance (MGUS) is much more common than myeloma, affecting about 6% of people over age 70 years; in general, MGUS is associated with a level of M component <20 g/L, low serum $\beta_2$-microglobulin, <10% marrow plasma cells, and no bone lesions. Lifetime risk of progression of MGUS to myeloma is about 25%.

## Staging

Disease stage influences survival (Table 66-4).

## TREATMENT MULTIPLE MYELOMA

About 10% of pts have very slowly progressive disease (the so-called smoldering myeloma) and do not require treatment until the paraprotein levels rise above 50 g/L or progressive bone disease occurs. Pts with solitary plasmacytoma and extramedullary plasmacytoma are usually cured with localized radiation therapy. Supportive care includes early treatment of infections; control of hypercalcemia with glucocorticoids, hydration, and natriuresis; chronic administration of bisphosphonates to antagonize skeletal destruction; and prophylaxis against urate nephropathy and dehydration. Therapy aimed at the tumor is usually palliative. Initial therapy is usually one of several approaches, based on whether the pt is a candidate for high-dose therapy and autologous stem cell transplant. Transplant eligible (avoid alkylating agents): thalidomide, 400 mg/d PO or 200 mg qhs, plus dexamethasone, 40 mg/d on days 1–4 each month, with or without bortezomib, or chemotherapy such as liposomal doxorubicin. Transplant ineligible: melphalan, 8 mg/m$^2$ orally for 4–7 days every 4–6 weeks, plus prednisone. About 60% of pts have significant symptomatic improvement plus a 75% decline in the M component. Bortezomib also appears to improve response rates to melphalan. Experimental approaches using sequential high-dose pulses of melphalan plus two successive autologous stem cell transplants have produced complete responses in about 50% of pts <65 years. Long-term follow-up is required to see whether survival is enhanced. Palliatively treated pts generally follow a chronic course for 2–5 years, followed by an acceleration characterized by organ infiltration with myeloma cells and marrow failure. More aggressive treatment may produce median survival of 6 years. New approaches to salvage treatment include bortezomib, 1.3 mg/m$^2$ on days 1, 4, 8, and 11 every 3 weeks, often used with dexamethasone, vincristine, and/or liposomal doxorubicin. Lenalidomide is also active and increasingly used as maintenance therapy.

## HODGKIN'S LYMPHOMA

About 9000 new cases are diagnosed each year. HD is a tumor of Reed-Sternberg cells, aneuploid cells that usually express CD30 and CD15 but may also express other B or T cell markers. Most tumors are derived from B cells in that immunoglobulin genes are rearranged but not expressed. Most of the cells in an enlarged node are normal lymphoid, plasma cells, monocytes, and eosinophils. The etiology is unknown, but the incidence in both identical twins is 99-fold increased over the expected concordance, suggesting a genetic susceptibility. Distribution of histologic subtypes is 75% nodular sclerosis, 20% mixed cellularity, with lymphocyte predominant and lymphocyte depleted representing about 5%.

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**TABLE 66-4 MYELOMA STAGING SYSTEMS**

| Durie-Salmon Staging System | | |
|---|---|---|
| **Stage** | **Criteria** | **Estimated tumor burden × $10^{12}$ cells/$m^2$** |
| I | All of the following:<br>1. Hemoglobin >100 g/L (>10 g/dL)<br>2. Serum calcium <3 mmol/L (<12 mg/dL)<br>3. Normal bone x-ray or solitary lesion<br>4. Low M-component production<br>a. IgG level <50 g/L (<5 g/dL)<br>b. IgA level <30 g/L (<3 g/dL)<br>c. Urine light chain <4 g/24 h | <0.6 (low) |
| II | Fitting neither I nor III | 0.6–1.20 (intermediate) |
| III | One or more of the following:<br>1. Hemoglobin <85 g/L (<8.5 g/dL)<br>2. Serum calcium >3 mmol/L (>12 mg/dL)<br>3. Advanced lytic bone lesions<br>4. High M-component production<br>a. IgG level >70 g/L (>7 g/dL)<br>b. IgA level >50 g/L (>5 g/dL)<br>c. Urine light chains >12 g/24 h | >1.20 (high) |
| **Level** | **Stage** | **Median Survival, Months** |
| **Subclassification based on serum creatinine levels** | | |
| A <177 µmol/L (<2 mg/dL) | IA | 61 |
| B >177 µmol/L (>2 mg/dL) | IIA, B | 55 |
| | IIIA | 30 |
| | IIIB | 15 |
| **International Staging System** | | |
| $\beta_2$M <3.5, alb ≥3.5 | I (28%) | 62 |
| $\beta_2$M <3.5, alb <3.5 *or* $\beta_2$M = 3.5–5.5 | II (39%) | 44 |
| $\beta_2$M >5.5 | III (33%) | 29 |

***Note:*** $\beta_2$M, serum $\beta_2$-microglobulin in mg/L; alb, serum albumin in g/dL; (#), % pts presenting at each stage.

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## Clinical Manifestations

Usually presents with asymptomatic lymph node enlargement or with adenopathy associated with fever, night sweats, weight loss, and sometimes pruritus. Mediastinal adenopathy (common in nodular sclerosing HD) may produce cough. Spread of disease tends to be to contiguous lymph node groups. Superior vena cava obstruction or spinal cord compression may be presenting manifestation. Involvement of bone marrow and liver is rare.

## Differential Diagnosis

- Infection: mononucleosis, viral syndromes, *Toxoplasma*, *Histoplasma*, primary tuberculosis
- Other malignancies: especially head and neck cancers
- Sarcoidosis: mediastinal and hilar adenopathy

## Immunologic and Hematologic Abnormalities

- Defects in cell-mediated immunity (remains even after successful treatment of lymphoma), cutaneous anergy, diminished antibody production to capsular antigens of *Haemophilus* and pneumococcus
- Anemia; elevated erythrocyte sedimentation rate, leukemoid reaction, eosinophilia, lymphocytopenia, fibrosis and granulomas in marrow

## Staging

The Ann Arbor staging classification is shown in Table 66-5. Disease is staged by performing physical examination, chest x-ray, thoracoabdominal CT, bone marrow biopsy, ultrasound examinations, and lymphangiogram. Staging laparotomy should be used, especially to evaluate the spleen, if pt has early-stage disease on clinical grounds and radiation therapy is being contemplated. Pathologic staging is unnecessary if the pt is treated with chemotherapy.

## TREATMENT HODGKIN'S DISEASE

About 85% of pts are curable. Therapy should be performed by experienced clinicians in centers with appropriate facilities. Most pts are clinically staged and treated with chemotherapy alone or combined-modality therapy. Those with stage II disease often receive either two or four cycles of doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) with or without involved-field radiation therapy or Stanford V, a combined-modality program using lower doses of chemotherapy. Those with stage III or IV disease receive six cycles of combination chemotherapy, usually ABVD. Pts with any stage disease accompanied by a large mediastinal mass (greater than one-third the greatest chest diameter) should receive combined-modality therapy with MOPP/ABVD or mechlorethamine, vincristine, procarbazine, prednisone (MOPP)-ABV hybrid followed by mantle field radiation therapy. (Radiation plus ABVD is too toxic to the lung.) A persistently positive midtreatment positron emission tomography scan may be an index of risk of relapse and need for additional therapy. About one-half of pts (or more) not cured by their initial chemotherapy regimen may be rescued by high-dose therapy and autologous stem cell transplant. Brentuximab vedotin, an anti-CD30 drug conjugate, has activity in pts relapsing after transplant.

With long-term follow-up, it has become clear that more pts are dying of late fatal toxicities related to radiation therapy (myocardial infarction, stroke, second cancers) than from HD. It may be possible to avoid radiation exposure by using combination chemotherapy alone in early-stage disease as well as in advanced-stage disease.

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**TABLE 66-5 THE ANN ARBOR STAGING SYSTEM FOR HODGKIN'S LYMPHOMA**

| Stage | Definition |
|---|---|
| I | Involvement of a single lymph node region or lymphoid structure (e.g., spleen, thymus, Waldeyer's ring) |
| II | Involvement of two or more lymph node regions on the same side of the diaphragm (the mediastinum is a single site; hilar lymph nodes should be considered "lateralized" and, when involved on both sides, constitute stage II disease) |
| III | Involvement of lymph node regions or lymphoid structures on both sides of the diaphragm |
| $III_1$ | Subdiaphragmatic involvement limited to spleen, splenic hilar nodes, celiac nodes, or portal nodes |
| $III_2$ | Subdiaphragmatic involvement includes paraaortic, iliac, or mesenteric nodes plus structures in $III_1$ |
| IV | Involvement of extranodal site(s) beyond that designated as "E" |
| | More than one extranodal deposit at any location |
| | Any involvement of liver or bone marrow |
| A | No symptoms |
| B | Unexplained weight loss of >10% of the body weight during the 6 months before staging investigation |
| | Unexplained, persistent, or recurrent fever with temperatures >38°C (100.5°F) during the previous month |
| | Recurrent drenching night sweats during the previous month |
| E | Localized, solitary involvement of extralymphatic tissue, excluding liver and bone marrow |

For a more detailed discussion, see Longo DL: Malignancies of Lymphoid Cells, Chap. 134, p. 695; Tefferi A, Longo DL: Less Common Hematologic Malignancies, Chap. 135e; Munshi NC, Longo DL, Anderson KC: Plasma Cell Disorders, Chap. 136, p. 710 in HPIM-19.

# 67 Skin Cancer

## MALIGNANT MELANOMA

Most dangerous cutaneous malignancy, high metastatic potential, poor prognosis with metastatic spread.

### Incidence

Melanoma has been diagnosed in 73,870 people in the United States in 2015 and caused 9940 deaths.

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**TABLE 67-1 FACTORS ASSOCIATED WITH INCREASED RISK OF MELANOMA**

| |
|---|
| Total body nevi (higher number = higher risk) |
| Family or personal history |
| Dysplastic nevi |
| Light skin/hair/eye color |
| Poor tanning ability |
| Freckling |
| UV exposure/sunburns/tanning booths |
| *CDKN2A* mutation |
| *MC1R* variants |

## Predisposing Factors (Table 67-1)

Fair complexion, sun exposure, family history of melanoma, dysplastic nevus syndrome (autosomal dominant disorder with multiple nevi of distinctive appearance and cutaneous melanoma may be associated with 9p deletion), and presence of a giant congenital nevus. Blacks have a low incidence.

## Prevention

Sun avoidance lowers risk. Sunscreens are not proven effective.

## Types

1. *Superficial spreading melanoma:* Most common; begins with initial radial growth phase before invasion.
2. *Lentigo maligna melanoma:* Very long radial growth phase before invasion, lentigo maligna (Hutchinson's melanotic freckle) is precursor lesion, most common in elderly and in sun-exposed areas (esp. face).
3. *Acral lentiginous:* Most common form in darkly pigmented pts; occurs on palms and soles, mucosal surfaces, in nail beds and mucocutaneous junctions; similar to lentigo maligna melanoma but with more aggressive biologic behavior.
4. *Nodular:* Generally poor prognosis because of invasive growth from onset.

## Biology

About half of melanomas carry an activating somatic mutation in the *BRAF* gene, often a valine to glutamate substitution at amino acid 600 (V600E). *N-ras* is mutated in about 20% and rare pts have activating mutations in *c-kit*. These mutations have been targeted by therapeutic agents that have antitumor activity.

## Clinical Appearance

Generally pigmented (rarely amelanotic); color of lesions varies, but red, white, and/or blue are common, in addition to brown and/or black. Suspicion should be raised by a pigmented skin lesion that is >6 mm in diameter, asymmetric, has an irregular surface or border, or has variation in color.

## Prognosis

Best with thin lesions without evidence of metastatic spread; with increasing thickness or evidence of spread, prognosis worsens. Stages I and II (primary tumor without spread) have 85% 5-year survival. Stage III (palpable regional nodes with tumor) has a 50% 5-year survival when only one node is involved and 15–20% when four or more are involved. Stage IV (disseminated disease) has <5% 5-year survival.

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## TREATMENT MALIGNANT MELANOMA

Early recognition and local excision for localized disease is best; 1- to 2-cm margins are as effective as 4- to 5-cm margins and do not usually require skin grafting. Elective lymph node dissection offers no advantage in overall survival compared with deferral of surgery until clinical recurrence. Pts with stage II disease may have improved disease-free survival with adjuvant interferon (IFN)-α 3 million units three times weekly for 12–18 months. In one study, pts with stage III disease had improved survival with adjuvant IFN, 20 million units IV daily × 5 for 4 weeks, then 10 million units SC three times weekly for 11 months. This result was not confirmed in a second study. Metastatic disease may be treated with chemotherapy or immunotherapy. Vemurafenib 960 mg PO bid or dabrafenib 150 mg PO bid induces responses in about 50% of pts with *BRAF* mutations. Median survival is about 16 months. Addition of a MET inhibitor (trametinib 2 mg/d) improved response rate to 64% and median overall survival to >20 months. The anti-CTLA4 antibody ipilimumab prolongs survival by about 4 months. The combination of ipilimumab and the PD-1 blocker nivolumab induced responses in both BRAF mutant and BRAF wild-type tumors. Response rate 58% with responses lasting about 12 months. Dacarbazine (250 mg/m$^2$ IV daily × 5 q3w) plus tamoxifen (20 mg/m$^2$ PO daily) may induce partial responses in one-quarter of pts. IFN and interleukin 2 (IL-2) at maximum tolerated doses induce partial responses in 15% of pts. Rare long remissions occur with IL-2. Temozolomide is an oral agent that has some activity. It can enter the central nervous system (CNS) and is being evaluated with radiation therapy for CNS metastases. No therapy for metastatic disease is curative. Vaccines and adoptive cellular therapies are being tested.

## BASAL CELL CARCINOMA (BCC)

Most common form of skin cancer; most frequently on sun-exposed skin, esp. face.

### Predisposing Factors

Fair complexion, chronic UV exposure, exposure to inorganic arsenic (i.e., Fowler's solution or insecticides such as Paris green), or exposure to ionizing radiation.

### Prevention

Avoidance of sun exposure and use of sunscreens lower risk.

### Types

Five general types: noduloulcerative (most common), superficial (mimics eczema), pigmented (may be mistaken for melanoma), morpheaform (plaquelike lesion with telangiectasia—with keratotic is most aggressive), keratotic (basosquamous carcinoma).

### Clinical Appearance

Classically a pearly, translucent, smooth papule with rolled edges and surface telangiectasia.

## TREATMENT BASAL CELL CARCINOMA

Local removal with electrodesiccation and curettage, excision, cryosurgery, or radiation therapy; metastases are rare but may spread locally. Exceedingly unusual for BCC to cause death. Locally advanced or metastatic disease may respond to vismodegib, an inhibitor of the hedgehog pathway often activated in this disease.

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### SQUAMOUS CELL CARCINOMA (SCC)

Less common than basal cell but more likely to metastasize.

#### Predisposing Factors

Fair complexion, chronic UV exposure, previous burn, or other scar (i.e., scar carcinoma), exposure to inorganic arsenic or ionizing radiation. Actinic keratosis is a premalignant lesion.

#### Types

Most commonly occurs as an ulcerated nodule or a superficial erosion on the skin. Variants include:

1. *Bowen's disease:* Erythematous patch or plaque, often with scale; noninvasive; involvement limited to epidermis and epidermal appendages (i.e., SCC in situ).
2. *Scar carcinoma:* Suggested by sudden change in previously stable scar, esp. if ulceration or nodules appear.
3. *Verrucous carcinoma:* Most commonly on plantar aspect of foot; low-grade malignancy but may be mistaken for a common wart.

#### Clinical Appearance

Hyperkeratotic papule or nodule or erosion; nodule may be ulcerated.

**TREATMENT SQUAMOUS CELL CARCINOMA**

Local excision and Mohs micrographic surgery are most common; radiation therapy in selected cases. Metastatic disease may be treated with radiation therapy or with combination biologic therapy; 13-*cis*-retinoic acid 1 mg/d PO plus IFN 3 million units/d SC.

#### Prognosis

Favorable if secondary to UV exposure; less favorable if in sun-protected areas or associated with ionizing radiation.

### SKIN CANCER PREVENTION

Most skin cancer is related to sun exposure. Encourage pts to avoid the sun and use sunscreen.

For a more detailed discussion, see Urba WJ, Curti BD: Cancer of the Skin, Chap. 105, p. 493, in HPIM-19.

# 68 Head and Neck Cancer

Epithelial cancers may arise from the mucosal surfaces of the head and neck including the sinuses, oral cavity, nasopharynx, oropharynx, hypopharynx, and larynx. These tumors are usually squamous cell cancers. Thyroid cancer is discussed in Chap. 170.

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## INCIDENCE AND EPIDEMIOLOGY

About 58,000 cases are diagnosed each year and 12,000 people die from the disease. Oral cavity, oropharynx, and larynx are the most frequent sites of primary lesions in the United States; nasopharyngeal primaries are more common in the Far East and Mediterranean countries. Alcohol and tobacco (including smokeless) abuse are risk factors. Human papillomavirus (usually types 16 and 18) is associated with about half of oropharynx cancers in Western countries.

## PATHOLOGY

Nasopharyngeal cancer in the Far East has a distinct histology, nonkeratinizing undifferentiated carcinoma with infiltrating lymphocytes called *lymphoepithelioma*, and a distinct etiology, Epstein-Barr virus. Squamous cell head and neck cancer may develop from premalignant lesions (erythroplakia, leukoplakia), and the histologic grade affects prognosis. Pts who have survived head and neck cancer commonly develop a second cancer of the head and neck, lung, or esophagus, presumably reflecting the exposure of the upper aerodigestive mucosa to similar carcinogenic stimuli.

## GENETIC ALTERATIONS

Chromosomal deletions and mutations have been found in chromosomes 3p, 9p, 17p, and 13q; mutations in p53 have been reported. Cyclin D1 may be overexpressed. Epidermal growth factor receptor is commonly overexpressed.

## CLINICAL PRESENTATION

Most occur in persons >50 years. Symptoms vary with the primary site. Nasopharynx lesions do not usually cause symptoms until late in the course and then cause unilateral serous otitis media or nasal obstruction or epistaxis. Oral cavity cancers present as nonhealing ulcers, sometimes painful. Oropharyngeal lesions also present late with sore throat or otalgia. Hoarseness may be an early sign of laryngeal cancer. Rare pts present with painless, rock-hard cervical or supraclavicular lymph node enlargement. Staging is based on the size of primary tumor and involvement of lymph nodes. Distant metastases occur in <10% of pts.

## TREATMENT HEAD AND NECK CANCER

Three categories of disease are common: localized, locally or regionally advanced, and recurrent or metastatic. *Localized disease* occurs in about one-third of pts and is treated with curative intent by surgery or radiation therapy. Radiation therapy is preferred for localized larynx cancer to preserve organ function; surgery is used more commonly for oral cavity lesions. Overall 5-year survival is 60–90%, and most recurrences occur within 2 years. *Locally advanced disease* is the most common presentation (>50%). Combined-modality therapy using induction chemotherapy, then surgery followed by concomitant chemotherapy and radiation therapy, is most effective. The use of three cycles of cisplatin (75 mg/m$^2$ IV day 1) and docetaxel (75 mg/m$^2$ IV day 1) plus 5-fluorouracil (5-FU) (750 [mg/m$^2$]/d by 96- to 120-h continuous infusion) before or during radiation therapy is more effective than surgery plus radiation therapy, although mucositis is also more severe; 5-year survival is 34–50%. Cetuximab plus radiation therapy may be more effective than radiation therapy alone. Head and neck cancer pts are frequently malnourished and often have intercurrent illness. Those who obtain a remission often develop hypothyroidism. Pts with *recurrent* or *metastatic disease* (about 10% of pts) are treated palliatively with cisplatin plus 5FU or paclitaxel (200–250 mg/m$^2$ with granulocyte colony-stimulating factor support) or with single-agent chemotherapy (a taxane, methotrexate, cisplatin, or carboplatin). Response rates are usually 30–50% and median survival of about 3 months.

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## PREVENTION

The most important intervention is to get the pts to stop smoking. Long-term survival is significantly better in those who stop smoking. Chemopreventive therapy with *cis*-retinoic acid (3 months of 1.5 [mg/kg]/d followed by 9 months of 0.5 [mg/kg]/d PO) may cause regression of leukoplakia but has no consistent effect on development of cancer.

For a more detailed discussion, see Vokes EE: Head and Neck Cancer, Chap. 106, p. 502, in HPIM-19.

# 69 Lung Cancer

## INCIDENCE

Lung cancer was diagnosed in about 115,610 men and 105,590 women in the United States in 2015, and 86% of pts die within 5 years. Lung cancer, the leading cause of cancer death, accounts for 28% of all cancer deaths in men and 26% in women. Peak incidence occurs between ages 55 and 65 years. Incidence is decreasing in men and increasing in women.

## HISTOLOGIC CLASSIFICATION

Four major types account for 88% of primary lung cancers: epidermoid (squamous), 29%; adenocarcinoma (including bronchioloalveolar), 35%; large cell, 9%; and small cell (or oat cell), 18%. Histology (small-cell versus non-small-cell types) is a major determinant of treatment approach. Small cell is usually widely disseminated at presentation, whereas non-small cell may be localized. Epidermoid and small cell typically present as central masses, whereas adenocarcinomas and large cell usually present as peripheral nodules or masses. Epidermoid and large cell cavitate in 20–30% of pts.

## ETIOLOGY

The major cause of lung cancer is tobacco use, particularly cigarette smoking. Lung cancer cells may have ≥10 acquired genetic lesions, most commonly point mutations in *ras* oncogenes; amplification, rearrangement, or transcriptional activation of *myc* family oncogenes; overexpression of *bcl*-2, *Her*2/*neu*, and telomerase; and deletions involving chromosomes 1p, 1q, 3p12-13, 3p14 (FHIT gene region), 3p21, 3p24-25, 3q, 5q, 9p (p16 and p15 cyclin-dependent kinase inhibitors), 11p13, 11p15, 13q14 (*rb* gene), 16q, and 17p13 (*p53* gene). Loss of 3p and 9p is the earliest event, detectable even in hyperplastic bronchial epithelium; *p53* abnormalities and *ras* point mutations are usually found only in invasive cancers. A small but significant subset of pts with adenocarcinoma have activating mutations in the gene for the epidermal growth factor (EGF) receptor, or activating fusion events involving the *alk* or *ros* gene. Driver mutations in lung cancer are depicted in Fig. 69-1.

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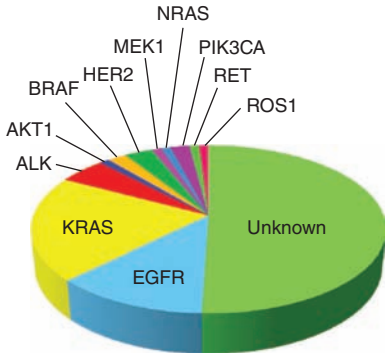


| Frequency of driver mutations in NSCLC | |
|---|---|
| AKT1 | 1% |
| ALK | 3–7% |
| BRAF | 1–3% |
| EGFR | 10–35% |
| HER2 | 2–4% |
| KRAS | 15–25% |
| MEK1 | 1% |
| NRAS | 1% |
| PIK3CA | 1–3% |
| RET | 1–2% |
| ROS1 | 1–2% |

**FIGURE 69-1** Driver mutations in adenocarcinomas.

## CLINICAL MANIFESTATIONS

Only 5–15% are detected while asymptomatic. Central endobronchial tumors cause cough, hemoptysis, wheeze, stridor, dyspnea, pneumonitis. Peripheral lesions cause pain, cough, dyspnea, symptoms of lung abscess resulting from cavitation. Metastatic spread of primary lung cancer may cause tracheal obstruction, dysphagia, hoarseness, Horner's syndrome. Other problems of regional spread include superior vena cava syndrome, pleural effusion, respiratory failure. Extrathoracic metastatic disease affects 50% of pts with epidermoid cancer, 80% with adenocarcinoma and large cell, and >95% with small cell. Clinical problems result from brain metastases, pathologic fractures, liver invasion, and spinal cord compression. Paraneoplastic syndromes may be a presenting finding of lung cancer or first sign of recurrence (Chap. 76). Systemic symptoms occur in 30% and include weight loss, anorexia, fever. Endocrine syndromes occur in 12% and include hypercalcemia (epidermoid), syndrome of inappropriate antidiuretic hormone secretion (small cell), gynecomastia (large cell). Skeletal connective tissue syndromes include clubbing in 30% (most often non-small cell) and hypertrophic pulmonary osteoarthropathy in 1–10% (most often adenocarcinomas), with clubbing, pain, and swelling.

## STAGING (TABLE 69-1)

Two parts to staging are: (1) determination of location (anatomic staging) and (2) assessment of pt's ability to withstand antitumor treatment (physiologic staging). Non-small-cell tumors are staged by the TNM/International Staging System (ISS). The T (tumor), N (regional node involvement), and M (presence or absence of distant metastasis) factors are taken together to define different stage groups. Small-cell tumors are staged by two-stage system: limited stage disease—confined to one hemithorax and regional lymph nodes; extensive disease—involvement beyond this. General staging procedures include careful ear, nose, and throat examination; chest x-ray (CXR); chest and abdominal CT scanning; and positron emission tomography scan. CT scans may suggest mediastinal lymph node involvement and pleural extension in non-small-cell lung cancer, but a definitive evaluation of mediastinal spread requires histologic examination. Routine radionuclide scans are not obtained in asymptomatic pts. If a mass lesion is on CXR and no obvious contraindications to curative surgical approach are noted, the mediastinum should be investigated. Major contraindications to curative surgery include extrathoracic metastases, superior vena cava syndrome, vocal cord and phrenic nerve paralysis, malignant pleural effusions, metastases to contralateral lung, and histologic diagnosis of small-cell cancer.

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**TABLE 69-1 TUMOR, NODE, METASTASIS INTERNATIONAL STAGING SYSTEM FOR LUNG CANCER**

Comparison of Survival by Stage in TNM Sixth and Seventh Editions

| Stage | TNM Sixth Edition | TNM Seventh Edition | 5-Year Survival, %[a] |
|---|---|---|---|
| IA | T1N0M0 | T1a-T1bN0M0 | 73 |
| IB | T2N0M0 | T2aN0M0 | 58 |
| IIA | T1N1M0 | T1a-T2aN1M0 *or* T2bN0M0 | 46 |
| IIB | T2N1M0 *or* T3N0M0 | T2bN1M0 *or* T3N0M0 | 36 |
| IIIA | T3N1M0 *or* T1-3N2M0 | T1a-T3N2M0 *or* T3N1M0 *or* T4N0-1M0 | 24 |
| IIIB | Any T N3M0<br>T4 Any N M0 | T4N2M0 *or* T1a-T4N3M0 | 9 |
| IV | Any T Any N M1 | Any T Any N M1a *or* M1b | 13 |
| | **Sixth Edition** | **Seventh Edition** | |
| **Tumor (T)** | | | |
| T1 | Tumor ≤3 cm diameter without invasion more proximal than lobar bronchus | Tumor ≤3 cm diameter, surrounded by lung or visceral pleura, without invasion more proximal than lobar bronchus | |
| T1a | | Tumor ≤2 cm in diameter | |
| T1b | | Tumor >2 cm but ≤3 cm in diameter | |
| T2 | Tumor >3 cm diameter *or* tumor of any size with any of the following: | Tumor >3 cm but ≤7 cm with any of the following: | |
| | Visceral pleural invasion | Involves main bronchus, ≥2 cm distal to carina | |
| | Atelectasis of less than entire lung | Invades visceral pleura | |
| | Proximal extent at least 2 cm from carina | Associated with atelectasis or obstructive pneumonitis extending to hilar region but not involving the entire lung | |
| T2a | | Tumor >3 cm but ≤5 cm in diameter | |
| T2b | | Tumor >5 cm but ≤7 cm in diameter | |
| T3 | Tumor of any size that invades any of the following: chest wall, diaphragm, mediastinal pleura, parietal pericardium | Tumor >7 cm or directly invades any of the following: chest wall (including superior sulcus tumors), phrenic nerve, mediastinal pleura, parietal pericardium | |
| | Tumor <2 cm distal to carina | Tumor <2 cm distal to carina but without involvement of carina | |
| | | Tumor with associated atelectasis or obstructive pneumonitis of entire lung | |
| | | Separate tumor nodule(s) in same lobe | |

(*Continued*)

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**TABLE 69-1 TUMOR, NODE, METASTASIS INTERNATIONAL STAGING SYSTEM FOR LUNG CANCER (*CONTINUED*)**

| | | |
|---|---|---|
| T4 | Tumor of any size that invades any of the following: mediastinum, heart or great vessels, trachea, esophagus, vertebral body, carina<br>Tumor with malignant pleural or pericardial effusion<br>Separate tumor nodules in same lobe | Tumor of any size that invades any of the following: mediastinum, heart or great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina<br>Separate tumor nodule(s) in a different ipsilateral lobe |
| **Nodes (N)** | | |
| N0 | No regional lymph node metastasis | No regional lymph node metastasis |
| N1 | Metastasis in ipsilateral peribronchial and/or hilar lymph node(s) | Metastasis in ipsilateral peribronchial and/or hilar lymph node(s) and intrapulmonary node(s), including involvement by direct extensions |
| N2 | Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s) | Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s) |
| N3 | Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular lymph node(s) | Metastasis in contralateral mediastinal, hilar, ipsilateral or contralateral scalene or supraclavicular lymph node(s) |
| **Metastasis (M)** | | |
| M0 | No distant metastasis | No distant metastasis |
| M1 | Distant metastasis (includes tumor nodules in different lobe from primary) | Distant metastasis |
| M1a | | Separate tumor nodules in a contralateral lobe<br>Tumor with pleural nodules or malignant pleural or pericardial effusion |
| M1b | | Distant metastasis |

[a]Survival according to the seventh edition.
***Abbreviation:*** TNM, tumor-node-metastasis.
***Source:*** Bottom portion of table reproduced with permission from P Goldstraw et al: *J Thorac Oncol* 2:706, 2007.

## TREATMENT LUNG CANCER (TABLE 69-2)

1. Surgery in pts with localized disease and non-small-cell cancer; however, majority initially thought to have curative resection ultimately succumb to metastatic disease. Adjuvant chemotherapy (cisplatin, four cycles at 100 mg/m$^2$ plus a second active agent [etoposide, vinblastine, vinorelbine, vindesine, a taxane]) in pts with total resection of stage IIA and IIB diseases may modestly extend survival.

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**TABLE 69-2 SUMMARY OF TREATMENT APPROACH TO PATIENTS WITH LUNG CANCER**

| |
|---|
| **Non-Small-Cell Lung Cancer** |
| Stages IA, IB, IIA, IIB, and some IIIA: |
| Surgical resection for stages IA, IB, IIA, and IIB |
| Surgical resection with complete-mediastinal lymph node dissection and consideration of neoadjuvant CRx for stage IIIA disease with "minimal N2 involvement" (discovered at thoracotomy or mediastinoscopy) |
| Consider postoperative RT for pts found to have N2 disease |
| Stage IB: discussion of risk/benefits of adjuvant CRx; not routinely given |
| Stage II: Adjuvant CRx |
| Curative potential RT for "nonoperable" pts |
| Stage IIIA with selected types of stage T3 tumors: |
| Tumors with chest wall invasion (T3): en bloc resection of tumor with involved chest wall and consideration of postoperative RT |
| Superior sulcus (Pancoast's) (T3) tumors: preoperative RT (30–45 Gy) and CRx followed by en bloc resection of involved lung and chest wall with postoperative RT |
| Proximal airway involvement (<2 cm from carina) without mediastinal nodes: sleeve resection if possible preserving distal normal lung or pneumonectomy |
| Stages IIIA "advanced, bulky, clinically evident N2 disease" (discovered preoperatively) and IIIB disease that can be included in a tolerable RT port: |
| Curative potential concurrent RT + CRx if performance status and general medical condition are reasonable; otherwise, sequential CRx followed by RT, or RT alone |
| Stage IIIB disease with carinal invasion (T4) but without N2 involvement: |
| Consider pneumonectomy with tracheal sleeve resection with direct reanastomosis to contralateral mainstem bronchus |
| Stage IV and more advanced IIIB disease: |
| RT to symptomatic local sites |
| CRx for ambulatory pts; consider CRx and bevacizumab for selected pts |
| Chest tube drainage of large malignant pleural effusions |
| Consider resection of primary tumor and metastasis for isolated brain or adrenal metastases |
| **Small-Cell Lung Cancer** |
| Limited stage (good performance status): combination CRx + concurrent chest RT |
| Extensive stage (good performance status): combination CRx |
| Complete tumor responders (all stages): consider prophylactic cranial RT |
| Poor-performance-status pts (all stages): |
| Modified-dose combination CRx |
| Palliative RT |
| **Bronchioloalveolar or Adenocarcinoma with EGF Receptor Mutations or ALK rearrangements** |
| Gefitinib or erlotinib, inhibitors of EGF receptor kinase activity |
| Crizotinib, an alk inhibitor, or ceritinib |

(*Continued*)

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**TABLE 69-2 SUMMARY OF TREATMENT APPROACH TO PATIENTS WITH LUNG CANCER (*CONTINUED*)**

| All Pts |
|---|
| RT for brain metastases, spinal cord compression, weight-bearing lytic bony lesions, symptomatic local lesions (nerve paralyses, obstructed airway, hemoptysis, intrathoracic large venous obstruction, in non-small-cell lung cancer and in small-cell cancer not responding to CRx) |
| Appropriate diagnosis and treatment of other medical problems and supportive care during CRx |
| Encouragement to stop smoking |
| Entrance into clinical trial, if eligible |

***Abbreviations:*** CRx, chemotherapy; EGF, epidermal growth factor; RT, radiotherapy.

2. Solitary pulmonary nodule: factors suggesting resection include cigarette smoking, age ≥35 years, relatively large (>2 cm) lesion, lack of calcification, chest symptoms, and growth of lesion compared with old CXR. See Fig. 69-1.
3. For unresectable stage II non-small-cell lung cancer, combined thoracic radiation therapy and cisplatin-based chemotherapy reduces mortality by about 25% at 1 year.
4. For unresectable non-small-cell cancer, metastatic disease, or refusal of surgery, consider for radiation therapy; addition of cisplatin/taxane-based chemotherapy may reduce death risk by 13% at 2 years and improve quality of life. Pemetrexed has activity in pts with progressive disease.
5. Small-cell cancer: combination chemotherapy is standard mode of therapy; response after 6–12 weeks predicts median- and long-term survival.
6. Addition of radiation therapy to chemotherapy in limited-stage small-cell lung cancer can increase 5-year survival from about 11% to 20%.
7. Prophylactic cranial irradiation improves survival of limited-stage small-cell lung cancer by another 5%.
8. Laser obliteration of tumor through bronchoscopy in presence of bronchial obstruction.
9. Radiation therapy for brain metastases, spinal cord compression, symptomatic masses, bone lesions.
10. Encourage cessation of smoking.
11. Pts with adenocarcinoma carcinoma (3% of all pts with lung cancer): 7% of these have activating mutations in the EGF receptor. These pts often respond to gefitinib or erlotinib, EGF receptor inhibitors. About 5% of these have activating rearrangements of the *alk* gene and may respond to crizotinib.

## PROGNOSIS

At time of diagnosis, only 20% of pts have localized disease. Overall 5-year survival is 30% for males and 50% for females with localized disease and 5% for pts with advanced disease. Survival as a function of stage is listed in Table 69-3.

## SCREENING

The National Cancer Institute study of lung cancer screening of high-risk pts (age 55–74 years with 30+ pack-year smoking history) with low-dose helical CT scan reduced lung cancer mortality by 20%, but had only a small effect on overall mortality.

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**TABLE 69-3 FIVE-YEAR SURVIVAL BY STAGE AND TNM CLASSIFICATION OF NON-SMALL-CELL LUNG CANCER (SEVENTH EDITION)**

| Stage | TNM Seventh Edition | 5-Year Survival (%) |
|---|---|---|
| IA | T1a-T1bN0M0 | 73% |
| IB | T2aN0M0 | 58% |
| IIA | T1a-T2aN1M0<br>T2bN0M0 | 46% |
| IIB | T2bN1M0<br>T3N0M0 | 36% |
| IIIA | T1a-T3N2M0<br>T3N1M0<br>T4N0-1M0 | 24% |
| IIIB | T4N2M0<br>T1a-T4N3M0 | 9% |
| IV | Any T<br>Any N plus M1a or M1b | 13% |

***Abbreviation:*** TNM, tumor-node-metastasis.

For a more detailed discussion, see Horn L, Lovly CM, Johnson DH: Neoplasms of the Lung, Chap. 107, p. 506, in HPIM-19.

# 70 Breast Cancer

## INCIDENCE AND EPIDEMIOLOGY

The most common tumor in women; 234,190 women in the United States were diagnosed in 2015 and 40,730 died with breast cancer. Men also get breast cancer; F:M is 150:1. Breast cancer is hormone dependent. Women with late menarche, early menopause, and first full-term pregnancy by age 18 years have a significantly reduced risk. The average American woman has about a one in nine lifetime risk of developing breast cancer. Dietary fat is a controversial risk factor. Oral contraceptives have little, if any, effect on risk and lower the risk of endometrial and ovarian cancer. Voluntary interruption of pregnancy does not increase risk. Estrogen replacement therapy may slightly increase the risk, but the beneficial effects of estrogen on quality of life, bone mineral density, and decreased risk of colorectal cancer appear to be somewhat outnumbered by increases in cardiovascular and thrombotic diseases. Women who received therapeutic radiation before age 30 years are at increased risk. Breast cancer risk is increased when a sister and mother also had the disease.

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## GENETICS

Perhaps 8–10% of breast cancer is familial. *BRCA-1* mutations account for about 5%. *BRCA-1* maps to chromosome 17q21 and appears to be involved in transcription-coupled DNA repair. Ashkenazi Jewish women have a 1% chance of having a common mutation (deletion of adenine and guanine at position 185). The *BRCA-1* syndrome includes an increased risk of ovarian cancer in women and prostate cancer in men. *BRCA-2* on chromosome 11 may account for 2–3% of breast cancer. Mutations are associated with an increased risk of breast cancer in men and women. Germ-line mutations in p53 (Li-Fraumeni syndrome) are very rare, but breast cancer, sarcomas, and other malignancies occur in such families. Germ-line mutations in *PALB2, hCHK2*, and *PTEN* may account for some familial breast cancer. Sporadic breast cancers show many genetic alterations, including overexpression of *HER2/neu* in 25% of cases, p53 mutations in 40%, and loss of heterozygosity at other loci.

## DIAGNOSIS

Breast cancer is usually diagnosed by biopsy of a nodule detected by mammogram or by palpation. Women should be strongly encouraged to examine their breasts monthly. In premenopausal women, questionable or nonsuspicious (small) masses should be reexamined in 2–4 weeks (Fig. 70-1). A mass in a premenopausal woman

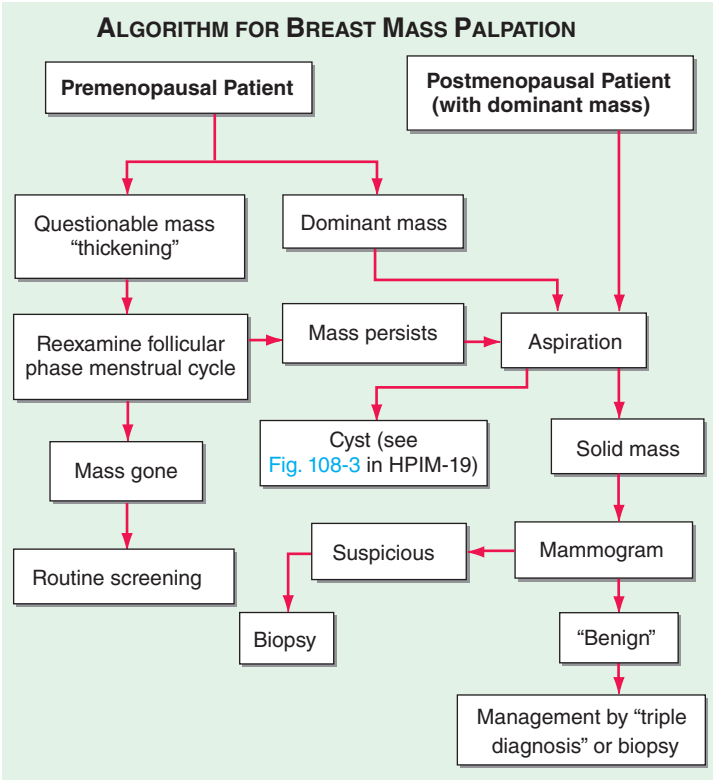


**FIGURE 70-1** Approach to a palpable breast mass.

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that persists throughout her cycle and any mass in a postmenopausal woman should be aspirated. If the mass is a cyst filled with nonbloody fluid that goes away with aspiration, the pt is returned to routine screening. If the cyst aspiration leaves a residual mass or reveals bloody fluid, the pt should have a mammogram and excisional biopsy. If the mass is solid, the pt should undergo a mammogram and excisional biopsy. Screening mammograms performed every other year beginning at age 50 years have been shown to save lives. The controversy regarding screening mammograms beginning at age 40 years relates to the following facts: (1) the disease is much less common in the 40- to 49-year age group, and screening is generally less successful for less common problems; (2) workup of mammographic abnormalities in the 40- to 49-year age group less commonly diagnoses cancer; and (3) about 50% of women who are screened annually during their forties have an abnormality at some point that requires a diagnostic procedure (usually a biopsy), yet very few evaluations reveal cancer. However, many believe in the value of screening mammography beginning at age 40 years. After 13–15 years of follow-up, women who start screening at age 40 years have a small survival benefit. Women with familial breast cancer more often have false-negative mammograms. MRI is a better screening tool in these women. Women with dense breasts (>50% fibroglandular tissue) are said to be at increased risk (1.2- to 2-fold), but it is not clear that they require increased surveillance.

## CLINICAL AND MOLECULAR STAGING

Therapy and prognosis are dictated by stage of disease (Table 70-1). Unless the breast mass is large or fixed to the chest wall, staging of the ipsilateral axilla is performed at the time of lumpectomy (see below). Within pts of a given stage, individual characteristics of the tumor may influence prognosis: expression of estrogen receptor improves prognosis, while overexpression of *HER2/neu*, mutations in p53,

**TABLE 70-1 STAGING OF BREAST CANCER**

| | |
|---|---|
| **Primary Tumor (T)** | |
| T0 | No evidence of primary tumor |
| TIS | Carcinoma in situ |
| T1 | Tumor ≤2 cm |
| T1a | Tumor >0.1 cm but ≤0.5 cm |
| T1b | Tumor >0.5 but ≤1 cm |
| T1c | Tumor >1 cm but ≤2 cm |
| T2 | Tumor >2 cm but ≤5 cm |
| T3 | Tumor >5 cm |
| T4 | Extension to chest wall, inflammation, satellite lesions, ulcerations |
| **Regional Lymph Nodes (N)** | |
| PN0(i–) | No regional lymph node metastasis histologically, negative IHC |
| PN0(i+) | No regional lymph node metastasis histologically, positive IHC, no IHC cluster >0.2 mm |
| PN0(mol–) | No regional lymph node metastasis histologically, negative molecular findings (RT-PCR) |
| PN0(mol+) | No regional lymph node metastasis histologically, positive molecular findings (RT-PCR) |
| PN1 | Metastasis in one to three axillary lymph nodes, or in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent |

(*Continued*)

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**TABLE 70-1 STAGING OF BREAST CANCER (*CONTINUED*)**

| | | | |
|---|---|---|---|
| PN1mi | Micrometastasis (>0.2 mm, none >2 mm) | | |
| PN1a | Metastasis in one to three axillary lymph nodes | | |
| PN1b | Metastasis in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not *clinically apparent* [a] | | |
| PN1c | Metastasis in one to three axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent.[a] (If associated with greater than three positive axillary lymph nodes, the internal mammary nodes are classified as pN3b to reflect increased tumor burden.) | | |
| pN2 | Metastasis in four to nine axillary lymph nodes, or in clinically apparent internal mammary lymph nodes in the *absence* of axillary lymph node metastasis | | |
| pN3 | Metastasis in 10 or more axillary lymph nodes, or in infraclavicular lymph nodes, or in clinically apparent[a] ipsilateral internal mammary lymph nodes in the *presence* of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes; or in ipsilateral subcarinal lymph nodes | | |
| **Distant Metastasis (M)** | | | |
| M0 | No distant metastasis | | |
| M1 | Distant metastasis (includes spread to ipsilateral supraclavicular nodes) | | |
| **Stage Grouping** | | | |
| Stage 0 | TIS | N0 | M0 |
| Stage I | T1 | N0 | M0 |
| Stage IIA | T0 | N1 | M0 |
| | T1 | N1 | M0 |
| | T2 | N0 | M0 |
| Stage IIB | T2 | N1 | M0 |
| | T3 | N0 | M0 |
| Stage IIIA | T0 | N2 | M0 |
| | T1 | N2 | M0 |
| | T2 | N2 | M0 |
| | T3 | N1, N2 | M0 |
| Stage IIIB | T4 | Any N | M0 |
| | Any T | N3 | M0 |
| Stage IIIC | Any T | N3 | M0 |
| Stage IV | Any T | Any N | M1 |

[a]Clinically apparent is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination.

***Abbreviations:*** IHC, immunohistochemistry; RT-PCR, reverse transcriptase/polymerase chain reaction.

***Source:*** Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Manual*, 7th ed. New York, Springer, 2010; *www.springeronline.com.*

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high growth fraction, and aneuploidy worsen the prognosis. Molecular profiling has identified genetically distinct subsets including luminal A and B (estrogen receptor positive), normal breast-like, *HER2*-amplified, and basal (or triple-negative based on no expression of hormone receptors or overexpression of HER2. These subsets differ in prognosis. Breast cancer can spread almost anywhere but commonly goes to bone, lungs, liver, soft tissue, and brain.

## TREATMENT BREAST CANCER

Five-year survival rate by stage is shown in Table 70-2. Treatment varies with stage of disease and expression of hormone receptors and HER2.

Ductal carcinoma in situ is noninvasive tumor present in the breast ducts. Treatment of choice is wide excision with breast radiation therapy. In one study, adjuvant tamoxifen further reduced the risk of recurrence.

Invasive breast cancer can be classified as operable, locally advanced, and metastatic. In operable breast cancer, the outcome of primary therapy is the same with modified radical mastectomy or lumpectomy followed by breast radiation therapy. Axillary dissection may be replaced with sentinel node biopsy to evaluate node involvement. The sentinel node is identified by injecting a dye in the tumor site at surgery; the first node in which dye appears is the sentinel node. Women with tumors <1 cm and negative axillary nodes require no additional therapy beyond their primary lumpectomy and breast radiation. Adjuvant combination chemotherapy for 6 months appears to benefit premenopausal women with positive lymph nodes, pre- and postmenopausal women with negative lymph nodes but with large tumors or poor prognostic features, and postmenopausal women with positive lymph nodes whose tumors do not express estrogen receptors. Estrogen receptor–positive tumors >1 cm with or without involvement of lymph nodes are treated with aromatase inhibitors. Women who began treatment with tamoxifen before aromatase inhibitors were approved should switch to an aromatase inhibitor after 5 years of tamoxifen and continue for another 5 years.

Adjuvant chemotherapy is added to hormonal therapy in estrogen receptor–positive, node-positive women and is used without hormonal therapy in estrogen receptor–negative node-positive women, whether they are pre- or postmenopausal. Various regimens have been used. The most effective regimen appears to be four cycles of doxorubicin, 60 mg/m$^2$, plus cyclophosphamide, 600 mg/m$^2$, IV on day 1 of each 3-week cycle followed by four cycles of paclitaxel, 175 mg/m$^2$, by 3-h infusion on day 1 of each 3-week cycle. In women with HER2+ tumors, trastuzumab augments the ability of chemotherapy to prevent recurrence. The activity of other combinations is being explored. In premenopausal women, ovarian ablation (e.g., with the luteinizing hormone–releasing hormone [LHRH] inhibitor goserelin) may be as effective as adjuvant chemotherapy.

**TABLE 70-2 A 5-YEAR SURVIVAL RATE FOR BREAST CANCER BY STAGE**

| Stage | 5-Year Survival (Percentage of Patients) |
|---|---|
| 0 | 99 |
| I | 92 |
| IIA | 82 |
| IIB | 65 |
| IIIA | 47 |
| IIIB | 44 |
| IV | 14 |

***Source:*** Modified from data of the National Cancer Institute—Surveillance, Epidemiology, and End Results (SEER).

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Tamoxifen adjuvant therapy (20 mg/d for 5 years) or an aromatase inhibitor (anastrozole, letrozole, exemestane) is used for postmenopausal women with tumors expressing estrogen receptors whose nodes are positive or whose nodes are negative but with large tumors or poor prognostic features. Breast cancer will recur in about half of pts with localized disease. High-dose adjuvant therapy with marrow support does not appear to benefit even women with high risk of recurrence.

Pts with locally advanced breast cancer benefit from neoadjuvant combination chemotherapy (e.g., CAF: cyclophosphamide 500 mg/m$^2$, doxorubicin 50 mg/m$^2$, and 5-fluorouracil 500 mg/m$^2$ all given IV on days 1 and 8 of a monthly cycle for 6 cycles) followed by surgery plus breast radiation therapy.

Treatment for metastatic disease depends on estrogen receptor status and treatment philosophy. No therapy is known to cure pts with metastatic disease. Randomized trials do not show that the use of high-dose therapy with hematopoietic stem cell support improves survival. Median survival is about 22 months with conventional treatment: aromatase inhibitors for estrogen receptor–positive tumors and combination chemotherapy for receptor-negative tumors. Pts whose tumors express *HER2/neu* have higher response rates by adding trastuzumab (anti-*HER2/neu*) to chemotherapy. Trastuzumab emtansine is a drug conjugate that targets HER2-expressing cells and has antitumor activity. Some advocate sequential use of active single agents in the setting of metastatic disease. Active agents in anthracycline- and taxane-resistant disease include capecitabine, vinorelbine, gemcitabine, irinotecan, and platinum agents. Pts progressing on adjuvant tamoxifen may benefit from an aromatase inhibitor such as letrozole or anastrozole. Half of pts who respond to one endocrine therapy will respond to another. Bisphosphonates reduce skeletal complications and may promote antitumor effects of other therapy. Radiation therapy is useful for palliation of symptoms.

## PREVENTION

Women with breast cancer have a 0.5% per year risk of developing a second breast cancer. Women at increased risk of breast cancer can reduce their risk by 49% by taking tamoxifen or an aromatase inhibitor for 5 years. Women with *BRCA-1* mutations can reduce the risk by 90% with simple mastectomy.

For a more detailed discussion, see Lippman ME: Breast Cancer, Chap. 108, p. 523, in HPIM-19.

# 71 Tumors of the Gastrointestinal Tract

## ESOPHAGEAL CARCINOMA

In 2015 in the United States, 16,980 cases and 15,590 deaths; less frequent in women than men. Highest incidence in focal regions of China, Iran, Afghanistan, Siberia, and Mongolia. In the United States, blacks more frequently affected than whites; usually

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presents sixth decade or later; 5-year survival <10% because most pts present with advanced disease.

### Pathology

20% squamous cell carcinoma, most commonly in upper two-thirds; 75% adenocarcinoma, usually in distal third, arising in region of columnar metaplasia (Barrett's esophagus), glandular tissue, or as direct extension of proximal gastric adenocarcinoma; lymphoma and melanoma rare. 5% of all esophageal cancers occur in the upper third, 20% in the middle third, and 75% in the lower third. 15% of tumors express *HER2/neu*.

### Risk Factors

Major risk factors for squamous cell carcinoma: ethanol abuse, smoking (combination is synergistic); other risks: lye ingestion and esophageal stricture, radiation exposure, head and neck cancer, achalasia, smoked opiates, Plummer-Vinson syndrome, tylosis, chronic ingestion of extremely hot tea, deficiency of vitamin A, zinc, molybdenum. Barrett's esophagus, chronic gastroesophageal reflux, obesity, and smoking are risk factors for adenocarcinoma.

### Clinical Features

Progressive dysphagia (first with solids, then liquids), rapid weight loss common, chest pain (from mediastinal spread), odynophagia, pulmonary aspiration (obstruction, tracheoesophageal fistula), hoarseness (laryngeal nerve palsy), hypercalcemia (parathyroid hormone–related peptide hypersecretion by squamous carcinomas); bleeding infrequent, occasionally severe; examination often unremarkable.

### Diagnosis

Double-contrast barium swallow useful as initial test in dysphagia; flexible esophagogastroscopy most sensitive and specific test; pathologic confirmation by combining endoscopic biopsy and cytologic examination of mucosal brushings (neither alone sufficiently sensitive); CT and endoscopic ultrasonography valuable to assess local and nodal spread. PET scanning can also assess mediastinal nodes and distant sites.

### TREATMENT ESOPHAGEAL CARCINOMA

Surgical resection feasible in only 40% of pts; associated with high complication rate (fistula, abscess, aspiration). *Squamous cell carcinoma*: Surgical resection after chemotherapy [5-fluorouracil (5FU), cisplatin] plus radiation therapy prolongs survival and may provide improved cure rate. *Adenocarcinoma*: Curative resection rarely possible; <20% of pts with resectable tumors survive 5 years. Palliative measures include laser ablation, mechanical dilatation, radiotherapy, and a luminal prosthesis to bypass the tumor. Gastrostomy or jejunostomy are frequently required for nutritional support. Preoperative chemotherapy with concurrent radiation therapy is somewhat more effective but more toxic therapy.

## GASTRIC CARCINOMA

Highest incidence in Japan, China, Chile, Ireland; incidence decreasing worldwide, eightfold in the United States over past 60 years; in 2015, 24,590 new cases and 10,720 deaths. Male:female = 2:1; peak incidence sixth and seventh decades; overall 5-year survival <15%.

### Risk Factors

Increased incidence in lower socioeconomic groups; environmental component is suggested by studies of migrants and their offspring. Several dietary factors

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correlated with increased incidence: nitrates, smoked foods, heavily salted foods; genetic component suggested by increased incidence in first-degree relatives of affected pts; other risk factors: atrophic gastritis, *Helicobacter pylori* infection, Billroth II gastrectomy, gastrojejunostomy, adenomatous gastric polyps, pernicious anemia, hyperplastic gastric polyps (latter two associated with atrophic gastritis), Ménétrier's disease, slight increased risk with blood group A.

## Pathology

Adenocarcinoma in 85%; usually focal (polypoid, ulcerative), two-thirds arising in antrum or lesser curvature, frequently ulcerative ("intestinal type"); less commonly diffuse infiltrative (linitis plastica) or superficial spreading (diffuse lesions more prevalent in younger pts; exhibit less geographic variation; have extremely poor prognosis); spreads primarily to local nodes, liver, peritoneum; systemic spread uncommon; lymphoma accounts for 15% (most frequent extranodal site in immunocompetent pts), either low-grade tumor of mucosa-associated lymphoid tissue (MALT) or aggressive diffuse large B cell lymphoma; leiomyosarcoma or gastrointestinal stromal tumor (GIST) is rare.

## Clinical Features

Most commonly presents with progressive upper abdominal discomfort, frequently with weight loss, anorexia, nausea; acute or chronic GI bleeding (mucosal ulceration) common; dysphagia (location in cardia); vomiting (pyloric and widespread disease); early satiety; examination often unrevealing early in course; later, abdominal tenderness, pallor, and cachexia most common signs; palpable mass uncommon; metastatic spread may be manifest by hepatomegaly, ascites, left supraclavicular or scalene adenopathy, periumbilical, ovarian, or prerectal mass (Blumer's shelf), low-grade fever, skin abnormalities (nodules, dermatomyositis, acanthosis nigricans, or multiple seborrheic keratoses). Laboratory findings: iron-deficiency anemia in two-thirds of pts; fecal occult blood in 80%; rarely associated with pancytopenia and microangiopathic hemolytic anemia (from marrow infiltration), leukemoid reaction, migratory thrombophlebitis, or acanthosis nigricans.

## Diagnosis

Double-contrast barium swallow useful but has been supplanted by the more sensitive and specific esophagogastroscopy and CT for staging and assessing resectability; pathologic confirmation by biopsy and cytologic examination of mucosal brushings; superficial biopsies less sensitive for lymphomas (frequently submucosal); important to differentiate benign from malignant gastric ulcers with multiple biopsies and follow-up examinations to demonstrate ulcer healing.

## TREATMENT GASTRIC CARCINOMA

*Adenocarcinoma*: Gastrectomy offers only chance of cure (only possible in less than one-third); the rare tumors limited to mucosa are resectable for cure in 80%; deeper invasion, nodal metastases decrease 5-year survival to 20% of pts with resectable tumors in absence of obvious metastatic spread (Table 71-1). Subtotal gastrectomy has similar efficacy to total gastrectomy for distal stomach lesions, but with less morbidity; no clear benefit for resection of spleen and a portion of the pancreas, or for radical lymph node removal. Adjuvant chemotherapy (5FU/leucovorin) plus radiation therapy following primary surgery leads to a 7-month increase in median survival. Neoadjuvant chemotherapy with epirubicin or docetaxel with cisplatin, and 5FU or capecitabine may downstage tumors and increase the efficacy of surgery. Palliative therapy for pain, obstruction, and bleeding includes surgery, endoscopic dilatation, radiation therapy, chemotherapy, and ramucirumab, an antiangiogenic antibody.

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**TABLE 71-1 STAGING SYSTEM FOR GASTRIC CARCINOMA**

| Stage | TNM | Features | Data from ACS: No. of Cases, % | Data from ACS: 5-Year Survival, % |
|---|---|---|---|---|
| 0 | $T_{is}N0M0$ | Node negative; limited to mucosa | 1 | 90 |
| IA | T1N0M0 | Node negative; invasion of lamina propria or submucosa | 7 | 59 |
| IB | T2N0M0<br>T1N1M0 | Node negative; invasion of muscularis propria | 10 | 44 |
| II | T1N2M0<br>T2N1M0 | Node positive; invasion beyond mucosa but within wall<br>*Or* | 17 | 29 |
| | T3N0M0 | Node negative; extension through wall | | |
| IIIA | T2N2M0<br>T3N1-2M0 | Node positive; invasion of muscularis propria or through wall | 21 | 15 |
| IIIB | T4N0-1M0 | Node negative; adherence to surrounding tissue | 14 | 9 |
| IIIC | T4N2-3M0 | >3 nodes positive; invasion of serosa or adjacent structures | | |
| | T3N3M0 | 7 or more positive nodes; penetrates wall without invading serosa or adjacent structures | | |
| IV | T4N2M0 | Node positive; adherence to surrounding tissue<br>*Or* | 30 | 3 |
| | T1-4N0-2-M1 | Distant metastases | | |

***Abbreviations:*** ACS, American Cancer Society; TNM, tumor-node-metastasis.

*Lymphoma*: Low-grade MALT lymphoma is caused by *H. pylori* infection, and eradication of the infection causes complete remissions in 50% of pts; rest are responsive to combination chemotherapy including cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) plus rituximab. Diffuse large B cell lymphoma may be treated with either CHOP plus rituximab or subtotal gastrectomy followed by chemotherapy; 50–60% 5-year survival.

*Leiomyosarcoma*: Surgical resection curative in most pts. Tumors expressing the *c-kit* tyrosine kinase (CD117)—GIST—respond to imatinib mesylate in a substantial fraction of cases.

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## BENIGN GASTRIC TUMORS

Much less common than malignant gastric tumors; hyperplastic polyps most common, with adenomas, hamartomas, and leiomyomas rare; 30% of adenomas and occasional hyperplastic polyps are associated with gastric malignancy; polyposis syndromes include Peutz-Jeghers and familial polyposis (hamartomas and adenomas), Gardner's (adenomas), and Cronkhite-Canada (cystic polyps). See "Colonic Polyps," below.

### Clinical Features

Usually asymptomatic; occasionally present with bleeding or vague epigastric discomfort.

**TREATMENT BENIGN GASTRIC TUMORS**

Endoscopic or surgical excision.

## SMALL-BOWEL TUMORS

### Clinical Features

Uncommon tumors (~5% of all GI neoplasms); usually present with bleeding, abdominal pain, weight loss, fever, or intestinal obstruction (intermittent or fixed); increased incidence of lymphomas in pts with gluten-sensitive enteropathy, Crohn's disease involving small bowel, AIDS, prior organ transplantation, autoimmune disorders.

### Pathology

Usually benign; most common are adenomas (usually duodenal), leiomyomas (intramural), and lipomas (usually ileal); 50% of malignant tumors are adenocarcinoma, usually in duodenum (at or near ampulla of Vater) or proximal jejunum, commonly coexisting with benign adenomas; primary intestinal lymphomas (non-Hodgkin's) account for 25% and occur as focal mass (Western type), which is usually a T cell lymphoma associated with prior celiac disease, or diffuse infiltration (Mediterranean type), which is usually immunoproliferative small-intestinal disease (IPSID; α-heavy chain disease), a B cell MALT lymphoma associated with *Campylobacter jejuni* infection, which can present as intestinal malabsorption; carcinoid tumors (usually asymptomatic) occasionally produce bleeding or intussusception (see below).

### Diagnosis

Endoscopy and biopsy most useful for tumors of duodenum and proximal jejunum; otherwise barium x-ray examination best diagnostic test; direct small-bowel instillation of contrast (enteroclysis) occasionally reveals tumors not seen with routine small-bowel radiography; angiography (to detect plexus of tumor vessels) or laparotomy often required for diagnosis; CT useful to evaluate extent of tumor (esp. lymphomas).

**TREATMENT SMALL-BOWEL TUMORS**

Surgical excision; adjuvant chemotherapy appears helpful for focal lymphoma; IPSID appears to be curable with combination chemotherapy used in aggressive lymphoma plus oral antibiotics (e.g., tetracycline); no proven role for chemotherapy or radiation therapy for other small-bowel tumors.

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## COLONIC POLYPS

### TUBULAR ADENOMAS

Present in ~30% of adults; pedunculated or sessile; usually asymptomatic; ~5% cause occult blood in stool; may cause obstruction; overall risk of malignant degeneration correlates with size (<2% if <1.5 cm in diameter; >10% if >2.5 cm in diameter) and is higher in sessile polyps; 65% found in rectosigmoid colon; diagnosis by barium enema, sigmoidoscopy, or colonoscopy. *Treatment*: Full colonoscopy to detect synchronous lesions (present in 30%); endoscopic resection (surgery if polyp large or inaccessible by colonoscopy); follow-up surveillance by colonoscopy every 2–3 years.

### VILLOUS ADENOMAS

Generally larger than tubular adenomas at diagnosis; often sessile; high risk of malignancy (up to 30% when >2 cm); more prevalent in left colon; occasionally associated with potassium-rich secretory diarrhea. *Treatment*: As for tubular adenomas.

### HYPERPLASTIC POLYPS

Asymptomatic; usually incidental finding at colonoscopy; rarely >5 mm; no malignant potential. No treatment required.

### HEREDITARY POLYPOSIS SYNDROMES

See Table 71-2.

**TABLE 71-2 HEREDITABLE (AUTOSOMAL DOMINANT) Gastrointestinal Polyposis Syndromes**

| Syndrome | Distribution of Polyps | Histologic Type | Malignant Potential | Associated Lesions |
|---|---|---|---|---|
| Familial adenomatous polyposis | Large intestine | Adenoma | Common | None |
| Gardner's syndrome | Large and small intestines | Adenoma | Common | Osteomas, fibromas, lipomas, epidermoid cysts, ampullary cancers, congenital hypertrophy of retinal pigment epithelium |
| Turcot's syndrome | Large intestine | Adenoma | Common | Brain tumors |
| Nonpolyposis syndrome (Lynch syndrome) | Large intestine (often proximal) | Adenoma | Common | Endometrial and ovarian tumors |
| Peutz-Jeghers syndrome | Small and large intestines, stomach | Hamartoma | Rare | Mucocutaneous pigmentation; tumors of the ovary, breast, pancreas, endometrium |
| Juvenile polyposis | Large and small intestines, stomach | Hamartoma, rarely progressing to adenoma | Rare | Various congenital abnormalities |

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1. *Familial polyposis coli* (FPC): Diffuse pancolonic adenomatous polyposis (up to several thousand polyps); autosomal dominant inheritance associated with deletion in adenomatous polyposis coli (*APC*) gene on chromosome 5; colon carcinoma from malignant degeneration of polyp in 100% by age 40. *Treatment*: Prophylactic total colectomy or subtotal colectomy with ileoproctostomy before age 30; subtotal resection avoids ileostomy but necessitates frequent proctoscopic surveillance; periodic colonoscopic or annual radiologic screening of siblings and offspring of pts with FPC until age 35; sulindac and other nonsteroidal anti-inflammatory drugs (NSAIDs) cause regression of polyps and inhibit their development.
2. *Gardner's syndrome:* Variant of FPC with associated soft tissue tumors (epidermoid cysts, osteomas, lipomas, fibromas, desmoids); higher incidence of gastroduodenal polyps, ampullary adenocarcinoma. *Treatment*: As for FPC; surveillance for small-bowel disease with fecal occult blood testing after colectomy.
3. *Turcot's syndrome:* Rare variant of FPC with associated malignant brain tumors. *Treatment*: As for FPC.
4. *Nonpolyposis syndrome:* Familial syndrome with up to 50% risk of colon carcinoma; peak incidence in fifth decade; associated with multiple primary cancers (esp. endometrial); autosomal dominant; due to defective DNA mismatch repair.
5. *Juvenile polyposis:* Multiple benign colonic and small-bowel hamartomas; intestinal bleeding common. Other symptoms: abdominal pain, diarrhea; occasional intussusception. Rarely recur after excision; low risk of colon cancer from malignant degeneration of interspersed adenomatous polyps. Prophylactic colectomy controversial.
6. *Peutz-Jeghers syndrome:* Numerous hamartomatous polyps of entire GI tract, though denser in small bowel than colon; GI bleeding common; somewhat increased risk for the development of cancer at GI and non-GI sites. Prophylactic surgery not recommended.

## COLORECTAL CANCER

Second most common internal cancer in humans; accounts for 10% of cancer-related deaths in United States; incidence increases dramatically above age 50, nearly equal in men and women. In 2015, 132,700 new cases, 49,700 deaths.

### Etiology and Risk Factors

Most colon cancers arise from adenomatous polyps. Genetic steps from polyp to dysplasia to carcinoma in situ to invasive cancer have been defined, including point mutation in K-*ras* proto-oncogene, hypomethylation of DNA leading to enhanced gene expression, allelic loss at the *APC* gene (a tumor suppressor), allelic loss at the *DCC* (deleted in colon cancer) gene on chromosome 18, and loss and mutation of p53 on chromosome 17. Hereditary nonpolyposis colon cancer arises from mutations in the DNA mismatch repair genes, *hMSH2* gene on chromosome 2 and *hMLH1* gene on chromosome 3. Mutations lead to colon and other cancers. Diagnosis requires three or more relatives with colon cancer, one of whom is a first-degree relative; one or more cases diagnosed before age 50; and involvement of at least two generations. Environmental factors also play a role including exposure to therapeutic radiation; smoking; increased prevalence in developed countries, urban areas, advantaged socioeconomic groups; increased risk in pts with hypercholesterolemia, coronary artery disease; correlation of risk with low-fiber, high-animal-fat diets, although direct effect of diet remains unproven; decreased risk with long-term dietary calcium supplementation and, possibly, daily aspirin ingestion. Risk increased in first-degree relatives of pts; families with increased prevalence of cancer; and pts with history of breast or gynecologic cancer, familial polyposis syndromes, >10-year history of ulcerative colitis or Crohn's colitis, >15-year history of ureterosigmoidostomy. Tumors in pts with strong family history of malignancy are frequently located in

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right colon and commonly present before age 50; high prevalence in pts with *Streptococcus bovis* bacteremia.

## Pathology

Nearly always adenocarcinoma; 75% located distal to the splenic flexure (except in association with polyposis or hereditary cancer syndromes); may be polypoid, sessile, fungating, or constricting; subtype and degree of differentiation do not correlate with course. Degree of invasiveness at surgery (Dukes' classification) is single best predictor of prognosis (Fig. 71-1). Rectosigmoid tumors may spread to lungs early because of systemic paravertebral venous drainage of this area. Other predictors of poor prognosis: preoperative serum carcinoembryonic antigen (CEA) >5 ng/mL (>5 μg/L), poorly differentiated histology, bowel perforation, venous invasion, adherence to adjacent organs, aneuploidy, specific deletions in chromosomes 5, 17, 18, and mutation of *ras* proto-oncogene. 15% have defects in DNA repair.

## Clinical Features

Left-sided colon cancers present most commonly with rectal bleeding, altered bowel habits (narrowing, constipation, intermittent diarrhea, tenesmus), and abdominal or back pain; cecal and ascending colon cancers more frequently present with symptoms of anemia, occult blood in stool, or weight loss; other complications: perforation, fistula, volvulus, inguinal hernia; laboratory findings: anemia in 50% of right-sided lesions.

## Diagnosis

Early diagnosis aided by screening asymptomatic persons with fecal occult blood testing (see below); >50% of all colon cancers are within reach of a 60-cm flexible sigmoidoscope; air-contrast barium enema will diagnose ~85% of colon cancers not within reach of sigmoidoscope; colonoscopy most sensitive and specific, permits tumor biopsy and removal of synchronous polyps (thus preventing neoplastic conversion), but is more expensive. Radiographic or virtual colonoscopy has not been shown to be a better diagnostic method than colonoscopy.

## TREATMENT COLORECTAL CANCER

*Local disease*: Surgical resection of colonic segment containing tumor; preoperative evaluation to assess prognosis and surgical approach includes full colonoscopy, chest films, biochemical liver tests, plasma CEA level, and possible abdominal CT. Resection of isolated hepatic metastases possible in selected cases. Adjuvant radiation therapy to pelvis (with or without concomitant 5FU chemotherapy) decreases local recurrence rate of rectal carcinoma (no apparent effect on survival); radiation therapy without benefit on colon tumors; preoperative radiation therapy may improve resectability and local control in pts with rectal cancer. Total mesorectal excision is more effective than conventional anteroposterior resection in rectal cancer. Adjuvant chemotherapy (5FU/leucovorin plus oxaliplatin, or FOLFOX plus bevacizumab, or 5FU/leucovorin plus irinotecan, or FOLFIRI) decreases recurrence rate and improves survival of stage C (III); survival benefit from adjuvant therapy is not so clear in stage B (II) tumors; periodic determination of serum CEA level useful to follow therapy and assess recurrence. *Follow-up after curative resection*: Yearly liver tests, complete blood count, follow-up radiologic or colonoscopic evaluation at 1 year—if normal, repeat every 3 years, with routine screening interim (see below); if polyps detected, repeat 1 year after resection. *Advanced tumor* (locally unresectable or metastatic): Systemic chemotherapy (5FU/leucovorin plus oxaliplatin plus bevacizumab), irinotecan usually used in second treatment; antibodies to the epidermal growth factor (EGF) receptor (cetuximab, panitumumab) appear to enhance the effect of chemotherapy

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Staging of colorectal cancer

| Stage | I | | II | III | | IV |
|---|---|---|---|---|---|---|
| | T1 | T2 | T3 | N1 | N2 | M |
| Extent of tumor | No deeper than submucosa | Not through muscularis | Through muscularis | 1–3 lymph node metastases | ≥4 lymph node metastases | Distant metastases |
| 5-year survival | >95% | >90% | 70–85% | 50–70% | 25–60% | <5% |
| Stage at presentation: Colon | 23% | | 31% | 26% | | 20% |
| Stage at presentation: Rectal | 34% | | 25% | 26% | | 15% |

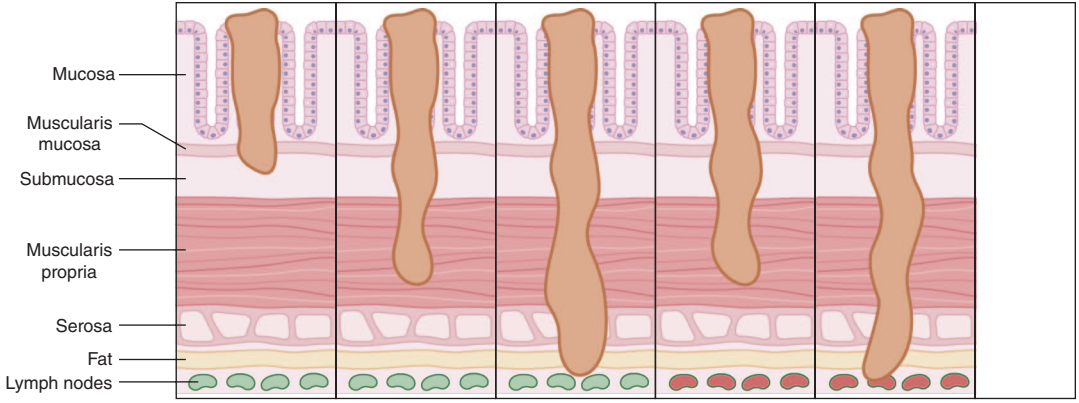


**FIGURE 71-1** Staging and prognosis for pts with colorectal cancer.



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but are ineffective in tumors with *ras* mutations; intraarterial chemotherapy [floxuridine (FUDR)] and/or radiation therapy may palliate symptoms from hepatic metastases. Solitary hepatic metastases may be resected by partial hepatectomy with 25% 5-year survival.

## Prevention

Early detection of colon carcinoma may be facilitated by routine screening of stool for occult blood (Hemoccult II, ColonCare, Hemosure); however, sensitivity only ~50% for carcinoma; specificity for tumor or polyp ~25–40%. Newer tests incorporating detection of blood and mutated genes may be more sensitive and specific. False positives: ingestion of red meat, iron, aspirin; upper GI bleeding. False negatives: vitamin C ingestion, intermittent bleeding. Annual digital rectal examination and fecal occult blood testing recommended for pts over age 40, screening by flexible sigmoidoscopy every 3 years after age 50, earlier in pts at increased risk (see above); careful evaluation of all pts with positive fecal occult blood tests (flexible sigmoidoscopy and air-contrast barium enema or colonoscopy alone) reveals polyps in 20–40% and carcinoma in ~5%; screening of asymptomatic persons allows earlier detection of colon cancer (i.e., earlier Dukes' stage) and achieves greater resectability rate; decreased overall mortality from colon carcinoma seen only after 13 years of follow-up. More intensive evaluation of first-degree relatives of pts with colon carcinoma frequently includes screening air-contrast barium enema or colonoscopy after age 40. NSAIDs and cyclooxygenase 2 inhibitors appear to prevent polyp development and induce regression in high-risk groups, but have not been recommended for average-risk pts at this time.

### ANAL CANCER

Accounts for 1–2% of large-bowel cancer, 7270 cases and 1010 deaths in 2015; associated with chronic irritation, e.g., from condyloma acuminata, perianal fissures/fistulas, chronic hemorrhoids, leukoplakia, trauma from anal intercourse. Women are more commonly affected than men. Homosexual men are at increased risk. Human papillomavirus is etiologic. Presents with bleeding, pain, and perianal mass. Radiation therapy plus chemotherapy (5FU and mitomycin) leads to complete response in 80% when the primary lesion is <3 cm. Abdominoperineal resection with permanent colostomy is reserved for those with large lesions or whose disease recurs after chemoradiotherapy.

## BENIGN LIVER TUMORS

Hepatocellular adenomas occur most commonly in women in the third or fourth decades who take birth control pills. Most are found incidentally but may cause pain; intratumoral hemorrhage may cause circulatory collapse. 10% may become malignant. Women with these adenomas should stop taking birth control pills. Large tumors near the liver surface may be resected. Focal nodular hyperplasia is also more common in women but seems not to be caused by birth control pills. Lesions are vascular on angiography and have septae and are usually asymptomatic.

## HEPATOCELLULAR CARCINOMA

About 35,660 cases in the United States in 2015, but worldwide this may be the most common tumor; 24,550 deaths in 2015 in United States. Male:female = 4:1; tumor usually develops in cirrhotic liver in persons in fifth or sixth decade. High incidence in Asia and Africa is related to etiologic relationship between this cancer and hepatitis B and C infections. Effective vaccines for hepatitis B prevention and successful chemotherapy of hepatitis C should reduce the incidence. Aflatoxin exposure

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contributes to etiology and leaves a molecular signature, a mutation in codon 249 of the gene for p53.

### Modes of Presentation

A pt with known liver disease develops an abnormality on ultrasound or rising α fetoprotein (AFP) or des-gamma-carboxy prothrombin (DCP) due to absence of vitamin K; abnormal liver function tests; cachexia, abdominal pain, fever.

### Physical Findings

Jaundice, asthenia, itching, tremors, disorientation, hepatomegaly, splenomegaly, ascites, peripheral edema.

**TREATMENT HEPATOCELLULAR CARCINOMA**

Surgical resection or liver transplantation is therapeutic option but rarely successful. Radiofrequency ablation, transcatheter arterial embolization (TACE), and $^{90}$Yttrium can cause regression of small tumors. Sorafenib may produce partial responses lasting a few months.

### Screening and Prevention

Screening populations at risk has given conflicting results. Hepatitis B vaccine prevents the disease. Interferon α (IFN-α) may prevent liver cancer in persons with chronic active hepatitis C disease and possibly in those with hepatitis B. Combination therapy with a viral protease inhibitor (e.g., ledipasvir) and a viral polumerase inhibitor (e.g., sofusbuvir) for 12–24 weeks cures most patients with chronic hepatitis C.

## PANCREATIC CANCER

In 2015 in the United States, about 48,960 new cases and 40,560 deaths. The incidence is decreasing somewhat, but nearly all diagnosed cases are fatal. The tumors are ductal adenocarcinomas and are not usually detected until the disease has spread. About 70% of tumors are in the pancreatic head, 20% in the body, and 10% in the tail. Mutations in K-*ras* have been found in 85% of tumors, and the p16 cyclin-dependent kinase inhibitor on chromosome 9 may also be implicated. Long-standing diabetes, chronic pancreatitis, and smoking increase the risk; coffee-drinking, alcoholism, and cholelithiasis do not. Pts present with pain and weight loss, the pain often relieved by bending forward. Jaundice commonly complicates tumors of the head, due to biliary obstruction. Curative surgical resections are feasible in about 10%. Adjuvant chemotherapy (5FU) may benefit some pts after resection. Gemcitabine plus erlotinib or capecitabine may palliate symptoms in pts with advanced disease. Fit patients may obtain some benefit from the combination regimen, FOLFIRINOX, that includes 5FU, irinotecan, and oxaliplatin.

## ENDOCRINE TUMORS OF THE GI TRACT AND PANCREAS

### CARCINOID TUMOR

Carcinoid tumor accounts for 75% of GI endocrine tumors; incidence is about 15 cases per million population. 90% originate in Kulchitsky cells of the GI tract, most commonly the appendix, ileum, and rectum. Carcinoid tumors of the small bowel and bronchus have a more malignant course than tumors of other sites. About 5% of pts with carcinoid tumors develop symptoms of the carcinoid syndrome, the classic triad being cutaneous flushing, diarrhea, and valvular heart disease. For tumors of GI tract origin, symptoms imply metastases to liver.

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Diagnosis can be made by detecting the site of tumor or documenting production of >15 mg/d of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the urine. Octreotide scintigraphy identifies sites of primary and metastatic tumor in about two-thirds of cases.

**TREATMENT CARCINOID TUMOR**

Surgical resection where feasible. Symptoms may be controlled with histamine blockers, serotonin receptor antagonists, and octreotide, 150–1500 mg/d in three doses. Hepatic artery embolization and chemotherapy (5FU plus streptozocin or doxorubicin) have been used for metastatic disease. IFN-α at 3–10 million units SC three times a week may relieve symptoms. Everolimus, an mTOR inhibitor, and sunitinib, a kinase inhibitor, have antitumor effects. Prognosis ranges from 95% 5-year survival for localized disease to 20% 5-year survival for those with liver metastases. Median survival of pts with carcinoid syndrome is 2.5 years from the first episode of flushing.

## PANCREATIC ISLET-CELL TUMORS

Gastrinoma, insulinoma, VIPoma, glucagonoma, and somatostatinoma account for the vast majority of pancreatic islet-cell tumors; their characteristics are shown in Table 71-3. The tumors are named for the dominant hormone they produce. They are generally slow-growing and produce symptoms related to hormone production. *Gastrinomas* and *peptic ulcer disease* constitute the Zollinger-Ellison syndrome. Gastrinomas are rare (4 cases per 10 million population), and in 25–50%, the tumor is a component of a multiple endocrine neoplasia type 1 (MEN 1) syndrome.

*Insulinoma* may present with Whipple's triad: fasting hypoglycemia, symptoms of hypoglycemia, and relief after IV glucose. Normal or elevated serum insulin levels

**TABLE 71-3 GASTROINTESTINAL ENDOCRINE TUMOR SYNDROMES**

| Syndrome | Cell Type | Clinical Features | Percentage Malignant | Major Products |
|---|---|---|---|---|
| Carcinoid syndrome | Entero-chromaffin, enterochro-maffin-like | Flushing, diarrhea, wheezing, hypotension | ~100 | Serotonin, histamine, miscellaneous peptides |
| Zollinger-Ellison, gastrinoma | Non-β islet cell, duodenal G cell | Peptic ulcers, diarrhea | ~70 | Gastrin |
| Insulinoma | Islet β cell | Hypoglycemia | ~10 | Insulin |
| VIPoma (Verner-Morrison, WDHA) | Islet $D_1$ cell | Diarrhea, hypokalemia, hypochlorhy-dria | ~60 | Vasoactive intestinal peptide |
| Glucagonoma | Islet A cell | Mild diabetes mellitus, ery-thema necro-lytica migrans, glossitis | >75 | Glucagon |
| Somatostati-noma | Islet D cell | Diabetes mel-litus, diarrhea, steatorrhea, gallstones | ~70 | Somatostatin |

***Abbreviation:*** WDHA, watery diarrhea, hypokalemia, achlorhydria.

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in the presence of fasting hypoglycemia are diagnostic. Insulinomas may also be associated with MEN 1.

Verner and Morrison described a syndrome of watery diarrhea, hypokalemia, achlorhydria, and renal failure associated with pancreatic islet tumors that produce vasoactive intestinal polypeptide (VIP). *VIPomas* are rare (1 case per 10 million) but often grow to a large size before producing symptoms.

*Glucagonoma* is associated with diabetes mellitus and necrolytic migratory erythema, a characteristic red, raised, scaly rash usually located on the face, abdomen, perineum, and distal extremities. Glucagon levels >1000 ng/L not suppressed by glucose are diagnostic.

The classic triad of *somatostatinoma* is diabetes mellitus, steatorrhea, and cholelithiasis.

Provocative tests may facilitate diagnosis of functional endocrine tumors: tolbutamide enhances somatostatin secretion by somatostatinomas; pentagastrin enhances calcitonin secretion from medullary thyroid (C cell) tumors; secretin enhances gastrin secretion from gastrinomas. If imaging techniques fail to detect tumor masses, angiography or selective venous sampling for hormone determination may reveal the site of tumor. Metastases to nodes and liver should be sought by CT or MRI.

### TREATMENT PANCREATIC ISLET-CELL TUMORS

Tumor is surgically removed, if possible. Everolimus 10 mg PO qd or sunitinib 37.5 mg PO qd may produce meaningful delay (~12 months) in progressive disease and prolong survival in pts with metastatic disease. Octreotide inhibits hormone secretion in the majority of cases. IFN-α may reduce symptoms. Streptozotocin plus doxorubicin combination chemotherapy may produce responses in 60–90% of cases. Embolization or chemoembolization of hepatic metastases may be palliative.

For a more detailed discussion, see Mayer RJ: Upper Gastrointestinal Tract Cancers, Chap. 109, p. 532; Mayer RJ: Lower Gastrointestinal Cancers, Chap. 110, p. 537; Carr BI: Tumors of the Liver and Biliary Tree, Chap. 111, p. 544; Smyth E, Cunningham D: Pancreatic Cancer, Chap. 112, p. 554; and Jensen RT: Endocrine Tumors of the Gastrointestinal Tract and Pancreas, Chap. 113, p. 557, in HPIM-19.

# 72 Genitourinary Tract Cancer

## BLADDER CANCER

### INCIDENCE AND EPIDEMIOLOGY

Annual incidence in the United States is about 74,000 cases with 16,000 deaths. Median age is 65 years. Smoking accounts for 50% of the risk. Exposure to polycyclic aromatic hydrocarbons increases the risk, especially in slow acetylators. Risk is

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increased in chimney sweeps, dry cleaners, and those involved in aluminum manufacturing. Chronic cyclophosphamide exposure increases risk ninefold. *Schistosoma haematobium* infection also increases risk, especially of squamous histology.

### ETIOLOGY

Lesions involving chromosome 9q are an early event. Deletions in 17p (p53), 18q (the DCC locus), 13q (RB), 3p, and 5q are characteristic of invasive lesions. Overexpression of epidermal growth factor receptors and *HER2/neu* receptors is common.

### PATHOLOGY

Over 90% of tumors are derived from transitional epithelium; 3% are squamous, 2% are adenocarcinomas, and <1% are neuroendocrine small cell tumors. Field effects are seen that place all sites lined by transitional epithelium at risk, including the renal pelvis, ureter, bladder, and proximal two-thirds of the urethra; 90% of tumors are in the bladder, 8% in the renal pelvis, and 2% in the ureter or urethra. Histologic grade influences survival. Lesion recurrence is influenced by size, number, and growth pattern of the primary tumor.

### CLINICAL PRESENTATION

Hematuria is the initial sign in 80–90%; however, cystitis is a more common cause of hematuria (22% of all hematuria) than is bladder cancer (15%). Pts are initially staged and treated by endoscopy. Superficial tumors are removed at endoscopy; muscle invasion requires more extensive surgery.

### TREATMENT BLADDER CANCER

Management is based on extent of disease: superficial, invasive, or metastatic. Frequency of presentation is 75% superficial, 20% invasive, and 5% metastatic. Superficial lesions are resected at endoscopy. Although complete resection is possible in 80%, 30–80% of cases recur; grade and stage progression occur in 30%. Intravesical instillation of bacille Calmette-Guérin (BCG) reduces the risk of recurrence by 40–45%. Recurrence is monitored every 3 months.

The standard management of muscle-invasive disease is radical cystectomy. 5-year survival is 70% for those without invasion of perivesicular fat or lymph nodes, 50% for those with invasion of fat but not lymph nodes, 35% for those with one node involved, and 10% for those with six or more involved nodes. Pts who cannot withstand radical surgery may have 30–35% 5-year survival with 5000- to 7000-cGy external beam radiation therapy. Bladder sparing may be possible in up to 45% of pts with two cycles of chemotherapy with CMV (methotrexate, 30 mg/m$^2$ days 1 and 8, vinblastine, 4 mg/m$^2$ days 1 and 8, cisplatin, 100 mg/m$^2$ day 2, q21d) followed by 4000-cGy radiation therapy given concurrently with cisplatin.

Metastatic disease is treated with combination chemotherapy. Useful regimens include CMV (see above), M-VAC (methotrexate, 30 mg/m$^2$ days 1, 15, 22; vinblastine, 3 mg/m$^2$ days 2, 15, 22; doxorubicin, 30 mg/m$^2$ day 2; cisplatin, 70 mg/m$^2$ day 2; q28d) or cisplatin (70 mg/m$^2$ day 2) plus gemcitabine (1000 mg/m$^2$ days 1, 8, 15 of a 28-day cycle) or carboplatin plus paclitaxel. About 70% of pts respond to treatment, and 20% have a complete response; 10–15% have long-term disease-free survival.

## RENAL CANCER

### INCIDENCE AND EPIDEMIOLOGY

Annual incidence in the United States is about 62,000 cases with 14,000 deaths. Cigarette smoking accounts for 20–30% of cases. Risk is increased in acquired renal

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cystic disease. There are two familial forms: a rare autosomal dominant syndrome and von Hippel–Lindau disease. About 35% of pts with von Hippel–Lindau disease develop renal cancer. Incidence is also increased in those with tuberous sclerosis and polycystic kidney disease.

### ETIOLOGY

Most cases are sporadic; however, the most frequent chromosomal abnormality (occurs in 60%) is deletion or rearrangement of 3p21-26. The von Hippel–Lindau gene has been mapped to that region and appears to have ubiquitin ligase activities that influence regulation of speed of transcription and turnover of damaged proteins. It is unclear how lesions in the gene lead to cancer.

### PATHOLOGY

Five variants are recognized: clear cell tumors (75%), papillary tumors (15%), chromophobic tumors (5%), oncocytic tumors (3%), and collecting duct tumors (2%). Clear cell tumors arise from cells of the proximal convoluted tubules. Papillary tumors tend to be bilateral and multifocal and often show trisomy 7 and/or trisomy 17. Chromophobic and eosinophilic tumors less frequently have chromosomal aberrations and follow a more indolent course.

### CLINICAL PRESENTATION

The classic triad of hematuria, flank pain, and flank mass is seen in only 10–20% of pts; hematuria (40%), flank pain (40%), palpable mass (33%), and weight loss (33%) are the most common individual symptoms. Paraneoplastic syndromes of erythrocytosis (3%), hypercalcemia (5%), and nonmetastatic hepatic dysfunction (Stauffer's syndrome) (15%) may also occur. Workup should include IV pyelography, renal ultrasonography, CT of abdomen and pelvis, chest x-ray (CXR), urinalysis, and urine cytology. Stage I is disease restricted to the kidney, stage II is disease contained within Gerota's fascia, stage III is locally invasive disease involving nodes and/or inferior vena cava, stage IV is invasion of adjacent organs or metastatic sites. Prognosis is related to stage: 66% 5-year survival for I, 64% for II, 42% for III, and 11% for IV.

### TREATMENT RENAL CANCER

Radical nephrectomy is standard for stage I, II, and most stage III pts. Surgery may also be indicated in the setting of metastatic disease for intractable local symptoms (bleeding, pain). Response rates of 40–48% have been noted with five different single agents, sunitinib (50 mg/d 4 weeks out of 6), sorafenib (400 mg bid), and temsirolimus (25 mg IV weekly) and the related drug, everolimus (10 mg PO daily), the PD1 inhibitor, nivolumab and cabozantinib (60 mg PO daily), an inhibitor of MET, AXL and the vascular endothelial growth factor receptor. Sunitinib and sorafenib are thought to be antiangiogenic through inhibition of kinases in tumor cells. Temsirolimus is an inhibitor of mTOR. Nivolumab allows activation of T cells that kill the tumor cells. About 10–15% of pts with advanced-stage disease may benefit from interleukin 2 and/or interferon α (IFN-α). Addition of bevacizumab to IFN-α improves the response rate. Some remissions are durable. Chemotherapy is of little or no benefit.

## TESTICULAR CANCER

### INCIDENCE AND EPIDEMIOLOGY

Annual incidence is about 8430 cases with 380 deaths. Peak age incidence is 20–40. Occurs 4–5 times more frequently in white than black men. Cryptorchid testes are

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at increased risk. Early orchiopexy may protect against testis cancer. Risk is also increased in testicular feminization syndromes, and Klinefelter syndrome is associated with mediastinal germ cell tumor.

## ETIOLOGY

The cause is unknown. Disease is associated with a characteristic cytogenetic defect, isochromosome 12p.

## PATHOLOGY

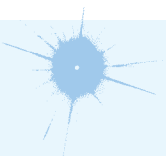
Two main subtypes are noted: seminoma and nonseminoma. Each accounts for ~50% of cases. Seminoma has a more indolent natural history and is highly sensitive to radiation therapy. Four subtypes of nonseminoma are defined: embryonal carcinoma, teratoma, choriocarcinoma, and endodermal sinus (yolk sac) tumor.

## CLINICAL PRESENTATION

Painless testicular mass is the classic initial sign. In the presence of pain, differential diagnosis includes epididymitis or orchitis; a brief trial of antibiotics may be undertaken. Staging evaluation includes measurement of serum tumor markers α fetoprotein (AFP) and β-human chorionic gonadotropin (hCG), CXR, and CT scan of abdomen and pelvis. Lymph nodes are staged at resection of the primary tumor through an inguinal approach. Stage I disease is limited to the testis, epididymis, or spermatic cord; stage II involves retroperitoneal nodes; and stage III is disease outside the retroperitoneum. Among seminoma pts, 70% are stage I, 20% are stage II, and 10% are stage III. Among nonseminoma germ cell tumor pts, 33% are found in each stage. hCG may be elevated in either seminoma or nonseminoma, but AFP is elevated only in nonseminoma. 95% of pts are cured if treated appropriately. Primary nonseminoma in the mediastinum is associated with acute leukemia or other hematologic disorders and has a poorer prognosis than testicular primaries (~33%).

## TREATMENT TESTICULAR CANCER (FIGURE 72-1)

For stages I and II seminoma, inguinal orchiectomy followed by retroperitoneal radiation therapy to 2500–3000 cGy is effective. For stages I and II nonseminoma germ cell tumors, inguinal orchiectomy followed by retroperitoneal lymph node dissection is effective. For pts of either histology with bulky nodes or stage III disease, chemotherapy is given. Cisplatin (20 mg/m$^2$ days 1–5), etoposide (100 mg/m$^2$ days 1–5), and bleomycin (30 U days 2, 9, 16) given every 21 days for four cycles is the standard therapy. If tumor markers return to zero, residual masses are resected. Most are necrotic debris or teratomas. Salvage therapy rescues about 25% of those not cured with primary therapy.



For a more detailed discussion, see Scher HI, Rosenberg JE, Motzer RJ: Bladder and Renal Cell Carcinomas, Chap. 114, p. 575; and Motzer RJ, Fedlman DR, Bosl GJ: Testicular Cancer, Chap. 116, p. 588, in HPIM-19.

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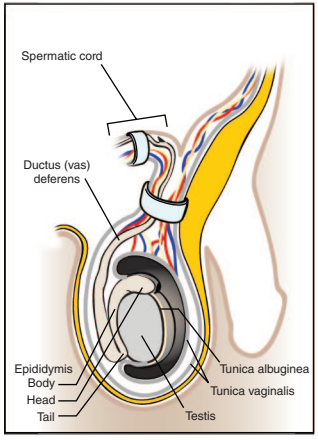
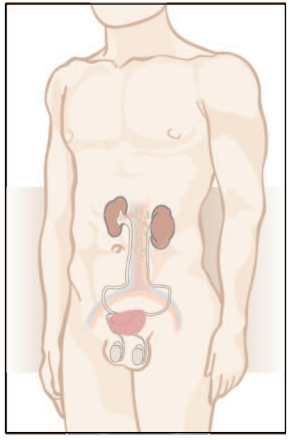



| Stage | Extent of Disease |
|---|---|
| pT1 | Tumor limited to the testis and epididymis without vascular/lymphatic invasion; tumor may invade into the tunica albuginea but not the tunica vaginalis |
| pT2 | Tumor limited to the testis and epididymis with vascular/lymphatic invasion; tumor extending through the tunica albuginea with involvement of the tunica vaginalis |
| pT3 | Tumor invades the spermatic cord with or without vascular/lymphatic invasion |
| pT4 | Tumor invades the scrotum with or without vascular/lymphatic invasion |



| | | Treatment Option | |
|---|---|---|---|
| Stage | Extent of Disease | Seminoma | Nonseminoma |
| IA | Testis only, no vascular/lymphatic invasion (T1) | Observation Chemotherapy or RT | Observation |
| IB | Testis only, with vascular/lymphatic invasion (T2), or extension through tunica albuginea (T2), or involvement of spermatic cord (T3) or scrotum (T4) | Observation Chemotherapy or RT | RPLND or Chemotherapy |
| IIA | Retroperitoneal Nodes <2 cm | RT | RPLND +/– adjuvant Chemotherapy or Chemotherapy, often followed by RPLND |
| IIB | Retroperitoneal Nodes 2–5 cm | RT or Chemotherapy | Chemotherapy, often followed by RPLND |
| IIC | Retroperitoneal Nodes >5 cm | Chemotherapy | Chemotherapy, often followed by RPLND |
| Distant Metastases | | | |
| III | Common sites include distant (or extra-abdominal) lymph nodes, lung, liver, bone, and brain | Chemotherapy | Chemotherapy, often followed by surgery (biopsy or resection) |

**FIGURE 72-1** Germ cell tumor staging and treatment. RPLND, retroperitoneal lymph node dissection; RT, radiotherapy.



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# 73 Gynecologic Cancer

## OVARIAN CANCER

### INCIDENCE AND EPIDEMIOLOGY

Annually in the United States, about 21,290 new cases are found and 14,180 women die of ovarian cancer. Incidence begins to rise in the fifth decade, peaking in the eighth decade. Risk is increased in nulliparous women and reduced by pregnancy (risk decreased about 10% per pregnancy) and oral contraceptives. About 5% of cases are familial.

### GENETICS

Mutations in *BRCA-1* and *BRCA-2* predispose women to both breast and ovarian cancer. Cytogenetic analysis of epithelial ovarian cancers that are not familial often reveals complex karyotypic abnormalities, including structural lesions on chromosomes 1 and 11 and loss of heterozygosity for loci on chromosomes 3q, 6q, 11q, 13q, and 17. C-*myc*, H-*ras*, K-*ras*, and *HER2/neu* are often mutated or overexpressed. Unlike in colon cancer, a stepwise pathway to ovarian carcinoma is not apparent. Ovarian cancers may also occur in the setting of Lynch syndrome, inherited nonpolyposis colorectal cancer, due to mutations in the genes that repair DNA mismatches. The subset of women with endometrioid histology often have a mutation in *ARID1A*, a DNA repair complex component.

### SCREENING

No benefit has been seen from screening women of average risk. Hereditary ovarian cancer accounts for 10% of all cases. Women with *BRCA-1* or *-2* mutations should consider prophylactic bilateral salpingo-oophorectomy by age 40.

### CLINICAL PRESENTATION

Most pts present with abdominal pain, bloating, urinary symptoms, and weight gain indicative of disease spread beyond the true pelvis. Localized ovarian cancer is usually asymptomatic and detected on routine pelvic examination as a palpable nontender adnexal mass. Most ovarian masses detected incidentally in ovulating women are ovarian cysts that resolve over one to three menstrual cycles. Adnexal masses in postmenopausal women are more often pathologic and should be surgically removed. CA-125 serum levels are ≥35 U/mL in 80–85% of women with ovarian cancer, but other conditions may also cause elevations.

### PATHOLOGY

Half of ovarian tumors are benign, one-third are malignant, and the rest are tumors of low malignant potential. These borderline lesions have cytologic features of malignancy but do not invade. Malignant epithelial tumors may be of five different types: serous (50%), mucinous (25%), endometrioid (15%), clear cell (5%), and Brenner tumors (1%, derived from urothelial or transitional epithelium). The remaining 4% of ovarian tumors are stromal or germ cell tumors, which are managed like testicular cancer in men (Chap. 72). Histologic grade is an important prognostic factor for the epithelial varieties.

### STAGING

Extent of disease is ascertained by a surgical procedure that permits visual and manual inspection of all peritoneal surfaces and the diaphragm. Total abdominal

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**TABLE 73-1 STAGING AND SURVIVAL IN GYNECOLOGIC MALIGNANCIES**

| Stage | Ovarian | 5-Year Survival, % | Endometrial | 5-Year Survival, % | Cervical | 5-Year Survival, % |
|---|---|---|---|---|---|---|
| 0 | — | | — | | Carcinoma in situ | 100 |
| I | Confined to ovary | 90–95 | Confined to corpus | 89 | Confined to uterus | 85 |
| II | Confined to pelvis | 70–80 | Involves corpus and cervix | 73 | Invades beyond uterus but not pelvic wall | 65 |
| III | Intraabdominal spread | 25–50 | Extends outside the uterus but not outside the true pelvis | 52 | Extends to pelvic wall and/or lower third of vagina, or hydronephrosis | 35 |
| IV | Spread outside abdomen | 1–5 | Extends outside the true pelvis or involves the bladder or rectum | 17 | Invades mucosa of bladder or rectum or extends beyond the true pelvis | 7 |

hysterectomy, bilateral salpingo-oophorectomy, partial omentectomy, pelvic and paraaortic lymph node sampling, and peritoneal washings should be performed. The staging system and its influence on survival are shown in Table 73-1. About 23% of pts are stage I, 13% are stage II, 47% are stage III, and 16% are stage IV.

## TREATMENT OVARIAN CANCER

Pts with stage I disease, no residual tumor after surgery, and well- or moderately differentiated tumors need no further treatment after surgery and have a 5-year survival of >95%. For stage II pts totally resected and stage I pts with poor histologic grade, adjuvant therapy with single-agent cisplatin or cisplatin plus paclitaxel produces 5-year survival of 80%. In the setting of bulky disease, maximal surgical cytoreduction is attempted. Those in whom no gross residual disease is left have a median survival of 39 months; those left with visible tumor, 17 months. Giving chemotherapy before definitive surgery (neoadjuvant) may increase the fraction of pts whose gross disease is resectable. Advanced-stage pts should receive paclitaxel, 175 mg/m$^2$ by 3-h infusion, followed by carboplatin dosed to an area under the curve (AUC) of 6 every 3 or 4 weeks. Carboplatin dose is calculated by the Calvert formula: dose = target AUC × (glomerular filtration rate + 25). Some data support intraperitoneal delivery of the chemotherapy. The complete response rate is about 55%, and median survival is 38 months.

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## ENDOMETRIAL CANCER

### INCIDENCE AND EPIDEMIOLOGY

The most common gynecologic cancer—54,870 cases are diagnosed in the United States and 10,170 pts die annually. It is primarily a disease of postmenopausal women. Obesity, altered menstrual cycles, infertility, late menopause, and postmenopausal bleeding are commonly encountered in women with endometrial cancer. Women taking tamoxifen to prevent breast cancer recurrence and those taking estrogen replacement therapy are at a modestly increased risk. Peak incidence is in the sixth and seventh decades.

### CLINICAL PRESENTATION

Abnormal vaginal discharge (90%), abnormal vaginal bleeding (80%), and leukorrhea (10%) are the most common symptoms.

### PATHOLOGY

Endometrial cancers are adenocarcinomas in 75–80% of cases. The remaining cases include mucinous carcinoma; papillary serous carcinoma; and secretory, ciliate, and clear cell varieties. Prognosis depends on stage, histologic grade, and degree of myometrial invasion.

### STAGING

Total abdominal hysterectomy and bilateral salpingo-oophorectomy constitute both the staging procedure and the treatment of choice. The staging scheme and its influence on prognosis are shown in Table 73-1. About 75% of pts are stage I, 13% are stage II, 9% are stage III, and 3% are stage IV.

### TREATMENT ENDOMETRIAL CANCER

In women with poor histologic grade, deep myometrial invasion, or extensive involvement of the lower uterine segment or cervix, intracavitary or external-beam radiation therapy is given. If cervical invasion is deep, preoperative radiation therapy may improve the resectability of the tumor. Stage III disease is managed with surgery and radiation therapy. Stage IV disease is usually treated palliatively. Progestational agents such as hydroxyprogesterone or megestrol and the antiestrogen tamoxifen may produce responses in 20% of pts. Doxorubicin, 60 mg/m$^2$ IV day 1, and cisplatin, 50 mg/m$^2$ IV day 1, every 3 weeks for 8 cycles produces a 45% response rate.

## CERVICAL CANCER

### INCIDENCE AND EPIDEMIOLOGY

In the United States, about 12,900 cases of invasive cervical cancer are diagnosed each year and 50,000 cases of carcinoma in situ are detected by Pap smear. Cervical cancer kills 4100 women a year, 85% of whom never had a Pap smear. It is a major cause of disease in underdeveloped countries and is more common in lower socioeconomic groups, in women with early sexual activity and/or multiple sexual partners, and in smokers. Human papilloma virus (HPV) types 16 and 18 are the major types associated with cervical cancer. The virus attacks the $G_1$ checkpoint of the cell cycle; its E7 protein binds and inactivates Rb protein, and E6 induces the degradation of p53. Risk factors include a large number of sexual partners, early age at first intercourse, a history of venereal disease, HIV infection, and heavy smoking.

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## SCREENING

Women should begin screening when they begin sexual activity or at age 20. After two consecutive negative annual Pap smears, the test should be repeated every 3 years. Abnormal smears dictate the need for a cervical biopsy, usually under colposcopy, with the cervix painted with 3% acetic acid, which shows abnormal areas as white patches. If there is evidence of carcinoma in situ, a cone biopsy is performed, which is therapeutic.

## PREVENTION

Women, men, and children age 9–26 should obtain vaccination with Gardasil to prevent infection with two serotypes of virus (16 and 18) that cause 70% of the cervical cancer in the United States.

## CLINICAL PRESENTATION

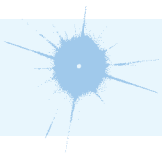
Pts present with abnormal bleeding or postcoital spotting or menometrorrhagia or intermenstrual bleeding. Vaginal discharge, low back pain, and urinary symptoms also may be present.

## STAGING

Staging is clinical and consists of a pelvic examination under anesthesia with cystoscopy and proctoscopy. Chest x-ray, IV pyelography, and abdominal CT are used to search for metastases. The staging system and its influence on prognosis are shown in Table 73-1. At presentation, 47% of pts are stage I, 28% are stage II, 21% are stage III, and 4% are stage IV.

## TREATMENT CERVICAL CANCER

Carcinoma in situ is cured with cone biopsy. Stage I disease may be treated with radical hysterectomy or radiation therapy. Stages II–IV disease are usually treated with radiation therapy, often with both brachytherapy and teletherapy, or combined-modality therapy. Pelvic exenteration is used uncommonly to control the disease, especially in the setting of centrally recurrent or persistent disease. Women with locally advanced (stage IIB–IVA) disease usually receive concurrent chemotherapy and radiation therapy. The chemotherapy acts as a radiosensitizer. Hydroxyurea, 5-fluorouracil (5FU), and cisplatin have all shown promising results given concurrently with radiation therapy. Cisplatin, 75 mg/m$^2$ IV over 4 h on day 1, and 5FU, 4 g given by 96-h infusion on days 1–5 of radiation therapy, is a common regimen. Relapse rates are reduced 30–50% by such therapy. Advanced-stage disease is treated palliatively with single agents (cisplatin, irinotecan, ifosfamide). Bevacizumab may improve the antitumor effects of chemotherapy.



For a more detailed discussion, see Seiden MV: Gynecologic Malignancies, Chap. 117, p. 592, in HPIM-19.

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# 74 Prostate Hyperplasia and Carcinoma

## PROSTATE HYPERPLASIA

Enlargement of the prostate is nearly universal in aging men. Hyperplasia usually begins by age 45 years, occurs in the area of the prostate gland surrounding the urethra, and produces urinary outflow obstruction. Symptoms develop on average by age 65 in whites and 60 in blacks. Symptoms develop late because hypertrophy of the bladder detrusor compensates for ureteral compression. As obstruction progresses, urinary stream caliber and force diminish, hesitancy in stream initiation develops, and postvoid dribbling occurs. Dysuria and urgency are signs of bladder irritation (perhaps due to inflammation or tumor) and are usually not seen in prostate hyperplasia. As the postvoid residual increases, nocturia and overflow incontinence may develop. Common medications such as tranquilizing drugs and decongestants, infections, or alcohol may precipitate urinary retention. Because of the prevalence of hyperplasia, the relationship to neoplasia is unclear.

On digital rectal examination (DRE), a hyperplastic prostate is smooth, firm, and rubbery in consistency; the median groove may be lost. Prostate-specific antigen (PSA) levels may be elevated but are ≤10 ng/mL unless cancer is also present (see below). Cancer may also be present at lower levels of PSA.

### TREATMENT PROSTATE HYPERPLASIA

Asymptomatic pts do not require treatment, and those with complications of urethral obstruction such as inability to urinate, renal failure, recurrent urinary tract infection, hematuria, or bladder stones clearly require surgical extirpation of the prostate, usually by transurethral resection (TURP). However, the approach to the remaining pts should be based on the degree of incapacity or discomfort from the disease and the likely side effects of any intervention. If the pt has only mild symptoms, watchful waiting is not harmful and permits an assessment of the rate of symptom progression. If therapy is desired by the pt, two medical approaches may be helpful: terazosin, an $\alpha_1$-adrenergic blocker (1 mg at bedtime, titrated to symptoms up to 20 mg/d), relaxes the smooth muscle of the bladder neck and increases urine flow; finasteride (5 mg/d) or dutasteride (2.5 mg/d), inhibitors of 5α-reductase, block the conversion of testosterone to dihydrotestosterone and cause an average decrease in prostate size of ~24%. TURP has the greatest success rate but also the greatest risk of complications. Transurethral microwave thermotherapy (TUMT) may be comparably effective to TURP. Direct comparison has not been made between medical and surgical management.

## PROSTATE CARCINOMA

Prostate cancer has been diagnosed in 220,800 men in 2015 in the United States—an incidence comparable to that of breast cancer. About 27,540 men have died of prostate cancer in 2015. The early diagnosis of cancers in mildly symptomatic men found on screening to have elevated serum levels of PSA has complicated management. Like most other cancers, incidence is age-related. The disease is more common in blacks than whites. Symptoms are generally similar to and indistinguishable from those of prostate hyperplasia, but those with cancer more often have dysuria and back or hip pain. On histology, 95% are adenocarcinomas. Biologic behavior is affected by histologic grade (Gleason score).

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In contrast to hyperplasia, prostate cancer generally originates in the periphery of the gland and may be detectable on DRE as one or more nodules on the posterior surface of the gland, hard in consistency and irregular in shape. An approach to diagnosis is shown in Fig. 74-1. Those with a negative DRE and PSA ≤4 ng/mL may be followed annually. Those with an abnormal DRE or a PSA >10 ng/mL should undergo transrectal ultrasound (TRUS)-guided biopsy. Those with normal DRE and PSA of 4.1–10 ng/mL may be handled differently in different centers. Some would perform TRUS and biopsy any abnormality or follow if no abnormality were found. Some would repeat the PSA in a year and biopsy if the increase over that period were >0.75 ng/mL. Other methods of using PSA to distinguish early cancer from hyperplasia include quantitating bound and free PSA and relating the PSA to the size of the prostate (PSA density). Perhaps one-third of persons with prostate cancer do not have PSA elevations.

Lymphatic spread is assessed surgically; it is present in only 10% of those with Gleason grade 5 or lower and in 70% of those with grade 9 or 10. PSA level also correlates with spread; only 10% of those with PSA <10 ng/mL have lymphatic spread. Bone is the most common site of distant metastasis. Whitmore-Jewett staging includes A: tumor not palpable but detected at TURP; B: palpable tumor in one (B1) or both (B2) lobes; C: palpable tumor outside capsule; and D: metastatic disease.

## TREATMENT PROSTATE CARCINOMA

For pts with stages A through C disease, surgery (radical retropubic prostatectomy) and radiation therapy (conformal three-dimensional fields) are said to have similar outcomes; however, most pts are treated surgically. Both modalities are associated with impotence. Surgery is more likely to lead to incontinence. Radiation therapy is more likely to produce proctitis, perhaps with bleeding or stricture. Addition of hormonal therapy (goserelin) to radiation therapy of pts with localized disease appears to improve results. Pts usually must have a 5-year life expectancy to undergo radical prostatectomy. Stage A pts have survival identical to age-matched controls without cancer. Stage B and C pts have a 10-year survival of 82% and 42%, respectively.

Pts treated surgically for localized disease who develop rising PSA may undergo Prostascint scanning (antibody to a prostate-specific membrane antigen). If no uptake is seen, the pt is observed. If uptake is seen in the prostate bed, local recurrence is implied and external beam radiation therapy is delivered to the site. (If the pt was initially treated with radiation therapy, this local recurrence may be treated with surgery.) However, in most cases, a rising PSA after local therapy indicates systemic disease. It is not clear when to intervene in such pts. Treatment is often initiated if the PSA doubling time is <12 months.

For pts with metastatic disease, androgen deprivation is the treatment of choice. Surgical castration is effective, but most pts prefer to take leuprolide, 7.5 mg depot form IM monthly (to inhibit pituitary gonadotropin production), plus flutamide, 250 mg PO tid (an androgen receptor blocker). The value of added flutamide is debated. Alternative approaches include adrenalectomy, hypophysectomy, estrogen administration, and medical adrenalectomy with aminoglutethimide. The median survival of stage D pts is 33 months. Pts occasionally respond to withdrawal of hormonal therapy with tumor shrinkage. Second hormonal manipulations act by blocking androgen production in the tumor; abiraterone, a CYP17 inhibitor that blocks androgen synthesis and enzalutamide, an antiandrogen, improve overall survival. Many pts who progress on hormonal therapy have androgen-independent tumors, often associated with genetic changes in the androgen receptor and new expression of *bcl*-2, which may contribute to chemotherapy resistance. Chemotherapy is used for palliation in prostate cancer. Mitoxantrone, estramustine, and taxanes, particularly cabazitaxel, appear to be active single agents, and combinations of drugs are being tested.

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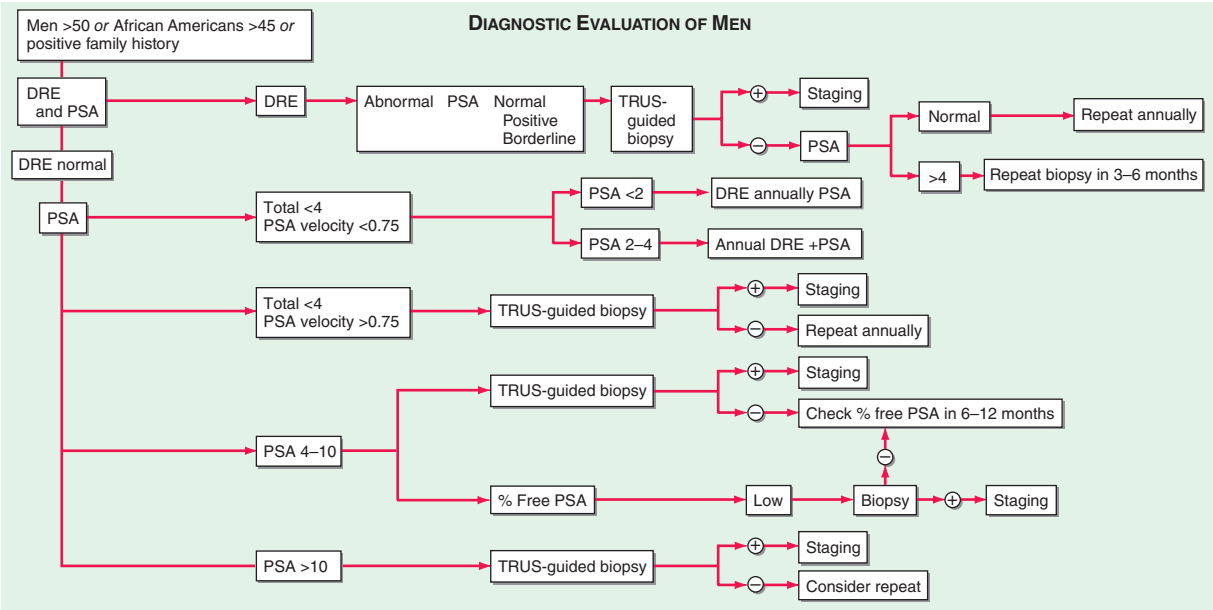


**FIGURE 74-1** The use of the annual digital rectal examination (DRE) and measurement of prostate-specific antigen (PSA) as guides for deciding which men should have transrectal ultrasound (TRUS)-guided prostate biopsy. There are at least three schools of thought about what to do if the DRE is negative and the PSA is equivocal (4.1–10 ng/mL).

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Chemotherapy-treated pts are more likely to have pain relief than those receiving supportive care alone. Sipuleucel-T, an active specific immunotherapy, improves survival by about 4 months in hormone-refractory disease without producing any measureable change in the tumor. Bone pain from metastases may be palliated with strontium-89 or samarium-153. Bisphosphonates decrease the incidence of skeletal events.

### PROSTATE CANCER PREVENTION

Finasteride and dutasteride have been shown to reduce the incidence of prostate cancer by 25%, but no effect on overall survival has been seen with limited follow-up. In addition, the cancers that do occur appear to be shifted to higher Gleason grades, but the clinical course of disease does not seem to be altered.

For a more detailed discussion, see Scher HI, Eastham JA: Benign and Malignant Diseases of the Prostate, Chap. 115, p. 579, in HPIM-19.

# 75 Cancer of Unknown Primary Site

Cancer of unknown primary site (CUPS) is defined as follows: biopsy-proven malignancy; primary site unapparent after history, physical examination, chest x-ray, abdominal and pelvic CT, complete blood count, chemistry survey, mammography (women), β-human chorionic gonadotropin (hCG) levels (men), α-fetoprotein (AFP) levels (men), and prostate-specific antigen (PSA) levels (men); and histologic evaluation not consistent with a primary tumor at the biopsy site. CUPS incidence is declining, probably because of better pathology diagnostic criteria; it accounts for about 3% of all cancers today, down from 10–15% 15 years ago. Most pts are over age 60. The tumors are often aneuploid. Cell lines derived from such tumors frequently have abnormalities in chromosome 1.

## Clinical Presentation

Pts may present with fatigue, weight loss, pain, bleeding, abdominal swelling, subcutaneous masses, and lymphadenopathy. Once metastatic malignancy is confirmed, diagnostic efforts should be confined to evaluating the presence of potentially curable tumors, such as lymphoma, Hodgkin's disease, germ cell tumor, ovarian cancer, head and neck cancer, and primitive neuroectodermal tumor, or tumors for which therapy may be of significant palliative value such as breast cancer or prostate cancer. In general, efforts to evaluate the presence of these tumor types depend more on the pathologist than on expensive clinical diagnostic testing. Localizing symptoms, a history of carcinogen exposure, or a history of fulguration of skin lesion may direct some clinical testing; however, the careful light microscopic, ultrastructural, immunologic, karyotypic, and molecular biologic examination of adequate volumes of tumor tissue is the most important feature of the diagnostic workup in the absence of suspicious findings on history and physical examination (Table 75-1).

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**TABLE 75-1 POSSIBLE PATHOLOGIC EVALUATION OF BIOPSY SPECIMENS FROM PATIENTS WITH METASTATIC CANCER OF UNKNOWN PRIMARY SITE**

| Evaluation/Findings | Suggested Primary Site or Neoplasm |
|---|---|
| **Histology (hematoxylin and eosin staining)** | |
| Psammoma bodies, papillary configuration | Ovary, thyroid |
| Signet ring cells | Stomach |
| **Immunohistology** | |
| Leukocyte common antigen (LCA, CD45) | Lymphoid neoplasm |
| Leu-M1 | Hodgkin's disease |
| Epithelial membrane antigen | Carcinoma |
| Cytokeratin | Carcinoma |
| CEA | Carcinoma |
| HMB45 | Melanoma |
| Desmin | Sarcoma |
| Thyroglobulin | Thyroid carcinoma |
| Calcitonin | Medullary carcinoma of the thyroid |
| Myoglobin | Rhabdomyosarcoma |
| PSA/prostatic acid phosphatase | Prostate |
| AFP | Liver, stomach, germ cell |
| Placental alkaline phosphatase | Germ cell |
| β-human chorionic gonadotropin | Germ cell |
| B, T cell markers | Lymphoid neoplasm |
| S-100 protein | Neuroendocrine tumor, melanoma |
| Gross cystic fluid protein | Breast, sweat gland |
| Estrogen and progesterone receptors | Breast |
| Factor VIII | Kaposi's sarcoma, angiosarcoma |
| Thyroid transcription factor 1 (TTF-1) | Lung adenocarcinoma, thyroid |
| Calretinin, mesothelin | Mesothelioma |
| URO-III, thrombomodulin | Bladder |
| **Flow Cytometry** | |
| B, T cell markers | Lymphoid neoplasm |
| **Ultrastructure** | |
| Actin-myosin filaments | Rhabdomyosarcoma |
| Secretory granules | Neuroendocrine tumors |
| Desmosomes | Carcinoma |
| Premelanosomes | Melanoma |
| **Cytogenetics** | |
| Isochromosome 12p; 12q(–) | Germ cell |
| t(11;22) | Ewing's sarcoma, primitive neuroectodermal tumor |
| t(8;14)[a] | Lymphoid neoplasm |
| 3p(–) | Small cell lung carcinoma; renal cell carcinoma, mesothelioma |
| t(X;18) | Synovial sarcoma |

(*Continued*)

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**TABLE 75-1 POSSIBLE PATHOLOGIC EVALUATION OF BIOPSY SPECIMENS FROM PATIENTS WITH METASTATIC CANCER OF UNKNOWN PRIMARY SITE (*CONTINUED*)**

| Evaluation/Findings | Suggested Primary Site or Neoplasm |
|---|---|
| t(12;16) | Myxoid liposarcoma |
| t(12;22) | Clear cell sarcoma (melanoma of soft parts) |
| t(2;13) | Alveolar rhabdomyosarcoma |
| 1p(–) | Neuroblastoma |
| **Receptor Analysis** | |
| Estrogen/progesterone receptor | Breast |
| **Molecular Biologic Studies** | |
| Immunoglobulin, *bcl*-2, T cell receptor gene rearrangement | Lymphoid neoplasm |

[a]Or any other rearrangement involving an antigen-receptor gene.
***Abbreviations:*** AFP, α-fetoprotein; CEA, carcinoembryonic antigen; PSA, prostate-specific antigen.

## Histology

About 60% of CUPS tumors are adenocarcinomas, 5% are squamous cell carcinomas, and 30% are poorly differentiated neoplasms not further classified on light microscopy. Expression of cytokeratin subtypes may narrow the range of possible diagnoses (Fig. 75-1).

## Prognosis

Pts with squamous cell carcinoma have a median survival of 9 months; those with adenocarcinoma or unclassifiable tumors have a median survival of 4–6 months. Pts in whom a primary site is identified usually have a better prognosis. Limited sites of involvement and neuroendocrine histology are favorable prognostic factors. Pts without a primary diagnosis should be treated palliatively with radiation therapy to symptomatic lesions. All-purpose chemotherapy regimens rarely produce responses but always produce toxicity. Certain clinical features may permit individualized therapy.

## SYNDROME OF UNRECOGNIZED EXTRAGONADAL GERM CELL CANCER

In pts <50 years with tumor involving midline structures, lung parenchyma, or lymph nodes and evidence of rapid tumor growth, germ cell tumor is a possible diagnosis. Serum tumor markers may or may not be elevated. Cisplatin, etoposide, and bleomycin (Chap. 72) chemotherapy may induce complete responses in ≥25%,

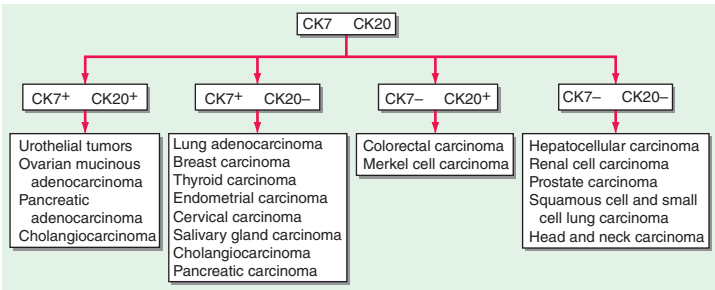


**FIGURE 75-1** Approach to cytokeratin (CK7 and CK20) markers used in CUP.

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and ~15% may be cured. A trial of such therapy should probably also be undertaken in pts whose tumors have abnormalities in chromosome 12.

### PERITONEAL CARCINOMATOSIS IN WOMEN

Women who present with pelvic mass or pain and an adenocarcinoma diffusely throughout the peritoneal cavity, but without a clear site of origin, have primary peritoneal papillary serous carcinoma. The presence of psammoma bodies in the tumor or elevated CA-125 levels may favor ovarian origin. Such pts should undergo debulking surgery followed by paclitaxel plus cisplatin or carboplatin combination chemotherapy (Chap. 73). About 20% of pts will respond, and 10% will survive at least 2 years.

### CARCINOMA IN AN AXILLARY LYMPH NODE IN WOMEN

Such women should receive adjuvant breast cancer therapy appropriate for their menopausal status even in the absence of a breast mass on physical examination or mammography and undetermined or negative estrogen and progesterone receptors on the tumor (Chap. 70). Unless the ipsilateral breast is radiated, up to 50% of these pts will later develop a breast mass. Although this is a rare clinical situation, long-term survival similar to women with stage II breast cancer is possible.

### OSTEOBLASTIC BONE METASTASES IN MEN

The probability of prostate cancer is high; a trial of empirical hormonal therapy (leuprolide and flutamide) is warranted (Chap. 74).

### CERVICAL LYMPH NODE METASTASES

Even if panendoscopy fails to reveal a head and neck primary, treatment of such pts with cisplatin and 5-fluorouracil chemotherapy may produce a response; some responses are long-lived (Chap. 68).

For a more detailed discussion, see Varadhachary GR, Abbruzzese JL: Carcinoma of Unknown Primary, Chap. 120e, in HPIM-19.

# 76 Paraneoplastic Endocrine Syndromes

Both benign and malignant tumors of nonendocrine tissue can secrete a variety of hormones, principally peptide hormones, and many tumors produce more than one hormone (Table 76-1). At the clinical level, ectopic hormone production is important for two reasons.

First, endocrine syndromes that result may either be the presenting manifestations of the neoplasm or occur late in the course. The endocrine manifestations in some instances are of greater significance than the tumor itself, as in pts with benign or slowly growing malignancies that secrete corticotropin-releasing hormone and cause fulminant Cushing's syndrome. The frequency with which ectopic hormone production is recognized varies with the criteria used for diagnosis. The most common syndromes of clinical import are those of adrenocorticotropic hormone

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**TABLE 76-1 PARANEOPLASTIC SYNDROMES CAUSED BY ECTOPIC HORMONE PRODUCTION**

| Paraneoplastic Syndrome | Ectopic Hormone | Typical Tumor Types[a] |
|---|---|---|
| **Common** | | |
| Hypercalcemia of malignancy | PTHrP | Squamous cell (head and neck, lung, skin), breast, genitourinary, gastrointestinal |
| | 1,25 dihydroxyvitamin D | Lymphomas |
| | PTH (rare) | Lung, ovary |
| | $PGE_2$ (rare) | Renal, lung |
| SIADH | Vasopressin | Lung (squamous, small cell), gastrointestinal, genitourinary, ovary |
| Cushing's syndrome | ACTH | Lung (small cell, bronchial carcinoid, adenocarcinoma, squamous), thymus, pancreatic islet, medullary thyroid carcinoma |
| | CRH (rare) | Pancreatic islet, carcinoid, lung, prostate |
| | Ectopic expression of GIP, LH/hCG, other G protein–coupled receptors (rare) | Macronodular adrenal hyperplasia |
| **Less common** | | |
| Nonislet cell hypoglycemia | IGF-II | Mesenchymal tumors, sarcomas, adrenal, hepatic, gastrointestinal, kidney, prostate |
| | Insulin (rare) | Cervix (small cell carcinoma) |
| Male feminization | hCG[b] | Testis (embryonal, seminomas), germinomas, choriocarcinoma, lung, hepatic, pancreatic islet |
| Diarrhea or intestinal hypermotility | Calcitonin[c] | Lung, colon, breast, medullary thyroid carcinoma |
| | VIP | Pancreas, pheochromocytoma, esophagus |
| **Rare** | | |
| Oncogenic osteomalacia | Phosphatonin (FGF23) | Hemangiopericytomas, osteoblastomas, fibromas, sarcomas, giant cell tumors, prostate, lung |
| Acromegaly | GHRH | Pancreatic islet, bronchial and other carcinoids |
| | GH | Lung, pancreatic islet |

(*Continued*)

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**TABLE 76-1 PARANEOPLASTIC SYNDROMES CAUSED BY ECTOPIC HORMONE PRODUCTION (*CONTINUED*)**

| Paraneoplastic Syndrome | Ectopic Hormone | Typical Tumor Types[a] |
|---|---|---|
| Hyperthyroidism | TSH | Hydatidiform mole, embryonal tumors, struma ovarii |
| Hypertension | Renin | Juxtaglomerular tumors, kidney, lung, pancreas, ovary |

[a]Only the most common tumor types are listed. For most ectopic hormone syndromes, an extensive list of tumors has been reported to produce one or more hormones.
[b]hCG is produced eutopically by trophoblastic tumors. Certain tumors produce disproportionate amounts of the hCG α or hCG β subunit. High levels of hCG rarely cause hyperthyroidism because of weak binding to the TSH receptor.
[c]Calcitonin is produced eutopically by medullary thyroid carcinoma and is used as a tumor marker.
***Abbreviations:*** ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; FGF23, fibroblast growth factor 23; GH, growth hormone; GHRH, Growth hormone–releasing hormone; GIP, gastric inhibitory peptide; hCG, human chorionic gonadotropin; IGF, insulin-like growth factor; LH, luteinizing hormone; $PGE_2$, prostaglandin $E_2$; PTH, parathyroid hormone; PTHrP, parathyroid hormone–related protein; SIADH, syndrome of inappropriate antidiuretic hormone secretion; TSH, thyroid-stimulating hormone; VIP, vasoactive intestinal peptide.

(ACTH) hypersecretion, hypercalcemia, and hypoglycemia. Indeed, ectopic ACTH secretion is responsible for 15–20% of pts with Cushing's syndrome, and ~50% of pts with persistent hypercalcemia have a malignancy rather than hyperparathyroidism. Because of the rapidity of development of hormone secretion in some rapidly growing tumors, diagnosis may require a high index of suspicion, and hormone levels may be elevated out of proportion to the manifestations.

Second, ectopic hormones serve as valuable peripheral markers for neoplasia. Because of the broad spectrum of ectopic hormone secretion, screening measurements of plasma hormone levels for diagnostic purposes are not cost effective. However, in pts with malignancies that are known to secrete hormones, serial measurements of circulating hormone levels can serve as markers for completeness of tumor excision and for effectiveness of radiation therapy or chemotherapy. Likewise, tumor recurrence may be heralded by reappearance of elevated plasma hormone levels before mass effects of the tumor are evident. However, some tumors at recurrence do not secrete hormones, so hormone measurements cannot be relied on as the sole evidence of tumor activity.

## TREATMENT PARANEOPLASTIC ENDOCRINE SYNDROMES

Therapy of ectopic hormone-secreting tumors should be directed when possible toward removal of the tumor. When the tumor cannot be removed or is incurable, specific therapy can be directed toward inhibiting hormone secretion (octreotide for ectopic acromegaly or mitotane to inhibit adrenal steroidogenesis in the ectopic ACTH syndrome) or blocking the action of the hormone at the tissue level (demeclocycline for inappropriate vasopressin secretion).

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## HYPERCALCEMIA

The most common paraneoplastic syndrome, hypercalcemia of malignancy accounts for 40% of all hypercalcemia. Of cancer pts with hypercalcemia, 80% have humoral hypercalcemia mediated by parathyroid hormone–related peptide; 20% have local osteolytic hypercalcemia mediated by cytokines such as interleukin 1 and tumor necrosis factor. Many tumor types may produce hypercalcemia (Table 76-1). Pts may have malaise, fatigue, confusion, anorexia, bone pain, polyuria, weakness, constipation, nausea, and vomiting. At high calcium levels, confusion, lethargy, coma, and death may ensue. Median survival of hypercalcemic cancer pts is 1–3 months. Treatment with saline hydration, furosemide diuresis, and pamidronate (60–90 mg IV) or zoledronate (4–8 mg IV) controls calcium levels within 2 days and suppresses calcium release for several weeks. Calcitonin (2–8 U/kg) may be useful if rapid action is needed. Oral bisphosphonates can be used for chronic treatment. In the setting of hematologic malignancies, hypercalcemia may respond to glucocorticoids.

## HYPONATREMIA

Most commonly discovered in asymptomatic individuals as a result of serum electrolyte measurements, hyponatremia is usually due to tumor secretion of arginine vasopressin, a condition called *syndrome of inappropriate antidiuretic hormone secretion* (SIADH). Atrial natriuretic hormone also may produce hyponatremia. SIADH occurs most commonly in small cell lung cancer (15%) and head and neck cancer (3%). A number of drugs may produce the syndrome. Symptoms of fatigue, poor attention span, nausea, weakness, anorexia, and headache may be controlled by restricting fluid intake to 500 mL/d or blocking the effects of the hormone with 600- to 1200-mg demeclocycline a day. Conivaptan, a vasopressin receptor blocker, is effective PO (20–120 mg bid) or IV (10–40 mg), especially in combination with fluid restriction. With severe hyponatremia (<115 meq/L) or in the setting of mental status changes, normal saline infusion plus furosemide may be required; rate of correction should be <1 meq/L per hour to prevent complications.

## ECTOPIC ACTH SYNDROME

When pro-opiomelanocortin mRNA in the tumor is processed into ACTH, excessive secretion of glucocorticoids and mineralocorticoids may ensue. Pts develop Cushing's syndrome with hypokalemic alkalosis, weakness, hypertension, and hyperglycemia. About half the cases occur in small cell lung cancer. ACTH production adversely affects prognosis. Ketoconazole (400–1200 mg/d) or metyrapone (1–4 g/d) may be used to inhibit adrenal steroid synthesis.

For a more detailed discussion, see Jameson JL, Longo, DL: Paraneoplastic Syndromes: Endocrinologic/Hematologic, Chap. 121, p. 608, in HPIM-19.

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# 77 Neurologic Paraneoplastic Syndromes

Paraneoplastic neurologic disorders (PNDs) are cancer-related syndromes that can affect any part of the nervous system; caused by mechanisms other than metastasis or by complications of cancer such as coagulopathy, stroke, metabolic and nutritional conditions, infections, and side effects of cancer therapy. In 60% of pts the neurologic symptoms precede cancer diagnosis. PNDs occur in 0.5–1% of all cancer pts, but they occur in 2–3% of pts with neuroblastoma or small cell lung cancer (SCLC), and in 30–50% of pts with thymoma or sclerotic myeloma.

## CLINICAL FEATURES

Recognition of a distinctive paraneoplastic syndrome (Table 77-1) should prompt a search for cancer, because treatment of tumor may improve the course of PNDs; many of these disorders also occur without cancer. Diagnosis is based on the clinical pattern, exclusion of other cancer-related disorders, confirmatory serum or CSF antibodies, or occasionally electrodiagnostic testing. Most PNDs are mediated by immune responses triggered by neuronal proteins expressed by tumors. PNDs associated with immune responses against intracellular antigens often respond poorly to treatment (Table 77-2), whereas those associated with antibodies to synaptic or neuronal cell surface proteins are more responsive to immunotherapy (Table 77-3). For any type of PND, if antibody testing is negative, the diagnosis rests on the

**TABLE 77-1 PARANEOPLASTIC SYNDROMES OF THE NERVOUS SYSTEM**

| Classic Syndromes: Usually Occur with Cancer Association | Nonclassic Syndromes: May Occur with and Without Cancer Association |
|---|---|
| Encephalomyelitis | Brainstem encephalitis |
| Limbic encephalitis | Stiff-person syndrome |
| Cerebellar degeneration (adults) | Necrotizing myelopathy |
| Opsoclonus-myoclonus | Motor neuron disease |
| Subacute sensory neuronopathy | Guillain-Barré syndrome |
| Gastrointestinal paresis or pseudo-obstruction | Subacute and chronic mixed sensory-motor neuropathies |
| Dermatomyositis (adults) | Neuropathy associated with plasma cell dyscrasias and lymphoma |
| Lambert-Eaton myasthenic syndrome | Vasculitis of nerve |
| Cancer- or melanoma-associated retinopathy | Pure autonomic neuropathy |
| | Acute necrotizing myopathy |
| | Polymyositis |
| | Vasculitis of muscle |
| | Optic neuropathy |
| | BDUMP |

***Abbreviation:*** BDUMP, bilateral diffuse uveal melanocytic proliferation.

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**TABLE 77-2 ANTIBODIES TO INTRACELLULAR ANTIGENS, SYNDROMES, AND ASSOCIATED CANCERS**

| Antibody | Associated Neurologic Syndrome(s) | Tumors |
|---|---|---|
| Anti-Hu (ANNA1) | Encephalomyelitis, subacute sensory neuronopathy | SCLC |
| Anti-Yo (PCA1) | Cerebellar degeneration | Ovary, breast |
| Anti-Ri (ANNA2) | Cerebellar degeneration, opsoclonus, brainstem encephalitis | Breast, gynecologic, SCLC |
| Anti-Tr | Cerebellar degeneration | Hodgkin's lymphoma |
| Anti-CRMP5 (CV2) | Encephalomyelitis, chorea, optic neuritis, uveitis, peripheral neuropathy | SCLC, thymoma, other |
| Anti-Ma proteins | Limbic, hypothalamic, brainstem encephalitis | Testicular (Ma2), other (Ma) |
| Anti-amphiphysin | Stiff-person syndrome, encephalomyelitis | Breast, SCLC |
| Recoverin, bipolar cell antibodies, others[a] | CAR<br>MAR | SCLC (CAR), melanoma (MAR) |
| Anti-GAD | Stiff-person, cerebellar syndromes, limbic encephalitis | Infrequent tumor association (thymoma) |

[a]A variety of target antigens have been identified.
***Abbreviations:*** CAR, cancer-associated retinopathy; CRMP, collapsing response-mediator protein; MAR, melanoma-associated retinopathy; SCLC, small cell lung cancer.

demonstration of cancer and the exclusion of other cancer-related or independent disorders. Combined whole-body CT and PET scans often uncover tumors undetected by other tests.

## PNDs of the Central Nervous System and Dorsal Root Ganglia

MRI and CSF studies are important to rule out neurologic complications due to direct spread of cancer. In most PNDs the MRI findings are nonspecific. CSF findings typically consist of mild to moderate pleocytosis (<200 mononuclear cells, predominantly lymphocytes), an increase in the protein concentration, and a variable presence of oligoclonal bands.

- *Paraneoplastic encephalomyelitis and focal encephalitis* describe an inflammatory process with multifocal involvement of the nervous system. Clinical manifestations depend on area involved, and syndromes may occur alone or in combination.
- *Cortical encephalitis*, which may present as "epilepsia partialis continua."
- *Limbic encephalitis*, characterized by confusion, depression, agitation, anxiety, severe short-term memory deficits, partial complex seizures, and sometimes dementia (the MRI usually shows unilateral or bilateral medial temporal lobe abnormalities).
- *Brainstem encephalitis* presents with eye movement disorders (nystagmus, opsoclonus, supranuclear or nuclear paresis), cranial nerve paresis, dysarthria, dysphagia, and central autonomic dysfunction.

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**TABLE 77-3 ANTIBODIES TO CELL SURFACE OR SYNAPTIC ANTIGENS, SYNDROMES, AND ASSOCIATED TUMORS**

| Antibody | Neurologic Syndrome | Tumor Type When Associated |
|---|---|---|
| Anti-AChR (muscle)[a] | Myasthenia gravis | Thymoma |
| Anti-AChR (neuronal)[a] | Autonomic ganglionopathy | SCLC |
| Anti-VGCC[b] | LEMS, cerebellar degeneration | SCLC |
| Anti-NMDAR[a] | Anti-NMDAR encephalitis | Teratoma in young women (children and men rarely have tumors) |
| Anti-LGI1[c] | Limbic encephalitis, hyponatremia, faciobrachial tonic, or dystonic seizures | Rarely thymoma |
| Anti-Caspr2[c] | Morvan's syndrome, neuromyotonia | Thymoma, prostate cancer |
| Anti-$GABA_BR$[d] | Limbic encephalitis, seizures | SCLC, neuroendocrine |
| Anti-$GABA_AR$[d] | Encephalitis with prominent seizures and status epilepticus; less often opsoclonus and stiff-person syndrome | Rarely thymoma |
| Anti-AMPAR[d] | Limbic encephalitis with relapses | SCLC, thymoma, breast |
| Glycine receptor[d] | Encephalomyelitis with rigidity, stiff-person syndrome | Rarely, thymoma, lung cancer |
| Anti-DPPX[d] | Agitation, myoclonus, tremor, seizures, hyperekplexia, encephalomyelitis with rigidity | No cancer, but frequent diarrhea or cachexia suggesting paraneoplasia |

[a]A direct pathogenic role of these antibodies has been demonstrated.
[b]Anti-VGCC antibodies are pathogenic for LEMS.
[c]Previously named voltage-gated potassium channel antibodies (VGKC); currently included under the term VGKC-complex proteins. Of note, the significance of antibodies to VGKC-complex proteins other than LGI1 and Caspr2 is uncertain (the antigens are unknown, and the response to immunotherapy is variable).
[d]These antibodies are strongly suspected to be pathogenic.
***Abbreviations:*** AChR, acetylcholine receptor; AMPAR, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor; Caspr2, contactin-associated protein-like 2; DPPX, dipeptidyl-peptidase-like protein-6; $GABA_BR$, γ-aminobutyric acid B receptor; GAD, glutamic acid decarboxylase; LEMS, Lambert-Eaton myasthenic syndrome; LGI1, leucine-rich glioma-inactivated 1; NMDAR, *N*-methyl-D-aspartate receptor; SCLC, small cell lung cancer; VGCC, voltage-gated calcium channel.

- *Opsoclonus-myoclonus syndrome* consists of involuntary, chaotic eye movements in all directions of gaze plus myoclonus; it is frequently associated with ataxia.
- *Paraneoplastic cerebellar degeneration* begins as dizziness, oscillopsia, blurry or double vision, nausea, and vomiting; a few days or weeks later, dysarthria, gait and limb ataxia, and variable dysphagia can appear.
- *Myelitis*, which may cause lower or upper motor neuron symptoms, myoclonus, muscle rigidity, and spasms.
- *Autonomic dysfunction* occurs as a result of involvement of the neuraxis at multiple levels, including hypothalamus, brainstem, and autonomic nerves. Cardiac

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arrhythmias, postural hypotension, and central hypoventilation are frequent causes of death.

- *Encephalitis with antibodies to cell-surface or synaptic proteins* can occur without tumor association and may occur predominantly in children or young adults. An example is *N*-methyl-D-aspartate (NMDA) receptor autoantibodies that present as a virus-like syndrome followed by a prominent psychiatric disturbance with involuntary movements; in young women, ovarian teratomas are frequently present. Despite dramatic severity at times, patients usually respond to treatment of the tumor (if found) and immunotherapy.
- *Cancer-associated retinopathies* involve cone and rod dysfunction with photosensitivity, progressive loss of vision and color perception, central or ring scotomas, night blindness, and attenuation of photopic and scotopic responses in the electroretinogram (ERG).
- *Dorsal root ganglionopathy* (sensory neuronopathy) is characterized by sensory deficits that may be symmetric or asymmetric, painful dysesthesias, radicular pain, and decreased or absent reflexes; all modalities of sensation can be involved.

## PNDs of Nerve and Muscle

These disorders may develop anytime during the course of the neoplastic disease. Serum and urine immunofixation studies should be considered in pts with peripheral neuropathy of unknown cause; detection of a monoclonal gammopathy suggests the need for additional studies to uncover a B cell or plasma cell malignancy. In paraneoplastic neuropathies, diagnostically useful antineuronal antibodies are limited to anti-$CV_2$/CRMP5 and anti-Hu.

Myasthenia gravis is discussed in Chap. 194 and dermatomyositis in Chap. 195.

## TREATMENT PARANEOPLASTIC NEUROLOGIC DISORDERS

- Treatment of PNDs focuses mainly on recognition and control of the underlying malignancy; a stabilization or improvement of symptoms has been reported in some pts with successful tumor control.
- Variable responses have been described following treatment with glucocorticoids and other immunosuppressive agents as well as intravenous immunoglobulin (IVIg) and plasma exchange.
- Those PNDs caused by antibodies to cell surface or synaptic antigens have a much more favorable response to therapy.

For a more detailed discussion, see Dalmau J, Rosenfeld MR: Paraneoplastic Neurologic Syndromes and Autoimmune Encephalitis, Chap. 122, p. 614, in HPIM-19.

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# 78 Infections Acquired in Health Care Facilities

Hospital-acquired or *nosocomial* infections (defined as those not present or incubating at the time of admission to the hospital) and other health care–associated infections affect an estimated 1.7 million pts, cost $28–33 billion, and contribute to 99,000 deaths in U.S. hospitals each year. Although efforts to lower infection risks have been challenged by the growing numbers of immunocompromised pts, antibiotic-resistant bacteria, fungal and viral superinfections, and invasive procedures and devices, the "zero-tolerance" viewpoint of consumer advocates holds that nearly all health care–associated infections should be avoidable. Accordingly, federal legislation now exists to prevent U.S. hospitals from upgrading Medicare charges to pay hospital costs resulting from at least 14 specific nosocomial events.

## PREVENTION OF HOSPITAL-ACQUIRED INFECTIONS

Nosocomial pathogens have reservoirs, are transmitted by largely predictable routes, and require susceptible hosts—features that allow the implementation of monitoring and prevention strategies.

- *Surveillance:* review of microbiology laboratory results, surveys of nursing wards, and use of other mechanisms to keep track of infections acquired after hospital admission. Most hospitals aim surveillance at infections associated with high-level morbidity or great expense. Results of surveillance are expressed as rates and should include a denominator indicating the number of pts exposed to a specific risk (e.g., pts using a mechanical ventilator) or the number of intervention days (e.g., 1000 pt days on a ventilator).
- *Prevention and control measures:* Hand hygiene is the single most important measure to prevent cross-infection.
  - Health care workers' rates of adherence to hand-hygiene recommendations are abysmally low at <50%.
  - Other measures include identifying and eradicating reservoirs of infection and minimizing use of invasive procedures and catheters.
- *Isolation techniques:* Isolation of infectious pts is a standard component of infection control programs.
  - *Standard precautions:* include hand hygiene and use of gloves when there is a potential for contact with blood, other body fluids, nonintact skin, or mucous membranes during the care of all pts. In certain cases, masks, eye protection, and gowns are used as well.
  - *Transmission-based guidelines:* Airborne, droplet, or contact precautions—for which personnel don (at a minimum) N95 respirators, surgical face masks, or gowns and gloves, respectively—are used to prevent transmission of disease from pts with contagious clinical syndromes. More than one precaution can be used for diseases that have more than one mode of transmission (e.g., contact and airborne isolation for varicella).



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## NOSOCOMIAL AND DEVICE-RELATED INFECTIONS

Nosocomial infections are due to the combined effect of the pt's own flora and the presence of invasive devices in 25–50% of cases. Intensive education, "bundling" of evidence-based interventions, and use of checklists to facilitate adherence can reduce infection rates. Table 78-1 summarizes effective interventions to reduce the incidence of the more common nosocomial infections.

- *Urinary tract infections:* Thirty to forty percent of nosocomial infections are UTIs, contributing ~15% to prolongation of hospital stay with an attributable cost of ~$1300.
  - Most nosocomial UTIs are associated with prior instrumentation or indwelling bladder catheterization. The 3–7% risk of infection for each day a catheter remains in place is due to the ascent of bacteria from the periurethral area or via intraluminal contamination of the catheter.
  - In men, condom catheters may lessen the risk of UTI.
  - The most common pathogens are *Escherichia coli*, nosocomial gram-negative bacilli, enterococci, and (particularly for pts in the ICU) *Candida*.
  - For suspected infection in the setting of chronic catheterization, the catheter should be replaced and a freshly voided urine specimen obtained for culture to confirm actual infection as opposed to simple colonization of the catheter.
  - As with all nosocomial infections, it is useful to repeat the culture to confirm the persistence of infection at the time therapy is initiated.
- *Pneumonia:* Accounting for 10–15% of nosocomial infections, pneumonia increases the duration of hospital stay by 10 days, accounts for ~$23,000 in extra costs, and is associated with more deaths than are infections at any other body site. Of pts using mechanical ventilation, 5–10% develop ventilator-associated events.
  - Bacterial nosocomial pneumonia is caused by aspiration of endogenous or hospital-acquired oropharyngeal flora.
  - Risk factors include events that increase colonization with potential pathogens, such as prior antibiotic use, contaminated ventilator equipment, or decreased gastric acidity; events that increase risk of aspiration, such as nasogastric or endotracheal intubation or decreased level of consciousness; and conditions that compromise host defense mechanisms in the lung, such as chronic obstructive pulmonary disease, extremes of age, or upper abdominal surgery.
  - Etiologic organisms include community-acquired pathogens (e.g., *Streptococcus pneumoniae*, *Haemophilus influenzae*) early during hospitalization and *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Enterobacter*, and *Acinetobacter* later in the hospital stay. In all, 20–40% of cases are polymicrobial.
  - Diagnosis can be difficult, as clinical criteria (e.g., fever, leukocytosis, purulent secretions, and new or changing pulmonary infiltrates on CXR) have high sensitivity but low specificity.
    - An etiology should be sought by studies of lower respiratory tract samples protected from upper-tract contamination; quantitative cultures have diagnostic sensitivities in the range of 80%.
    - Febrile pts with nasogastric or nasotracheal tubes should also have sinusitis or otitis media ruled out.
- *Surgical wound infections:* Making up ~15–20% of nosocomial infections, surgical wound infections increase the length of hospital stay by 7–10 days and increase costs by $3000–$29,000.
  - These infections often become evident after pts have left the hospital; thus, it is difficult to assess the true incidence.
  - Risk factors include the pt's underlying conditions (e.g., diabetes mellitus or obesity) and age, inappropriate timing of antibiotic prophylaxis, the presence of drains, prolonged preoperative hospital stays, shaving of the operative site the day before surgery (rather than just before the procedure), long duration of surgery, and infection at remote sites.

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**TABLE 78-1 EXAMPLES OF EVIDENCE-BASED "BUNDLED INTERVENTIONS" TO PREVENT COMMON HEALTH CARE–ASSOCIATED INFECTIONS AND OTHER ADVERSE EVENTS**

| |
|---|
| **Prevention of Central Venous Catheter Infections** |
| *Catheter insertion bundle:* |
| Educate personnel about catheter insertion and care. |
| Use chlorhexidine to prepare the insertion site. |
| Use maximal barrier precautions and asepsis during catheter insertion. |
| Consolidate insertion supplies (e.g., in an insertion kit or cart). |
| Use a checklist to enhance adherence to the "insertion bundle." |
| Empower nurses to halt insertion if asepsis is breached. |
| *Catheter maintenance bundle:* |
| Cleanse pts daily with chlorhexidine. |
| Maintain clean, dry dressings. |
| Enforce hand hygiene among health care workers. |
| Ask daily: Is the catheter needed? Remove catheter if not needed or used. |
| **Prevention of Ventilator-Associated Events** |
| Elevate head of bed to 30–45°. |
| Decontaminate oropharynx regularly with chlorhexidine (controversial). |
| Give "sedation vacation" and assess readiness to extubate daily. |
| Use peptic ulcer disease prophylaxis. |
| Use deep-vein thrombosis prophylaxis (unless contraindicated). |
| **Prevention of Surgical-Site Infections** |
| Choose a surgeon wisely. |
| Administer prophylactic antibiotics within 1 h before surgery; discontinue within 24 h. |
| Limit any hair removal to the time of surgery; use clippers or do not remove hair at all. |
| Prepare surgical site with chlorhexidine-alcohol. |
| Maintain normal perioperative glucose levels (cardiac surgery pts).[a] |
| Maintain perioperative normothermia (colorectal surgery pts).[a] |
| **Prevention of Urinary Tract Infections** |
| Place bladder catheters only when absolutely needed (e.g., to relieve obstruction), not solely for the provider's convenience. |
| Use aseptic technique for catheter insertion and urinary tract instrumentation. |
| Minimize manipulation or opening of drainage systems. |
| Ask daily: Is the bladder catheter needed? Remove catheter if not needed. |
| **Prevention of Pathogen Cross-Transmission** |
| Cleanse hands with alcohol hand rub before and after all contacts with pts or their environments. |

[a]These components of care are supported by clinical trials and experimental evidence in the specified populations; they may prove valuable for other surgical pts as well.

***Source:*** Adapted from information presented at the following websites: *www.cdc.gov/hicpac/pubs.html*; *www.cdc.gov/HAI/prevent/prevention.html*; *www.ihi.org*.

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  - These infections are typically caused by the pt's endogenous or hospital-acquired flora.
    - *S. aureus*, coagulase-negative staphylococci, and enteric and anaerobic bacteria are the most common pathogens.
    - A group A streptococcal or clostridial etiology should be considered in rapidly progressing postoperative infections (manifesting within 24–48 h of a procedure).
  - Clinical assessment of the surgical site may reveal obvious cellulitis or abscess formation; diagnosis of deeper infections requires a high index of suspicion and radiographic imaging.
  - Treatment of postoperative wound infections requires source control (drainage or surgical excision of infected or necrotic material) and use of antibiotics aimed at the most likely or laboratory-confirmed pathogens.
- *Intravascular device infections:* Intravascular device–related infections cause 10–15% of nosocomial infections, increase the duration of hospital stay by 12 days, add $3700–$29,000 to hospital costs, and have an attributable mortality rate of 12–25%.
  - Catheterization of the femoral vessels is associated with a higher risk of infection in adults.
    - These infections are largely due to the skin flora at the site of catheter insertion, with pathogens migrating extraluminally to the catheter tip.
    - Contamination of the infusate is rare.
    - Coagulase-negative staphylococci, *S. aureus* (≥50% methicillin-resistant isolates), enterococci, nosocomial gram-negative bacilli, and *Candida* are the pathogens most frequently associated with these bacteremias.
  - Infection is suspected on the basis of the catheter site's appearance and/or the presence of fever or bacteremia without another source. The diagnosis is confirmed by isolation of the same bacteria from peripheral-blood cultures and from semiquantitative or quantitative cultures of samples from the vascular catheter tip.
  - In addition to the initiation of appropriate antibiotic treatment, considerations include the level of risk for endocarditis (relatively high in pts with *S. aureus* bacteremia) and the decision regarding catheter removal, which is often necessary to cure infection.
    - The decision to remove a surgically implanted catheter should be based on the severity of the pt's illness, the strength of evidence that the device is infected, the presence of local or systemic complications, an assessment of the specific pathogens, and the pt's response to antimicrobial therapy if the catheter is initially retained.
    - If salvage of the catheter is attempted, the "antibiotic lock" technique (allowing a concentrated antibiotic solution to dwell in the catheter lumen along with systemic antibiotic administration) should be used.

## EPIDEMIC AND EMERGING PROBLEMS

Although outbreaks and emerging pathogens often receive a great deal of press, they account for <5% of nosocomial infections.

- *Influenza:* The main components of infection control—vaccination of the general public and health care workers, early use of antiviral agents for control of outbreaks, and adherence to surveillance and droplet precautions for symptomatic pts—have been effective in controlling influenza, including the 2009 H1N1 pandemic.
- *Nosocomial diarrhea:* Rates of health care–associated diarrhea have been increasing in recent years.
  - Rates of infection with *Clostridium difficile*—particularly the more virulent BI/NAP1/027 strain—are increasing, especially among older pts. Important

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infection-control components include judicious use of antibiotics (particularly fluoroquinolones); heightened suspicion in cases with atypical presentations; and early diagnosis, treatment, and implementation of contact precautions.
  - Outbreaks of norovirus infection should be suspected in bacterial culture–negative diarrheal syndromes in which nausea and vomiting are prominent aspects. Contact precautions may need to be augmented by environmental cleaning and active exclusion of ill staff and visitors, who often represent index cases.
- *Chickenpox:* Routine vaccination of children and VZV-susceptible employees has made nosocomial spread less common.
  - If VZV exposure occurs, postexposure prophylaxis with varicella-zoster immune globulin (VZIG) is considered for immunocompromised or pregnant contacts.
  - Varicella vaccine or preemptive administration of acyclovir is an alternative for other susceptible persons.
  - Susceptible employees are furloughed for 8–21 days (or for 28 days if VZIG has been given).
- *Tuberculosis:* Prompt recognition and isolation of cases, use of negative-pressure private rooms with 100% exhaust and at least 6–12 air changes per hour, use of approved N95 respirators, and follow-up serologic or skin testing of susceptible, exposed personnel are required.
- *Group A streptococcal infections:* One or two nosocomial cases, usually involving surgical wounds and the presence of an asymptomatic carrier in the operating room, should trigger an investigation. Health care workers linked to nosocomial transmission of group A streptococci should not be permitted to return to pt care settings until eradication of carriage via antimicrobial therapy has been documented.
- *Fungal infections:* Hospital renovations and disturbance of dusty surfaces can cause fungal spores to become airborne. Routine surveillance of neutropenic pts for infections with filamentous fungi (e.g., *Aspergillus*, *Fusarium*) helps determine whether there are extensive environmental risks.
- *Legionellosis:* If nosocomial cases are detected, environmental samples (e.g., tap water) should be cultured; eradication measures should be pursued if typing of clinical and environmental isolates reveals a correlation.
- *Antibiotic-resistant bacterial infection:* Close laboratory surveillance, strict infection-control practices, and aggressive antibiotic-control policies are the cornerstones of resistance-control efforts.
  - Molecular typing can help distinguish an outbreak of a single isolate (which necessitates an emphasis on hand hygiene and an evaluation of common-source exposures) from a polyclonal outbreak (which necessitates re-emphasis on antibiotic prudence and device bundles).
  - Organisms that raise concerns include methicillin-resistant *S. aureus*, gram-negative organisms that produce carbapenemases and/or extended-spectrum β-lactamases, pan-resistant strains of *Acinetobacter*, and vancomycin-resistant enterococci.
- *Bioterrorism preparedness:* Education, effective systems of internal and external communication, and risk assessment capabilities are key features.

For a more detailed discussion, see Weinstein RA: Infections Acquired in Health Care Facilities, Chap. 168, p. 911, in HPIM-19.

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# 79 Infections in the Immunocompromised Host

The immunocompromised pt is at increased risk for infection with both common and opportunistic pathogens.

## INFECTIONS IN CANCER PTS

Table 79-1 lists the normal barriers to infection whose disruption may permit infections in immunocompromised pts, with particular relevance for the noted cancers. Infection-associated mortality rates among cancer pts have decreased as a result of an evolving approach entailing early use of empirical broad-spectrum antibiotics; empirical antifungal therapy in neutropenic pts who, after 4–7 days of antibiotic treatment, remain febrile without positive cultures; and use of antibiotics for afebrile neutropenic pts as broad-spectrum prophylaxis against infections.

### SYSTEM-SPECIFIC SYNDROMES

- *Skin infections:* Skin lesions of various types are common in pts with cancer and may be the first sign of bacterial or fungal sepsis, particularly in neutropenic pts (those with <500 functional neutrophils/μL).
  - *Cellulitis:* most often caused by group A *Streptococcus* and *Staphylococcus aureus*. Unusual organisms (e.g., *Escherichia coli*, *Pseudomonas*, fungi) may be involved in neutropenic pts.
  - *Macules or papules:* due to bacteria (e.g., *Pseudomonas aeruginosa* causing ecthyma gangrenosum) or fungi (e.g., *Candida*)
  - *Sweet's syndrome or febrile neutrophilic dermatosis:* Most often seen in neutropenic pts (particularly those with acute myeloid leukemia), it presents as red or bluish-red papules or nodules that form sharply bordered plaques; high fever; and an elevated ESR. The skin lesions are most common on the face, neck, and arms.
  - *Erythema multiforme with mucous membrane involvement:* Often due to HSV infection, it is distinct from Stevens-Johnson syndrome, which is associated with drugs and has a more widespread distribution. Both conditions are common in pts with cancer.
  - *Drug rashes:* Rashes associated with drugs, particularly cytokines used in cancer therapy, complicate the differential diagnosis of rashes in pts with cancer.
- *Catheter-related infections:* Exit-site infections, often with erythema around the insertion site, are most common.
  - Infections caused by coagulase-negative staphylococci can often be treated medically without catheter removal.
  - Infections caused by other organisms, including *S. aureus*, *P. aeruginosa*, *Candida*, *Stenotrophomonas*, and *Bacillus*, usually require catheter removal.
  - If a red streak develops over the SC part of a "tunneled" catheter, the device must be removed to prevent extensive cellulitis and tissue necrosis.
- *Upper GI infections:* Breakdown of mucosal surfaces due to chemotherapy and infection is common.
  - Oral mucositis is associated with viridans streptococci and HSV.
  - Oral candidal infections (thrush) are common.
  - Esophagitis can be caused by *Candida albicans* and HSV.
- *Lower GI infections:* Transmigration of bowel flora across the intestinal epithelium can lead to severe conditions.

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**TABLE 79-1 DISRUPTION OF NORMAL BARRIERS THAT MAY PREDISPOSE TO INFECTIONS IN PTS WITH CANCER**

| Type of Defense | Specific Lesion | Cells Involved | Organisms | Cancer Association(s) | Disease(s) |
|---|---|---|---|---|---|
| Physical barrier | Breaks in skin | Skin epithelial cells | Staphylococci, streptococci | Head and neck, squamous cell carcinoma | Cellulitis, extensive skin infection |
| Emptying of fluid collections | Occlusion of orifices: ureters, bile duct, colon | Luminal epithelial cells | Gram-negative bacilli | Renal, ovarian, biliary tree, metastatic diseases of many cancers | Rapid, overwhelming bacteremia; urinary tract infection |
| Lymphatic function | Node dissection | Lymph nodes | Staphylococci, streptococci | Breast cancer surgery | Cellulitis |
| Splenic clearance of microorganisms | Splenectomy | Splenic reticuloendothelial cells | *Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis, Babesia, Capnocytophaga canimorsus* | Hodgkin's disease, leukemia | Rapid, overwhelming sepsis |
| Phagocytosis | Lack of granulocytes | Granulocytes (neutrophils) | Staphylococci, streptococci, enteric organisms, fungi | Acute myeloid and acute lymphocytic leukemias, hairy cell leukemia | Bacteremia |
| Humoral immunity | Lack of antibody | B cells | *S. pneumoniae, H. influenzae, N. meningitidis* | Chronic lymphocytic leukemia, multiple myeloma | Infections with encapsulated organisms, sinusitis, pneumonia |
| Cellular immunity | Lack of T cells | T cells and macrophages | *Mycobacterium tuberculosis, Listeria,* herpesviruses, fungi, intracellular parasites | Hodgkin's disease, leukemia, T-cell lymphoma | Infections with intracellular bacteria, fungi, parasites; virus reactivation |

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- *Chronic disseminated candidiasis:* results from seeding of organs (e.g., liver, spleen, kidneys) during neutropenia in pts with hematologic malignancy and generally presents symptomatically when neutropenia resolves. Pts have persistent fever unresponsive to antibiotics, abdominal pain, and increased alkaline phosphatase levels. Although biopsies may reveal granulomas, yeasts, or pseudohyphae, the diagnosis is often made on the basis of radiographic studies (CT, MRI). Treatment should be directed to the causative agent; *C. albicans* is usually responsible, but *C. tropicalis* or other *Candida* species are sometimes involved.
- *Typhlitis (necrotizing colitis):* more common among children than among adults and among pts with acute myeloid leukemia or acute lymphocytic leukemia than among pts with other forms of cancer. Pts have fever, RLQ tenderness, and diarrhea that is often bloody. The diagnosis is confirmed by documentation of a thickened cecal wall via imaging. Treatment should include antibiotics directed against bowel flora and surgery (in the case of perforation).

- *CNS infections:* The susceptibility of pts to specific infections depends on whether they have prolonged neutropenia, defects in cellular immunity (e.g., due to high-dose glucocorticoid therapy or cytotoxic chemotherapy), or defects in humoral immunity (e.g., pts with chronic lymphocytic leukemia, those who have previously undergone splenectomy or bone marrow transplantation [BMT]).
  - *Meningitis:* Consider *Cryptococcus* or *Listeria*, particularly for pts with defects in cellular immunity. Pts with defects in humoral immunity are also at risk for infection with encapsulated bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*.
  - *Encephalitis:* Pts with defects in cellular immunity are particularly prone to infection with VZV, JC virus (the cause of progressive multifocal leukoencephalopathy), CMV, *Listeria*, HSV, and human herpesvirus type 6.
  - *Brain masses:* most often present as headache with or without fever or neurologic abnormalities. Pts with prolonged neutropenia are at increased risk for a brain abscess due to *Aspergillus*, *Nocardia*, or *Cryptococcus*. Pts with defects in cellular immunity are at increased risk for infection with *Toxoplasma* and EBV (lymphoproliferative disease). A definitive diagnosis may require a biopsy.
- *Pulmonary infections:* Pneumonia can be difficult to diagnose in immunocompromised pts, given that many of the conventional findings (e.g., purulent sputum, physical findings suggestive of chest consolidation) rely on the presence of neutrophils. Radiographic patterns of infiltration can help narrow the differential diagnosis.
  - *Localized infiltrate:* Consider bacterial pneumonia (including *Legionella* and mycobacteria), local hemorrhage or embolism, and tumor.
  - *Nodular infiltrate:* Consider fungal infection (e.g., *Aspergillus*, *Mucor*), *Nocardia* infection, and recurrent tumor. In pts with *Aspergillus* infection, hemoptysis may be an ominous sign. A biopsy performed with direct visualization may be required for definitive diagnosis.
  - *Diffuse infiltrates:* Consider infection with viruses (particularly CMV), *Chlamydia*, *Pneumocystis*, *Toxoplasma*, or mycobacteria. Viruses that cause URIs in immunocompetent hosts (e.g., influenza, respiratory syncytial) can cause fatal pneumonitis in immunocompromised pts. Noninfectious causes include radiation pneumonitis, CHF, diffuse alveolar hemorrhage (after BMT), and drug-induced lung injury (e.g., bleomycin, alkylating agents).
- *Renal and ureteral infections:* These infections are usually associated with obstructing tumor masses.
  - *Candida* has a predilection for the kidneys, reaching this site via either hematogenous seeding or retrograde spread from the bladder. Persistent funguria should prompt a search for infection in the kidney (e.g., fungus ball).
  - BK virus and adenovirus can cause hemorrhagic cystitis.

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## APPROACH TO THE PATIENT:
## Febrile Neutropenia

**Approach to Diagnosis and Treatment of Febrile Neutropenic Pts** Figure 79-1 presents an algorithm for the diagnosis and treatment of pts with febrile neutropenia.

- The initial regimen should be refined on the basis of culture data; surface cultures of skin and mucous membranes may be misleading.
- Adding antibiotics to the initial regimen is not appropriate unless there is a clinical or microbiologic reason to do so. Administering additional antibiotics

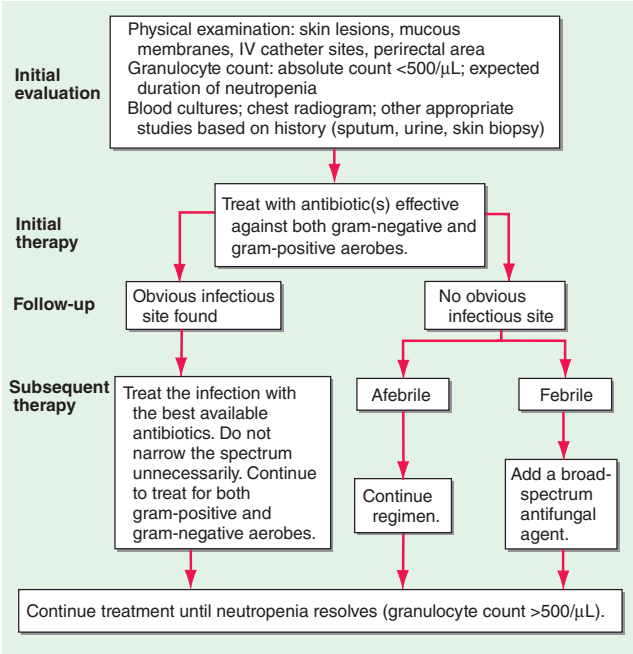


**FIGURE 79-1** Algorithm for the diagnosis and treatment of fever and neutropenia. Several general guidelines are useful in the initial treatment of febrile neutropenic pts: (1) The agents used should reflect both the epidemiology and the antibiotic resistance pattern of the hospital. (2) A single third-generation cephalosporin constitutes an appropriate initial regimen in many hospitals (if the pattern of resistance justifies its use). (3) Most standard regimens are designed for pts who have not previously received prophylactic antibiotics. The development of fever in a pt who has received antibiotics affects the choice of subsequent therapy (which should target resistant organisms and organisms known to cause infections in pts being treated with the antibiotics already administered). (4) Randomized trials have indicated that it is safe to use oral antibiotic regimens to treat "low-risk" pts who have fever and neutropenia. Outpatients who are expected to remain neutropenic for <10 days and who have no concurrent medical problems (such as hypotension, pulmonary compromise, or abdominal pain) can be classified as low risk and treated with a broad-spectrum oral regimen.

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for fear of a gram-negative infection (e.g., "double coverage," synergistic addition of aminoglycosides to β-lactam therapy) does not enhance efficacy (but does increase toxicity), even for infections involving *P. aeruginosa*.

- For empirical antifungal treatment, amphotericin B deoxycholate is being supplanted by liposomal formulations of amphotericin B, newer azoles (e.g., voriconazole or posaconazole), and echinocandins (e.g., caspofungin). Echinocandins are useful against infections with azole-resistant *Candida*.
- Clinical experience related to antiviral therapy is most extensive with acyclovir for HSV and VZV infections. Newer agents (e.g., cidofovir, foscarnet) with a broader spectrum of action have heightened the focus on treatment of viral infections.
  - Prophylactic antibiotics (e.g., fluoroquinolones) in pts expected to have prolonged neutropenia or antifungal agents (e.g., fluconazole) in pts with hematopoietic stem cell transplants (see below) may prevent infections. *Pneumocystis* prophylaxis is mandatory for pts with acute lymphocytic leukemia and for those receiving glucocorticoid-containing regimens.

## INFECTIONS IN TRANSPLANT RECIPIENTS

Evaluation of infections in transplant recipients must involve consideration of infectious agents harbored by the donor organ and the recipient's immunosuppressive drug regimen, which increases susceptibility to latent infections (among other infections).

- Pretransplantation evaluation of the donor should include a thorough serologic evaluation for viral pathogens (e.g., HSV-1, HSV-2, VZV, CMV, EBV, HIV, and hepatitis A, B, and C viruses) and mycobacterial disease; other evaluations should be directed by the donor's history, including diet, exposures, and travel.
- Pretransplantation evaluation of the recipient is generally more comprehensive than that of the donor and should include assessment for respiratory viruses and GI pathogens. Given the effects of underlying chronic disease and chemotherapy, serologic testing of the recipient may not be reliable.

### HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)

- *Pathogenesis:* The myeloablative processes involved in HSCT result in the complete absence of innate and adaptive immune cells. This transient state of complete immunologic incompetence and the reconstitution that follows make the host extremely susceptible to infections.
- *Etiology:* Most infections occur in a predictable time frame after HSCT (Table 79-2).
  - *Bacterial infections:* Neutropenia-related infectious complications are most common during the first month. Some centers give prophylactic antibiotics (e.g., quinolones) that may decrease the risk of gram-negative bacteremia but increase the risk of *Clostridium difficile* colitis.
    - Skin and bowel flora (e.g., *S. aureus*, coagulase-negative staphylococci, *E. coli*) are responsible for most infections in the first few days following HSCT, after which nosocomial pathogens and filamentous bacteria (e.g., vancomycin-resistant enterococci, *Acinetobacter*, antibiotic-resistant gram-negative bacteria, and *Nocardia* species) become more common.
    - In the late posttransplantation period (>6 months after reconstitution), bacteremia due to encapsulated organisms is most common, particularly among pts who are asplenic or hypogammaglobulinemic.
  - *Fungal infections:* Fungal infections are increasingly common beyond the first week after HSCT, particularly among pts who receive broad-spectrum antibiotics. Infections with *Candida* species are most common, although resistant fungi (e.g.,

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**TABLE 79-2 COMMON SOURCES OF INFECTIONS AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION**

| | Period after Transplantation | | |
|---|---|---|---|
| **Infection Site** | **Early (<1 Month)** | **Middle (1–4 Months)** | **Late (>6 Months)** |
| Disseminated | Aerobic bacteria (gram-negative, gram-positive) | *Candida, Aspergillus,* EBV | Encapsulated bacteria (*Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis*) |
| Skin and mucous membranes | HSV | HHV-6 | VZV, HPV (warts) |
| Lungs | Aerobic bacteria (gram-negative, gram-positive), *Candida, Aspergillus,* other molds, HSV | CMV, seasonal respiratory viruses, *Pneumocystis, Toxoplasma* | *Pneumocystis, Nocardia, S. pneumoniae* |
| Gastrointestinal tract | *Clostridium difficile* | CMV, adenovirus, *Bradyrhizobium enterica* (cord blood cells) | EBV, CMV, *B. enterica* (cord blood cells) |
| Kidney | | BK virus, adenovirus | |
| Brain | | HHV-6, *Toxoplasma* | *Toxoplasma,* JC virus (rare) |
| Bone marrow | | CMV, HHV-6 | CMV, HHV-6 |

***Abbreviations:*** HHV-6, human herpesvirus type 6; HPV, human papillomavirus.

*Aspergillus*, *Fusarium*) are becoming more common because of the increased use of prophylactic fluconazole.

- Prolonged treatment with glucocorticoids or other immunosuppressive agents increases the risk of infection with *Candida* or *Aspergillus* and of reactivation of endemic fungi even after resolution of neutropenia.
- Maintenance prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX; 160/800 mg/d starting 1 month after engraftment and continuing for at least 1 year) is recommended to prevent *Pneumocystis jirovecii* pneumonia.

– *Parasitic infections:* Prophylaxis with TMP-SMX is also protective against disease caused by *Toxoplasma* as well as against late infections caused by certain bacteria, including *Nocardia*, *Listeria monocytogenes*, *S. pneumoniae*, and *H. influenzae*.

- Given increasing international travel, parasitic diseases (e.g., caused by *Strongyloides*, *Leishmania*, *Giardia*, *Cryptosporidium*) that are typically restricted to particular environments may be more likely to be reactivated in pts after HSCT.

– *Viral infections:* Prophylactic acyclovir or valacyclovir for HSV-seropositive pts reduces rates of mucositis and prevents pneumonia and other HSV manifestations.

- Zoster generally occurs several months after HSCT and usually is managed readily with acyclovir.
- Human herpesvirus type 6 delays monocyte and platelet engraftment and may be linked to encephalitis or pneumonitis; the efficacy of antiviral treatment has not been well studied.

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- CMV disease (e.g., interstitial pneumonia, bone marrow suppression, colitis, and graft failure) usually occurs 30–90 days after HSCT. Severe disease is more common among allogeneic transplant recipients and is often associated with graft-versus-host disease, with pneumonia as the foremost cause of death. Preemptive therapy (initiation of antiviral therapy only after CMV is detected in blood) has supplanted prophylactic therapy (treatment of all transplant recipients when either the recipient or the donor is seropositive) because of the toxic side effects associated with ganciclovir.
- EBV lymphoproliferative disease as well as infections caused by respiratory viruses (e.g., respiratory syncytial virus, parainfluenza virus, metapneumovirus, influenza virus, adenovirus) can occur. BK virus (a polyomavirus) has been found in the urine of pts after HSCT and may be associated with hemorrhagic cystitis.

## SOLID ORGAN TRANSPLANTATION

- *Pathogenesis:* After solid organ transplantation, pts do not go through a stage of neutropenia like that seen after HSCT; thus the infections in these two groups of pts differ. However, solid organ transplant recipients are immunosuppressed for longer periods with agents that chronically impair T-cell immunity. Moreover, the persistent HLA mismatch between recipient immune cells (e.g., effector T cells) and the donor organ (allograft) places the organ at permanently increased risk of infection.
- *Etiology:* As in HSCT, the infection risk depends on the interval since transplantation.
  - *Early infections (<1 month):* Infections are most commonly caused by extracellular organisms, which originate in surgical wound or anastomotic sites.
  - *Middle-period infections (1–6 months):* The consequences of suppressing cell-mediated immunity become apparent, and infections result from acquisition—or reactivation—of viruses, mycobacteria, endemic fungi, and parasites.
    - CMV can cause severe systemic disease or infection of transplanted organs; the latter increases the risk of organ rejection, prompting increased immunosuppression that, in turn, increases CMV replication.
    - Diagnosis, treatment, and prophylaxis of CMV infection are the keys to interrupting this cycle.
  - *Late infections (>6 months):* Infections in this period are similar to those in pts with chronically impaired T-cell immunity (e.g., *Listeria*, *Nocardia*, *Rhodococcus*, mycobacteria, various fungi, other intracellular organisms).
    - EBV lymphoproliferative disease occurs most commonly in pts who receive a heart or lung transplant (as well as the most intense immunosuppressive regimens); in these cases, immunosuppression should be decreased or discontinued, if possible, and consideration should be given to treatment with anti–B cell antibodies.
    - Prophylaxis against *Pneumocystis* pneumonia for at least 1 year is generally recommended for all solid organ transplant recipients.
    - The incidence of tuberculosis within the first 12 months after solid organ transplantation is greater than that after HSCT and reflects the prevalence of tuberculosis in the local population.
- *Specific issues:* While the above information is generally valid for all organ transplants, there are some organ-specific considerations.
  - *Kidney transplantation:* TMP-SMX prophylaxis for the first 4–6 months decreases the incidence of early and middle-period infections, particularly UTIs related to anatomic alterations resulting from surgery. CMV is the predominant pathogen in the middle period; disease is evident in 50% of renal transplant pts presenting with fever 1–4 months after transplantation, prompting many centers to use valganciclovir prophylaxis for high-risk pts. BK viruria and viremia, often diagnosed as a late-onset disease, are associated with ureteral strictures, nephropathy, and vasculopathy and require a reduction of immunosuppression to lower rates of graft loss.
  - *Heart transplantation:* Mediastinitis, generally caused by typical skin flora and rarely caused by *Mycoplasma hominis*, is an early complication of heart transplantation. The overall incidence of toxoplasmosis (a middle-period infec-

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tion) is so high in the setting of heart transplantation that serologic screening and some prophylaxis (e.g., TMP-SMX) are always warranted.

– *Lung transplantation:* Pts receiving a lung transplant are predisposed to pneumonia and mediastinitis in the early period. The high incidence of CMV disease (75–100% if either the donor or the recipient is seropositive) indicates the importance of antiviral prophylaxis; late disease may occur once prophylaxis is discontinued, although the pt is generally better able to handle it because of reduced immunosuppression.

– *Liver transplantation:* Bacterial abscesses and peritonitis are common early complications and often result from biliary leaks. Pts receiving a liver transplant have a high incidence of fungal infections correlated with preoperative glucocorticoid use, long-term antimicrobial use, and a high degree of immunosuppression. Recurrent (reactivated) hepatitis B and C infections are problematic; while hepatitis B immunoglobulin administration and prophylaxis with antiviral agents active against hepatitis B virus have been successful in preventing reinfection with hepatitis B virus, reinfection with hepatitis C virus occurs in all pts.

## IMMUNIZATIONS IN IMMUNOSUPPRESSED PTS

Recommendations for vaccination of cancer pts receiving chemotherapy, pts with Hodgkin's disease, and hematopoietic stem cell transplant recipients are listed in Table 79-3. In solid organ transplant recipients, the usual vaccines and boosters should be given before immunosuppression. Pts with continued immunosuppression should have pneumococcal vaccination repeated every 5 years and should not receive live vaccines.

**TABLE 79-3 VACCINATION OF CANCER AND TRANSPLANT PTS RECEIVING CHEMOTHERAPY[a]**

| | Use in Indicated Pts | | |
|---|---|---|---|
| **Vaccine** | **Intensive Chemotherapy** | **Hodgkin's Disease** | **Hematopoietic Stem Cell Transplantation** |
| Diphtheria-tetanus[b] | Primary series and boosters as necessary | No special recommendation | Three doses given 6–12 months after transplantation |
| Poliomyelitis[c] | Complete primary series and boosters | No special recommendation | Three doses given 6–12 months after transplantation |
| *Haemophilus influenzae* type b conjugate | Primary series and booster for children | Single dose for adults | Three doses given 6–12 months after transplantation (separated by 1 month) |
| HPV | Quadrivalent HPV vaccine is approved for males and females 9–26 years of age. Check CDC website (*www.cdc.gov/vaccines*) for updated recommendations. | Quadrivalent HPV vaccine is approved for males and females 9–26 years of age. Check CDC website (*www.cdc.gov/vaccines*) for updated recommendations. | Quadrivalent HPV vaccine is approved for males and females 9–26 years of age. Check CDC website (*www.cdc.gov/vaccines*) for updated recommendations. |

(*Continued*)

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**TABLE 79-3 VACCINATION OF CANCER AND TRANSPLANT PTS RECEIVING CHEMOTHERAPY[a] (*CONTINUED*)**

| Vaccine | Use in Indicated Pts | | |
|---|---|---|---|
| | **Intensive Chemotherapy** | **Hodgkin's Disease** | **Hematopoietic Stem Cell Transplantation** |
| Hepatitis A | As indicated for normal hosts on the basis of occupation and lifestyle | As indicated for normal hosts on the basis of occupation and lifestyle | As indicated for normal hosts on the basis of occupation and lifestyle |
| Hepatitis B | Same as for normal hosts | As indicated for normal hosts on the basis of occupation and lifestyle | Three doses given 6–12 months after transplantation |
| PCV13<br>PPSV23[d] | Finish series prior to chemotherapy if possible | Pts with splenectomy should receive PPSV23. | Three doses of PCV13, beginning 3–6 months after transplantation, are followed by a dose of PPSV23 at least 8 weeks later. A second PPSV23 dose can be given 5 years later. |
| Quadrivalent meningococcal vaccine[e] | Should be administered to splenectomized pts and to pts living in endemic areas, including college students in dormitories | Should be administered to splenectomized pts and to pts living in endemic areas, including college students in dormitories. An additional dose can be given after 5 years. | Should be administered to splenectomized pts and to pts living in endemic areas, including college students in dormitories. An additional dose can be given after 5 years. |
| Influenza | Seasonal immunization | Seasonal immunization | Seasonal immunization (A seasonal dose is recommended and can be given as early as 4 months after transplantation; if given <6 months after transplantation, an additional dose is recommended.) |
| Measles/mumps/rubella | Contraindicated | Contraindicated during chemotherapy | After 24 months in pts without graft-versus-host disease |

(*Continued*)

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**TABLE 79-3 VACCINATION OF CANCER AND TRANSPLANT PTS RECEIVING CHEMOTHERAPY[a] (*CONTINUED*)**

| | Use in Indicated Pts | | |
|---|---|---|---|
| **Vaccine** | **Intensive Chemotherapy** | **Hodgkin's Disease** | **Hematopoietic Stem Cell Transplantation** |
| Varicella-zoster virus[f] | Contraindicated[g] | Contraindicated | Contraindicated (CDC recommends use on a case-by-case basis following reevaluation.) |

[a]The latest recommendations by the Advisory Committee on Immunization Practices and the CDC guidelines can be found at *http://www.cdc.gov/vaccines*.
[b]A single dose of tetanus–diphtheria–acellular pertussis (TDaP), followed by a booster dose of tetanus-diphtheria (Td) every 10 years, is recommended for adults.
[c]Live-virus vaccine is contraindicated; inactivated vaccine should be used.
[d]Two types of vaccine are used to prevent pneumococcal disease. A conjugate vaccine active against 13 serotypes (13-valent pneumococcal conjugate vaccine, or PCV13) is currently administered in three separate doses to all children. A polysaccharide vaccine active against 23 serotypes (23-valent pneumococcal polysaccharide vaccine, or PPSV23) elicits titers of antibody lower than those achieved with the conjugate vaccine, and immunity may wane more rapidly. Because the ablative chemotherapy given to recipients of hematopoietic stem cell transplants eradicates immunologic memory, revaccination is recommended for all such pts. Vaccination is much more effective once immunologic reconstitution has occurred; however, because of the need to prevent serious disease, pneumococcal vaccine should be administered 6–12 months after transplantation in most cases. Because PPSV23 includes serotypes not present in PCV13, recipients of stem cell transplants should receive a dose of PPSV23 at least 8 weeks after the last dose of PCV13. Although antibody titers from PPSV23 clearly decay, experience with multiple doses of PPSV23 is limited, as are data on the safety, toxicity, or efficacy of such a regimen. For this reason, the CDC currently recommends the administration of one additional dose of PPSV23 at least 5 years after the last dose to immunocompromised pts, including transplant recipients, as well as pts with Hodgkin's disease, multiple myeloma, lymphoma, or generalized malignancies. Beyond this single additional dose, further doses are not recommended at this time.
[e]Meningococcal conjugate vaccine MenACWY is recommended for adults ≤55 years old, and meningococcal polysaccharide vaccine (MPSV4) is recommended for those ≥ 56 years old.
[f]Includes both varicella vaccine for children and zoster vaccine for adults.
[g]Contact the manufacturer for more information on use in children with acute lymphocytic leukemia.
***Abbreviations:*** CDC, Centers for Disease Control and Prevention; HPV, human papillomavirus; PCV, pneumococcal conjugate vaccine; PPSV, pneumococcal polysaccharide vaccine.

For a more detailed discussion, see Finberg RW: Infections in Patients with Cancer, Chap. 104, p. 484; and Finberg RW, Fingeroth J: Infections in Transplant Recipients, Chap. 169, p. 919, in HPIM-19.

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# 80 Infective Endocarditis

*Acute* endocarditis is a febrile illness that rapidly damages cardiac structures, seeds extracardiac sites hematogenously, and can progress to death within weeks. *Subacute* endocarditis follows an indolent course, rarely causes metastatic infection, and progresses gradually unless complicated by a major embolic event or a ruptured mycotic aneurysm.

- *Epidemiology:* In developed countries, the incidence of endocarditis ranges from 4 to 7 cases per 100,000 population per year, with higher rates among the elderly.
  - Predisposing conditions include congenital heart disease, illicit IV drug use, degenerative valve disease, and the presence of intracardiac devices.
  - Chronic rheumatic heart disease is a risk factor in low-income countries.
  - Of endocarditis cases, 16–30% involve prosthetic valves, with the greatest risk during the first 6–12 months after valve replacement.
- *Etiology and microbiology:* Because of their different portals of entry, the causative microorganisms vary among clinical types of endocarditis.
  - In native valve endocarditis (NVE), viridans streptococci, staphylococci, and HACEK organisms (*Haemophilus* spp., *Aggregatibacter spp.*, *Cardiobacterium hominis*, *Eikenella corrodens,* and *Kingella kingae*) enter the bloodstream from oral, skin, and upper respiratory tract portals. *Streptococcus gallolyticus* subspecies *gallolyticus* (formerly *S. bovis* biotype 1) originates from the gut and is associated with polyps or colon cancer.
  - Health care–associated NVE, frequently due to *Staphylococcus aureus*, coagulase-negative staphylococci (CoNS), and enterococci, may have a nosocomial onset (55%) or a community onset (45%) in pts who have had extensive contact with the health care system in the preceding 90 days.
  - Prosthetic valve endocarditis (PVE) developing within 2 months of surgery is due to intraoperative contamination or a bacteremic postoperative complication and is typically caused by CoNS, *S. aureus*, facultative gram-negative bacilli, diphtheroids, or fungi. Cases beginning >1 year after valve surgery are caused by the same organisms that cause community-acquired NVE. PVE due to CoNS that presents 2–12 months after surgery often represents delayed-onset nosocomial infection.
  - Cardiovascular implantable electronic device (CIED)–related endocarditis involves the device itself or the endothelium at points of device contact, with occasional concurrent aortic or mitral valve infection. One-third of cases of CIED endocarditis present within 3 months after device implantation or manipulation, one-third present at 4–12 months, and one-third present at >1 year. *S. aureus* and CoNS (often methicillin-resistant strains) cause the majority of cases.
  - Endocarditis occurring among IV drug users, especially that involving the tricuspid valve, is commonly caused by *S. aureus* (often a methicillin-resistant strain). Left-sided valve infections among IV drug users are caused by *Pseudomonas aeruginosa* and *Candida*, *Bacillus*, *Lactobacillus*, and *Corynebacterium* spp. in addition to the usual causes of endocarditis.
  - About 5–15% of endocarditis cases are culture negative, and one-third to one-half of these cases are due to prior antibiotic exposure. The remainder of culture-negative cases represent infection by fastidious organisms, such as the nutritionally variant bacteria *Granulicatella* and *Abiotrophia* spp., HACEK organisms, *Coxiella burnetii*, *Brucella* spp., and *Tropheryma whipplei*.
- *Pathogenesis:* Endothelial injury allows direct infection by more virulent pathogens (e.g., *S. aureus*) or the development of a platelet-fibrin thrombus [referred to as *nonbacterial thrombotic endocarditis* (NBTE)] that may become infected during

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transient bacteremia. NBTE arises from cardiac conditions (e.g., mitral regurgitation, aortic stenosis, aortic regurgitation), hypercoagulable states (giving rise to marantic endocarditis, which consists of uninfected vegetations), and the antiphospholipid antibody syndrome. After entering the bloodstream, organisms adhere to the endothelium or sites of NBTE via surface adhesin molecules. The clinical manifestations of endocarditis arise from cytokine production, damage to intracardiac structures, embolization of vegetation fragments, hematogenous infection of sites during bacteremia, and tissue injury due to the deposition of immune complexes.

- *Clinical manifestations:* The clinical syndrome is variable and spans a continuum between acute and subacute presentations. The temporal course of disease is dictated in large part by the causative organism: *S. aureus*, β-hemolytic streptococci, pneumococci, and *Staphylococcus lugdunensis* typically present acutely, whereas viridans streptococci, enterococci, CoNS (other than *S. lugdunensis*), and the HACEK group typically present subacutely.
  - *Constitutional symptoms:* generally nonspecific, but may include fever, chills, weight loss, myalgias, or arthralgias
  - *Cardiac manifestations:* Heart murmurs, particularly new or worsened regurgitant murmurs, are ultimately heard in 85% of pts with acute NVE.
    - CHF develops in 30–40% of pts and is usually due to valvular dysfunction.
    - Extension of infection can result in perivalvular abscesses, which in turn may cause intracardiac fistulae. Abscesses may burrow from the aortic root into the ventricular septum and interrupt the conduction system or may burrow through the epicardium and cause pericarditis.
  - *Noncardiac manifestations:* Arterial emboli, one-half of which precede the diagnosis of endocarditis, are present in 50% of pts, with hematogenously seeded focal infection most often evident in the skin, spleen, kidneys, bones, and meninges.
    - The risk of embolization increases with endocarditis caused by *S. aureus*, vegetations >10 mm in diameter, and infection involving the mitral valve (particularly the anterior leaflet).
    - Cerebrovascular emboli presenting as stroke or encephalopathy complicate 15–35% of cases, with one-half of these cases preceding the diagnosis of endocarditis.
      - The incidence of stroke decreases dramatically with antibiotic therapy and does not correlate with change in vegetation size; 3% of strokes occur after 1 week of effective therapy, but these late-occurring embolic events do not specifically constitute evidence of failed antimicrobial therapy.
      - Other neurologic complications include aseptic or purulent meningitis, intracranial hemorrhage due to ruptured mycotic aneurysms (focal dilations of arteries at points in the artery wall that have been weakened by infection or where septic emboli have lodged) or hemorrhagic infarcts, seizures, and microabscesses (especially with *S. aureus*).
    - Immune complex deposition on the glomerular basement membrane causes glomerulonephritis and renal dysfunction, which improve with antibiotic therapy.
    - Nonsuppurative peripheral manifestations of subacute endocarditis (e.g., Janeway lesions, Roth's spots) are related to duration of infection and are now rare because of early diagnosis and treatment.
  - *Manifestations of specific predisposing conditions:* Underlying conditions may affect the presenting signs and symptoms.
    - *IV drug use:* ~50% of endocarditis cases associated with IV drug use are limited to the tricuspid valve and present as fever, faint or no murmur, septic pulmonary emboli (evidenced by cough, pleuritic chest pain, nodular pulmonary infiltrates, or occasional pyopneumothorax), and the absence of peripheral manifestations. Pts with left-sided cardiac infections present with the typical clinical features of endocarditis.
    - *Health care–associated endocarditis:* Manifestations are typical in the absence of a retained intracardiac device. Endocarditis associated with a transvenous

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pacemaker or an implanted defibrillator may be associated with a generator pocket infection and result in fever, minimal murmur, and pulmonary symptoms due to septic emboli.
  - *PVE:* In cases of endocarditis occurring within 60 days of valve surgery, typical symptoms may be masked by comorbidity associated with recent surgery. Paravalvular infection is common in PVE, resulting in partial valve dehiscence, regurgitant murmurs, CHF, or disruption of the conduction system.
- *Diagnosis:* A diagnosis of infective endocarditis is established definitively only when vegetations are examined histologically and microbiologically.
  - The modified Duke criteria (Table 80-1) constitute a highly sensitive and specific diagnostic schema that emphasizes the roles of bacteremia and echocardiographic findings.
    - A clinical diagnosis of definite endocarditis requires fulfillment of two major criteria, one major criterion plus three minor criteria, or five minor criteria.
    - A diagnosis of possible endocarditis requires documentation of one major criterion plus one minor criterion or three minor criteria.
  - For antibiotic-naïve pts, three 2-bottle sets of blood culture samples—separated from one another by at least 2 h—should be obtained from different sites within the first 24 h. If blood cultures are negative after 48–72 h, two or three additional sets of samples should be cultured.
  - Serology is helpful in implicating *Brucella, Bartonella*, *Legionella*, *Chlamydia psittaci*, or *C. burnetii* in endocarditis. Examination of the vegetation by histology, culture, direct fluorescent antibody techniques, and/or PCR may be helpful in identifying the causative organism in the absence of a positive blood culture.
  - Echocardiography should be performed to confirm the diagnosis, to verify the size of vegetations, to detect intracardiac complications, and to assess cardiac function.
    - Transthoracic echocardiography (TTE) does not detect vegetations <2 mm in diameter, is not adequate for evaluation of prosthetic valves or detection of intracardiac complications, and is technically inadequate in 20% of pts because of emphysema or body habitus; however, TTE may suffice when pts have a low pretest likelihood of endocarditis.
    - Transesophageal echocardiography (TEE) detects vegetations in >90% of cases of definite endocarditis and is optimal for evaluation of prosthetic valves and detection of abscesses, valve perforation, or intracardiac fistulas.
    - When endocarditis is likely, a negative TEE result does not exclude the diagnosis but warrants repetition of the study once or twice in 7–10 days.
    - Routine echocardiography (preferably TEE) is recommended in pts with *S. aureus* bacteremia.

## TREATMENT ENDOCARDITIS

### ANTIMICROBIAL THERAPY

- Antimicrobial therapy must be bactericidal and prolonged. See Table 80-2 for organism-specific regimens.
  - Blood cultures should be repeated until sterile, and results should be rechecked if there is recrudescent fever and at 4–6 weeks after therapy to document cure.
  - If pts are febrile for 7 days despite antibiotic therapy, an evaluation for paravalvular or extracardiac abscesses should be performed.
- Pts with acute endocarditis require antibiotic treatment as soon as three sets of blood culture samples are obtained, but pts with subacute disease who are clinically stable should have antibiotics withheld until a diagnosis is made.
- Pts treated with vancomycin or an aminoglycoside should have serum drug levels monitored. Tests to detect renal, hepatic, and/or hematologic toxicity should be performed periodically.

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**TABLE 80-1 THE MODIFIED DUKE CRITERIA FOR THE CLINICAL DIAGNOSIS OF INFECTIVE ENDOCARDITIS[a]**

**Major Criteria**

1. Positive blood culture
   - Typical microorganism for infective endocarditis from two separate blood cultures
     - Viridans streptococci, *Streptococcus gallolyticus*, HACEK group organisms, *Staphylococcus aureus*, *or*
     - Community-acquired enterococci in the absence of a primary focus,
     - ***or***
   - Persistently positive blood culture, defined as recovery of a microorganism consistent with infective endocarditis from:
     - Blood cultures drawn >12 h apart; *or*
     - All of 3 or a majority of ≥4 separate blood cultures, with first and last drawn at least 1 h apart
     - ***or***
   - Single positive blood culture for *Coxiella burnetii* or phase I IgG antibody titer of >1:800
2. Evidence of endocardial involvement
   - Positive echocardiogram[b]
     - Oscillating intracardiac mass on valve or supporting structures or in the path of regurgitant jets or in implanted material, in the absence of an alternative anatomic explanation, *or*
     - Abscess, *or*
     - New partial dehiscence of prosthetic valve,
     - ***or***
   - New valvular regurgitation (increase or change in preexisting murmur not sufficient)

**Minor Criteria**

1. Predisposition: predisposing heart conditions[c] or injection drug use
2. Fever ≥38.0°C (≥100.4°F)
3. Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions
4. Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, rheumatoid factor
5. Microbiologic evidence: positive blood culture but not meeting major criterion, as noted previously,[d] *or* serologic evidence of active infection with an organism consistent with infective endocarditis

[a]Definite endocarditis is defined by documentation of two major criteria, of one major criterion and three minor criteria, or of five minor criteria. See text for further details.
[b]Transesophageal echocardiography is required for optimal assessment of possible prosthetic valve endocarditis or complicated endocarditis.
[c]Valvular disease with stenosis or regurgitation, presence of a prosthetic valve, congenital heart disease including corrected or partially corrected conditions (except isolated atrial septal defect, repaired ventricular septal defect, or closed patent ductus arteriosus), prior endocarditis, or hypertrophic cardiomyopathy.
[d]Excluding single positive cultures for coagulase-negative staphylococci and diphtheroids, which are common culture contaminants, or for organisms that do not cause endocarditis frequently, such as gram-negative bacilli.
***Source:*** Adapted from JS Li et al: *Clin Infect Dis* 30:633, 2000. With permission from Oxford University Press.

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**TABLE 80-2 ANTIBIOTIC TREATMENT FOR INFECTIVE ENDOCARDITIS CAUSED BY COMMON ORGANISMS[a]**

| Organism | Drug (Dose, Duration) | Comments |
|---|---|---|
| **Streptococci** | | |
| Penicillin-susceptible[b] streptococci, *S. gallolyticus* | • Penicillin G (2–3 mU IV q4h for 4 weeks) | — |
| | • Ceftriaxone (2 g/d IV as a single dose for 4 weeks) | Can use ceftriaxone in pts with nonimmediate penicillin allergy. |
| | • Vancomycin[c] (15 mg/kg IV q12h for 4 weeks) | Use vancomycin in pts with severe or immediate β-lactam allergy. |
| | • Penicillin G (2–3 mU IV q4h) *or* ceftriaxone (2 g IV qd) for 2 weeks<br>***plus***<br>Gentamicin[d] (3 mg/kg qd IV or IM, as a single dose[e] or divided into equal doses q8h for 2 weeks) | Avoid 2-week regimen when risk of aminoglycoside toxicity is increased and in prosthetic valve or complicated endocarditis. |
| Relatively penicillin-resistant[f] | • Penicillin G (4 mU IV q4h) *or* ceftriaxone (2 g IV qd) for 4 weeks<br>***plus***<br>Gentamicin[d] (3 mg/kg qd IV or IM, as a single dose[e] or divided into equal doses q8h for 2 weeks) | Penicillin alone at this dose for 6 weeks or with gentamicin during the initial 2 weeks is preferred for prosthetic valve endocarditis caused by streptococci with penicillin MICs of ≤0.1 μg/mL. |
| | • Vancomycin[c] as noted above for 4 weeks | — |
| Moderately penicillin-resistant[g] streptococci, nutritionally variant organisms, or *Gemella* species | • Penicillin G (4–5 mU IV q4h) *or* ceftriaxone (2 g IV qd) for 6 weeks<br>***plus***<br>Gentamicin[d] (3 mg/kg qd IV or IM as a single dose[e] *or* divided into equal doses q8h for 6 weeks) | Preferred for prosthetic valve endocarditis caused by streptococci with penicillin MICs of >0.1 μg/mL |
| | • Vancomycin[c] as noted above for 4 weeks | Regimen is preferred by some. |
| Enterococci[h] | | |
| | • Penicillin G (4–5 mU IV q4h) *plus* gentamicin[d] (1 mg/kg IV q8h), both for 4–6 weeks | Can use streptomycin (7.5 mg/kg q12h) in lieu of gentamicin if there is not high-level resistance to streptomycin |
| | • Ampicillin (2 g IV q4h) *plus* gentamicin[d] (1 mg/kg IV q8h), both for 4–6 weeks | — |

(*Continued*)

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**TABLE 80-2 ANTIBIOTIC TREATMENT FOR INFECTIVE ENDOCARDITIS CAUSED BY COMMON ORGANISMS[a] (*CONTINUED*)**

| Organism | Drug (Dose, Duration) | Comments |
|---|---|---|
| | • Vancomycin[c] (15 mg/kg IV q12h) *plus* gentamicin[d] (1 mg/kg IV q8h), both for 4–6 weeks | Use vancomycin plus gentamicin for penicillin-allergic pts (or desensitize to penicillin) and for isolates resistant to penicillin/ampicillin. |
| | • Ampicillin (2 g IV q4h) *plus* ceftriaxone (2 g IV q12h), both for 6 weeks | Use for *E. faecalis* isolates with high-level resistance to gentamicin and streptomycin or for pts at high risk for aminoglycoside nephrotoxicity |
| *Staphylococci* | | |
| MSSA infecting native valves (no foreign devices) | • Nafcillin, oxacillin, *or* flucloxacillin (2 g IV q4h for 4–6 weeks) | Can use penicillin (4 mU q4h) if isolate is penicillin-susceptible (does not produce β-lactamase). |
| | • Cefazolin (2 g IV q8h for 4–6 weeks) | Can use cefazolin regimen for pts with nonimmediate penicillin allergy |
| | • Vancomycin[c] (15 mg/kg IV q12h for 4–6 weeks) | Use vancomycin for pts with immediate (urticarial) or severe penicillin allergy. |
| MRSA infecting native valves (no foreign devices) | • Vancomycin[c] (15 mg/kg IV q8–12h for 4–6 weeks) | No role for routine use of rifampin. Consider alternative treatment (see text) for MRSA with vancomycin MIC >1.0 or persistent bacteremia during vancomycin therapy. |
| MSSA infecting prosthetic valves | • Nafcillin, oxacillin, *or* flucloxacillin (2 g IV q4h for 6–8 weeks)<br>***plus***<br>Gentamicin[d] (1 mg/kg IM or IV q8h for 2 weeks)<br>***plus***<br>• Rifampin[i] (300 mg PO q8h for 6–8 weeks) | Use gentamicin during initial 2 weeks; determine susceptibility to gentamicin before initiating rifampin; if pt is highly allergic to penicillin, use regimen for MRSA; if β-lactam allergy is of the minor nonimmediate type, cefazolin can be substituted for oxacillin/nafcillin. |
| MRSA infecting prosthetic valves | • Vancomycin[c] (15 mg/kg IV q12h for 6–8 weeks)<br>***plus***<br>Gentamicin[d] (1 mg/kg IM or IV q8h for 2 weeks)<br>***plus***<br>Rifampin[i] (300 mg PO q8h for 6–8 weeks) | Use gentamicin during initial 2 weeks; determine gentamicin susceptibility before initiating rifampin. |

(*Continued*)

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**TABLE 80-2 ANTIBIOTIC TREATMENT FOR INFECTIVE ENDOCARDITIS CAUSED BY COMMON ORGANISMS[a] (*CONTINUED*)**

| Organism | Drug (Dose, Duration) | Comments |
|---|---|---|
| HACEK Organisms | | |
| | • Ceftriaxone (2 g/d IV as a single dose for 4 weeks) | Can use another third-generation cephalosporin at comparable dosage |
| | • Ampicillin/sulbactam (3 g IV q6h for 4 weeks) | — |
| *Coxiella burnetii* | | |
| | • Doxycycline (100 mg PO q12h) *plus* hydroxychloroquine (200 mg PO q8h), both for 18 (native valve) or 24 (prosthetic valve) months | Follow serology to monitor response during treatment (anti–phase I IgG and IgA decreased 4-fold and IgM anti–phase II negative) and thereafter for relapse. |
| *Bartonella* spp. | | |
| | • Ceftriaxone (2 g IV q24h) *or* ampicillin (2 g IV q4h) *or* doxycycline (100 mg PO q12h) for 6 weeks<br>***plus***<br>Gentamicin (1 mg/kg IV q8h for 3 weeks) | If pt is highly allergic to β-lactams, use doxycycline. |

[a]Doses are for adults with normal renal function. Doses of gentamicin, streptomycin, and vancomycin must be adjusted for reduced renal function. Ideal body weight is used to calculate doses of gentamicin and streptomycin per kilogram (men = 50 kg + 2.3 kg per inch over 5 feet; women = 45.5 kg + 2.3 kg per inch over 5 feet).
[b]MIC, ≤0.1 μg/mL.
[c]Vancomycin dose is based on actual body weight. Adjust for trough level of 10–15 μg/mL for streptococcal and enterococcal infections and 15–20 μg/mL for staphylococcal infections.
[d]Aminoglycosides should not be administered as single daily doses for enterococcal endocarditis and should be introduced as part of the initial treatment. Target peak and trough serum concentrations of divided-dose gentamicin 1 h after a 20- to 30-min infusion or IM injection are ~3.5 μg/mL and ≤1 μg/mL, respectively; target peak and trough serum concentrations of streptomycin (timing as with gentamicin) are 20–35 μg/mL and <10 μg/mL, respectively.
[e]Netilmicin (4 mg/kg qd, as a single dose) can be used in lieu of gentamicin.
[f]MIC, >0.1 μg/mL and <0.5 μg/mL.
[g]MIC, ≥0.5 μg/mL and <8 μg/mL.
[h]Antimicrobial susceptibility must be evaluated; see text.
[i]Rifampin increases warfarin and dicumarol requirements for anticoagulation.
***Abbreviations:*** MIC, minimal inhibitory concentration; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-sensitive *S. aureus*.

## ORGANISM-SPECIFIC THERAPIES

- Endocarditis due to group B, C, or G streptococci should be treated with the regimen recommended for relatively penicillin-resistant streptococci (Table 80-2).
- Killing of enterococci requires the synergistic activity of a cell wall–active agent and an aminoglycoside (gentamicin or streptomycin) to which the isolate does

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not exhibit high-level resistance. The aminoglycoside can be discontinued in those pts who have responded satisfactorily if toxicity develops after 2–3 weeks of treatment. If there is high-level resistance to both aminoglycosides, the cell wall–active agent should be given alone for 8–12 weeks, or—for *Enterococcus faecalis*—high-dose ampicillin plus ceftriaxone or cefotaxime can be given. If the isolate is resistant to all commonly used agents, surgical therapy is advised (see below and Table 80-3).

- For staphylococcal NVE, the addition of 3–5 days of gentamicin to a β-lactam antibiotic does not improve survival rates and is not recommended.
- Although this regimen has not yet been approved by the U.S. Food and Drug Administration, daptomycin (6 mg/kg IV qd; or, as some experts prefer, 8–10 mg/kg IV qd) has been recommended for endocarditis caused by *S. aureus* isolates with a vancomycin minimal inhibitory concentration (MIC) of ≥2 μg/mL. These isolates should be tested to document daptomycin sensitivity.

**TABLE 80-3 TIMING OF CARDIAC SURGICAL INTERVENTION IN PTS WITH ENDOCARDITIS**

| | Indication for Surgical Intervention | |
|---|---|---|
| **Timing** | **Strong Supporting Evidence** | **Conflicting Evidence, but Majority of Opinions Favor Surgery** |
| Emergent (same day) | Acute aortic regurgitation plus preclosure of mitral valve | |
| | Sinus of Valsalva abscess ruptured into right heart | |
| | Rupture into pericardial sac | |
| Urgent (within 1–2 days) | Valve obstruction by vegetation | Major embolus plus persisting large vegetation (>10 mm in diameter) |
| | Unstable (dehisced) prosthesis | |
| | Acute aortic or mitral regurgitation with heart failure (New York Heart Association class III or IV) | |
| | Septal perforation | |
| | Perivalvular extension of infection with or without new electrocardiographic conduction system changes | |
| | Lack of effective antibiotic therapy | |
| Elective (earlier usually preferred) | Vegetation diameter >10 mm plus severe aortic or mitral valve dysfunction[a] | Staphylococcal prosthetic valve endocarditis |
| | Progressive paravalvular prosthetic regurgitation | Early prosthetic valve endocarditis (≤2 months after valve surgery) |
| | Valve dysfunction plus persisting infection after ≥7–10 days of antimicrobial therapy | Fungal endocarditis (*Candida* spp.) |
| | Fungal (mold) endocarditis | Antibiotic-resistant organisms |

[a]Supported by a single-institution randomized trial showing benefit from early surgery. Implementation requires clinical judgment.

***Source:*** Adapted from L Olaison, G Pettersson: *Infect Dis Clin North Am* 16:453, 2002.

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- Staphylococcal PVE is treated for 6–8 weeks with a multidrug regimen. Rifampin is important because it kills organisms adherent to foreign material. The inclusion of two other agents in addition to rifampin helps prevent the emergence of rifampin resistance in vivo. Testing for gentamicin susceptibility should be performed before rifampin is given; if the strain is resistant, another aminoglycoside, a fluoroquinolone, or another active agent should be substituted.
- Empirical therapy (either before culture results are known or when cultures are negative) depends on epidemiologic clues to etiology (e.g., endocarditis in an IV drug user, health care–associated endocarditis).
  - In the setting of no prior antibiotic therapy and negative blood cultures, *S. aureus*, CoNS, and enterococcal infection are unlikely; empirical therapy in this situation should target nutritionally variant organisms, the HACEK group, and *Bartonella*.
  - If negative cultures are confounded by prior antibiotic therapy, broader empirical therapy is indicated and should cover pathogens inhibited by the prior therapy.

## SURGICAL TREATMENT

- The timing and indications for surgical intervention are listed in Table 80-3; most of these indications are not absolute, and recommendations are derived from observational studies and expert opinion. Moderate or severe refractory CHF is the major indication for surgical treatment of endocarditis.
- Cardiac surgery should be delayed for 2–3 weeks if possible when the pt has had a nonhemorrhagic embolic stroke and for 4 weeks when the pt has had a hemorrhagic embolic stroke. Ruptured mycotic aneurysms should be treated prior to cardiac surgery.
- The duration of antibiotic therapy after cardiac surgery depends on the indication for surgery.
  - For cases of uncomplicated NVE caused by susceptible organisms with negative valve cultures at surgery, the duration of pre- and postoperative treatment should equal the total duration of recommended therapy, with ~2 weeks of treatment given postoperatively.
  - For endocarditis with paravalvular abscess, partially treated PVE, or culture-positive valves, pts should receive a full course of therapy postoperatively.

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- *Outcome:* Death and other poor outcomes are related not to failure of antibiotic therapy but rather to interactions of comorbidities and endocarditis-related end-organ complications.
  - Survival rates are 85–90% for NVE due to viridans streptococci, HACEK organisms, or enterococci as opposed to 55–70% for NVE due to *S. aureus* in pts who are not IV drug users.
  - PVE beginning within 2 months of valve replacement results in mortality rates of 40–50%, whereas rates are only 10–20% in later-onset cases.
- *Prevention:* The American Heart Association and the European Society of Cardiology have narrowed recommendations for antibiotic prophylaxis, limiting its use to pts at highest risk of severe morbidity and death from endocarditis.
  - Prophylaxis is recommended only for those dental procedures involving manipulation of gingival tissue or the periapical region of the teeth or perforation of the oral mucosa (including respiratory tract surgery). Prophylaxis is not advised for pts undergoing GI or genitourinary tract procedures unless the genitourinary tract is infected.
  - Table 80-4 lists the high-risk cardiac lesions for which prophylaxis is advised, and Table 80-5 lists the recommended antibiotic regimens for this purpose.

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**TABLE 80-4 HIGH-RISK CARDIAC LESIONS FOR WHICH ENDOCARDITIS PROPHYLAXIS IS ADVISED BEFORE DENTAL PROCEDURES**

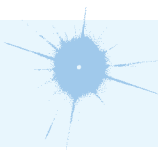
| |
|---|
| Prosthetic heart valves |
| Prior endocarditis |
| Unrepaired cyanotic congenital heart disease, including palliative shunts or conduits |
| Completely repaired congenital heart defects during the 6 months after repair |
| Incompletely repaired congenital heart disease with residual defects adjacent to prosthetic material |
| Valvulopathy developing after cardiac transplantation[a] |

[a]Not a target population for prophylaxis according to recommendations of the European Society for Cardiology.
***Source:*** Table created using the guidelines published by the American Heart Association and the European Society of Cardiology (W Wilson et al: *Circulation* 116:1736, 2007; and G Habib et al: *Eur Heart J* 30:2369, 2009).

**TABLE 80-5 ANTIBIOTIC REGIMENS FOR PROPHYLAXIS OF ENDOCARDITIS IN ADULTS WITH HIGH-RISK CARDIAC LESIONS[a,b]**

A. Standard oral regimen
   Amoxicillin: 2 g PO 1 h before procedure
B. Inability to take oral medication
   Ampicillin: 2 g IV or IM within 1 h before procedure
C. Penicillin allergy
   1. Clarithromycin or azithromycin: 500 mg PO 1 h before procedure
   2. Cephalexin[c]: 2 g PO 1 h before procedure
   3. Clindamycin: 600 mg PO 1 h before procedure
D. Penicillin allergy, inability to take oral medication
   1. Cefazolin[c] or ceftriaxone[c]: 1 g IV or IM 30 min before procedure
   2. Clindamycin: 600 mg IV or IM 1 h before procedure

[a]Dosing for children: for amoxicillin, ampicillin, cephalexin, or cefadroxil, use 50 mg/kg PO; cefazolin, 25 mg/kg IV; clindamycin, 20 mg/kg PO or 25 mg/kg IV; clarithromycin, 15 mg/kg PO; and vancomycin, 20 mg/kg IV.
[b]For high-risk lesions, see Table 80-4. Prophylaxis is not advised for other lesions.
[c]Do not use cephalosporins in pts with immediate hypersensitivity (urticaria, angioedema, anaphylaxis) to penicillin.
***Source:*** Table created using the guidelines published by the American Heart Association and the European Society of Cardiology (W Wilson et al: *Circulation* 116:1736, 2007; and G Habib et al: *Eur Heart J* 30:2369, 2009).



For a more detailed discussion, see Karchmer AW: Infective Endocarditis, Chap. 155, p. 816, in HPIM-19.

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# 81 Intraabdominal Infections

Intraperitoneal infections result when normal anatomic barriers are disrupted. Organisms contained within the bowel or an intraabdominal organ enter the sterile peritoneal cavity, causing peritonitis and—if the infection goes untreated and the pt survives—abscesses.

## PERITONITIS

Peritonitis is a life-threatening event that is often accompanied by bacteremia and sepsis. Primary peritonitis has no apparent source, whereas secondary peritonitis is caused by spillage from an intraabdominal viscus; the etiologic organisms and the clinical presentations of these two processes are different.

### PRIMARY (SPONTANEOUS) BACTERIAL PERITONITIS

- *Epidemiology:* Primary bacterial peritonitis (PBP) is most common among pts with cirrhosis (usually due to alcoholism) and preexisting ascites, but ≤10% of these pts develop PBP. PBP is also described in other settings (e.g., malignancy, hepatitis).
- *Pathogenesis:* PBP is due to hematogenous spread of organisms to ascitic fluid in pts in whom a diseased liver and altered portal circulation compromise the liver's filtration function.
- *Microbiology:* Enteric gram-negative bacilli such as *Escherichia coli* or gram-positive organisms such as streptococci, enterococci, and pneumococci are the most common etiologic agents.
  - A single organism is typically isolated.
  - If a polymicrobial infection including anaerobes is identified, the diagnosis of PBP should be reconsidered and a source of secondary peritonitis sought.
- *Clinical manifestations:* Although some pts experience acute-onset abdominal pain or signs of peritoneal irritation, other pts have only nonspecific and nonlocalizing manifestations (e.g., malaise, fatigue, encephalopathy). Fever is common (~80% of pts).
- *Diagnosis:* PBP is diagnosed if peritoneal fluid is sampled and contains >250 PMNs/μL.
  - Culture yield is improved if a 10-mL volume of peritoneal fluid is placed directly into blood culture bottles.
  - Blood cultures should be performed because bacteremia is common.
- *Prevention:* Up to 70% of pts have a recurrence of PBP within 1 year. Prophylaxis with fluoroquinolones (e.g., ciprofloxacin, 750 mg weekly) or trimethoprim-sulfamethoxazole (TMP-SMX; one double-strength tablet daily) reduces this rate to 20%, but increases the risk of serious staphylococcal infections over time.

### TREATMENT PRIMARY (SPONTANEOUS) BACTERIAL PERITONITIS

A third-generation cephalosporin (e.g., ceftriaxone, 2 g q24h IV; or cefotaxime, 2 g q8h IV) or piperacillin/tazobactam (3.375 g qid IV) constitutes appropriate empirical treatment.

- The regimen should be narrowed after the etiology is identified.
- Treatment should continue for at least 5 days, but longer courses (up to 2 weeks) may be needed for pts with coexisting bacteremia or for those whose improvement is slow.
- Albumin (1.5 g/kg of body weight within 6 h of detection and 1.0 g/kg on day 3) improves survival rates among pts with serum creatinine levels ≥1 mg/dL, BUN levels ≥30 mg/dL, or total bilirubin levels ≥4 mg/dL.

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## SECONDARY PERITONITIS

- *Pathogenesis:* Secondary peritonitis develops when bacteria contaminate the peritoneum as a result of spillage from an intraabdominal viscus.
- *Microbiology:* Infection almost always involves a mixed flora in which gram-negative bacilli and anaerobes predominate, especially when the contaminating source is colonic. The specific organisms depend on the flora present at the site of the initial process.
- *Clinical manifestations:* Initial symptoms may be localized or vague and depend on the primary organ involved. Once infection has spread to the peritoneal cavity, pain increases; pts lie motionless, often with knees drawn up to avoid stretching the nerve fibers of the peritoneal cavity. Coughing or sneezing causes severe, sharp pain. There is marked voluntary and involuntary guarding of anterior abdominal musculature, tenderness (often with rebound), and fever.
- *Diagnosis:* Although recovery of organisms from peritoneal fluid is easier in secondary than in primary peritonitis, radiographic studies to find the source of peritoneal contamination or immediate surgical intervention should usually be part of the initial diagnostic evaluation. Abdominal taps are done only to exclude hemoperitoneum in trauma cases.

### TREATMENT SECONDARY PERITONITIS

- Antibiotics aimed at the inciting flora—e.g., penicillin/β-lactamase inhibitor combinations or a combination of a fluoroquinolone or a third-generation cephalosporin plus metronidazole—should be administered early.
  - For critically ill pts in the ICU, imipenem (500 mg q6h IV) or dr*ug combinations such as ampicillin plus metronidazol*e plus ciprofloxacin should be used.
  - Surgical intervention is often needed.

## PERITONITIS IN PTS UNDERGOING CAPD

- *Pathogenesis:* In a phenomenon similar to that seen in intravascular device–related infections, organisms migrate along the catheter, a foreign body that serves as an entry point.
- *Microbiology:* CAPD-associated peritonitis usually involves skin organisms, with *Staphylococcus* spp. such as coagulase-negative staphylococci and *Staphylococcus aureus* accounting for ~45% of cases; gram-negative bacilli and fungi (e.g., *Candida*) are occasionally identified. A polymicrobial infection should prompt evaluation for secondary peritonitis.
- *Clinical manifestations:* CAPD-associated peritonitis presents similarly to secondary peritonitis, in that diffuse pain and peritoneal signs are common.
- *Diagnosis:* Several hundred milliliters of removed dialysis fluid should be centrifuged and sent for culture.
  - Use of blood culture bottles improves the diagnostic yield.
  - The dialysate is usually cloudy and contains >100 WBCs/μL, with >50% neutrophils; the percentage of neutrophils is more important than the absolute WBC count.

### TREATMENT PERITONITIS IN PTS UNDERGOING CAPD

- Empirical therapy should be directed against staphylococcal species and gram-negative bacilli (e.g., cefazolin plus a fluoroquinolone or a third-generation cephalosporin such as ceftazidime). Vancomycin should be used instead of cefazolin if methicillin resistance is prevalent, if the pt has an overt exit-site infection, or if the pt appears toxic.
  - Antibiotics are given by the IP route either continuously (e.g., with each exchange) or intermittently (e.g., once daily, with the dose allowed to remain

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in the peritoneal cavity for 6 h). Severely ill pts should be given the same regimen by the IV route.
  - Catheter removal should be considered in fungal infection, for pts with exit-site or tunnel infection, or if the pt's condition does not improve within 48–96 h.
  - Uncomplicated CAPD-associated peritonitis should be treated for 14 days; up to 21 days may be necessary in pts with exit-site or tunnel infection.

## INTRAABDOMINAL ABSCESSES

Intraabdominal abscesses are generally diagnosed through radiographic studies, of which abdominal CT is typically most useful.

### INTRAPERITONEAL ABSCESSES

- *Epidemiology:* Of intraabdominal abscesses, 74% are IP or retroperitoneal, not visceral.
- *Pathogenesis:* Most IP abscesses arise from colonic sources. Abscesses develop in untreated peritonitis as an extension of the disease process and represent host defense activity aimed at containing the infection.
- *Microbiology:* Infection is typically polymicrobial; the most frequently isolated anaerobe is *Bacteroides fragilis*.

**TREATMENT INTRAPERITONEAL ABSCESSES**

- Antimicrobial therapy is adjunctive to drainage and/or surgical correction of an underlying lesion or process.
  - Diverticular abscesses usually wall off locally, and surgical intervention is not routinely needed.
  - Antimicrobial agents with activity against gram-negative bacilli and anaerobic organisms are indicated (see "Secondary Peritonitis," above).

### VISCERAL ABSCESSES

#### Liver Abscess

- *Epidemiology, Pathogenesis, and Microbiology:* Liver abscesses account for up to half of visceral intraabdominal abscesses and are caused most commonly by biliary tract disease (due to aerobic gram-negative bacilli or enterococci) and less often by local spread from pelvic and other IP sources (due to mixed flora including aerobic and anaerobic species, among which *B. fragilis* is most common) or hematogenous seeding (infection with a single species, usually *S. aureus* or streptococci such as *S. milleri*).
  - Amebic liver abscesses are not uncommon, with positive serology in >95% of affected pts.
- *Clinical manifestations:* Pts have fever, anorexia, weight loss, nausea, and vomiting, but only ~50% have signs localized to the RUQ, such as tenderness, hepatomegaly, and jaundice. Serum levels of alkaline phosphatase are elevated in ~70% of pts, and leukocytosis is common. One-third to one-half of pts are bacteremic.

**TREATMENT LIVER ABSCESS**

- Drainage is the mainstay of treatment, but medical management with long courses of antibiotics can be successful.
  - Empirical therapy is the same as for intraabdominal sepsis and secondary bacterial peritonitis.

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– Percutaneous drainage tends to fail in cases with multiple, sizable abscesses; with viscous abscess contents that plug the pigtail catheter; with associated disease (e.g., of the biliary tract) requiring surgery; with the presence of yeast; or with lack of response in 4–7 days.

## Splenic Abscess

- *Epidemiology and Pathogenesis:* Splenic abscesses are much less common than liver abscesses and usually develop via hematogenous spread of infection (e.g., due to endocarditis). The diagnosis is often made only after the pt's death; the condition is frequently fatal if left untreated.
- *Microbiology:* Splenic abscesses are most often caused by streptococci; *S. aureus* is the next most common cause. Gram-negative bacilli can cause splenic abscess in pts with urinary tract foci, with associated bacteremia, or with infection from another intraabdominal source; salmonellae are fairly commonly isolated, particularly from pts with sickle cell disease.
- *Clinical manifestations:* Abdominal pain or splenomegaly occurs in ~50% of cases and pain localized to the LUQ in ~25%. Fever and leukocytosis are common.

### TREATMENT SPLENIC ABSCESS

Pts with multiple or complex multilocular abscesses should undergo splenectomy, receive adjunctive antibiotics, and be vaccinated against encapsulated organisms (*Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*). Percutaneous drainage has been successful for single, small (<3-cm) abscesses and may also be useful for pts at high surgical risk.

## Perinephric and Renal Abscesses

- *Epidemiology and Pathogenesis:* Perinephric and renal abscesses are uncommon. More than 75% of these abscesses are due to ascending infection and are preceded by pyelonephritis. The most important risk factor is the presence of renal calculi that produce local obstruction to urinary flow.
- *Microbiology: E. coli*, *Proteus* spp. (associated with struvite stones), and *Klebsiella* spp. are the most common etiologic agents; *Candida* spp. are sometimes identified.
- *Clinical manifestations:* Clinical signs are nonspecific and include flank pain, abdominal pain, and fever. This diagnosis should be considered if pts with pyelonephritis have persistent fever after 4 or 5 days of treatment, if a urine culture yields a polymicrobial flora, if the pt has known renal stone disease, or if fever and pyuria occur in conjunction with a sterile urine culture.

### TREATMENT PERINEPHRIC AND RENAL ABSCESSES

Drainage and the administration of antibiotics active against the organisms recovered are essential. Percutaneous drainage is usually successful for perinephric abscesses.

For a more detailed discussion, see Barshak MB, Kasper DL: Intraabdominal Infections and Abscesses, Chap. 159, p. 846, in HPIM-19.

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# 82 Infectious Diarrheas

Acute diarrheal disease, which is associated with ~1.4 million deaths per year, is the second most common infectious cause of death worldwide among children <5 years old (after lower respiratory tract infection). The wide range of clinical manifestations is matched by the wide variety of infectious agents involved (Table 82-1). An approach to pts with infectious diarrhea is presented in Fig. 82-1.

## NONINFLAMMATORY DIARRHEA

### BACTERIAL FOOD POISONING

If there is evidence of a common-source outbreak, questions concerning the ingestion of specific foods and the timing of diarrhea after a meal can provide clues to the bacterial cause of the illness.

**TABLE 82-1 GASTROINTESTINAL PATHOGENS CAUSING ACUTE DIARRHEA**

| Mechanism | Location | Illness | Stool Findings | Examples of Pathogens Involved |
|---|---|---|---|---|
| Noninflammatory (enterotoxin) | Proximal small bowel | Watery diarrhea | No fecal leukocytes; mild or no increase in fecal lactoferrin | *Vibrio cholerae*, enterotoxigenic *Escherichia coli* (LT and/or ST), enteroaggregative *E. coli*, *Clostridium perfringens*, *Bacillus cereus*, *Staphylococcus aureus*, *Aeromonas hydrophila*, *Plesiomonas shigelloides*, rotavirus, norovirus, enteric adenoviruses, *Giardia lamblia*, *Cryptosporidium* spp., *Cyclospora* spp., microsporidia |
| Inflammatory (invasion or cytotoxin) | Colon or distal small bowel | Dysentery or inflammatory diarrhea | Fecal polymorphonuclear leukocytes; substantial increase in fecal lactoferrin | *Shigella* spp., *Salmonella* spp., *Campylobacter jejuni*, enterohemorrhagic *E. coli*, enteroinvasive *E. coli*, *Yersinia enterocolitica*, *Listeria monocytogenes*, *Vibrio parahaemolyticus*, *Clostridium difficile*, *A. hydrophila*, *P. shigelloides*, *Entamoeba histolytica*, *Klebsiella oxytoca* |
| Penetrating | Distal small bowel | Enteric fever | Fecal mononuclear leukocytes | *Salmonella typhi*, *Y. enterocolitica* |

***Abbreviations:*** LT, heat-labile enterotoxin; ST, heat-stable enterotoxin.

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- *Staphylococcus aureus:* Enterotoxin is elaborated in food left at room temperature (e.g., at picnics).
  - The incubation period is 1–6 h. Disease lasts <12 h and consists of diarrhea, nausea, vomiting, and abdominal cramping, usually without fever.
  - Most cases are due to contamination from infected human carriers.
- *Bacillus cereus:* Either an *emetic* or a *diarrheal* form of food poisoning can occur.
  - The emetic form presents like *S. aureus* food poisoning, is due to a staphylococcal type of enterotoxin, has an incubation period of 1–6 h, and is associated with contaminated fried rice.
  - The diarrheal form has an incubation period of 8–16 h, is caused by an enterotoxin resembling *Escherichia coli* heat-labile toxin (LT), and presents as diarrhea and abdominal cramps without vomiting.
- *Clostridium perfringens:* Ingestion of heat-resistant spores in undercooked meat, poultry, or legumes leads to toxin production in the intestinal tract. The incubation period is 8–14 h, after which pts develop ≤24 h of diarrhea and abdominal cramps, without vomiting or fever.

## CHOLERA

### Microbiology

Cholera is caused by *Vibrio cholerae* serogroups O1 (classic and El Tor biotypes) and O139—highly motile, facultatively anaerobic, curved gram-negative rods. The natural habitat of *V. cholerae* is coastal salt water and brackish estuaries. Toxin production causes disease manifestations.

### Epidemiology

Currently, >90% of cases reported to the World Health Organization (WHO) are from Africa; however, most cases go unreported or do not have a specific bacterial etiology identified.

- It is estimated that there are >3 million cases annually, with >100,000 deaths.
- Spread takes place by fecal contamination of water and food sources. Infection requires ingestion of a relatively large inoculum (compared with that required for other pathogens) of $>10^5$ organisms.

### Clinical Manifestations

After an incubation period of 24–48 h, pts develop painless watery diarrhea and vomiting that can cause profound, rapidly progressive dehydration and death within hours.

- Volume loss can be >250 mL/kg in the first day.
- Stool has a characteristic "rice-water" appearance: gray cloudy fluid with flecks of mucus; no blood; and a fishy, inoffensive odor.

### Diagnosis

Stool cultures on selective medium (e.g., thiosulfate–citrate–bile salts–sucrose [TCBS] agar) can isolate the organism. A point-of-care antigen-detection assay is available for field use.

**TREATMENT CHOLERA**

Rapid fluid replacement is critical, preferably with the WHO's reduced-osmolarity oral rehydration solution (ORS), which contains (per liter of water) $Na^+$, 75 mmol; $K^+$, 20 mmol; $Cl^-$, 65 mmol; citrate, 10 mmol; and glucose, 75 mmol.

- If available, rice-based ORS is considered superior to standard ORS for cholera.

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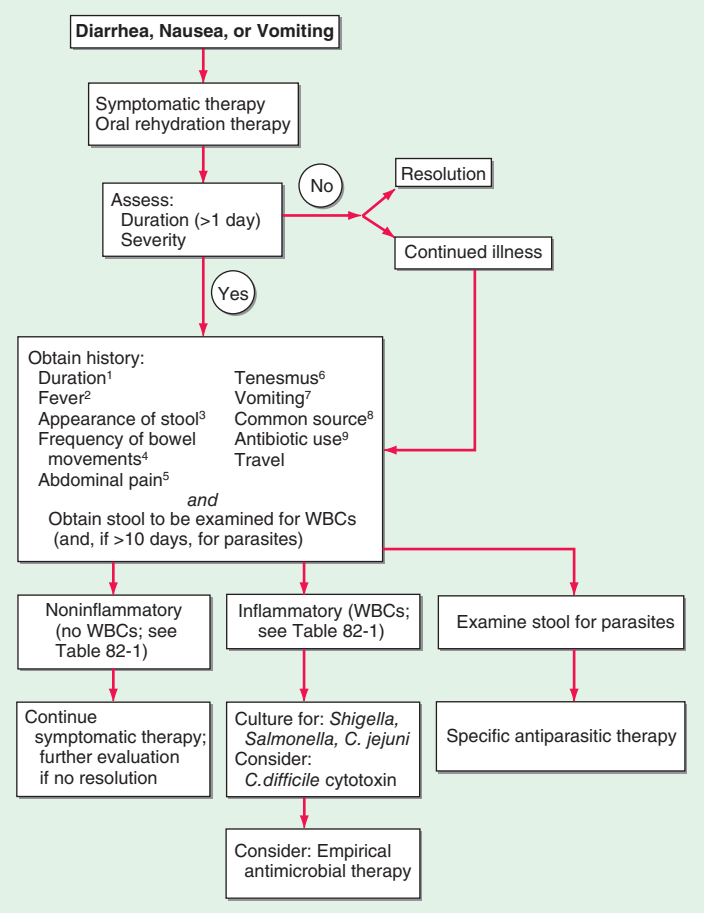


**FIGURE 82-1** Clinical algorithm for the approach to pts with community-acquired infectious diarrhea or bacterial food poisoning. Key to superscripts: **1.** Diarrhea lasting >2 weeks is generally defined as chronic; in such cases, many of the causes of acute diarrhea are much less likely, and a new spectrum of causes needs to be considered. **2.** Fever often implies invasive disease, although fever and diarrhea may also result from infection outside the GI tract, as in malaria. **3.** Stools that contain blood or mucus indicate ulceration of the large bowel. Bloody stools without fecal leukocytes should alert the laboratory to the possibility of infection with Shiga toxin–producing enterohemorrhagic *Escherichia coli*. Bulky white stools suggest a small-intestinal process that is causing malabsorption. Profuse "rice-water" stools suggest cholera or a similar toxigenic process. **4.** Frequent stools over a given period can provide the first warning of impending dehydration. **5.** Abdominal pain may be most severe in inflammatory processes like those due to *Shigella, Campylobacter*, and necrotizing toxins. Painful abdominal muscle cramps, caused by electrolyte loss, can develop in severe cases of cholera. Bloating is common in giardiasis. An appendicitis-like syndrome should prompt a culture for *Yersinia enterocolitica* with cold enrichment. **6.** Tenesmus (painful rectal spasms with a strong urge to defecate but little passage of stool) may be a feature of cases with proctitis, as in shigellosis or amebiasis. **7.** Vomiting implies

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- If ORS is not available, a substitute can be made by adding 0.5 teaspoon of table salt (NaCl; 3.5 g) and 6 teaspoons of table sugar (sucrose) to 1 L of safe water, with potassium provided separately (e.g., in orange juice or coconut water).
- Severely dehydrated pts should be managed initially with IV hydration (preferably with Ringer's lactate), with the total fluid deficit replaced in the first 3–4 h (half within the first hour).
- Antibiotic therapy (azithromycin, a single 1-g dose; erythromycin, 250 mg PO qid for 3 days; tetracycline, 500 mg PO qid for 3 days; or ciprofloxacin, 500 mg PO bid for 3 days) diminishes the duration and volume of stool.

## *VIBRIO PARAHAEMOLYTICUS* AND NON-O1 *V. CHOLERAE*

These infections are linked to ingestion of contaminated seawater or undercooked seafood. After an incubation period of 4 h to 4 days, watery diarrhea, abdominal cramps, nausea, vomiting, and occasionally fever and chills develop. The disease lasts <7 days. Dysentery is a less common presentation. Pts with comorbid disease (e.g., liver disease) sometimes have extraintestinal infections that require antibiotic treatment.

## NOROVIRUSES AND RELATED HUMAN CALICIVIRUSES

### Microbiology and Epidemiology

These single-stranded RNA viruses are common causes of traveler's diarrhea and of viral gastroenteritis in pts of all ages as well as of epidemics worldwide, with a higher prevalence in cold-weather months. In the United States, >90% of outbreaks of nonbacterial gastroenteritis are caused by noroviruses. Very small inocula are required for infection. Thus, although the fecal-oral route is the primary mode of transmission, aerosolization, fomite contact, and person-to-person contact can also result in infection.

### Clinical Manifestations

After a 24-h incubation period (range, 12–72 h), pts experience the sudden onset of nausea, vomiting, diarrhea, and/or abdominal cramps with constitutional symptoms (e.g., fever, headache, chills). Stools are loose, watery, and without blood, mucus, or leukocytes. Disease lasts 12–60 h.

### Diagnosis

PCR assays have been developed to detect these viruses in stool and other body fluids. Because of poor sensitivity, enzyme immunoassays (EIAs) have limited clinical utility outside of outbreaks.

an acute infection (e.g., a toxin-mediated illness or food poisoning) but can also be prominent in a variety of systemic illnesses (e.g., malaria) and in intestinal obstruction. **8.** Asking pts whether anyone else they know is sick is a more efficient means of identifying a common source than is constructing a list of recently eaten foods. If a common source seems likely, specific foods can be investigated. **9.** Current antibiotic therapy or a recent history of treatment suggests *Clostridium difficile* diarrhea. Stop antibiotic treatment if possible and consider tests for *C. difficile* toxins. Antibiotic use may increase the risk of chronic intestinal carriage after salmonellosis. *(After Steiner TS, Guerrant RL: Principles and syndromes of enteric infection, in Mandell, Douglas, and Bennett's* Principles and Practice of Infectious Diseases, *7th ed, GL Mandell et al [eds]. Philadelphia, Churchill Livingstone, 2010, pp 1335–1351; RL Guerrant, DA Bobak: N Engl J Med 325:327, 1991; with permission.)*

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**TREATMENT INFECTIONS WITH NOROVIRUSES AND RELATED HUMAN CALICIVIRUSES**

Only supportive measures are required.

## ROTAVIRUSES

### Microbiology and Epidemiology

Rotavirus is a segmented, double-stranded RNA virus that infects nearly all children worldwide by 3–5 years of age; adults can become infected if exposed.

- Reinfections are progressively less severe.
- Large quantities of virus are shed in the stool during the first week of infection, and transmission takes place both via the fecal-oral route and from person to person.
- Disease incidence peaks in the cooler fall and winter months.

### Clinical Manifestations

After an incubation period of 1–3 days, disease onset is abrupt. Vomiting often precedes diarrhea (loose, watery stools without blood or fecal leukocytes), and about one-third of pts have temperatures >39°C (102.2°F). Symptoms resolve within 3–7 days.

### Diagnosis

EIAs or viral RNA detection techniques, such as PCR, can identify rotavirus in stool samples.

**TREATMENT ROTAVIRUS INFECTIONS**

Only supportive treatment is needed. Dehydration can be severe, and IV hydration may be needed in pts with frequent vomiting. Avoid antibiotics and antimotility agents.

### Prevention

Rotavirus vaccines, two of which are available, are included in the routine vaccination schedule for U.S. infants. Vaccination has led to a >70% decline in hospital visits due to rotavirus illness. Notably, the efficacy of rotavirus vaccines is lower (50–65%) in low-resource settings.

## GIARDIASIS

### Microbiology and Epidemiology

*Giardia lamblia* (also known as *G. intestinalis* or *G. duodenalis*) is a protozoal parasite that inhabits the small intestines of humans and other mammals.

- Cysts are ingested from the environment, excyst in the small intestine, and release flagellated trophozoites that remain in the proximal small intestine. Some trophozoites encyst, with the resulting cysts excreted in feces.
- Transmission occurs via the fecal-oral route, by ingestion of contaminated food and water, or from person to person in settings with poor fecal hygiene (e.g., day-care centers, institutional settings). Infection results from as few as 10 cysts.
- Viable cysts can be eradicated from water by either boiling or filtration. Standard chlorination techniques used to control bacteria do not destroy cysts.
- Young pts, newly exposed pts, and pts with hypogammaglobulinemia are at increased risk—a pattern suggesting a role for humoral immunity in resistance.

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## Clinical Manifestations

After an incubation period of 5 days to 3 weeks, the manifestations of infection range from asymptomatic carriage (most common) to fulminant diarrhea and malabsorption.

- Prominent early symptoms include diarrhea, abdominal pain, bloating, belching, flatus, nausea, and vomiting and usually last >1 week. Fever is rare, as is blood or mucus in stool.
- Chronic giardiasis can be continual or episodic; diarrhea may not be prominent, but increased flatulence, sulfurous belching, and weight loss can occur.
- In some cases, disease can be severe, with malabsorption, growth retardation, dehydration, and/or extraintestinal manifestations (e.g., anterior uveitis, arthritis).

## Diagnosis

Giardiasis can be diagnosed by parasite antigen detection in feces, by identification of cysts (oval, with four nuclei) or trophozoites (pear-shaped, flattened parasites with two nuclei and four pairs of flagella) in stool specimens, or by nucleic acid amplification tests. Given variability in cyst excretion, multiple samples may need to be examined.

**TREATMENT GIARDIASIS**

- Cure rates with metronidazole (250 mg tid for 5 days) and albendazole (400 mg/d for 5–10 days) are >90%; tinidazole (2 g PO once) may be more effective. Nitazoxanide (500 mg bid for 3 days) is an alternative agent.
- If symptoms persist, continued infection should be documented before retreatment, and possible sources of reinfection should be sought. Prolonged therapy with metronidazole (750 mg tid for 21 days) has been successful.

# CRYPTOSPORIDIOSIS

## Microbiology and Epidemiology

Cryptosporidial infections are caused by *Cryptosporidium hominis* and *C. parvum*.

- Oocysts are ingested and subsequently excyst, enter intestinal cells, and generate oocysts that are excreted in feces. The 50% infectious dose in immunocompetent individuals is ~132 oocysts.
- Person-to-person transmission of infectious oocysts can occur among close contacts and in day-care settings. Waterborne transmission is common. Oocysts are not killed by routine chlorination.

## Clinical Manifestations

After an incubation period of ~1 week, pts may remain asymptomatic or develop watery, nonbloody diarrhea, occasionally with abdominal pain, nausea, anorexia, fever, and/or weight loss lasting 1–2 weeks. In immunocompromised hosts (particularly those with $CD4^+$ T cell counts <100/μL), diarrhea can be profuse and chronic, resulting in severe dehydration, weight loss, and wasting; the biliary tract can be involved.

## Diagnosis

On multiple days, fecal samples should be examined for oocysts (4–5 μm in diameter, smaller than most parasites). Although conventional stool examination for ova and parasites does not detect *Cryptosporidium*, modified acid-fast staining, direct immunofluorescent techniques, and EIAs can facilitate diagnosis.

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**TREATMENT CRYPTOSPORIDIOSIS**

- Nitazoxanide (500 mg bid for 3 days) is effective for immunocompetent pts but not for HIV-infected pts; improved immune status due to antiretroviral therapy can alleviate symptoms in the latter pts.
- In addition to antiprotozoal agents, supportive measures include replacement of fluid and electrolytes and use of antidiarrheal agents.

### CYSTOISOSPORIASIS

*Cystoisospora belli* (formerly *Isospora belli*) infection is acquired by oocyst ingestion and is most common in tropical and subtropical countries. Acute infection can begin suddenly with fever, abdominal pain, and watery, nonbloody diarrhea and can last for weeks or months. Eosinophilia may occur. Compromised (e.g., HIV-infected) pts may have chronic disease that resembles cryptosporidiosis. Detection of large oocysts (~25 μm) in stool by modified acid-fast staining confirms the diagnosis.

**TREATMENT CYSTOISOSPORIASIS**

- Trimethoprim-sulfamethoxazole (TMP-SMX; 160/800 mg qid for 10 days) is effective in immunocompetent pts.
  - HIV-infected pts should receive prolonged therapy with TMP-SMX (160/800 mg qid for 10 days, followed by 160/800 mg tid for 3 weeks).
  - Pyrimethamine (50–75 mg/d) can be given to pts intolerant of TMP-SMX.
  - Pts with AIDS may need suppressive maintenance therapy (TMP-SMX, 160/800 mg 3 times per week) to prevent relapses.

### CYCLOSPORIASIS

*Cyclospora cayetanensis* can be transmitted through water or food (e.g., basil, raspberries). Clinical manifestations include diarrhea, flulike symptoms, flatulence, and burping. Disease can be self-limited or can persist for >1 month. Diagnosis is made by detection of oocysts (spherical, 8–10 μm) in stool; targeted diagnostic studies must be specifically requested.

**TREATMENT CYCLOSPORIASIS**

TMP-SMX (160/800 mg bid for 7–10 days) is effective. Pts with AIDS may need suppressive maintenance therapy to prevent relapses.

## INFLAMMATORY DIARRHEA

### SALMONELLOSIS

#### Microbiology and Pathogenesis

Salmonellae are facultatively anaerobic gram-negative bacilli that cause infection when between 200 and $10^6$ organisms are ingested.

- Conditions that reduce gastric acidity or intestinal integrity increase susceptibility to infection.
- Organisms penetrate the small-intestinal mucus layer and traverse the intestinal epithelium through M cells overlying Peyer's patches.
  - *S. typhi* and *S. paratyphi* survive within macrophages, then disseminate throughout the body via lymphatics, and ultimately colonize reticuloendothelial tissues.

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– Nontyphoidal salmonellae most commonly cause gastroenteritis, invading the large- and small-intestinal mucosa and resulting in massive PMN infiltration (as opposed to the mononuclear-cell infiltration seen with typhoid fever).

## Epidemiology and Clinical Manifestations

Depending on the specific species, salmonellosis results in typhoid fever or gastroenteritis.

- *Typhoid (enteric) fever:* Typhoid fever is a systemic disease characterized by fever and abdominal pain and caused by dissemination of *S. typhi* or *S. paratyphi*, for which humans are the only hosts.
  - Disease results from ingestion of food or water contaminated by chronic carriers and is rare in developed nations. Worldwide, there are ~27 million cases, with 200,000–600,000 deaths annually.
  - After an incubation period of 5–21 days, prolonged fever (>75% of cases), headache (80%), chills (35–45%), anorexia (55%), and abdominal pain (30–40%) are common. Other signs and symptoms may include sweating, cough, malaise, arthralgias, nausea, vomiting, and diarrhea—or, less often, constipation.
  - Physical findings include *rose spots* (a faint, salmon-colored, blanching, maculopapular rash), hepatosplenomegaly, epistaxis, and relative bradycardia.
  - Intestinal perforation and/or GI hemorrhage can occur in the third and fourth weeks of illness; neurologic manifestations (e.g., meningitis, Guillain-Barré syndrome) occur in 2–40% of pts.
  - Long-term *Salmonella* carriage (i.e., for >1 year) in urine or stool develops in 1–5% of pts.
- *Nontyphoidal salmonellosis (NTS)*: Most commonly caused by *S. typhimurium* or *S. enteritidis*, NTS typically presents within 6–48 h of exposure as gastroenteritis (nausea, vomiting, nonbloody diarrhea, abdominal cramping, and fever) that lasts 3–7 days.
  - In the United States, NTS causes ~12 million illnesses annually.
  - Disease is acquired from multiple animal reservoirs. The main mode of transmission is via contaminated food products, such as eggs (*S. enteritidis*), poultry, undercooked meat, dairy products, manufactured or processed foods, and fresh produce. Infection is also acquired during exposure to pets, especially reptiles.
  - Stool cultures remain positive for 4–5 weeks and—in rare cases of chronic carriage—for >1 year.
  - Bacteremia, usually due to *S. choleraesuis* and *S. dublin*, develops in 8% of pts; of these pts, 5–10% develop localized infections (e.g., hepatosplenic abscesses, meningitis, pneumonia, osteomyelitis).
  - Reactive arthritis can follow *Salmonella* gastroenteritis, particularly in persons with the HLA-B27 histocompatibility antigen.

## Diagnosis

Positive cultures of blood, stool, or other specimens are required for diagnosis.

### TREATMENT SALMONELLOSIS

- *Typhoid fever*: A fluoroquinolone (e.g., ciprofloxacin, 500 mg PO bid for 5–7 days) is most effective against susceptible organisms.
  - Pts infected with nalidixic acid–resistant strains (whose susceptibility to ciprofloxacin is reduced) should be treated with ceftriaxone (2 g/d IV for 10–14 days), azithromycin (1 g/d PO for 5 days), or high-dose ciprofloxacin (750 mg PO bid or 400 mg IV q8h for 10–14 days).
  - Dexamethasone may be of benefit in severe cases.

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- *NTS*: Antibiotic treatment is not recommended in most cases as it does not shorten the duration of symptoms and is associated with increased rates of relapse, a prolonged carrier state, and adverse drug reactions.
  - Antibiotic treatment may be required for infants ≤3 months of age; pts >50 years of age with suspected atherosclerosis; pts with immunosuppression; pts with cardiac, valvular, or endovascular abnormalities; and pts with significant joint disease.
  - Fluoroquinolones or third-generation cephalosporins are given for 3–7 days or until defervescence (if the pt is immunocompetent) or for 1–2 weeks (if the pt is immunocompromised).
  - HIV-infected pts are at high risk for *Salmonella* bacteremia and should receive 4 weeks of oral fluoroquinolone therapy after 1–2 weeks of IV treatment. In cases of relapse, long-term suppression with a fluoroquinolone or TMP-SMX should be considered.
  - Pts with endovascular infections or endocarditis should receive 6 weeks of treatment with a third-generation cephalosporin.

## CAMPYLOBACTERIOSIS

### Microbiology

Campylobacters are motile, curved gram-negative rods that are a common bacterial cause of gastroenteritis in the United States. Most cases are caused by *C. jejuni*.

### Epidemiology

Campylobacters are common commensals in the GI tract of many food animals and household pets. In developed countries, ingestion of contaminated poultry accounts for 30–70% of cases. Transmission to humans occurs via contact with or ingestion of raw or undercooked food products or direct contact with infected animals.

### Clinical Manifestations

An incubation period of 2–4 days (range, 1–7 days) is followed by a prodrome of fever, headache, myalgia, and/or malaise. Within the next 12–48 h, diarrhea (with stools containing blood, mucus, and leukocytes), cramping abdominal pain, and fever develop.

- Most cases are self-limited, but illness persists for >1 week in 10–20% of pts and may be confused with inflammatory bowel disease.
- Species other than *C. jejuni* (e.g., *C. fetus*) can cause a similar illness in normal hosts or prolonged relapsing systemic disease without a primary focus in immunocompromised pts.
  - The course may be fulminant, with bacterial seeding of many organs, particularly vascular sites.
  - Fetal death can result from infection in a pregnant pt.
- Three patterns of extraintestinal infection have been noted: (1) transient bacteremia in a normal host with enteritis (benign course, no specific treatment needed); (2) sustained bacteremia or focal infection in a normal host; and (3) sustained bacteremia or focal infection in a compromised host.
- Complications include reactive arthritis (particularly in persons with the HLA-B27 phenotype) and Guillain-Barré syndrome (in which campylobacters are associated with 20–40% of cases).

### Diagnosis

The diagnosis is confirmed by cultures of stool, blood, or other specimens on special media and/or with selective techniques.

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**TREATMENT CAMPYLOBACTERIOSIS**

- Fluid and electrolyte replacement is the mainstay of therapy.
- Use of antimotility agents is not recommended, as they are associated with toxic megacolon.
- Antibiotic treatment (erythromycin, 250 mg PO qid for 5–7 days) should be reserved for pts with high fever, bloody or severe diarrhea, persistence for >1 week, and worsening of symptoms. Azithromycin and fluoroquinolones are alternative regimens, although resistance to fluoroquinolones is increasing.

## SHIGELLOSIS AND INFECTION WITH SHIGA TOXIN–PRODUCING/ENTEROHEMORRHAGIC/SHIGA TOXIN–PRODUCING ENTEROAGGREGATIVE *E. COLI* (STEC/EHEC/STEAEC)

### Microbiology and Epidemiology

Shigellae are small, gram-negative, nonmotile bacilli that are very closely related to *E. coli*. The four most common *Shigella* serotypes are *S. dysenteriae* type 1, *S. flexneri*, *S. boydii*, and *S. sonnei* (which is more prevalent in the industrialized world). Humans are the major reservoir, but *Shigella* can be found in other higher primates and STEC/EHEC in cows.

- Person-to-person spread via the fecal-oral route is most common for *Shigella* (and occasionally STEC/EHEC/STEAEC); ingestion of contaminated food and water is the more common route of transmission of STEC/EHEC/STEAEC (and occasionally *Shigella*).
- The ability of as few as 100 organisms to cause infection helps explain the high rate of secondary household transmission.
- Shiga toxin and Shiga-like toxins produced by some strains of *E. coli* (including O157:H7) are important factors in disease severity. The toxins target endothelial cells and play a significant role in the microangiopathic complications of *Shigella* and *E. coli* infections, such as hemolytic-uremic syndrome (HUS; i.e., Coombs-negative hemolytic anemia, thrombocytopenia, and acute renal failure) and thrombotic thrombocytopenic purpura.
- An analysis of *Shigella* cases occurring in 1966–1997 revealed an annual incidence of 165 million cases (of which 69% affected children <5 years of age) with 0.5–1.1 million deaths; these numbers have likely decreased since then, but multidrug-resistant strains have emerged.

### Clinical Manifestations

After an incubation period of 1–4 days, shigellosis evolves through three phases: watery diarrhea, dysentery (bloody mucopurulent stools), and the postinfectious phase.

- Most episodes resolve in 1 week without treatment; with appropriate treatment, recovery takes place within a few days, with no sequelae.
- Complications are largely intestinal (e.g., toxic megacolon, intestinal perforation, rectal prolapse) or metabolic (e.g., hypoglycemia, hyponatremia). Shiga toxin produced by *S. dysenteriae* type 1 is linked to HUS in developing countries but is rare in industrialized countries, where *E. coli* O157:H7 is a more common cause.

### Diagnosis

Shigellosis is diagnosed directly by stool culture. STEC/EHEC infection is diagnosed by simultaneous culture (assaying for *E. coli* strains that do not ferment sorbitol, with subsequent serotyping for O157) and assay for the detection of Shiga toxin (which can rapidly detect non-O157 STEC/EHEC and sorbitol-fermenting strains of O157:H7).

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**TREATMENT SHIGELLOSIS AND INFECTION WITH STEC/EHEC**

- In the United States, because of the ready transmissibility of *Shigella*, antibiotics are recommended. Fluoroquinolones (e.g., ciprofloxacin, 500 mg bid) are effective, as are ceftriaxone, azithromycin, pivmecillinam, and some fifth-generation quinolones.
  - *S. dysenteriae* infection should be treated for 5 days and non-*dysenteriae Shigella* infection for 3 days.
  - Immunocompromised pts should receive 7–10 days of treatment.
- Antibiotic treatment for STEC/EHEC infections should be avoided, since antibiotics may increase the incidence of HUS.
- Rehydration usually is not needed; *Shigella* infection rarely causes significant dehydration. If required, rehydration should be oral, and nutrition should be started as soon as possible. Use of antimotility agents may prolong fever and increase the risk of HUS and toxic megacolon.

## YERSINIOSIS

### Microbiology and Clinical Manifestations

*Y. enterocolitica* and *Y. pseudotuberculosis* are nonmotile gram-negative rods that cause enteritis or enterocolitis with self-limited diarrhea that lasts an average of 2 weeks as well as mesenteric adenitis (especially common with *Y. pseudotuberculosis*) and terminal ileitis (especially common with *Y. enterocolitica*), either of which can resemble acute appendicitis. Septicemia can occur in pts with chronic liver disease, malignancy, diabetes mellitus, and other underlying illnesses. Infection has been linked to reactive arthritis in HLA-B27-positive pts.

### Diagnosis

Stool culture studies for *Yersinia* must be specifically requested and require the use of special media.

**TREATMENT YERSINIOSIS**

Antibiotics are not indicated for diarrhea caused by yersiniae; supportive measures suffice.

## AMEBIASIS

### Microbiology and Epidemiology

*Entamoeba histolytica*, the cause of amebiasis, infects ~10% of the world's population and is the third most common cause of death from parasitic disease (after schistosomiasis and malaria). Infection follows ingestion of cysts from fecally contaminated water, food, or hands. Motile trophozoites are released from cysts in the small intestine and then cause infection in the large bowel. Trophozoites may be shed in stool (in active dysentery) or encyst. Excreted cysts survive for weeks in a moist environment.

### Clinical Manifestations

Most pts harboring *Entamoeba* species are asymptomatic, but some pts develop inflammatory colitis 2–6 weeks after ingestion of amebic cysts.

- Dysentery may develop, with daily passage of 10–12 small stools consisting mostly of blood and mucus. Fewer than 40% of pts have fever.
- Fulminant amebic colitis—characterized by more profuse diarrhea, severe abdominal pain with peritoneal signs, and fever—is more common among children.
- Liver abscess is the most common type of extraintestinal infection and can arise months after exposure to *E. histolytica*. Pts present with RUQ pain, fever, right-sided pleural

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effusion, and hepatic tenderness and typically do not have active colitis. The abscess can rupture through the diaphragm and metastasize elsewhere (e.g., lung, heart).

### Diagnosis

Microscopic examination of three stool samples, often combined with serologic testing, remains the standard diagnostic approach.

- Up to 10% of pts with acute amebic liver abscess may have negative serologies; testing should be repeated in 1 week if clinical suspicion remains high.

**TREATMENT AMEBIASIS**

- Tinidazole (2 g/d PO for 3 days) or metronidazole (750 mg PO or IV tid for 5–10 days) is recommended for amebic colitis and amebic liver abscess.
  - Within 3 days of treatment initiation, >90% of pts respond clinically.
  - Drainage of liver abscesses is rarely needed. Indications for aspiration include the need to rule out pyogenic abscess, a lack of response to treatment in 3–5 days, an imminent threat of liver-abscess rupture, or the need to prevent left-lobe abscess rupture into the pericardium.
- Pts with either colitis or liver abscesses should also receive a luminal agent to ensure eradication of the infection. Paromomycin (500 mg PO tid for 10 days) is the preferred agent; iodoquinol (650 mg PO tid for 20 days) is an alternative.

## *CLOSTRIDIUM DIFFICILE* INFECTION (CDI)

### Microbiology and Epidemiology

*C. difficile* is an obligately anaerobic, gram-positive, spore-forming bacillus and causes diarrheal illness that is most commonly acquired in the hospital. The disease is acquired almost exclusively in association with antimicrobial treatment; virtually all antibiotics carry a risk of CDI.

- After *C. difficile* colonizes the gut, its spores vegetate, multiply, and secrete toxin A (an enterotoxin) and toxin B (a cytotoxin), causing diarrhea and pseudomembranous colitis. The rate of fecal colonization is often ≥20% among adult pts hospitalized for >1 week; in contrast, the rate is 1–3% among community residents.
- Spores can persist on environmental surfaces in the hospital for months and on the hands of hospital personnel who do not practice adequate hand hygiene.
- Rates and severity of CDI in the United States, Canada, and Europe have increased markedly in the past decade. The epidemic NAP1/BI/027 strain accounts for much of the increase and is characterized by production of 16–23 times as much toxin A and toxin B as is documented for control strains, by the presence of a third toxin (binary toxin), and by high-level resistance to fluoroquinolones.

### Clinical Manifestations

Most commonly, pts develop diarrhea, with stools that are not grossly bloody and are soft to watery, with a characteristic odor. Pts may have up to 20 bowel movements per day. Fever, abdominal pain, and leukocytosis are common.

- Constipation due to an adynamic ileus can occur. Unexplained leukocytosis (≥15,000 WBCs/μL) in this setting should prompt evaluation for CDI. These pts are at high risk for complications such as toxic megacolon and sepsis.
- *C. difficile* diarrhea recurs after treatment in ~15–30% of cases.

### Diagnosis

CDI is diagnosed in a pt with diarrhea (≥3 unformed stools per 24 h for ≥2 days) by detection of the organism, toxin A, or toxin B in stool or identification of pseudomembranes in the colon.

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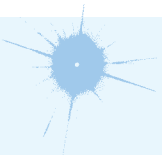
- Most laboratory tests for toxin (e.g., ELISAs) lack sensitivity, but repeat testing is not recommended. PCR assays are rapid, sensitive, and highly specific.
- Testing of asymptomatic pts (including a test of cure for those who have completed therapy) is not recommended.

## TREATMENT *C. DIFFICILE* INFECTION

- *Primary CDI:* When feasible, discontinuation of ongoing antimicrobial treatment is an effective cure in 15–23% of cases. Prompt initiation of specific therapy is recommended.
  - For mild to moderate disease, metronidazole (500 mg tid for 10 days) is recommended, with extension of therapy if the clinical response is slow.
  - For severe disease (e.g., >15,000 WBCs/μL, serum creatinine levels ≥1.5 times baseline), vancomycin (125 mg qid PO for 10–14 d) is the agent of choice. Fidaxomicin is an alternative and results in lower rates of recurrent disease.
- *Recurrent CDI:* The first recurrence should be treated the same as the initial episode.
  - For the second recurrence, an extended, tapered vancomycin regimen (125 mg qid for 10–14 d, then bid for 1 week, then daily for 1 week, then q2–3d for 2–8 weeks) should be used.
  - For multiple recurrences, there is no standard treatment course. Consider repetition of the tapered vancomycin regimen, administration of vancomycin (500 mg qid for 10 days) with *Saccharomyces boulardii* (500 mg bid for 28 d), administration of sequential therapy with vancomycin (125 mg qid for 10–14 d) followed by rifaximin (400 mg bid for 2 weeks), treatment with nitazoxanide (500 mg bid for 10 d), or treatment with IV immunoglobulin (400 mg/kg). On the basis of recent successful clinical trials, fecal transplantation is increasingly being used for recurrent CDI.
- *Fulminant CDI:* Medical management is complicated by ineffective delivery of oral antibiotics to the intestinal lumen in the setting of ileus. Vancomycin (given via nasogastric tube and by retention enema) combined with IV metronidazole has been used with some success, as has IV tigecycline. Surgical colectomy can be life-saving.



For a more detailed discussion, see LaRocque RC, Ryan ET, Calderwood SB: Acute Infectious Diarrheal Diseases and Bacterial Food Poisoning, Chap. 160, p. 852; Gerding DN, Johnson S: *Clostridium difficile* Infection, Including Pseudomembranous Colitis, Chap. 161, p. 857; Russo TA, Johnson JR: Diseases Caused by Gram-Negative Enteric Bacilli, Chap. 186, p. 1025; Pegues DA, Miller SI: Salmonellosis, Chap. 190, p. 1049; Sansonetti PJ, Bergounioux J: Shigellosis, Chap. 191, p. 1055; Blaser MJ: Infections Due to *Campylobacter* and Related Organisms, Chap. 192, p. 1058; Waldor MK, Ryan ET: Cholera and Other Vibrioses, Chap. 193, p. 1061; Prentice MB: Plague and Other *Yersinia* Infections, Chap. 196, p. 1070; Parashar UD, Glass RI: Viral Gastroenteritis, Chap. 227, p. 1285; Andrade M, Reed SL: Amebiasis and Infection with Free-Living Amebas, Chap. 247, p. 1363; and Weller PF: Protozoal Intestinal Infections and Trichomoniasis, Chap. 254, p. 1405, in HPIM-19.

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# 83 Sexually Transmitted and Reproductive Tract Infections

## GENERAL PRINCIPLES

- Worldwide, most adults acquire at least one sexually transmitted infection (STI).
- Three factors determine the initial rate of spread of any STI within a population: rate of sexual exposure of susceptible to infectious people, efficiency of transmission per exposure, and duration of infectivity of those infected.
- STI care and management begin with risk assessment and proceed to clinical assessment, diagnostic testing or screening, syndrome-based treatment to cover the most likely causes, and prevention and control. The "4 C's" of control are *c*ontact tracing, ensuring *c*ompliance with treatment, and *c*ounseling on risk reduction, including *c*ondom promotion and provision.

## SPECIFIC SYNDROMES

### URETHRITIS IN MEN

#### Microbiology and Epidemiology

Most cases are caused by either *Neisseria gonorrhoeae* or *Chlamydia trachomatis*. Other causative organisms include *Mycoplasma genitalium*, *Ureaplasma urealyticum*, *Trichomonas vaginalis*, and HSV. *Chlamydia* causes 30–40% of nongonococcal urethritis (NGU) cases. *M. genitalium* is the probable cause in many *Chlamydia*-negative cases of NGU.

#### Clinical Manifestations

Urethritis in men produces urethral discharge, dysuria, or both, usually without frequency of urination.

#### Diagnosis

Pts present with a mucopurulent urethral discharge that can usually be expressed by milking of the urethra; alternatively, a Gram's-stained smear of an anterior urethral specimen containing ≥5 PMNs/1000× field confirms the diagnosis.

- Centrifuged sediment of the day's first 20–30 mL of voided urine can be examined instead.
- *N. gonorrhoeae* can be presumptively identified if intracellular gram-negative diplococci are present in Gram's-stained samples.
- Early-morning, first-voided urine should be used in "multiplex" nucleic acid amplification tests (NAATs) for *N. gonorrhoeae* and *C. trachomatis*.

**TREATMENT** URETHRITIS IN MEN

- Treatment should be given promptly, while test results are pending.
  - Unless these diseases have been excluded, gonorrhea is treated with a single dose of ceftriaxone (250 mg IM) plus azithromycin (1 g PO once), and *Chlamydia* infection is treated with azithromycin (1 g PO once) or doxycycline (100 mg bid for 7 days); azithromycin may be more effective for *M. genitalium*.
  - Sexual partners of the index case should receive the same treatment.
- For recurrent symptoms: With re-exposure, both pt and partner are re-treated. Without re-exposure, infection with *T. vaginalis* (with culture or NAATs of a

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urethral swab and early-morning, first-voided urine) or doxycycline-resistant *M. genitalium* or *Ureaplasma* should be considered; treatment with metronidazole or tinidazole (a single PO dose of 2 g) plus azithromycin (1 g PO once) is recommended, and the azithromycin component is especially important if this drug was not used for the primary episode.

## EPIDIDYMITIS

### Microbiology

In sexually active men <35 years old, epididymitis is caused most frequently by *C. trachomatis* and less commonly by *N. gonorrhoeae*.

- In older men or after urinary tract instrumentation, urinary pathogens are most common.
- In men who practice insertive rectal intercourse, Enterobacteriaceae may be responsible.

### Clinical Manifestations

Acute epididymitis—almost always unilateral—produces pain, swelling, and tenderness of the epididymis, with or without symptoms or signs of urethritis. Epididymitis must be differentiated from testicular torsion, tumor, and trauma. If symptoms persist after treatment, a testicular tumor or a chronic granulomatous disease (e.g., tuberculosis) should be considered.

**TREATMENT EPIDIDYMITIS**

- Ceftriaxone (250 mg IM once) followed by doxycycline (100 mg PO bid for 10 days) is effective for epididymitis due to *C. trachomatis* or *N. gonorrhoeae*.
- Oral cephalosporins and fluoroquinolones are no longer recommended because of increasing resistance in *N. gonorrhoeae*.
- If Enterobacteriaceae are suspected as the cause and such organisms are detected in a urine culture, levofloxacin (500 mg PO daily for 10 days) can be used.

## URETHRITIS (THE URETHRAL SYNDROME) IN WOMEN

### Microbiology and Clinical Manifestations

*C. trachomatis*, *N. gonorrhoeae*, and occasionally HSV cause symptomatic urethritis—known as *the urethral syndrome* in women—that is characterized by "internal" dysuria (usually without urinary urgency or frequency), pyuria, and an absence of *Escherichia coli* and other uropathogens at counts $\geq 10^2$/mL in urine.

### Diagnosis

Specific tests (e.g., NAATs of vaginal secretions collected with a swab) are used to evaluate for infection with *N. gonorrhoeae* or *C. trachomatis*.

**TREATMENT URETHRITIS (THE URETHRAL SYNDROME) IN WOMEN**

See "Urethritis in Men," above.

## VULVOVAGINAL INFECTIONS

### Microbiology

A variety of organisms are associated with vulvovaginal infections, including *N. gonorrhoeae* and *C. trachomatis* (particularly when they cause cervicitis), *T. vaginalis*, *Candida albicans*, *Gardnerella vaginalis*, and HSV.

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## Clinical Manifestations

Vulvovaginal infections encompass a wide array of specific conditions, each of which has different presenting symptoms.

- Unsolicited reporting of abnormal vaginal discharge suggests trichomoniasis or bacterial vaginosis (BV).
  - *Trichomoniasis* is characterized by vulvar irritation and a profuse white or yellow, homogeneous vaginal discharge with a pH that is typically ≥5.
  - *BV* is characterized by vaginal malodor and a slight to moderate increase in white or gray, homogeneous vaginal discharge that uniformly coats the vaginal walls and typically has a pH >4.5.
  - Vaginal trichomoniasis and BV early in pregnancy are associated with premature onset of labor.
- Vulvar conditions such as genital herpes or vulvovaginal candidiasis can cause vulvar pruritus, burning, irritation, or lesions as well as external dysuria (as urine passes over the inflamed vulva or areas of epithelial disruption) or vulvar dyspareunia.

## Diagnosis

Evaluation of vulvovaginal symptoms includes a pelvic examination (with a speculum examination) and simple rapid diagnostic tests.

- Abnormal vaginal discharge is assessed for pH, a fishy odor after mixing with 10% KOH (BV), evidence on microscopy of motile trichomonads and/or clue cells of BV (vaginal epithelial cells coated with coccobacillary organisms) when the specimen is mixed with saline, or hyphae or pseudohyphae on microscopy when 10% KOH is added (vaginal candidiasis).
- A DNA probe test (the Affirm test) can detect *T. vaginalis*, *C. albicans*, and increased concentrations of *G. vaginalis*. A NAAT for *T. vaginalis* is available.

### TREATMENT VULVOVAGINAL INFECTIONS

- *Vulvovaginal candidiasis:* Miconazole (a single 1200-mg vaginal suppository), clotrimazole (two 100-mg vaginal tablets daily for 3 days), or fluconazole (150 mg PO once) are all effective.
- *Trichomoniasis:* Metronidazole (2 g PO once) or tinidazole is effective. Treatment of sexual partners with the same regimen reduces the risk of reinfection and is the standard of care.
- *BV:* Metronidazole (500 mg PO bid for 7 days), 2% clindamycin cream (one full applicator vaginally each night for 7 days), or 0.75% metronidazole gel (one full applicator vaginally bid for 5 days) is effective, but recurrence is common regardless of the regimen used.

# MUCOPURULENT CERVICITIS

## Microbiology

*N. gonorrhoeae*, *C. trachomatis*, and *M. genitalium* are the primary causes of mucopurulent cervicitis. Of note, NAATs for these pathogens, HSV, and *T. vaginalis* have been negative in nearly half of cases.

## Clinical Manifestations

Mucopurulent cervicitis represents the "silent partner" of urethritis in men and results from inflammation of the columnar epithelium and subepithelium of the endocervix.

## Diagnosis

Yellow mucopurulent discharge from the cervical os, with ≥20 PMNs/1000× field on Gram's stain of cervical mucus, indicates endocervicitis. The presence of intracellular

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gram-negative diplococci on Gram's stain of cervical mucus is specific but <50% sensitive for gonorrhea; thus NAATs for *N. gonorrhoeae* and *C. trachomatis* are always indicated.

**TREATMENT MUCOPURULENT CERVICITIS**

See "Urethritis in Men," above.

## PELVIC INFLAMMATORY DISEASE (PID)

### Microbiology

The agents most often implicated in acute PID—infection that ascends from the cervix or vagina to the endometrium and/or fallopian tubes—include the primary causes of endocervicitis (e.g., *N. gonorrhoeae* and *C. trachomatis*); other organisms (e.g., *M. genitalium*, *Prevotella* spp., peptostreptococci, *E. coli, Haemophilus influenzae*, and group B streptococci) account for 25–33% of cases.

### Epidemiology

In 2011, there were 90,000 visits to physicians' offices for PID in the United States; there are ~70,000–100,000 hospitalizations related to PID annually.

- Risk factors for PID include cervicitis, BV, a history of salpingitis or recent vaginal douching, menstruation, and recent insertion of an intrauterine contraceptive device (IUD).
- Oral contraceptive pills decrease risk.

### Clinical Manifestations

The presenting symptoms depend on the extent to which the infection has spread.

- *Endometritis:* Pts present with midline abdominal pain and abnormal vaginal bleeding. Lower-quadrant, adnexal, or cervical motion or abdominal rebound tenderness is less severe in women with endometritis alone than in women who also have salpingitis.
- *Salpingitis:* Symptoms evolve from mucopurulent cervicitis to endometritis and then to bilateral lower abdominal and pelvic pain caused by salpingitis. Nausea, vomiting, and increased abdominal tenderness may occur if peritonitis develops.
- *Perihepatitis* (Fitz-Hugh–Curtis syndrome): 3–10% of women present with pleuritic upper abdominal pain and tenderness in the RUQ due to perihepatic inflammation. Most cases are due to chlamydial salpingitis.
- *Periappendicitis:* ~5% of pts can have appendiceal serositis without involvement of the intestinal mucosa as a result of gonococcal or chlamydial salpingitis.

### Diagnosis

Speculum examination shows evidence of mucopurulent cervicitis in the majority of pts with gonococcal or chlamydial PID; cervical motion tenderness, uterine fundal tenderness, and/or abnormal adnexal tenderness also is usually present. Vaginal or endocervical swab specimens should be examined by NAATs for *N. gonorrhoeae* and *C. trachomatis*.

**TREATMENT PELVIC INFLAMMATORY DISEASE**

- Empirical treatment for PID should be initiated in sexually active young women and in other women who are at risk for PID and who have pelvic or lower abdominal pain with no other explanation as well as cervical motion, uterine, or adnexal tenderness.
- Hospitalization should be considered when (1) the diagnosis is uncertain and surgical emergencies cannot be excluded, (2) the pt is pregnant, (3) pelvic

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abscess is suspected, (4) severe illness precludes outpatient management, (5) the pt has HIV infection, (6) the pt is unable to follow or tolerate an outpatient regimen, or (7) the pt has failed to respond to outpatient therapy.

- *Outpatient regimen*: Ceftriaxone (250 mg IM once) plus doxycycline (100 mg PO bid for 14 days) plus metronidazole (500 mg PO bid for 14 days) is effective. Women treated as outpatients should be clinically reevaluated within 72 h.
- *Parenteral regimens*: Parenteral treatment with the two regimens listed below should be given for ≥48 h after clinical improvement. A 14-day course should be completed with doxycycline (100 mg PO bid); if the clindamycin-containing regimen is used, this drug can be given by the oral route (450 mg PO qid).
  - Cefotetan (2 g IV q12h) or cefoxitin (2 g IV q6h) plus doxycycline (100 mg IV/PO q12h)
  - Clindamycin (900 mg IV q8h) plus gentamicin (loading dose of 2.0 mg/kg IV/IM followed by 1.5 mg/kg q8h)
- Male sex partners should be evaluated and treated empirically for gonorrhea and chlamydial infection.

## Prognosis

Late sequelae include infertility (11% after one episode of PID, 23% after two, and 54% after three or more); ectopic pregnancy (sevenfold increase in risk); chronic pelvic pain; and recurrent salpingitis.

# ULCERATIVE GENITAL LESIONS

The most common etiologies for ulcerative genital lesions in the United States are genital herpes, syphilis, and chancroid. See Table 83-1 and the sections on individual pathogens below for specific clinical manifestations. Pts with persistent genital ulcers that do not resolve with syndrome-based antimicrobial therapy should have their HIV serologic status assessed if such testing has not previously been performed. Immediate treatment (before all test results are available) is often appropriate to improve response, reduce transmission, and cover pts who might not return for follow-up visits.

# PROCTITIS, PROCTOCOLITIS, ENTEROCOLITIS, AND ENTERITIS

## Microbiology and Epidemiology

Acquisition of HSV, *N. gonorrhoeae*, or *C. trachomatis* (including lymphogranuloma venereum [LGV] strains of *C. trachomatis*) during receptive anorectal intercourse causes most cases of infectious proctitis in women and in men who have sex with men (MSM). Sexually acquired proctocolitis is most often due to *Campylobacter* or *Shigella* spp. In MSM without HIV infection, enteritis is often attributable to *Giardia lamblia*.

## Clinical Manifestations

Anorectal pain and mucopurulent, bloody rectal discharge suggest proctitis or proctocolitis. Proctitis is more likely to cause tenesmus and constipation, whereas proctocolitis and enteritis more often cause diarrhea.

- HSV proctitis and LGV proctocolitis can cause severe pain, fever, and systemic manifestations.
- Sacral nerve root radiculopathy, with urinary retention or anal sphincter dysfunction, is associated with primary HSV infection.

## Diagnosis

Pts should undergo anoscopy to examine the rectal mucosa and exudates and to obtain specimens for diagnosis.

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**TABLE 83-1 CLINICAL FEATURES OF GENITAL ULCERS**

| Feature | Syphilis | Herpes | Chancroid | Lymphogranuloma Venereum | Donovanosis |
|---|---|---|---|---|---|
| Incubation period | 9–90 days | 2–7 days | 1–14 days | 3 days–6 weeks | 1–4 weeks (up to 6 months) |
| Early primary lesions | Papule | Vesicle | Pustule | Papule, pustule, or vesicle | Papule |
| No. of lesions | Usually one | Multiple | Usually multiple, may coalesce | Usually one; often not detected, despite lymphadenopathy | Variable |
| Diameter | 5–15 mm | 1–2 mm | Variable | 2–10 mm | Variable |
| Edges | Sharply demarcated, elevated, round, or oval | Erythematous | Undermined, ragged, irregular | Elevated, round, or oval | Elevated, irregular |
| Depth | Superficial or deep | Superficial | Excavated | Superficial or deep | Elevated |
| Base | Smooth, nonpurulent, relatively nonvascular | Serous, erythematous, nonvascular | Purulent, bleeds easily | Variable, nonvascular | Red and velvety, bleeds readily |
| Induration | Firm | None | Soft | Occasionally firm | Firm |
| Pain | Uncommon | Frequently tender | Usually very tender | Variable | Uncommon |
| Lymphadenopathy | Firm, nontender, bilateral | Firm, tender, often bilateral with initial episode | Tender, may suppurate, loculated, usually unilateral | Tender, may suppurate, loculated, usually unilateral | None; pseudobuboes |

***Source:*** From RM Ballard, in KK Holmes et al (eds): *Sexually Transmitted Diseases*, 4th ed. New York, McGraw-Hill, 2008.

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**TREATMENT** PROCTITIS, PROCTOCOLITIS, ENTEROCOLITIS, ENTERITIS

- Pending test results, pts should receive empirical treatment for gonorrhea and chlamydial infection with ceftriaxone (250 mg IM once) followed by doxycycline (100 mg bid for 7 days); therapy for syphilis or herpes should be given as indicated.
- If LGV proctitis is proven or suspected, doxycycline (100 mg PO bid for 21 days) should be given.

## INDIVIDUAL PATHOGENS

### GONORRHEA

#### Microbiology

*N. gonorrhoeae*, the causative agent of gonorrhea, is a gram-negative, nonmotile, non-spore-forming organism that grows singly and in pairs (i.e., as diplococci).

#### Epidemiology

The ~311,000 cases reported in the United States in 2012 probably represent only half the true number of cases because of underreporting, self-treatment, and nonspecific treatment without a laboratory diagnosis.

- 60% of reported cases in the United States occur in 15- to 19-year-old women and 20- to 24-year-old men.
- Gonorrhea is transmitted from males to females more efficiently than in the opposite direction, with 50–70% of women acquiring gonorrhea during a single unprotected sexual encounter with an infected man. Roughly two-thirds of all infected men are asymptomatic.
- Drug-resistant strains are widespread. Penicillin, ampicillin, and tetracycline are no longer reliable therapeutic agents, and oral cephalosporins and fluoroquinolones are no longer routinely recommended. In addition, strains highly resistant to ceftriaxone have been isolated in Japan and some European countries.

#### Clinical Manifestations

Except in disseminated disease, the sites of infection typically reflect areas involved in sexual contact.

- *Urethritis* and *cervicitis* have an incubation period of 2–7 days and ~10 days, respectively. See above for details.
- *Anorectal gonorrhea* can cause acute proctitis in women (due to the spread of cervical exudate to the rectum) and MSM.
- *Pharyngeal gonorrhea* is usually mild or asymptomatic and results from oral–genital sexual exposure (typically fellatio). Pharyngeal infection almost always coexists with genital infection, resolves spontaneously, and is rarely transmitted to sexual contacts.
- *Ocular gonorrhea* is typically caused by autoinoculation and presents as a markedly swollen eyelid, hyperemia, chemosis, and profuse purulent discharge.
- *Gonorrhea in pregnancy* can have serious consequences for both the mother and the infant.
  - Salpingitis and PID are associated with fetal loss.
  - Third-trimester disease can cause prolonged rupture of membranes, premature delivery, chorioamnionitis, funisitis, and neonatal sepsis.
  - *Ophthalmia neonatorum*, the most common form of gonorrhea among neonates, is preventable by prophylactic ophthalmic ointments (e.g., containing erythromycin or tetracycline), but treatment requires systemic antibiotics.
- *Gonococcal arthritis* results from dissemination of organisms due to gonococcal bacteremia. Pts present during a bacteremic phase (relatively uncommon) or with

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suppurative arthritis involving one or two joints (most commonly the knees, wrists, ankles, and elbows), with tenosynovitis and skin lesions. Menstruation and complement deficiencies of the membrane attack complex (C5–C9) are risk factors for disseminated disease.

## Diagnosis

NAATs, culture, and microscopic examination (for intracellular diplococci) of urogenital samples are used to diagnose gonorrhea; NAAT of urine samples is most sensitive. A single culture of endocervical discharge has a sensitivity of 80–90%.

## TREATMENT GONORRHEA

See Table 83-2.

**TABLE 83-2 RECOMMENDED TREATMENT FOR GONOCOCCAL INFECTIONS: ADAPTED FROM THE 2010 GUIDELINES OF THE CENTERS FOR DISEASE CONTROL AND PREVENTION**

| Diagnosis | Treatment of Choice[a] |
|---|---|
| Uncomplicated gonococcal infection of the cervix, urethra, pharynx[b], or rectum | |
| First-line regimen | Ceftriaxone (250 mg IM, single dose)<br>*plus*<br>Treatment for *Chlamydia* if chlamydial infection is not ruled out:<br>Azithromycin (1 g PO, single dose)<br>*or*<br>Doxycycline (100 mg PO bid for 7 days) |
| Alternative regimens[c] | Cefixime (400 mg PO, single dose)<br>*or*<br>Ceftizoxime (500 mg IM, single dose)<br>*or*<br>Cefotaxime (500 mg IM, single dose)<br>*or*<br>Spectinomycin (2 g IM, single dose)[d, e]<br>*or*<br>Cefotetan (1 g IM, single dose) *plus* probenecid (1 g PO, single dose)[d]<br>*or*<br>Cefoxitin (2 g IM, single dose) *plus* probenecid (1 g PO, single dose)[d] |
| Epididymitis | Ceftriaxone (250 mg IM once) *followed by* doxycycline (100 mg PO bid for 10 days) is effective for epididymitis due to *Chlamydia trachomatis* or *Neisseria gonorrhoeae.* |
| Pelvic inflammatory disease | See **Chap. 163 in HPIM-19** |
| Outpatient | Ceftriaxone (250 mg IM once)<br>*plus*<br>Doxycycline (100 mg PO bid for 14 days)<br>*plus*<br>Metronidazole (500 mg PO bid for 14 days) |

(*Continued*)

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**TABLE 83-2 RECOMMENDED TREATMENT FOR GONOCOCCAL INFECTIONS: ADAPTED FROM THE 2010 GUIDELINES OF THE CENTERS FOR DISEASE CONTROL AND PREVENTION (*CONTINUED*)**

| Diagnosis | Treatment of Choice[a] |
|---|---|
| Inpatient | Cefotetan (2 g IV q12h) or cefoxitin (2 g IV q6h)<br>*plus*<br>doxycycline (100 mg IV/PO q12h)<br>*or*<br>Clindamycin (900 mg IV q8h)<br>*plus*<br>gentamicin (loading dose of 2.0 mg/kg IV/IM followed by 1.5 mg/kg q8h) |
| Gonococcal conjunctivitis in an adult | Ceftriaxone (1 g IM, single dose)[f] |
| Ophthalmia neonatorum[g] | Ceftriaxone (25–50 mg/kg IV, single dose, not to exceed 125 mg) |
| Disseminated gonococcal infection[h] | |
| Initial therapy[i] | |
| Pt tolerant of β-lactam drugs | Ceftriaxone (1 g IM or IV q24h; recommended)<br>*or*<br>Cefotaxime (1 g IV q8h)<br>*or*<br>Ceftizoxime (1 g IV q8h) |
| Pts allergic to β-lactam drugs | Spectinomycin (2 g IM q12h)[d] |
| Continuation therapy[i] | Cefixime (400 mg PO bid) |
| Meningitis or endocarditis | Ceftriaxone (1–2 g IV bid) for 10–14 days (meningitis) or ≥4 weeks (endocarditis)[j] |

[a]True failure of treatment with a recommended regimen is rare and should prompt an evaluation for reinfection, infection with a drug-resistant strain, or an alternative diagnosis.
[b]Ceftriaxone is the only agent recommended for treatment of pharyngeal infection.
[c]Persons given an alternative regimen should return for a test of cure targeting the infected anatomic site, with a culture strongly preferred over a NAAT. All positive cultures for test of cure should undergo antimicrobial susceptibility testing.
[d]Spectinomycin, cefotetan, and cefoxitin, which are alternative agents, currently are unavailable or in short supply in the United States.
[e]Spectinomycin may be ineffective for the treatment of pharyngeal gonorrhea.
[f]Plus lavage of the infected eye with saline solution (once).
[g]Ocular neonatal instillation of a prophylactic agent (e.g., 1% silver nitrate eye drops or ophthalmic preparations containing erythromycin or tetracycline) prevents ophthalmia neonatorum but is not effective for its treatment, which requires systemic antibiotics.
[h]Hospitalization is indicated if the diagnosis is uncertain, if the pt has frank arthritis with an effusion, or if the pt cannot be relied on to adhere to treatment.
[i]All initial regimens should be continued for 24–48 h after clinical improvement begins, at which time the switch may be made to an oral agent (e.g., cefixime or a quinolone) if antimicrobial susceptibility can be documented by culture of the causative organism. If no organism is isolated and the diagnosis is secure, then treatment with ceftriaxone should be continued for at least 1 week. Treatment for chlamydial infection (as above) should be given if this infection has not been ruled out.
[j]Hospitalization is indicated to exclude suspected meningitis or endocarditis.

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## INFECTIONS WITH *CHLAMYDIA TRACHOMATIS*

### Microbiology

*C. trachomatis* organisms are obligate intracellular bacteria that are divided into two biovars: trachoma and LGV. The trachoma biovar causes ocular trachoma and urogenital infections; the LGV biovar causes lymphogranuloma venereum.

### Epidemiology

The World Health Organization (WHO) estimates that >106.4 million cases of *C. trachomatis* infection occur annually worldwide; it is the most prevalent of all bacterial STIs. The estimated 2–3 million cases per year that occur in the United States make *C. trachomatis* infection the most commonly reported infectious disease in this country.

### Clinical Manifestations

80–90% of women and >50% of men with *C. trachomatis* genital infections lack symptoms; other pts have very mild symptoms.

- Urethritis, epididymitis, cervicitis, salpingitis, PID, and proctitis are all discussed above.
- Reactive arthritis (conjunctivitis, urethritis or cervicitis, arthritis, and mucocutaneous lesions) occurs in 1–2% of NGU cases, many of which are due to *C. trachomatis*. More than 80% of pts have the HLA-B27 phenotype.
- LGV is an invasive, systemic STI that—in heterosexual individuals—presents most commonly as painful inguinal lymphadenopathy beginning 2–6 weeks after presumed exposure. Progressive periadenitis results in fluctuant, suppurative nodes with development of multiple draining fistulas. Spontaneous resolution occurs after several months. See Table 83-1 for additional clinical details.

### Diagnosis

NAATs of urine or urogenital swabs are the diagnostic tests of choice. Serologic testing may be helpful in the diagnosis of LGV and neonatal pneumonia caused by *C. trachomatis*, but it is not useful in diagnosing uncomplicated urogenital infections.

**TREATMENT** INFECTIONS WITH *CHLAMYDIA TRACHOMATIS*

- See "Specific Syndromes," above.
- LGV should be treated with doxycycline (100 mg PO bid) or erythromycin base (500 mg PO qid) for at least 3 weeks.

## INFECTIONS DUE TO MYCOPLASMAS

### Microbiology and Epidemiology

Mycoplasmas are the smallest free-living organisms known and lack a cell wall. *M. hominis*, *M. genitalium*, *Ureaplasma parvum*, and *U. urealyticum* cause urogenital tract disease. These organisms are commonly present in the vagina of asymptomatic women.

### Clinical Manifestations

Ureaplasmas are a common cause of *Chlamydia*-negative NGU. *M. hominis* and *M. genitalium* are associated with PID; *M. hominis* is implicated in 5–10% of cases of postpartum or postabortal fever.

### Diagnosis

PCR is most commonly used for detection of urogenital mycoplasmas; culture is possible but can be done primarily at reference laboratories. Serologic testing is not helpful.

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## TREATMENT INFECTIONS DUE TO MYCOPLASMAS

Recommendations for treatment of NGU and PID listed above are appropriate for genital mycoplasmas.

## SYPHILIS

### Microbiology and Epidemiology

*Treponema pallidum* subspecies *pallidum*—the cause of syphilis—is a thin, spiral organism with a cell body surrounded by a trilaminar cytoplasmic membrane. Humans are the only natural host, and the organism cannot be cultured in vitro.

- Cases are acquired by sexual contact with infectious lesions (chancre, mucous patch, skin rash, condyloma latum); nonsexual acquisition through close personal contact, infection in utero, blood transfusion, and organ transplantation is less common.
- There are ~12 million new infections per year worldwide.
  - In the United States, 31,575 cases were reported in 2000.
  - The reported cases of primary and secondary syphilis combined (which better indicate disease activity) increased from <6000 in 2000 to >14,000 in 2012, primarily affecting MSM, 20–70% of whom were co-infected with HIV.
- One-third to one-half of sexual contacts of persons with infectious syphilis become infected—a figure that underscores the importance of treating all recently exposed sexual contacts.

### Pathogenesis

*T. pallidum* penetrates intact mucous membranes or microscopic abrasions and, within hours, enters lymphatics and blood to produce systemic infection and metastatic foci. After a median incubation period of ~21 days (range, 2–6 weeks), the primary lesion (chancre) appears at the site of inoculation, persists for 4–6 weeks, and then heals spontaneously. Generalized parenchymal, constitutional, and mucocutaneous manifestations of secondary syphilis appear 6–8 weeks later despite high antibody titers, subsiding in 2–6 weeks. After a latent period, one-third of untreated pts eventually develop tertiary disease (syphilitic gummas, cardiovascular disease, neurologic disease).

### Clinical Manifestations

Syphilis progresses through three phases with distinct clinical presentations.

- *Primary syphilis:* A chancre at the site of inoculation (penis, rectum or anal canal, mouth, cervix, labia) is characteristic but often goes unnoticed. See Table 83-1 for clinical details. Regional adenopathy can persist long after the chancre heals.
- *Secondary syphilis:* The protean manifestations of the secondary stage usually include mucocutaneous lesions and generalized nontender lymphadenopathy.
  - Skin lesions can be subtle but are often pale red or pink, nonpruritic macules that are widely distributed over the trunk and extremities, including the palms and soles.
  - In moist intertriginous areas, papules can enlarge and erode to produce broad, highly infectious lesions called *condylomata lata*.
  - Superficial mucosal erosions (*mucous patches*) and constitutional symptoms (e.g., sore throat, fever, malaise) can occur.
  - Less common findings include hepatitis, nephropathy, arthritis, and ocular findings (e.g., optic neuritis, anterior uveitis, iritis).
- *Latent syphilis:* Pts without clinical manifestations but with positive syphilis serology have latent disease. *Early latent* syphilis is limited to the first year after infection, whereas *late latent* syphilis is defined as that of ≥1 year's (or unknown) duration.

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- *Tertiary syphilis:* The classic forms of tertiary syphilis include neurosyphilis, cardiovascular syphilis, and gummas.
  - *Neurosyphilis* represents a continuum, with asymptomatic disease occurring early after infection and potentially progressing to general paresis and tabes dorsalis. Symptomatic disease has three main presentations, all of which are now rare (except in pts with advanced HIV infection). *Meningeal* syphilis presents as headache, nausea, vomiting, neck stiffness, cranial nerve involvement, seizures, and changes in mental status within 1 year of infection. *Meningovascular* syphilis presents up to 10 years after infection as a subacute encephalitic prodrome followed by a gradually progressive vascular syndrome. *Parenchymatous* involvement presents at 20 years for general paresis and 25–30 years for tabes dorsalis. A general mnemonic for paresis is *p*ersonality, *a*ffect, *r*eflexes (hyperactive), *e*ye (Argyll Robertson pupils, which react to accommodation but not to light), *s*ensorium (illusions, delusions, hallucinations), *i*ntellect (decrease in recent memory and orientation, judgment, calculations, insight), and *s*peech. Tabes dorsalis is a demyelination of posterior columns, dorsal roots, and dorsal root ganglia, with ataxic, wide-based gait and footslap; paresthesia; bladder disturbances; impotence; areflexia; and loss of position, deep pain, and temperature sensations.
  - *Cardiovascular syphilis* develops in ~10% of untreated pts 10–40 years after infection. Endarteritis obliterans of the vasa vasorum providing the blood supply to large vessels results in aortitis, aortic regurgitation, saccular aneurysm, and coronary ostial stenosis.
  - *Gummas* are usually solitary lesions showing granulomatous inflammation with central necrosis. Common sites include the skin and skeletal system; however, any organ (including the brain) may be involved.
- *Congenital syphilis:* Syphilis can be transmitted throughout pregnancy, but fetal disease does not become manifest until after the fourth month of gestation. All pregnant women should be tested for syphilis early in pregnancy.

## Diagnosis

Serologic tests—both nontreponemal and treponemal—are the mainstays of diagnosis; changes in antibody titers can also be used to monitor response to therapy.

- Nontreponemal serologic tests that measure IgG and IgM antibodies to a cardiolipin–lecithin–cholesterol antigen complex (e.g., rapid plasma reagin [RPR], Venereal Disease Research Laboratory [VDRL]) are recommended for screening or for quantitation of serum antibody. After therapy for early syphilis, a persistent fall in titer by ≥4-fold is considered an adequate response.
- Treponemal tests, including the agglutination assay (e.g., the Serodia TP-PA test), the fluorescent treponemal antibody–absorbed (FTA-ABS) test, and treponemal enzyme or chemiluminescence immunoassays (EIAs/CIAs), are used to confirm results from nontreponemal tests and should not be used as a screening test because of high false-positive rates. Results remain positive even after successful treatment.
- LP is recommended for pts with syphilis and neurologic signs or symptoms, an RPR or VDRL titer ≥1:32, or suspected treatment failure and for HIV-infected pts with a $CD4^+$ T cell count <350/μL.
  - CSF exam demonstrates pleocytosis (>5 WBCs/μL) and increased protein levels (>45 mg/dL). A positive CSF VDRL test is specific but not sensitive; an unabsorbed FTA test is sensitive but not specific. A negative unabsorbed FTA test excludes neurosyphilis.
- Pts with syphilis should be evaluated for HIV disease.

## TREATMENT SYPHILIS

- See **Table 83-3** for treatment recommendations.
- The Jarisch-Herxheimer reaction is a dramatic reaction to treatment that is most common with initiation of therapy for primary (~50% of pts) or secondary

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**TABLE 83-3 RECOMMENDATIONS FOR THE TREATMENT OF SYPHILIS[a]**

| Stage of Syphilis | Patients without Penicillin Allergy | Patients with Confirmed Penicillin Allergy[b] |
|---|---|---|
| Primary, secondary, or early latent | *CSF normal or not examined:* Penicillin G benzathine (single dose of 2.4 mU IM)<br>*CSF abnormal:* Treat as neurosyphilis | *CSF normal or not examined:* Tetracycline HCl (500 mg PO qid) or doxycycline (100 mg PO bid) for 2 weeks<br>*CSF abnormal:* Treat as neurosyphilis |
| Late latent (or latent of uncertain duration), cardiovascular, or benign tertiary | *CSF normal or not examined:* Penicillin G benzathine (2.4 mU IM weekly for 3 weeks)<br>*CSF abnormal:* Treat as neurosyphilis | *CSF normal and pt not infected with HIV:* Tetracycline HCl (500 mg PO qid) or doxycycline (100 mg PO bid) for 4 weeks<br>*CSF normal and pt infected with HIV:* Desensitization and treatment with penicillin if compliance cannot be ensured<br>*CSF abnormal:* Treat as neurosyphilis |
| Neurosyphilis (asymptomatic or symptomatic) | Aqueous crystalline penicillin G (18–24 mU/d IV, given as 3–4 mU q4h or continuous infusion) for 10–14 days<br>*or*<br>Aqueous procaine penicillin G (2.4 mU/d IM) *plus* oral probenecid (500 mg qid), both for 10–14 days | Desensitization and treatment with penicillin[c] |
| Syphilis in pregnancy | According to stage | Desensitization and treatment with penicillin |

[a]See text for indications for CSF examination.
[b]Because of the documented presence of macrolide resistance in many *T. pallidum* strains in North America, Europe, and China, azithromycin or other macrolides should be used with caution only when treatment with penicillin or doxycycline is not feasible. Azithromycin should not be used for men who have sex with men or for pregnant women.
[c]Limited data suggest that ceftriaxone (2 g/d either IM or IV for 10–14 days) can be used; however, cross-reactivity between penicillin and ceftriaxone is possible.
***Abbreviations:*** mU, million units.
***Source:*** Adapted from the 2010 Sexually Transmitted Diseases Treatment Guidelines from the Centers for Disease Control and Prevention.

(~90%) syphilis. The reaction is associated with fever, chills, myalgias, tachycardia, headache, tachypnea, and vasodilation. Symptoms subside within 12–24 h without treatment.

- Response to treatment should be monitored by determination of RPR or VDRL titers at 6 and 12 months in primary and secondary syphilis and at 6, 12, and 24 months in tertiary or latent syphilis.

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– HIV-infected pts should undergo repeat serologic testing at 3, 6, 9, 12, and 24 months, irrespective of the stage of syphilis.
– Re-treatment should be considered if serologic responses are not adequate (a persistent antibody fall by ≥4-fold) or if clinical signs persist or recur. For these pts, CSF should be examined, with treatment for neurosyphilis if CSF is abnormal and treatment for late latent syphilis if CSF is normal.
– In treated neurosyphilis, CSF cell counts should be monitored every 6 months until normal. In adequately treated HIV-uninfected pts, an elevated CSF cell count falls to normal in 3–12 months.

## HERPES SIMPLEX VIRUS INFECTIONS

### Microbiology and Epidemiology

HSV is a linear, double-strand DNA virus, with two subtypes (HSV-1 and HSV-2).

- Exposure to HSV at mucosal surfaces or abraded skin sites permits viral entry into cells of the epidermis and dermis, viral replication, entry into neuronal cells, and centrifugal spread throughout the body.
- More than 90% of adults have antibodies to HSV-1 by age 40; 15–20% of the U.S. population has antibodies to HSV-2, with a higher prevalence in low-income countries.
- Unrecognized carriage of HSV-2 and frequent asymptomatic reactivations of virus from the genital tract foster the continued spread of HSV disease.
- Genital lesions caused by HSV-1 have lower recurrence rates in the first year (~55%) than those caused by HSV-2 (~90%).

### Clinical Manifestations

See Table 83-1 for clinical details. First episodes of genital herpes due to HSV-1 and HSV-2 present similarly and can be associated with fever, headache, malaise, and myalgias. More than 80% of women with primary genital herpes have cervical or urethral involvement. Local symptoms include pain, dysuria, vaginal and urethral discharge, and tender inguinal lymphadenopathy.

### Diagnosis

Isolation of HSV in tissue culture or demonstration of HSV antigens or DNA in scrapings from lesions is the most accurate diagnostic method. PCR is increasingly being used for detection of HSV DNA and is more sensitive than culture at mucosal sites. Staining of scrapings from the base of the lesion with Wright's, Giemsa's (Tzanck preparation), or Papanicolaou's stain to detect giant cells or intranuclear inclusions is well described, but most clinicians are not skilled in these techniques, which furthermore do not differentiate between HSV and VZV.

**TREATMENT HSV GENITAL INFECTIONS**

- *First episodes*: Oral acyclovir (400 mg tid), valacyclovir (1 g bid), or famciclovir (250 mg bid) for 7–14 days is effective.
- *Symptomatic recurrent episodes*: Oral acyclovir (800 mg tid for 2 days), valacyclovir (500 mg bid for 3 days), or famciclovir (750 or 1000 mg bid for 1 day, 1500 mg once, or 500 mg stat followed by 250 mg q12h for 3 days) effectively shortens lesion duration.
- *Suppression of recurrent episodes*: Oral acyclovir (400–800 mg bid) or valacyclovir (500 mg qd) is given. Pts with >9 episodes per year should take valacyclovir (1 g qd or 500 mg bid) or famciclovir (250–500 mg bid). Daily valacyclovir appears to be more effective at reducing subclinical shedding than daily famciclovir.

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## CHANCROID (*HAEMOPHILUS DUCREYI* INFECTION)

*H. ducreyi* is the etiologic agent of chancroid, an STI characterized by genital ulceration and inguinal adenitis. In addition to being a cause of morbidity in itself, chancroid increases the efficiency of transmission of and degree of susceptibility to HIV infection. See Table 83-1 for clinical details. Culture of *H. ducreyi* from the lesion confirms the diagnosis; PCR is starting to become available. In the setting of a compatible clinical presentation (including one or more painful genital ulcers) and negative tests for syphilis and HSV infection, a probable diagnosis of chancroid can be made.

**TREATMENT CHANCROID (*HAEMOPHILUS DUCREYI* INFECTION)**

- Regimens recommended by the Centers for Disease Control and Prevention (CDC) include azithromycin (1 g PO once), ciprofloxacin (500 mg PO bid for 3 days), ceftriaxone (250 mg IM once), and erythromycin base (500 mg tid for 1 week).
- Sexual partners within 10 days preceding the pt's onset of symptoms should be identified and treated, regardless of symptoms.

## DONOVANOSIS (*KLEBSIELLA GRANULOMATIS* INFECTION)

### Microbiology and Epidemiology

Also known as *granuloma inguinale*, donovanosis is caused by *K. granulomatis*. The infection is endemic in Papua New Guinea, parts of southern Africa, India, the Caribbean, French Guyana, Brazil, and Aboriginal communities in Australia; few cases are reported in the United States.

### Clinical Manifestations

See Table 83-1 for clinical details. Four types of lesions have been described: (1) the classic ulcerogranulomatous lesion that bleeds readily when touched; (2) a hypertrophic or verrucous ulcer with a raised irregular edge; (3) a necrotic, offensive-smelling ulcer causing tissue destruction; and (4) a sclerotic or cicatricial lesion with fibrous and scar tissue. The genitals are affected in 90% of pts and the inguinal region in 10%.

### Diagnosis and Treatment

Diagnosis is often based on identification of typical Donovan bodies (gram-negative intracytoplasmic cysts filled with deeply staining bodies that may have a safety-pin appearance) within large mononuclear cells in smears from lesions or biopsy specimens. PCR is also available.

**TREATMENT DONOVANOSIS (*KLEBSIELLA GRANULOMATIS* INFECTION)**

Pts should be treated with azithromycin (1 g on day 1, then 500 mg qd for 7 days or 1 g weekly for 4 weeks); alternative therapy consists of a 14-day course of doxycycline (100 mg bid), trimethoprim-sulfamethoxazole (960 mg bid), erythromycin (500 mg qid), or tetracycline (500 mg qid). If any of the 14-day treatment regimens are chosen, the pt should be monitored until lesions have healed completely.

## HUMAN PAPILLOMAVIRUS (HPV) INFECTIONS

### Microbiology

Papillomaviruses are nonenveloped, double-strand DNA viruses. More than 125 HPV types are recognized, and individual types are associated with specific clinical manifestations. For example, HPV types 16 and 18 have been most strongly associated with cervical and anal cancers, causing 70–85% and ~90% of cases, respectively; HPV types 6 and 11 cause genital warts (*condylomata acuminata*).

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## Epidemiology and Clinical Manifestations

- HPV is transmitted by sexual intercourse, by oral sex, and possibly by touching of a partner's genitalia.
- The interval between initial infection and the diagnosis of HPV-associated cancer may be >20 years, with HIV infection accelerating this progression.
- The physical appearance of warts varies with their anatomic location, ranging from soft, whitish papules on the vulva to raised, keratotic, pigmented plaques on the penis.
- Although subclinical cervical HPV infections are common, pts with cervical cancer present early on with eroded carcinomas that bleed easily; more advanced carcinomas present as ulcerated lesions or as an exophytic lesion.
- Anal cancer typically presents as rectal bleeding and pain or a mass sensation, although 20% of pts are asymptomatic.

## Diagnosis

Most visible warts are diagnosed correctly by history and physical examination alone. The primary method used for cervical cancer screening is cytology via Pap smear every 3 years beginning at age 21; for women ≥30 years of age, the testing interval can be lengthened to 5 years if co-testing for HPV DNA is negative. There is no clear consensus regarding screening for anal cancer.

### TREATMENT HUMAN PAPILLOMAVIRUS INFECTIONS

- Many lesions resolve spontaneously. Current treatment is not completely effective, and some agents have significant side effects.
- Provider-administered therapy can include cryotherapy, surgical excision, intralesionally administered interferon, or laser surgery.
- Pt-administered therapy consists of podophyllotoxin (0.05% solution or gel or 0.15% cream applied bid for 3 days; can be repeated up to 4 times with 4 days between treatment courses); imiquimod (5% or 3.75% cream applied 3 times per week for up to 16 weeks); and sinecatechins (15% ointment applied tid for up to 4 months).

## Prevention

- A quadrivalent vaccine (Gardasil, Merck) containing HPV types 6, 11, 16, and 18 and a bivalent vaccine (Cervarix, GlaxoSmithKline) containing HPV types 16 and 18 are available. The CDC recommends administration of the quadrivalent vaccine to all boys and girls at 11–12 years of age as well as to young men and women 13–26 years of age who have not previously completed the full series.

For a more detailed discussion, see Marrazzo JM, Holmes KK: Sexually Transmitted Infections: Overview and Clinical Approach, Chap. 163, p. 869; Ram S, Rice PA: Gonococcal Infections, Chap. 181, p. 1003; Murphy TF: *Haemophilus* and *Moraxella* Infections, Chap. 182, p. 1010; O'Farrell N: Donovanosis, Chap. 198e; Lukehart SA: Syphilis, Chap. 206, p. 1132; Hardy RD: Infections Due to Mycoplasmas, Chap. 212, p. 1163; Gaydos CA, Quinn TC: Chlamydial Infections, Chap. 213, p. 1165; Corey L: Herpes Simplex Virus Infections, Chap. 216, p. 1175; and Ermel AC, Brown DR: Human Papillomavirus Infections, Chap. 222, p. 1197, in HPIM-19.

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# 84 Infections of the Skin, Soft Tissues, Joints, and Bones

## SKIN AND SOFT TISSUE INFECTIONS

Skin and soft tissue infections are diagnosed principally by a careful history (e.g., temporal progression, travel, animal exposure, bites, trauma, underlying medical conditions) and physical examination (appearance of lesions and distribution). Treatment of common skin infections is summarized in Table 84-1; parenteral treatment is

**TABLE 84-1 TREATMENT OF COMMON INFECTIONS OF THE SKIN**

| Diagnosis/ Condition | Primary Treatment | Alternative Treatment | See Also Chap(s). |
|---|---|---|---|
| Animal bite (prophylaxis or early infection)[a] | Amoxicillin/ clavulanate, 875/ 125 mg PO bid | Doxycycline, 100 mg PO bid | 27 |
| Animal bite[a] (established infection) | Ampicillin/sulbactam, 1.5–3 g IV q6h | Clindamycin, 600–900 mg IV q8h, *plus* Ciprofloxacin, 400 mg IV q12h, *or* cefoxitin, 2 g IV q6h | 27 |
| Bacillary angiomatosis | Erythromycin, 500 mg PO qid | Doxycycline, 100 mg PO bid | 91 |
| Herpes simplex (primary genital) | Acyclovir, 400 mg PO tid for 10 days | Famciclovir, 250 mg PO tid for 5–10 days, *or* Valacyclovir, 1000 mg PO bid for 10 days | 99 |
| Herpes zoster (immunocompetent host >50 years of age) | Acyclovir, 800 mg PO 5 times daily for 7–10 days | Famciclovir, 500 mg PO tid for 7–10 days, *or* Valacyclovir, 1000 mg PO tid for 7 days | 99 |
| Cellulitis (staphylococcal or streptococcal[b,c]) | Nafcillin or oxacillin, 2 g IV q4–6h | Cefazolin, 1–2 g q8h, *or* Ampicillin/sulbactam, 1.5–3 g IV q6h, *or* Erythromycin, 0.5–1 g IV q6h, *or* Clindamycin, 600–900 mg IV q8h | 86, 87 |

(*Continued*)

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**TABLE 84-1 TREATMENT OF COMMON INFECTIONS OF THE SKIN (*CONTINUED*)**

| Diagnosis/ Condition | Primary Treatment | Alternative Treatment | See Also Chap(s). |
|---|---|---|---|
| MRSA skin infection[d] | Vancomycin, 1 g IV q12h | Linezolid, 600 mg IV q12h | 86 |
| Necrotizing fasciitis (group A streptococcal[b]) | Clindamycin, 600–900 mg IV q6–8h, *plus* Penicillin G, 4 million units IV q4h | Clindamycin, 600–900 mg IV q6–8h, *plus* Cephalosporin (first- or second-generation) | 87 |
| Necrotizing fasciitis (mixed aerobes and anaerobes) | Ampicillin, 2 g IV q4h, *plus* Clindamycin, 600–900 mg IV q6–8h, *plus* Ciprofloxacin, 400 mg IV q6–8h | Vancomycin, 1 g IV q6h, *plus* Metronidazole, 500 mg IV q6h, *plus* Ciprofloxacin, 400 mg IV q6–8h | 92 |
| Gas gangrene | Clindamycin, 600–900 mg IV q6–8h, *plus* Penicillin G, 4 million units IV q4–6h | Clindamycin, 600–900 mg IV q6–8h, *plus* Cefoxitin, 2 g IV q6h | 92 |

[a]*Pasteurella multocida*, a species commonly associated with both dog and cat bites, is resistant to cephalexin, dicloxacillin, clindamycin, and erythromycin. *Eikenella corrodens*, a bacterium commonly associated with human bites, is resistant to clindamycin, penicillinase-resistant penicillins, and metronidazole but is sensitive to trimethoprim-sulfamethoxazole and fluoroquinolones.
[b]The frequency of erythromycin resistance in group A *Streptococcus* is currently ~5% in the United States but has reached 70–100% in some other countries. Most, but not all, erythromycin-resistant group A streptococci are susceptible to clindamycin. Approximately 90% of *Staphylococcus aureus* strains are sensitive to clindamycin, but resistance—both intrinsic and inducible—is increasing.
[c]Severe hospital-acquired *S. aureus* infections or community-acquired *S. aureus* infections that are not responding to the β-lactam antibiotics recommended in this table may be caused by methicillin-resistant strains, requiring a switch to vancomycin, daptomycin, or linezolid.
[d]Some strains of methicillin-resistant *S. aureus* (MRSA) remain sensitive to tetracycline and trimethoprim-sulfamethoxazole. Daptomycin (4 mg/kg IV q24h) or tigecycline (100-mg loading dose followed by 50 mg IV q12h) is an alternative treatment for MRSA.

usually given until systemic signs and symptoms have improved. Types of skin lesions include the following:

1. *Vesicles:* due to proliferation of organisms, usually viruses, within the epidermis (e.g., VZV, HSV, coxsackievirus, poxviruses, *Rickettsia akari*)
2. *Bullae:* caused by toxin-producing organisms. Different entities affect different skin levels. For example, staphylococcal scalded-skin syndrome and toxic epidermal necrolysis cause cleavage of the stratum corneum and the stratum

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germinativum, respectively. Bullae are also seen in necrotizing fasciitis, gas gangrene, and *Vibrio vulnificus* infections.

3. *Crusted lesions:* Impetigo caused by either *Streptococcus pyogenes* (impetigo contagiosa) or *Staphylococcus aureus* (bullous impetigo) usually starts with a bullous phase before development of a golden-brown crust. Crusted lesions are also seen in some systemic fungal infections, dermatophytic infections, and cutaneous mycobacterial infections. It is important to recognize impetigo contagiosa because of its relation to poststreptococcal glomerulonephritis.
4. *Folliculitis:* Localized infection of hair follicles is usually due to *S. aureus*. "Hot-tub folliculitis" is a diffuse condition caused by *Pseudomonas aeruginosa*. Freshwater avian schistosomes cause an allergic reaction after penetrating hair follicles, resulting in "swimmer's itch."
5. *Papular and nodular lesions:* Raised lesions of the skin occur in many different forms and can be caused by *Bartonella henselae* (cat-scratch disease and bacillary angiomatosis), *Treponema pallidum*, human papillomavirus, mycobacteria, and helminths.
6. *Ulcers, with or without eschars:* can be caused by cutaneous anthrax, ulceroglandular tularemia, plague, and mycobacterial infection. Ulcerated lesions on the genitals can be caused by chancroid (painful) or syphilis (painless).
7. *Erysipelas*: abrupt onset of fiery red swelling of the face or extremities, with well-defined indurated margins, intense pain, and rapid progression. *S. pyogenes* is the exclusive cause.

## CELLULITIS

- *Pathogenesis:* Bacteria gain access to the epidermis through breaks in the skin, whether accidental (e.g., cuts, scratches, burns) or iatrogenic (e.g., surgical incisions, IV catheters). The expanding area of erythema may be due to extracellular toxins and/or the host immune response rather than to increasing bacterial numbers.
- *Microbiology:* Etiologic causes include commensal flora (e.g., *S. aureus*, *S. pyogenes*) or a wide variety of exogenous flora. With the latter, a thorough history and epidemiologic data may help identify the cause.
  - Examples of exogenous bacteria causing cellulitis include the following: *Pasteurella multocida* after a cat or dog bite; *Capnocytophaga canimorsus* after a dog bite; *Eikenella corrodens* after a human bite; *P. aeruginosa* in association with ecthyma gangrenosum in neutropenic pts, a penetrating injury (stepping on a nail), or hot-tub folliculitis; *Aeromonas hydrophila* after a laceration sustained in fresh water; or *Erysipelothrix rhusiopathiae* after contact with domestic swine and fish.
- *Clinical manifestations:* This acute inflammatory condition of the skin is characterized by localized pain, erythema, swelling, and heat.
  - Cellulitis due to *S. aureus* often spreads from a central site of localized infection, such as an abscess or an infected foreign body, and is referred to as "purulent cellulitis."
  - *S. pyogenes* can cause nonpurulent cellulitis, a rapidly spreading, diffuse process that often occurs with fever and lymphangitis.
- *Diagnosis:* If there is drainage, an open wound, or an obvious portal of entry, Gram's staining and culture may identify the etiology. Aspiration or biopsy of the leading edge of the cellulitic tissue yields a diagnosis in only 20% of cases.
- *Treatment:* See Table 84-1.

## NECROTIZING FASCIITIS

- *Pathogenesis:* Infection, either apparent or inapparent, results from a breach in integrity of the skin or mucous membrane barriers and can be associated with malignancy, a diverticulum, hemorrhoids, or an anal fissure.

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  - In the case of infections with no obvious portal of entry, transient bacteremia is thought to seed sites of nonpenetrating trauma (e.g., bruise, muscle strain).
  - Infection spreads to the deep fascia and along fascial planes through venous channels and lymphatics.
- *Microbiology:* Necrotizing fasciitis is caused by *S. pyogenes*, mixed aerobic and anaerobic bacteria, or *Clostridium perfringens*; methicillin-resistant *S. aureus* (MRSA) strains that produce the Panton-Valentine leukocidin have also been reported as an occasional cause.
- *Clinical manifestations:* The timing of cutaneous manifestations (e.g., violaceous bullae; friable, necrotic skin; induration; brawny edema) depends on whether the infection began superficially (rapid onset) or in deeper structures (slower onset).
  - Early in the disease course, severe pain and unexplained fever may be the only findings.
  - Thrombosis of blood vessels in dermal papillae leads to ischemia of peripheral nerves and anesthesia of the affected area.
  - In later stages, pts appear toxic and often develop shock and multiorgan failure.
- *Diagnosis:* Diagnosis is based on clinical presentation. Other findings may include gas detected in deep tissues by imaging studies (particularly with clostridial species but rarely with *S. pyogenes*) and markedly elevated serum CPK levels (in the case of concomitant myositis).
- *Treatment:* Emergent surgical exploration to deep fascia and muscle, with removal of necrotic tissue, is essential. Table 84-1 provides recommendations for adjunctive antibiotic therapy.

## MYOSITIS/MYONECROSIS

- *Clinical manifestations and microbiology:* Infections involving the muscle have differing manifestations, depending on the etiology.
  - *Myositis:* can be caused by bacteria (clostridia, streptococci), viruses (influenza virus, dengue virus, coxsackievirus), or parasites (*Trichinella*, *Taenia solium*, *Toxoplasma*). This condition usually manifests with myalgias, but pain can be severe in coxsackievirus, *Trichinella*, and bacterial infections.
  - *Pyomyositis:* a localized muscle infection usually due to *S. aureus*, common in tropical areas, and typically with no known portal of entry
  - *Myonecrosis:* can be caused by clostridial species (*C. perfringens*, *C. septicum*, *C. histolyticum*, *C. sordellii*) or by mixed aerobic and anaerobic bacteria. Myonecrosis is usually related to trauma; however, spontaneous gangrene—usually due to *C. septicum*—can occur in pts with neutropenia, GI malignancy, or diverticulosis. Myonecrosis of the uterus, typically due to *C. sordellii*, occurs in women after spontaneous or medically induced abortion and in healthy postpartum women; infection is rapidly and almost uniformly fatal as there are few or no localizing clinical findings.
- *Diagnosis and Treatment:* Emergent surgical intervention to visualize deep structures, obtain materials for culture and sensitivity testing, remove necrotic tissue, and reduce compartment pressure is both diagnostic and therapeutic.
  - Empirical antibiotic treatment should target likely etiologies—e.g., vancomycin (1 g IV q12h) for pyomyositis and ampicillin/sulbactam (2–3 g IV q6h) for mixed aerobic–anaerobic infections.
  - For treatment of clostridial myonecrosis (gas gangrene), see Table 84-1.

## INFECTIOUS ARTHRITIS

- *Pathogenesis:* Joints become infected by hematogenous seeding (the most common route), by spread from a contiguous site of infection, or by direct inoculation (e.g., during trauma or surgery). Acute bacterial infection can rapidly destroy articular cartilage as a result of increased intraarticular pressure and the elicited host immune response.

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- *Microbiology:* The predominant etiologic agents differ with the pt's age; *S. aureus* is the most common nongonococcal isolate in adults of all ages.
  - In children <5 years old, *S. aureus*, *S. pyogenes*, and *Kingella kingae* predominate.
  - In young adults, *Neisseria gonorrhoeae* is the most common etiology.
  - In adults, *S. aureus* predominates, but gram-negative bacilli, pneumococci, and β-hemolytic streptococci are involved in one-third of cases in older adults.
  - Other causes of septic arthritis include *Borrelia burgdorferi* (Lyme disease), tuberculosis and other mycobacterial infections, fungal infections (e.g., coccidioidomycosis, histoplasmosis), and viral infections (e.g., rubella, mumps, hepatitis B, parvovirus infection).
- *Epidemiology and clinical manifestations:* The risk factors and presentation differ depending on whether *N. gonorrhoeae* is the cause.
  - *Nongonococcal bacterial arthritis:* Risk is increased in pts with rheumatoid arthritis, diabetes mellitus, glucocorticoid therapy, hemodialysis, malignancy, and IV drug use.
    - In 90% of pts, one joint is involved—most often the knee, which is followed in frequency by the hip, shoulder, wrist, and elbow; IV drug users often have spinal, sacroiliac, or sternoclavicular joint involvement.
    - Pts have moderate to severe pain, effusion, decreased range of motion, and fever.
  - *Gonococcal arthritis:* Women are 2–3 times more likely than men to develop disseminated gonococcal infection (DGI) and arthritis, particularly during menses and during pregnancy (see Chap. 83).
    - DGI presents as fever, chills, rash, and articular symptoms (migratory arthritis). The cutaneous and articular findings result from an immune reaction to circulating gonococci and immune-complex deposition; thus synovial fluid cultures are consistently negative.
    - In true gonococcal arthritis (which always follows DGI), a single joint (hip, knee, ankle, or wrist) is usually involved.
  - *Prosthetic joint infections:* complicate 1–4% of joint replacements and are usually acquired intra- or perioperatively
    - Acute presentations are seen in infections caused by *S. aureus*, pyogenic streptococci, and enteric bacilli.
    - Indolent presentations are seen in infections caused by coagulase-negative staphylococci and diphtheroids.
  - *Reactive arthritis:* follows ~1% of cases of nongonococcal urethritis and 2% of enteric infections (e.g., *Yersinia enterocolitica*, *Shigella flexneri*, *Campylobacter jejuni*, *Salmonella* spp.). Only a minority of pts have the other classic findings associated with reactive arthritis, including urethritis, conjunctivitis, uveitis, oral ulcers, and rash.
- *Diagnosis:* If there is concern about joint infection, examination of synovial fluid from the affected joint is essential. There is considerable overlap in the cell counts due to different etiologies, but synovial fluid culture and examination for crystals (to rule out gout and pseudogout) can help narrow the diagnosis.
  - *Normal* synovial fluid contains <180 cells (mostly mononuclear)/μL. *Acute bacterial infection* of joints results in synovial fluid cell counts averaging 100,000/μL (range, 25,000–250,000/μL), with >90% PMNs. Synovial fluid in *gonococcal arthritis* contains >50,000 cells/μL, but results of Gram's staining are usually negative, and cultures of synovial fluid are positive in <40% of cases. Other mucosal sites should be cultured to diagnose gonorrhea. Pts with septic arthritis due to *mycobacteria* or *fungi* can have 10,000–30,000 cells/μL in synovial fluid, with 50–70% PMNs. Synovial fluid cell counts in *noninfectious inflammatory arthritides* are typically <30,000–50,000/μL.
  - Gram's staining of synovial fluid should be performed. Injection directly into blood culture bottles can increase the yield of synovial fluid cultures.
  - Blood cultures are positive in 50–70% of cases due to *S. aureus* but are less commonly positive with other organisms.

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– Plain radiographs show soft tissue swelling, joint space widening, and displacement of tissue planes by distended capsule. Narrowing of the joint space and bony erosions suggest advanced disease.

## TREATMENT INFECTIOUS ARTHRITIS

- Drainage of pus and necrotic debris is needed to cure infection and to prevent destruction of cartilage, postinfectious degenerative arthritis, and joint deformity or instability.
- A third-generation cephalosporin (cefotaxime, 1 g IV q8h; or ceftriaxone, 1–2 g IV q24h) provides adequate empirical coverage for most community-acquired infections in adults when smears demonstrate no organisms. Vancomycin (1 g IV q12h) should be used to cover the possibility of MRSA when there are gram-positive cocci on the smear.
  – In IV drug users and other susceptible pts, treatment for gram-negative organisms such as *P. aeruginosa* should be considered.
  – If a pathogen is identified by culture, treatment should be adjusted according to the specific bacterial organism and its antibiotic susceptibility.
- Treatment for *S. aureus* should be given for 4 weeks, that for enteric gram-negative bacilli for 3–4 weeks, and that for pneumococci or streptococci for 2 weeks. Treatment for gonococcal arthritis should commence with ceftriaxone (1 g/d) until improvement; depending on the susceptibilities of the isolate, the 7-day course can be completed with an oral fluoroquinolone (e.g., ciprofloxacin, 500 mg bid) or amoxicillin (500 mg tid).
- Prosthetic joint infections should be treated with surgery and high-dose IV antibiotics for 4–6 weeks. The prosthesis often has to be removed; to avoid joint removal, antibiotic suppression of infection may be tried. A 3- to 6-month course of ciprofloxacin and rifampin has been successful in *S. aureus* prosthetic-joint infections of relatively short duration, although prospective trials confirming the efficacy of this regimen are still needed.

## OSTEOMYELITIS

- *Pathogenesis and epidemiology:* Osteomyelitis cases can be classified by pathogenesis, duration of infection, location of infection, and whether prosthetic material is present. Osteomyelitis is typically caused by hematogenous spread, spread from a contiguous site following surgery, and/or secondary infection in the setting of vascular insufficiency or concomitant neuropathy (e.g., in diabetes). The most common primary foci of infection are the urinary tract, skin and soft tissues, intravascular catheterization sites, and the endocardium. Hematogenous osteomyelitis in adults most commonly results in vertebral infection, with 6.5 cases/100,000 at ages >70 years.
- *Microbiology:* Irrespective of the anatomic location involved, *S. aureus* is the most common cause, accounting for ~40–50% of cases.
  – Gram-negative bacilli account for 10–20% of cases.
- *Clinical manifestations:* Pts generally have a febrile illness, with localized pain and tenderness. A history of surgery or trauma in the affected region—even in the remote past—should raise suspicion.
- *Diagnosis:* Radiographic studies and occasionally invasive sampling of lesions are needed to confirm the diagnosis.
  – Blood cultures are positive in 30–78% of cases, with lower rates if the pt has previously received antibiotics.
  – CT and especially MRI scans offer increased sensitivity in detecting osteomyelitis.
- *Treatment:* Table 84-2 lists antibiotics for the treatment of osteomyelitis in the absence of implants.

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**TABLE 84-2 ANTIBIOTIC THERAPY FOR OSTEOMYELITIS IN ADULTS WITHOUT IMPLANTS[a]**

| Microorganism | Antimicrobial Agent (Dose,[b] Route) |
|---|---|
| *Staphylococcus* spp. | |
| Methicillin-susceptible | Nafcillin *or* oxacillin[c] (2 g IV q6h)<br>***followed by***<br>Rifampin (300–450 mg PO q12h)<br>*plus*<br>levofloxacin (750 mg PO q24h or 500 mg PO q12h) |
| Methicillin-resistant | Vancomycin[d] (15 mg/kg IV q12h) *or* daptomycin (>6–8 mg/kg IV q24h)<br>***followed by***<br>Rifampin (300–450 mg PO q12h)<br>***plus***<br>Levofloxacin (750 mg PO q24h or 500 mg PO q12h) *or* TMP-SMX[e] (1 double-strength tablet PO q8h) *or* fusidic acid (500 mg PO q8h) |
| *Streptococcus* spp. | Penicillin G[c] (5 million units IV q6h) *or* ceftriaxone (2 g IV q24h) |
| Enterobacteriaceae | |
| Quinolone-susceptible | Ciprofloxacin (750 mg PO q24h) |
| Quinolone-resistant[f] | Imipenem (500 mg IV q6h) |
| *Pseudomonas aeruginosa* | Cefepime *or* ceftazidime (2 g IV q8h)<br>*plus*<br>an aminoglycoside[g]<br>***or***<br>Piperacillin-tazobactam (4.5 g IV q8h)<br>*plus*<br>an aminoglycoside[g] for 2–4 weeks<br>***followed by***<br>Ciprofloxacin[h] (750 mg PO q12h) |
| Anaerobes | Clindamycin (600 mg IV q6–8h) for 2–4 weeks<br>***followed by***<br>Clindamycin[i] (300 mg PO q6h) |

[a]Unless otherwise indicated, the total duration of antimicrobial treatment is generally 6 weeks.
[b]All dosages are for adults with normal renal function.
[c]When the pt has delayed-type penicillin hypersensitivity, cefuroxime (1.5 g IV q6–8h) can be administered. When the pt has immediate-type penicillin hypersensitivity, the penicillin should be replaced by vancomycin (1 g IV q12h).
[d]Target vancomycin trough level: 15–20 μg/mL.
[e]Trimethoprim-sulfamethoxazole. A double-strength tablet contains 160 mg of trimethoprim and 800 mg of sulfamethoxazole.
[f]Including isolates producing extended-spectrum β-lactamase.
[g]The need for addition of an aminoglycoside has not yet been proven. However, this addition may decrease the risk of emergence of resistance to the β-lactam.
[h]The rationale for starting ciprofloxacin treatment only after pretreatment with a β-lactam is the increased risk of emergence of quinolone resistance in the presence of a heavy bacterial load.
[i]Alternatively, penicillin G (5 million units IV q6h) or ceftriaxone (2 g IV q24h) can be used against gram-positive anaerobes (e.g., *Propionibacterium acnes*), and metronidazole (500 mg IV/PO q8h) can be used against gram-negative anaerobes (e.g., *Bacteroides* spp.).
***Source:*** From W Zimmerli: *N Engl J Med* 362:1022, 2010. © Massachusetts Medical Society. Reprinted with permission.

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– The optimal route and duration of therapy remain controversial, but a 6-week course of IV therapy is usually recommended for acute osteomyelitis. If evidence indicates clinical efficacy of an oral antibiotic to which the organism is susceptible and if the pt has normal intestinal function (without vomiting), a transition from IV to PO therapy can be considered.
– Serial measurements of inflammatory markers (ESR, C-reactive protein) can serve as surrogates for response to treatment in some infections (particularly those due to *S. aureus*).
– Surgical intervention is usually required in chronic osteomyelitis and cases involving prosthetic implants.

For a more detailed discussion, see Stevens DL: Infections of the Skin, Muscles, and Soft Tissues, Chap. 156, p. 827; Madoff LC: Infectious Arthritis, Chap. 157, p. 833; and Zimmerli W: Osteomyelitis, Chap. 158, p. 838, in HPIM-19.

# 85 Pneumococcal Infections

## MICROBIOLOGY

- *Streptococcus pneumoniae* (the pneumococcus) is a gram-positive coccus that grows in chains, causes $\alpha$-hemolysis on blood agar, is bile soluble, and is sensitive to optochin.
- Nearly every clinical isolate has a polysaccharide capsule that protects the bacteria from phagocytosis in the absence of type-specific antibody; 93 distinct capsules have been identified.

## EPIDEMIOLOGY

- In industrialized countries, children serve as the major vectors of pneumococcal transmission: 20–50% of children <5 years old have asymptomatic nasopharyngeal colonization with *S. pneumoniae* (compared with 5–15% of young and middle-aged adults). Colonization rates for all age groups are even higher in low-income countries.
- Rates of pneumococcal disease vary by season (higher in winter), gender (higher for males), and underlying medical condition (e.g., higher with splenic dysfunction; chronic respiratory, heart, liver, and kidney disease; immunosuppression).
- The introduction and widespread use (in industrialized countries) of pneumococcal conjugate vaccines have led to dramatic changes in the epidemiology of invasive pneumococcal disease; rates have fallen by >75% among infants and children in the United States.

## PATHOGENESIS

- Nasopharyngeal colonization can persist for many months, resulting in the development of type-specific serum IgG that ultimately leads to pneumococcal clearance

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from the nasopharynx. Accordingly, pneumococcal disease is usually associated with recent acquisition of a new colonizing serotype.
- Once the nasopharynx has been colonized, the bacteria spread either via the bloodstream to distant sites (e.g., brain, joint, bones) or locally to contiguous areas (e.g., middle ear, lungs).
- Local cytokine production, particularly after intercurrent viral infections, facilitates pneumococcal adherence. Bacterial factors such as peptidoglycan and teichoic acid induce inflammation, result in characteristic pathology, and permit bacterial invasion.

## CLINICAL MANIFESTATIONS AND DIAGNOSIS

The clinical manifestations of pneumococcal disease depend on the site of infection and the duration of illness.

### Pneumonia

Pneumococcal pneumonia—the most common serious pneumococcal syndrome—is difficult to distinguish from pneumonia of other etiologies on the basis of clinical findings.

- Pts often present with fever, abrupt-onset cough and dyspnea, and sputum production.
  - Pts may also have pleuritic chest pain, shaking chills, or myalgias.
  - Among the elderly, presenting signs and symptoms may be less specific, with confusion and malaise but without fever or cough.
- On physical examination, adults may have tachypnea (>30 breaths/min) and tachycardia, crackles on chest auscultation, and dullness to percussion of the chest in areas of consolidation.
  - In some cases, hypotension, bronchial breathing, a pleural rub, or cyanosis may be present.
  - Upper abdominal pain may be present if the diaphragmatic pleura is involved.
- Pneumococcal pneumonia is generally diagnosed by Gram's staining and culture of sputum.
  - While culture results are awaited, chest x-rays—which classically demonstrate lobar or segmental consolidation—may provide some adjunctive evidence, although they may be normal early in the course of illness or with dehydration.
  - Blood cultures are positive for pneumococci in <30% of cases.
  - Leukocytosis (>15,000/μL) is common; leukopenia is documented in <10% of cases and is associated with a fatal outcome.
  - A positive pneumococcal urinary antigen test has a high predictive value among adults, in whom the prevalence of nasopharyngeal colonization is low.
- Empyema occurs in <5% of cases and should be considered when a pleural effusion is accompanied by fever and leukocytosis after 4–5 days of appropriate antibiotic therapy. Pleural fluid with frank pus, bacteria, or a pH of ≤7.1 indicates empyema and requires aggressive drainage.

### Meningitis

*S. pneumoniae* is among the most common causes of meningitis in both adults and children. Pneumococcal meningitis can present as a primary syndrome or as a complication of other pneumococcal conditions (e.g., otitis media, infected skull fracture, bacteremia). Pneumococcal meningitis is clinically indistinguishable from pyogenic meningitis of other etiologies.

- Pts have fever, headache, neck stiffness, photophobia, and occasionally seizures and confusion.
- On examination, pts have a toxic appearance, altered consciousness, bradycardia, and hypertension (indicative of increased intracranial pressure). Kernig's or Brudzinski's sign or cranial nerve palsies (particularly of the third and sixth cranial nerves) are noted in a small fraction of adult pts.

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- Diagnosis of pneumococcal meningitis relies on examination of CSF, which reveals an elevated protein level, elevated WBC count, and reduced glucose concentration. The etiologic agent can be specifically identified by culture, antigen testing, or PCR. A blood culture positive for *S. pneumoniae* in conjunction with clinical manifestations of meningitis is also considered confirmatory.

## Other Invasive Syndromes

*S. pneumoniae* can affect virtually any body site and cause invasive syndromes, including bacteremia, osteomyelitis, septic arthritis, endocarditis, pericarditis, and peritonitis. The essential diagnostic approach is collection of fluid from the site of infection by sterile technique and examination by Gram's staining, culture, and—when relevant—capsular antigen assay or PCR. Hemolytic-uremic syndrome can complicate invasive pneumococcal disease.

## Noninvasive Syndromes

Sinusitis and otitis media are the two most common noninvasive syndromes caused by *S. pneumoniae*; the latter is the most common pneumococcal syndrome and most often affects young children. See Chap. 58 for more detail.

## TREATMENT PNEUMOCOCCAL INFECTIONS

- Penicillin remains the cornerstone of treatment for pneumococcal disease caused by sensitive isolates, with daily doses ranging from 50,000 U/kg for minor infections to 300,000 U/kg for meningitis. Macrolides and cephalosporins are alternatives for penicillin-allergic pts but otherwise offer no advantage over penicillin.
- Strains resistant to β-lactam drugs are increasing in frequency, and antibiotic recommendations are typically based on the minimal inhibitory concentration against the isolate, particularly in cases of invasive disease.

### PNEUMONIA

- *Outpatient treatment:* Amoxicillin (1 g PO q8h) is effective for virtually all cases of pneumococcal pneumonia. Fluoroquinolones (e.g., levofloxacin, 500–750 mg/d; or moxifloxacin, 400 mg/d) are also highly likely to be effective in the United States, although they are much more expensive than amoxicillin. Clindamycin and azithromycin are effective in 90% and 80% of cases, respectively.
- *Inpatient treatment:* For pts with noncritical illness, β-lactam antibiotics are recommended—e.g., penicillin (3–4 mU IV q4h) or ceftriaxone (1 g IV q12–24h). For pts with critical illness, vancomycin may be added, with its use reviewed once susceptibility data are available.
- *Treatment duration:* The optimal duration of treatment is uncertain, but continuation of antibiotics for at least 5 days after the pt becomes afebrile seems prudent.

### MENINGITIS

- Because of the increased prevalence of resistant pneumococci, first-line therapy should include vancomycin (1 g IV q12h) plus a third-generation cephalosporin (ceftriaxone, 2 g IV q12h; or cefotaxime, 2 g IV q4h). Rifampin (600 mg/d) can be substituted for the third-generation cephalosporin in pts hypersensitive to β-lactam agents.
- The antibiotic regimen should be adjusted appropriately once susceptibility data are available. If the isolate is resistant to penicillin and cephalosporins, both vancomycin and the cephalosporin should be continued.
- A repeat LP should be considered after 48 h if the organism is not sensitive to penicillin and information on cephalosporin sensitivity is not yet available, if the pt's clinical condition does not improve or deteriorates, or if the pt has received dexamethasone, which may compromise clinical evaluation.

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- In adults with community-acquired bacterial meningitis, dexamethasone should be given before or in conjunction with the first dose of antibiotics, as glucocorticoids have been demonstrated to significantly reduce rates of mortality, severe hearing loss, and neurologic sequelae. The data are not clear as to whether this practice is also beneficial in children.

## PREVENTION

- All persons ≥65 years old and those 2–64 years old who are at increased risk of pneumococcal disease should receive the 23-valent pneumococcal polysaccharide vaccine (PPSV23), which contains capsular polysaccharide from the 23 most prevalent serotypes of *S. pneumoniae*.
  - Persons >2 years old with continuing increased risk should be revaccinated every 5 years.
  - Persons whose only indication for vaccination is an age of ≥65 years do not need to be revaccinated.
- The efficacy of PPSV23 is controversial; it appears to be effective against invasive pneumococcal disease but less effective or ineffective against nonbacteremic pneumococcal pneumonia.
- The duration of protection conferred by PPSV23 is ~5 years.
- The poor response of infants and young children to pneumococcal polysaccharide vaccines prompted the development of pneumococcal conjugate vaccines. In the United States, the current recommendation is for infants to be routinely vaccinated with the conjugate vaccine PCV13, which contains the 13 serotypes most associated with disease.
  - All immunocompromised children and adults should receive PCV13 prior to receiving PPSV23.
  - Pneumococcal conjugate vaccines are highly effective at providing protection against vaccine-serotype invasive pneumococcal disease, pneumonia, otitis media, nasopharyngeal colonization, and all-cause mortality.
  - In the United States, there has been a >90% reduction in vaccine-serotype invasive pneumococcal disease among the whole population, including indirect protection of unvaccinated adults.

For a more detailed discussion, see Goldblatt D, O'Brien KL: Pneumococcal Infections, Chap. 171, p. 946, in HPIM-19.

# 86 Staphylococcal Infections

## MICROBIOLOGY

Staphylococci are gram-positive cocci that form grapelike clusters on Gram's stain; they are catalase positive (unlike streptococci), nonmotile, aerobic, and facultatively anaerobic. *Staphylococcus aureus*, which is distinguished from other staphylococci by its production of coagulase, is the most virulent species.

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## *S. AUREUS* INFECTIONS

### Epidemiology

*S. aureus* is an important cause of community-acquired infections and a leading cause of nosocomial infections.

- *S. aureus* is a component of the normal human flora, most frequently colonizing the anterior nares and oropharynx but also colonizing the skin (particularly damaged skin), vagina, axilla, and perineum. These sites of colonization are reservoirs for future infection.
- Of healthy persons, ~30% are transiently colonized with *S. aureus*, while ~10% are persistently colonized. The rate is elevated among insulin-dependent diabetic pts, HIV-infected persons, injection drug users, hemodialysis pts, and pts with skin damage.
- Transmission of *S. aureus* most frequently results from direct personal contact, although spread via respiratory secretions has been reported. Most *S. aureus* infections are caused by a strain that is already a component of the pt's own microbiota.
- Methicillin-resistant *S. aureus* (MRSA) is common in hospitals, and its prevalence is increasing dramatically in community settings among individuals without prior medical exposure.
  - In the United States, strain USA300 (defined by pulsed-field gel electrophoresis) causes most community-acquired MRSA (CA-MRSA) infections and can cause severe disease in immunocompetent pts.

### Pathogenesis

*S. aureus* is a pyogenic pathogen known for its capacity to induce abscess formation.

- *Invasive disease:* For invasive *S. aureus* infection to occur, some or all of the following steps are necessary:
  - *Colonization/inoculation:* Bacteria colonize tissue surfaces or are inoculated directly into tissue—e.g., as a result of minor abrasions or via IV access catheters.
  - *Invasion:* Bacteria replicate at the site of infection and elaborate enzymes that facilitate survival and local spread. CA-MRSA isolates that produce the Panton-Valentine leukocidin toxin have been linked to more serious infections.
  - *Evasion of host defense mechanisms: S. aureus* possesses an antiphagocytic polysaccharide microcapsule that facilitates evasion of host defenses and plays a role in abscess formation. Organisms can survive intracellularly and then cause recrudescent infections when conditions are suitable.
  - *Metastatic spread: S. aureus* can survive in PMNs and may use these cells to spread to and seed other tissue sites.
- *Toxin-mediated disease: S. aureus* produces three types of toxin: cytotoxins, pyrogenic toxin superantigens, and exfoliative toxins.
  - Antitoxin antibodies are protective against toxin-mediated staphylococcal illness.
  - Enterotoxins and toxic shock syndrome toxin 1 (TSST-1) act as "superantigens" or T-cell mitogens and cause the release of large amounts of inflammatory mediators, producing multisystem disease that includes fever, rash, and hypotension.

### Diagnosis

*S. aureus* infections are readily diagnosed by Gram's stain and microscopic examination of infected tissue.

- Routine cultures of infected material usually yield positive results, and blood cultures are sometimes positive even when infections are localized to extravascular sites.
- PCR assays have been developed for rapid testing and are increasingly being used.

### Clinical Syndromes

**Skin and Soft Tissue Infections** *S. aureus* causes a variety of cutaneous infections characterized by pus-containing blisters, many of which can also be caused by group A

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streptococci and other streptococcal species. Predisposing factors include skin disease (e.g., eczema), skin damage (e.g., minor trauma), injections, and poor personal hygiene.

- Infections can be superficial (e.g., folliculitis, cellulitis, impetigo) or deep and painful (e.g., furuncles, carbuncles, hidradenitis suppurativa).
  - Carbuncles (often located in the lower neck) are more severe and painful than furuncles (boils that extend from hair follicles) and are due to coalesced lesions extending to deeper SC tissue.
  - Mastitis in lactating women can range from superficial cellulitis to abscess.

**Musculoskeletal Infections** See Chap. 84 for additional details.

- *S. aureus* is among the most common causes of *osteomyelitis* arising from either hematogenous dissemination or contiguous spread from a soft tissue site (e.g., diabetic or vascular ulcers).
  - Hematogenous osteomyelitis in adults is often vertebral and occurs in pts with endocarditis, pts undergoing hemodialysis, injection drug users, or diabetics. Intense back pain and fever can occur, but infections may also be clinically occult.
  - *Epidural abscess* is a serious complication that can present as trouble voiding or walking or as radicular pain in addition to symptoms of osteomyelitis; neurologic compromise can develop in the absence of timely treatment, which often requires surgical intervention.
  - Osteomyelitis from contiguous soft tissue infections is suggested by exposure of bone, a draining fistulous tract, failure to heal, or continued drainage.
- *S. aureus* is the most common cause of *septic arthritis* in native joints of both adults and children. *S. aureus* septic arthritis in adults may result from trauma, surgery, or hematogenous dissemination.
  - The joints most commonly affected are the knees, shoulders, hips, and phalanges.
  - Examination of synovial fluid reveals >50,000 PMNs/μL and gram-positive cocci in clusters on Gram's stain.
- *Pyomyositis*, an infection of skeletal muscles that is seen in tropical climates and in immunocompromised pts (e.g., HIV-infected pts), causes fever, swelling, and pain overlying involved muscle and is usually due to *S. aureus*.

**Respiratory Tract Infections**

- Newborns and infants can develop serious infections characterized by fever, dyspnea, and respiratory failure; pneumatoceles (shaggy, thin-walled cavities), pneumothorax, and empyema are known complications.
- Community-acquired pneumonia usually follows viral infections (e.g., influenza) and manifests as fever, bloody sputum production, and midlung-field pneumatoceles or multiple patchy pulmonary infiltrates.
  - Blood cultures are usually negative.
- Nosocomial pneumonia is common in intubated pts and is indistinguishable from pneumonia of other bacterial etiologies.
  - Pts produce an increased volume of purulent sputum and develop fever, new pulmonary infiltrates, and respiratory distress.

**Bacteremia and Sepsis** The incidence of metastatic seeding during bacteremia has been estimated to be as high as 31%, with bones, joints, kidneys, and lungs most commonly infected.

- Diabetes, HIV infection, and renal insufficiency are often seen in association with *S. aureus* bacteremia and increase the risk of complications.

**Infective Endocarditis** See Chap. 80 for additional details.

- *S. aureus* is the leading cause of endocarditis worldwide and accounts for 25–35% of cases.

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- The incidence is increasing as a result of injection drug use, hemodialysis, intravascular prosthetic devices, and immunosuppression.
- Mortality rates range from 20% to 40% despite the availability of effective antibiotics.
- The four clinical settings in which *S. aureus* endocarditis is encountered are (1) right-sided endocarditis in association with injection drug use, (2) left-sided native-valve endocarditis, (3) prosthetic-valve endocarditis, and (4) nosocomial endocarditis.

**Urinary Tract Infections** UTIs due to *S. aureus* are uncommon and suggest hematogenous dissemination.

**Prosthetic Device–Related Infections** Compared with coagulase-negative staphylococci (CoNS), *S. aureus* causes more acute disease, with localized and systemic manifestations that tend to be rapidly progressive. Successful treatment usually involves removal of the prosthetic device.

**CA-MRSA Infections** While the skin and soft tissues are the most common sites of infection associated with CA-MRSA, 5–10% of these infections are invasive and potentially life threatening (e.g., necrotizing fasciitis, necrotic pneumonia, sepsis, purpura fulminans).

**Toxin-Mediated Disease** Each class of toxin produced by *S. aureus* results in a characteristic syndrome.

- *Food poisoning:* results from inoculation of toxin-producing *S. aureus* into food by colonized food handlers, with subsequent toxin elaboration in growth-promoting foods (e.g., custard, potato salad, processed meat)
  - The heat-stable toxin is not destroyed even if heating kills the bacteria.
  - Because the disease is caused by preformed toxins, its onset is rapid and explosive, occurring within 1–6 h of ingestion of contaminated food.
  - The chief signs and symptoms are nausea and vomiting, but diarrhea, hypotension, and dehydration may occur. Fever is absent.
  - Symptoms resolve within 8–10 h; treatment is entirely supportive.
- *Toxic shock syndrome (TSS):* results from elaboration of an enterotoxin (many nonmenstrual TSS cases) or TSST-1 (some nonmenstrual cases and >90% of menstrual cases)
  - Although the specific toxin may differ, the clinical presentation is similar in menstrual and nonmenstrual cases.
  - Diagnosis is based on a constellation of clinical findings. Table 86-1 summarizes the case definition for staphylococcal TSS.
  - Menstrual cases occur 2–3 days after menses begin.
  - Illness occurs only in people who lack antibody to the toxin.
- *Staphylococcal scalded-skin syndrome (SSSS):* most often affects newborns and children. Fragility of the skin, with tender, thick-walled, fluid-filled bullae, can lead to exfoliation of most of the skin surface. *Nikolsky's sign* is positive when gentle pressure on bullae causes rupture of lesions and leaves denuded underlying skin.

## Prevention

Hand washing and careful attention to appropriate isolation procedures prevent the spread of *S. aureus* infection. Elimination of nasal carriage of *S. aureus* (e.g., with mupirocin) has reduced the incidence of postsurgical infection.

# INFECTIONS CAUSED BY COAGULASE-NEGATIVE STAPHYLOCOCCI

## Microbiology

CoNS are generally less virulent than *S. aureus* but are important and common causes of prosthetic-device infections.

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**TABLE 86-1 CASE DEFINITION OF *S. AUREUS* TOXIC SHOCK SYNDROME**

1. Fever: temperature of ≥38.9°C (≥102°F)
2. Hypotension: systolic blood pressure of ≤90 mmHg or orthostatic hypotension (orthostatic drop in diastolic blood pressure by ≥15 mmHg, orthostatic syncope, or orthostatic dizziness)
3. Diffuse macular rash, with desquamation 1–2 weeks after onset (including the palms and soles)
4. Multisystem involvement
   a. Hepatic: bilirubin or aminotransferase levels ≥2 times normal
   b. Hematologic: platelet count ≤100,000/μL
   c. Renal: blood urea nitrogen or serum creatinine level ≥2 times the normal upper limit
   d. Mucous membranes: vaginal, oropharyngeal, or conjunctival hyperemia
   e. Gastrointestinal: vomiting or diarrhea at onset of illness
   f. Muscular: severe myalgias or serum creatine phosphokinase level ≥2 times the normal upper limit
   g. Central nervous system: disorientation or alteration in consciousness without focal neurologic signs and in the absence of fever and hypotension
5. Negative serologic or other tests for measles, leptospirosis, and Rocky Mountain spotted fever, as well as negative blood or cerebrospinal fluid cultures for organisms other than *S. aureus*

***Source:*** M Wharton et al: Case definitions for public health surveillance. *MMWR* 39:1, 1990; with permission.

- Of CoNS species, *S. epidermidis* most often causes disease. This organism is a normal component of the skin, oropharyngeal, and vaginal flora.
- *S. saprophyticus* is a common cause of UTIs.
- *S. lugdunensis* and *S. schleiferi* are more virulent than other CoNS species and cause serious infections, possibly because they apparently share more virulence determinants with *S. aureus* than do other CoNS species.

## Pathogenesis

CoNS are uniquely adapted to cause prosthetic-device infections because they can elaborate an extracellular polysaccharide (glycocalyx or slime) that forms a biofilm on the device surface, protecting bacteria from host defenses as well as from antibiotic treatment while allowing bacterial survival.

## Clinical Syndromes

CoNS cause diverse prosthetic device–related infections. Signs of localized infection are usually subtle, disease progression is slow, and systemic findings are limited. Fever and mild leukocytosis may be documented. Infections not associated with prosthetic devices are infrequent, but up to 5% of native-valve endocarditis cases have been due to CoNS in some series.

## Diagnosis

CoNS are readily detected by standard methods, but distinguishing infection from colonization is often problematic because CoNS are common contaminants of cultures of blood and other sites. Only 10–25% of blood cultures positive for CoNS reflect true bacteremia.

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## TREATMENT STAPHYLOCOCCAL INFECTIONS

- Suppurative collections should be surgically drained. The emergence of CA-MRSA has increased the importance of culturing material from all collections to identify the pathogen and determine its antimicrobial susceptibility.
- In most cases of prosthetic-device infection, the device should be removed, although some CoNS infections can be managed medically.
- Antibiotic therapy for *S. aureus* infection is generally prolonged (i.e., 4–8 weeks), particularly if blood cultures remain positive 96 h after initiation of therapy, if the infection was acquired in the community, if a removable focus of infection is not removed, or if cutaneous or embolic manifestations of infection occur. For immunocompetent pts in whom shorter therapy is planned, a transesophageal echocardiogram to rule out endocarditis is warranted.
- Antimicrobial therapy for serious staphylococcal infections is summarized in Table 86-2.
  - Penicillinase-resistant β-lactams, such as nafcillin, oxacillin, and cephalosporins, are highly effective against penicillin-resistant strains.
  - The incidence of MRSA is high in hospital settings, and strains intermediately or fully resistant to vancomycin have been described. In general, vancomycin is less reliably bactericidal than the β-lactams and should be used only when absolutely indicated.
  - Among newer antistaphylococcal agents, ceftaroline is a fifth-generation cephalosporin with bactericidal activity against MRSA; daptomycin is bactericidal but is not effective in pulmonary infections; quinupristin/dalfopristin is typically bactericidal but is only bacteriostatic against isolates resistant to erythromycin or clindamycin; linezolid is bacteriostatic and offers similar bioavailability after oral or parenteral administration; and telavancin—a derivative of vancomycin—is active against strains with reduced susceptibility to vancomycin (i.e., vancomycin-intermediate *S. aureus*, or VISA). Tigecycline, a broad-spectrum minocycline analogue, is bacteriostatic against MRSA.
    - Other alternatives include the quinolones, but resistance to these drugs is increasing, especially among MRSA strains.
    - Trimethoprim-sulfamethoxazole (TMP-SMX) and minocycline have been used successfully to treat MRSA infections in cases of vancomycin toxicity or intolerance.
    - Combinations of antistaphylococcal agents have been used to enhance bactericidal activity (e.g., daptomycin plus a β-lactam antibiotic) and, in selected instances (e.g., right-sided endocarditis), to shorten the duration of therapy.

Special considerations for treatment include:

- *Uncomplicated skin and soft tissue infections:* Oral agents are usually adequate.
- *Native-valve endocarditis:* A β-lactam is recommended for methicillin-sensitive *S. aureus* and vancomycin (1 g q12h) or daptomycin (6 mg/kg q24h) for MRSA. Treatment should continue for 4–6 weeks.
- *Prosthetic-valve endocarditis:* Surgery is often needed in addition to antibiotics. A β-lactam drug (or either vancomycin or daptomycin if MRSA is involved) with gentamicin and rifampin is indicated.
- *Hematogenous osteomyelitis or septic arthritis:* A 4-week treatment course is adequate for children, but adults require longer courses. Joint infections require repeated aspiration or arthroscopy to prevent damage from inflammatory cells.
- *Chronic osteomyelitis:* Surgical debridement—in addition to antibiotic therapy—is needed in most cases.
- *Prosthetic-joint infections:* Ciprofloxacin and rifampin have been used successfully in combination, particularly when the prosthesis cannot be removed.

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**TABLE 86-2 ANTIMICROBIAL THERAPY FOR STAPHYLOCOCCAL INFECTIONS[a]**

| Sensitivity/ Resistance of Isolate | Drug of Choice | Alternative(s) | Comments |
|---|---|---|---|
| **Parenteral Therapy for Serious Infections** | | | |
| Sensitive to penicillin | Penicillin G (4 mU q4h) | Nafcillin or oxacillin (2 g q4h), cefazolin (2 g q8h), vancomycin (1 g q12h[b]) | Fewer than 5% of isolates are sensitive to penicillin. The clinical microbiology laboratory must verify that the strain is not a β-lactamase producer. |
| Sensitive to methicillin | Nafcillin or oxacillin (2 g q4h) | Cefazolin (2 g q8h), vancomycin (15–20 mg/kg q8–12h[b]) | Pts with penicillin allergy can be treated with a cephalosporin if the allergy does not involve an anaphylactic or accelerated reaction; desensitization to β-lactams may be indicated in selected cases of serious infection when maximal bactericidal activity is needed (e.g., prosthetic-valve endocarditis[c]). Type A β-lactamase may rapidly hydrolyze cefazolin and reduce its efficacy in endocarditis. Vancomycin is a less effective option. |
| Resistant to methicillin | Vancomycin (15–20 mg/kg q8–12h[b]), daptomycin (6 mg/kg IV q24h[b,d]) for bacteremia, endocarditis, and complicated skin infections | Linezolid (600 mg q12h PO or IV), ceftaroline (600 mg IV q12h) | Sensitivity testing is necessary before an alternative drug is selected. For some serious infections, higher doses of daptomycin have been used. Quinupristin/dalfopristin is bactericidal against methicillin-resistant isolates unless the strain is resistant to erythromycin or clindamycin. The efficacy of adjunctive therapy is not well established in many settings. Both linezolid and quinupristin/dalfopristin have had in vitro activity against most VISA and VRSA strains. See footnote for treatment of prosthetic-valve endocarditis.[c] |

(*Continued*)



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**TABLE 86-2 ANTIMICROBIAL THERAPY FOR STAPHYLOCOCCAL INFECTIONS[a] (*CONTINUED*)**

| Sensitivity/ Resistance of Isolate | Drug of Choice | Alternative(s) | Comments |
|---|---|---|---|
| Resistant to methicillin with intermediate or complete resistance to vancomycin[e] | Daptomycin (6 mg/kg q24h[b,d]) for bacteremia, endocarditis, and complicated skin infections | Same as for methicillin-resistant strains; check antibiotic susceptibilities<br>***or***<br>Ceftaroline (600 mg IV q12h)<br>Newer agents include tedizolid (200 mg administered once daily either IV or orally) or dalbavancin (two IV doses: 1000 mg followed in 1 week by 500 mg). Both drugs are approved only for the treatment of skin and soft tissue infections. | Same as for methicillin-resistant strains; check antibiotic susceptibilities. Ceftaroline is used either alone or in combination with daptomycin. |
| Not yet known (i.e., empirical therapy) | Vancomycin (15–20 mg/kg q8–12h[b]), daptomycin (6 mg/kg q24h[b,d]) for bacteremia, endocarditis, and complicated skin infections | — | Empirical therapy is given when the susceptibility of the isolate is not known. Vancomycin is recommended for suspected community- or hospital-acquired *Staphylococcus aureus* infections because of the increased frequency of methicillin-resistant strains in the community. |

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| Oral Therapy for Skin and Soft Tissue Infections | | | |
|---|---|---|---|
| Sensitive to methicillin | Dicloxacillin (500 mg qid), cephalexin (500 mg qid) | Minocycline or doxycycline (100 mg q12h[b]), TMP-SMX (1 or 2 ds tablets bid), clindamycin (300–450 mg/kg tid), linezolid (600 mg PO q12h), tedizolid (200 mg PO q24h) | It is important to know the antibiotic susceptibility of isolates in the specific geographic region. All drainage should be cultured. |
| Resistant to methicillin | Clindamycin (300–450 mg/kg tid), TMP-SMX (1 or 2 ds tablets bid), minocycline or doxycycline (100 mg q12h[b]), linezolid (600 mg bid), or tedizolid (200 mg once daily) | Same options as under "Drug of Choice" | It is important to know the antibiotic susceptibility of isolates in the specific geographic region. All drainage should be cultured. |

[a]Recommended dosages are for adults with normal renal and hepatic function.
[b]The dosage must be adjusted for pts with reduced creatinine clearance.
[c]For the treatment of prosthetic-valve endocarditis, the addition of gentamicin (1 mg/kg q8h) and rifampin (300 mg PO q8h) is recommended, with adjustment of the gentamicin dosage if the creatinine clearance rate is reduced.
[d]Daptomycin cannot be used for the treatment of pneumonia.
[e]Vancomycin-resistant *S. aureus* isolates from clinical infections have been reported.
***Abbreviations:*** ds, double-strength; TMP-SMX, trimethoprim-sulfamethoxazole; VISA, vancomycin-intermediate *S. aureus;* VRSA, vancomycin-resistant *S. aureus.*
***Source:*** Modified with permission from FD Lowy: *N Engl J Med* 339:520, 1998 (© 1998 Massachusetts Medical Society. All rights reserved.); C Liu et al: *Clin Infect Dis* 52:285, 2011; DL Stevens et al: *Clin Infect Dis 59:148, 2014; Med Lett Drugs Ther* 56:39, 2014.



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- *TSS:* Supportive therapy and removal of tampons or other packing material or debridement of an infected site are most important. The role of antibiotics is less clear, but a clindamycin/semisynthetic penicillin combination is often recommended.
  - Clindamycin is recommended because it is a protein synthesis inhibitor and has been shown to decrease toxin synthesis in vitro; its efficacy in vivo is less clear.
  - Anecdotally, IV immunoglobulin is helpful.

For a more detailed discussion, see Lowy FD: Staphylococcal Infections, Chap. 172, p. 954, in HPIM-19.

# 87 Streptococcal/Enterococcal Infections, Diphtheria, and Infections Caused by Other Corynebacteria and Related Species

## STREPTOCOCCAL AND ENTEROCOCCAL INFECTIONS

### MICROBIOLOGY

Streptococci and enterococci are gram-positive cocci that form chains when grown in liquid media.

- Culture on blood agar reveals three hemolytic patterns:
  - α-Hemolysis results in partial hemolysis that imparts a greenish appearance to agar. This pattern is seen with *S. pneumoniae* and viridans streptococci.
  - β-Hemolysis results in complete hemolysis around a colony. This pattern is seen with streptococci of Lancefield groups A, B, C, and G. Lancefield grouping is based on cell-wall carbohydrate antigens.
  - γ-Hemolysis describes the absence of hemolytic ability. This pattern is typical of enterococci, nonenterococcal group D streptococci, and anaerobic streptococci.
- Streptococci and enterococci colonize the respiratory, GI, and genitourinary tracts as part of the normal flora. Several of these species are also important causes of human diseases.

### GROUP A *STREPTOCOCCUS* (GAS)

#### Epidemiology and Pathogenesis

GAS (*S. pyogenes*) causes suppurative infections and is associated with postinfectious syndromes such as acute rheumatic fever (ARF) and poststreptococcal glomerulonephritis (PSGN).

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- Up to 20% of people may have asymptomatic pharyngeal colonization with GAS.
  - Pharyngitis due to GAS is one of the most common bacterial infections of childhood.
  - GAS accounts for 20–40% of all cases of exudative pharyngitis in children >3 years of age.
- The incidence of all GAS infections is ~10-fold higher in low-income than in high-income countries. Worldwide, GAS contributes to ~500,000 deaths per year.
- The major surface protein (M protein) and the hyaluronic acid polysaccharide capsule protect GAS against phagocytic ingestion and killing.
- GAS makes a large number of extracellular products that may contribute to local and systemic toxicity; these include streptolysins S and O, streptokinase, DNases, and the pyrogenic exotoxins that cause the rash of scarlet fever and contribute to the pathogenesis of toxic shock syndrome (TSS) and necrotizing fasciitis.
- Respiratory droplets provide the usual route of transmission, although other mechanisms have been described.

## Clinical Manifestations

**Pharyngitis** After an incubation period of 1–4 days, pts develop sore throat, fever, chills, malaise, and GI manifestations.

- Examination may reveal an erythematous and swollen pharyngeal mucosa, purulent exudates over the posterior pharynx and tonsillar pillars, and tender anterior cervical adenopathy.
- Viral pharyngitis is the more likely diagnosis when pts have cough, coryza, hoarseness, conjunctivitis, or mucosal ulcers.
- Throat culture is the gold standard for diagnosis.
  - Latex agglutination or enzyme immunoassay is highly specific (>95%) and can be relied on for a rapid, definitive diagnosis.
  - Given a variable sensitivity of 55–90%, a negative rapid-assay result should be confirmed with a throat culture.

### TREATMENT GAS PHARYNGITIS

- See Table 87-1 for recommended treatments.
  - The primary goal of treatment is to prevent suppurative complications (e.g., lymphadenitis, abscess, sinusitis, bacteremia, pneumonia) and ARF; therapy does not seem to significantly reduce the duration of symptoms or to prevent PSGN.
  - Follow-up cultures after completion of therapy are not routinely recommended.
- Asymptomatic pharyngeal GAS carriage usually is not treated; however, when the pt is a potential source of infection in others (e.g., health care workers), either clindamycin (300 mg PO tid for 10 days) or penicillin V (500 mg PO qid for 10 days) with rifampin (300 mg PO bid for the first 4 days) is used.

**Scarlet Fever** Scarlet fever is the designation for GAS infection—usually pharyngitis—associated with a characteristic rash. It is much less common now than in the past.

- The rash typically appears in the first 2 days of illness over the upper trunk and spreads to the extremities but not to the palms and soles. The skin has a sandpaper feel.
- Other findings include circumoral pallor, strawberry tongue (enlarged papillae on a coated tongue), and Pastia's lines (accentuation of rash in skin folds).
- Rash improves in 6–9 days, with desquamation on palms and soles.

**Skin and Soft Tissue Infections** See Chap. 84 for further discussion of clinical manifestations and treatment.

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**TABLE 87-1 TREATMENT OF GROUP A STREPTOCOCCAL INFECTIONS**

| Infection | Treatment[a] |
|---|---|
| Pharyngitis | Benzathine penicillin G (1.2 mU IM) *or* penicillin V (250 mg PO tid or 500 mg PO bid) × 10 days (Children <27 kg: Benzathine penicillin G [600,000 units IM] *or* penicillin V [250 mg PO bid or tid] × 10 days) |
| Impetigo | Same as pharyngitis |
| Erysipelas/cellulitis | Severe: Penicillin G (1–2 mU IV q4h)<br>Mild to moderate: Procaine penicillin (1.2 mU IM bid) |
| Necrotizing fasciitis/ myositis | Surgical debridement *plus* penicillin G (2–4 mU IV q4h) *plus* clindamycin[b] (600–900 mg IV q8h) |
| Pneumonia/empyema | Penicillin G (2–4 mU IV q4h) *plus* drainage of empyema |
| Streptococcal toxic shock syndrome | Penicillin G (2–4 mU IV q4h) *plus* clindamycin[b] (600–900 mg IV q8h) *plus* IV immunoglobulin[b] (2 g/kg as a single dose) |

[a]Penicillin allergy: A first-generation cephalosporin, such as cephalexin or cefadroxil, may be substituted for penicillin in cases of penicillin allergy if the nature of the allergy is not an immediate hypersensitivity reaction (anaphylaxis or urticaria) or another potentially life-threatening manifestation (e.g., severe rash and fever). Alternative agents for oral therapy are erythromycin (10 mg/kg PO qid, up to a maximum of 250 mg per dose) and azithromycin (a 5-day course at a dose of 12 mg/kg once daily, up to a maximum of 500 mg/d). Vancomycin is an alternative for parenteral therapy.
[b]Efficacy unproven, but recommended by several experts. See text for discussion.

- *Impetigo:* A superficial skin infection, impetigo is most often seen in young children in warmer months or climates and under poor hygienic conditions.
  - Red papular lesions evolve into pustules that ultimately form characteristic honeycomb-like crusts, usually affecting the facial areas around the nose and mouth and the legs. Pts are usually afebrile.
  - GAS impetigo is associated with PSGN but not with ARF.
  - For treatment, see Table 87-1. Given an increasing incidence of impetigo due to *Staphylococcus aureus*, empirical antibiotic therapy should cover GAS and *S. aureus*.
    - Thus dicloxacillin or cephalexin (250 mg PO qid for 10 days) is used.
    - Topical mupirocin ointment is also effective.
- *Cellulitis:* GAS cellulitis develops at anatomic sites where normal lymphatic drainage has been disrupted (e.g., by surgery or prior cellulitis). When skin integrity is breached, organisms may enter at sites distant from the area of cellulitis.
  - GAS may cause rapidly developing postoperative wound infections with a thin exudate.
  - *Erysipelas* is a form of cellulitis characterized by pain, fever, and acute onset of bright red swelling that is sharply demarcated from normal skin.
    - It usually involves the malar facial area or the lower extremities and is caused almost exclusively by β-hemolytic streptococci, usually GAS.
    - The skin often has a *peau d'orange* texture, and blebs or bullae may form after 2 or 3 days.
  - For treatment of erysipelas or cellulitis known to be due to GAS, see Table 87-1; empirical treatment should be directed against GAS and *S. aureus*.

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- *Necrotizing fasciitis:* See Chap. 84 for details. GAS causes ~60% of cases of necrotizing fasciitis. For treatment, see Table 87-1.

**Pneumonia and Empyema** GAS is an occasional cause of pneumonia in previously healthy pts.

- Pts have pleuritic chest pain, fever, chills, and dyspnea; ~50% have accompanying pleural effusions that—unlike the sterile parapneumonic effusions of pneumococcal pneumonia—are almost always infected and should be drained quickly to avoid loculation.
- For treatment, see Table 87-1.

**Bacteremia** In most cases of GAS bacteremia, a focus is readily identifiable. Bacteremia occurs occasionally with cellulitis or pneumonia and frequently with necrotizing fasciitis.
- If no focus is immediately evident, a diagnosis of endocarditis, occult abscess, or osteomyelitis should be considered.

**Toxic Shock Syndrome** Unlike those with TSS due to *S. aureus*, pts with streptococcal TSS generally lack a rash, have bacteremia, and have an associated soft tissue infection (cellulitis, necrotizing fasciitis, or myositis).

- Table 87-2 presents a proposed case definition for streptococcal TSS.
- The mortality rate for streptococcal TSS is ≥30%, with most deaths due to shock and respiratory failure.
- For treatment, see Table 87-1.

## Prevention

Although household contacts of individuals with invasive GAS infection are at increased risk of infection, the attack rate is low enough that antibiotic prophylaxis is not routinely recommended.

**TABLE 87-2 PROPOSED CASE DEFINITION FOR THE STREPTOCOCCAL TOXIC SHOCK SYNDROME[a]**

I. Isolation of group A streptococci (*Streptococcus pyogenes*)
   A. From a normally sterile site
   B. From a nonsterile site
II. Clinical signs of severity
   A. Hypotension *and*
   B. ≥2 of the following signs
      1. Renal impairment
      2. Coagulopathy
      3. Liver function impairment
      4. Adult respiratory distress syndrome
      5. A generalized erythematous macular rash that may desquamate
      6. Soft tissue necrosis, including necrotizing fasciitis or myositis; *or* gangrene

[a]An illness fulfilling criteria IA, IIA, and IIB is defined as a *definite* case. An illness fulfilling criteria IB, IIA, and IIB is defined as a *probable* case if no other etiology for the illness is identified.
***Source:*** Modified from Working Group on Severe Streptococcal Infections: *JAMA* 269:390, 1993.

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## STREPTOCOCCI OF GROUPS C AND G

- Streptococci of groups C and G cause infections similar to those caused by GAS, including cellulitis, bacteremia (particularly in elderly or chronically ill pts), pneumonia, and soft tissue infections.
- Strains that form small colonies (<0.5 mm) on blood agar are generally of the *S. milleri* group (*S. intermedius*, *S. anginosus*); large-colony groups C and G streptococci are now considered a single species (*S. dysgalactiae* subsp. *equisimilis*).
- Treatment is the same as for similar syndromes due to GAS.
  - Although it has not been shown to be superior, the addition of gentamicin (1 mg/kg IV q8h) is recommended by some experts for endocarditis or septic arthritis due to group C or G streptococci because of a poor clinical response to penicillin alone.
  - Joint infections can require repeated aspiration or open drainage for cure.

## GROUP B *STREPTOCOCCUS* (GBS)

- GBS is a major cause of meningitis and sepsis in neonates and a common cause of peripartum fever in women.
  - About half of the infants delivered vaginally to mothers colonized with GBS (5–40% of women) become colonized, but only 1–2% develop infection.
  - With maternal colonization, the risk of neonatal GBS infection is high if delivery is preterm or if the mother has an early rupture of membranes (>24 h before delivery), prolonged labor, fever, or chorioamnionitis.
- Widespread prenatal screening for GBS has reduced the incidence of neonatal infection to 0.6 case per 1000 live births; adults now account for a larger proportion of invasive GBS infections than do newborns.

### Neonatal Infections

- *Early-onset infection* occurs within the first week of life (median age, 20 h). The infection is acquired within the maternal genital tract during birth.
  - Neonates typically have respiratory distress, lethargy, and hypotension.
  - Bacteremia is noted in ~100% of cases, pneumonia in one-third to one-half, and meningitis in one-third.
- *Late-onset infection* develops in infants >1 week old and generally ≤3 months of age (mean age, 3–4 weeks). The organism is acquired during delivery or during later contact with a source.
  - Meningitis is the most common manifestation.
  - Infants present with lethargy, fever, irritability, poor feeding, and occasionally seizures.

**TREATMENT GBS INFECTIONS IN NEONATES**

- Penicillin is the agent of choice for all GBS infections.
  - Empirical therapy for suspected bacterial sepsis consists of ampicillin and gentamicin while cultures are pending.
  - Many physicians continue to give gentamicin until the pt improves clinically.

- *Prevention:* Identification of high-risk mothers and prophylactic administration of ampicillin or penicillin during delivery reduce the risk of neonatal infection.
- Maternal screening for anogenital colonization with GBS at 35–37 weeks of pregnancy is currently recommended.
- Women who have previously given birth to an infant with GBS disease, who have a history of GBS bacteriuria during pregnancy, or who have an unknown culture

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status but risk factors noted above should receive intrapartum prophylaxis (usually 5 mU of penicillin G followed by 2.5 mU q4h until delivery).
  - Cefazolin can be used for pts with a penicillin allergy who are at low risk for anaphylaxis.
  - If the mother is at risk for anaphylaxis and the GBS isolate is known to be susceptible, clindamycin can be used; otherwise, vancomycin is indicated.

## Infections in Adults

Most GBS infections in adults are related to pregnancy and parturition. Other GBS infections are seen in the elderly, especially pts with underlying conditions such as diabetes mellitus or cancer.

- Cellulitis and soft tissue infection, UTI, pneumonia, endocarditis, and septic arthritis are most common.
- Penicillin (12 mU/d for localized infections and 18–24 mU/d for endocarditis or meningitis, in divided doses) is recommended. Vancomycin is an acceptable alternative for penicillin-allergic pts.
- Relapse or recurrent invasive infection occurs in ~4% of cases.

### NONENTEROCOCCAL GROUP D STREPTOCOCCI

The main nonenterococcal group D streptococci that cause human infections are *S. gallolyticus* and *S. infantarius* (previously classified together as *S. bovis*), each of which has two subspecies.

- These organisms have been associated with GI malignancies and other bowel lesions, which are found in ≥60% of pts presenting with group D streptococcal endocarditis.
- Unlike enterococcal endocarditis, group D streptococcal endocarditis can be adequately treated with penicillin alone.

### VIRIDANS STREPTOCOCCI

- Many viridans streptococcal species are part of the normal oral flora, residing in close association with the teeth and gingiva. Minor trauma such as flossing or toothbrushing can cause transient bacteremia.
- Viridans streptococci have a predilection to cause endocarditis. Moreover, they are often part of a mixed flora in sinus infections and brain and liver abscesses.
- Bacteremia is common in neutropenic pts, who can develop a sepsis syndrome with high fever and shock. Risk factors in these pts include chemotherapy with high-dose cytosine arabinoside, prior treatment with trimethoprim-sulfamethoxazole (TMP-SMX) or a fluoroquinolone, mucositis, or therapy with antacids or histamine antagonists.
- The *S. milleri* group (including *S. intermedius*, *S. anginosus*, and *S. constellatus*) differs from other viridans streptococci in both hemolytic pattern (i.e., they may be α-, β-, or γ-hemolytic) and clinical syndromes. These organisms commonly cause suppurative infections, especially abscesses of brain and viscera, as well as infections of the oral cavity and respiratory tract such as peritonsillar abscess, empyema, and lung abscess.
- Neutropenic pts should receive vancomycin pending susceptibility testing; other pts may be treated with penicillin.

### *ABIOTROPHIA* AND *GRANULICATELLA* SPECIES (NUTRITIONALLY VARIANT STREPTOCOCCI)

- The organisms formerly known as nutritionally variant streptococci are now classified as *Abiotrophia defectiva* and three species within the genus *Granulicatella*. These fastidious organisms require media that are enriched (e.g., with vitamin $B_6$) for growth.

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- These organisms are more frequently associated with treatment failure and relapse in cases of endocarditis than are viridans streptococci. Thus, gentamicin (1 mg/kg q8h) must be added to the penicillin regimen.

## ENTEROCOCCI

### Microbiology

Enterococci are gram-positive cocci that are observed as single cells, diplococci, or short chains.

- Enterococci share many morphologic and phenotypic characteristics with streptococci and thus were previously classified as the latter.
- Enterococci are generally nonhemolytic when cultured on blood agar plates.
- Enterococci are inherently resistant to a variety of commonly used antibiotics. *E. faecium* is the most resistant species, with >80% of US isolates resistant to vancomycin (VRE) and >90% resistant to ampicillin. In contrast, only ~7% of *E. faecalis* isolates are resistant to vancomycin and ~4% to ampicillin.

### Epidemiology

Although 18 enterococcal species have been isolated from human infections, *E. faecalis* and *E. faecium* cause the overwhelming majority of enterococcal infections.

- Enterococci are the second most common cause of nosocomial infection (after staphylococci), with roughly equal numbers of cases caused by *E. faecalis* and *E. faecium*.
- Colonization with VRE (as opposed to antibiotic-susceptible strains) predisposes to enterococcal infection. Risk factors for VRE colonization include prolonged hospitalization; long antibiotic courses; hospitalization in long-term care facilities, surgical units, and/or ICUs; organ transplantation; renal failure; high APACHE scores; and physical proximity to pts colonized with VRE.

### Clinical Manifestations

Enterococci cause UTIs, especially in pts who have undergone instrumentation; chronic prostatitis; bacteremia related to intravascular catheters; bacterial endocarditis of both native and prosthetic valves (usually with a subacute presentation); meningitis, particularly in pts who have undergone neurosurgery; soft tissue infections, particularly involving surgical wounds; and neonatal infections. These organisms can also be a component of mixed intraabdominal infections.

## TREATMENT ENTEROCOCCAL INFECTIONS

- Given low cure rates with β-lactam monotherapy, combination therapy with a β-lactam plus gentamicin or streptomycin is recommended for serious enterococcal infections. High-level resistance to aminoglycosides (i.e., minimal inhibitory concentrations of >500 and >2000 μg/mL for gentamicin and streptomycin, respectively) abolishes the synergism otherwise obtained by adding an aminoglycoside to a cell wall–active agent. This phenotype must be assessed in isolates from serious infections.
- There is burgeoning evidence that ampicillin plus ceftriaxone is as effective as ampicillin plus gentamicin in the treatment of *E. faecalis* endocarditis, with less risk of toxicity.
- For *E. faecium* isolates resistant to ampicillin:
  - Daptomycin, quinupristin/dalfopristin, or linezolid plus another active agent (doxycycline with rifampin, tigecycline, or a fluoroquinolone) may be used.
  - If daptomycin is used and if high-level resistance is not noted, an aminoglycoside should be added to the regimen.

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- If high-level aminoglycoside resistance is present, two other active agents should be used.

## CORYNEBACTERIAL AND RELATED INFECTIONS

### DIPHTHERIA

#### Microbiology

*Corynebacterium diphtheriae,* the causative agent of the nasopharyngeal and skin infection known as diphtheria, is a club-shaped, gram-positive, unencapsulated, nonmotile, nonsporulating rod.

- The bacteria often form clusters of parallel arrays (palisades) in culture, referred to as *Chinese characters*.
- Some strains produce diphtheria toxin, which can cause myocarditis, polyneuropathy, and other systemic toxicities and is associated with the formation of pseudomembranes in the pharynx during respiratory infection.

#### Epidemiology and Pathogenesis

As a result of routine immunization, fewer than five cases of diphtheria are diagnosed per year in the United States.

- Low-income countries in Africa and Asia continue to have significant outbreaks; globally, there were ~7000 cases of diphtheria in 2008 and ~5000 deaths related to diphtheria in 2004.
- *C. diphtheriae* is transmitted via the aerosol route, primarily during close contact.
- Diphtheria toxin—the primary virulence factor—irreversibly inhibits protein synthesis, thereby causing the death of the cell.

#### Clinical Manifestations

- *Respiratory diphtheria:* Upper respiratory tract illness due to *C. diphtheriae* typically has a 2- to 5-day incubation period and is diagnosed on the basis of a constellation of sore throat; low-grade fever; and a tonsillar, pharyngeal, or nasal pseudomembrane.
  - Unlike that of GAS pharyngitis, the pseudomembrane of diphtheria is tightly adherent; dislodging the membrane usually causes bleeding.
  - Massive swelling of the tonsils and "bull-neck" diphtheria resulting from submandibular and paratracheal edema can develop. This illness is further characterized by foul breath, thick speech, and stridorous breathing.
  - Respiratory tract obstruction due to swelling and sloughing of the pseudomembrane can be fatal.
  - Neurologic manifestations may appear during the first 2 weeks of illness, beginning with dysphagia and nasal dysarthria and progressing to cranial nerve involvement (e.g., weakness of the tongue, facial numbness, blurred vision due to ciliary paralysis).
    - Several weeks later, generalized sensorimotor polyneuropathy with prominent autonomic dysfunction (including hypotension) may occur.
    - Pts who survive the acute phase gradually improve.
- *Cutaneous diphtheria:* This variable dermatosis is generally characterized by punched-out ulcerative lesions with necrotic sloughing or pseudomembrane formation. Pts typically present to medical care because of nonhealing or enlarging ulcers; the lesions rarely exceed 5 cm in diameter.

#### Diagnosis

A definitive diagnosis is based on compatible clinical findings and detection of *C. diphtheriae* or toxigenic *C. ulcerans* (by isolation or histologic identification) in local lesions.

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- The laboratory should be notified that diphtheria is being considered, and appropriate selective media must be used.
- In the United States, respiratory diphtheria is a notifiable disease; cutaneous diphtheria is not.

**TREATMENT DIPHTHERIA**

- Diphtheria antitoxin is the most important component of treatment and should be given as soon as possible. To obtain antitoxin, contact the Emergency Operations Center at the Centers for Disease Control and Prevention (CDC) (770-488-7100). See *http://www.cdc.gov/diphtheria/dat.html* for further information.
- Antibiotic therapy is administered for 14 days to prevent transmission to contacts. The recommended options are (1) procaine penicillin G (600,000 U IM q12h in adults; 12,500–25,000 U/kg IM q12h in children) until the pt can take oral penicillin V (125–250 mg qid); or (2) erythromycin (500 mg IV q6h in adults; 40–50 mg/kg per day IV in 2–4 divided doses in children) until the pt can take oral erythromycin (500 mg qid).
  - Rifampin and clindamycin are other options for pts who cannot tolerate penicillin or erythromycin.
  - Cultures should document eradication of the organism 1 and 14 days after completion of antibiotic therapy. If the organism is not eradicated after 2 weeks of therapy, an additional 10-day course followed by repeat cultures is recommended.
- Respiratory isolation and close monitoring of cardiac and respiratory functions should be instituted.

## Prognosis

Risk factors for death include a long interval between onset of local disease and antitoxin administration; bull-neck diphtheria; myocarditis with ventricular tachycardia; atrial fibrillation; complete heart block; an age of >60 years or <6 months; alcoholism; extensive pseudomembrane elongation; and laryngeal, tracheal, or bronchial involvement.

## Prevention

- DTaP (diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed) is recommended for primary immunization of children up to age 7 years; Tdap (tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis) is recommended as the booster vaccine for children 11–12 years old and as the catch-up vaccine for children 7–10 and 13–18 years old.
- Td (tetanus and diphtheria toxoids) is recommended for routine booster use in adults at 10-year intervals or for tetanus-prone wounds. When >10 years have elapsed since the last Td dose, adults 19–64 years old should receive a single dose of Tdap.
- Close contacts of pts with respiratory diphtheria should have throat specimens cultured for *C. diphtheriae*, should receive a 7- to 10-day course of oral erythromycin or one dose of benzathine penicillin (1.2 mU for persons ≥6 years old; 600,000 U for children <6 years old), and should be vaccinated if immunization status is uncertain.

## OTHER CORYNEBACTERIA AND RELATED ORGANISMS

Nondiphtherial *Corynebacterium* species and related organisms are common components of the normal human flora. Although frequently considered contaminants, these bacteria are associated with invasive disease in immunocompromised hosts.

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- *C. ulcerans* infection is a zoonosis that causes diphtheria-like illness and requires similar treatment.
- *C. jeikeium* infects pts with cancer or severe immunodeficiency and can cause severe sepsis, endocarditis, device-related infections, pneumonia, and soft tissue infections. Treatment consists of removal of the source of infection and administration of vancomycin.
- *C. urealyticum* is a cause of sepsis and nosocomial UTI, including *alkaline-encrusted cystitis* (a chronic inflammatory bladder infection associated with deposition of ammonium magnesium phosphate on the surface and walls of ulcerating lesions in the bladder). Vancomycin is an effective therapeutic agent.
- *Rhodococcus* species appear as spherical to long, curved, clubbed gram-positive rods that are often acid fast. The most common presentation—nodular cavitary pneumonia of the upper lobe (similar to tuberculosis and nocardiosis) in an immunocompromised host—often occurs in conjunction with HIV infection. Vancomycin is the drug of choice, but macrolides, clindamycin, rifampin, and TMP-SMX have also been used to treat these infections.
- *Arcanobacterium haemolyticum* can cause pharyngitis and chronic skin ulcers, often in association with a scarlatiniform rash similar to that caused by GAS. The organism is susceptible to β-lactam agents, macrolides, fluoroquinolones, clindamycin, vancomycin, and doxycycline. Penicillin resistance has been reported.

For a more detailed discussion, see Wessels MR: Streptococcal Infections, Chap. 173, p. 963; Arias CA, Murray BE: Enterococcal Infections, Chap. 174, p. 971; Bishai WR, Murphy JR: Diphtheria and Other Corynebacterial Infections, Chap. 175, p. 977, in HPIM-19.

# 88 Meningococcal and Listerial Infections

## MENINGOCOCCAL INFECTIONS

- *Etiology and microbiology: Neisseria meningitidis* is a catalase- and oxidase-positive, gram-negative aerobic diplococcus with a polysaccharide capsule that colonizes humans only.
  - Of the 13 identified serogroups, only 6—A, B, C, X, Y, and W (formerly W135)—account for the majority of cases of invasive disease.
  - Serogroups A, X, and W cause recurrent epidemics in sub-Saharan Africa. Serogroup B can cause hyperendemic disease, and serogroups C and Y cause sporadic disease and small outbreaks.
- *Epidemiology:* Up to 500,000 cases of meningococcal disease occur worldwide each year, with a mortality rate of ~10%.

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- Most commonly, meningococci asymptomatically colonize the nasopharynx; such asymptomatic nasopharyngeal carriage is detected in >25% of healthy adolescents and ~10% of adults.
- Patterns of meningococcal disease include epidemics, outbreaks (e.g., in colleges, refugee camps), hyperendemic disease, and sporadic or endemic cases.
- Although most countries have predominantly sporadic cases (0.3–5 cases per 100,000 population), epidemics in sub-Saharan Africa can have rates as high as 1000 cases per 100,000 population.
- Rates of meningococcal disease are highest among infants, with a second peak in adolescents and young adults (15–25 years of age).
- Other risk factors for meningococcal disease include complement deficiency (e.g., C5–C9, properdin, factor D), close contact with carriers, exposure to tobacco smoke, and a recent URI caused by a virus or *Mycoplasma* species.

• *Pathogenesis:* Meningococci colonizing the upper respiratory tract invade the bloodstream through the mucosa only rarely, usually within a few days after an invasive strain is acquired.
- The capsule is an important virulence factor, providing resistance to phagocytosis and helping prevent desiccation during transmission between hosts.
- Severity of disease is related to the degree of endotoxemia and the magnitude of the inflammatory response.
- Endothelial injury leads to increased vascular permeability and hypovolemia, resulting in vasoconstriction and ultimately in decreased cardiac output.
- Intravascular thrombosis caused by activation of procoagulant pathways and downregulation of anticoagulant pathways results in the characteristic purpura fulminans often seen in meningococcemia.

• *Clinical manifestations:* The most common clinical syndromes are meningitis and meningococcal septicemia, with disease usually developing within 4 days of organism acquisition.
- A nonblanching rash (petechial or purpuric) develops in >80% of cases; early in the illness, the rash is often absent or may be indistinguishable from viral rashes.
- Meningococcal meningitis alone (without septicemia) accounts for 30–50% of cases.
  - This meningitis is indistinguishable from other forms of bacterial meningitis unless there is an associated petechial or purpuric rash.
  - Classic signs of meningitis (e.g., headache, neck stiffness, photophobia) are often absent or difficult to discern in infants and young children.
- Meningococcal septicemia alone accounts for ~20% of cases and initially may present as an influenza-like illness (e.g., fever, headache, myalgias, vomiting, abdominal pain).
  - May progress to shock (e.g., tachycardia, poor peripheral perfusion, oliguria), decreased level of consciousness due to decreased cerebral perfusion, spontaneous hemorrhage (pulmonary, gastric, or cerebral), and ultimately multiorgan failure and death
  - Poor prognostic factors include an absence of meningismus, hypotension, relatively low temperature (<38°C [100.4°F]), leukopenia, and thrombocytopenia.
- Chronic meningococcemia, which is rarely recognized, presents as repeated episodes of petechial rash associated with fever, joint pain, features of arthritis, and splenomegaly that may progress to acute meningococcal septicemia if untreated.
  - This condition is occasionally associated with complement deficiencies or inadequate sulfonamide therapy.
- Postmeningococcal reactive disease is immune complex–mediated and occurs 4–10 days after onset of meningococcal disease.
  - Manifestations can include a maculopapular or vasculitic rash (2% of cases), arthritis (≤8% of cases), iritis (1% of cases), or serositis. These features resolve spontaneously without sequelae.

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- Less common clinical manifestations include pneumonia, pyogenic arthritis, osteomyelitis, purulent pericarditis, endophthalmitis, conjunctivitis, or primary peritonitis.

- *Diagnosis:* Although meningococcal infections are often diagnosed on clinical grounds, blood cultures are positive in ~75% of cases and should be performed to confirm the diagnosis and to facilitate public health investigations.
  - In the setting of fever and petechial rash, elevations in the WBC count and inflammatory marker levels suggest meningococcal disease.
  - With antibiotic pretreatment, blood cultures are generally negative; in contrast, PCR analysis of whole-blood samples is effective for several days after initiation of antibiotics and increases the diagnostic yield by >40%.
  - Unless contraindicated on clinical grounds, LP should be performed in cases of suspected meningococcal meningitis.
    - Gram's staining of CSF is ~80% sensitive, and CSF culture is 90% sensitive. Latex agglutination testing of CSF is insensitive and should be avoided.
    - LP should be avoided in pts with meningococcal septicemia, as positioning for the procedure may adversely affect circulatory status.

## TREATMENT MENINGOCOCCAL INFECTIONS

- Initial therapy should focus on urgent clinical issues (e.g., hypovolemic shock, increased intracranial pressure, airway patency) and administration of antibiotics.
- Empirical antibiotic therapy for suspected meningococcal disease consists of a third-generation cephalosporin such as ceftriaxone (75–100 mg/kg per day [maximum, 4 g/d] in one or two divided IV doses) or cefotaxime (200 mg/kg per day [maximum, 8 g/d] in four divided IV doses) to provide coverage both for meningococci and for other, potentially penicillin-resistant organisms that may produce an indistinguishable clinical syndrome.
- Meningococcal meningitis and meningococcal septicemia are conventionally treated for 7 days.
  - A single dose of ceftriaxone has been used successfully in resource-poor settings.
  - Treatment for meningococcal disease at other foci (e.g., pneumonia, arthritis) is usually continued until clinical and laboratory evidence of infection has resolved; cultures usually become sterile within 24 h of initiation of antibiotics.
- Little evidence supports other adjunctive therapies (e.g., antibody to lipopolysaccharide, recombinant bactericidal/permeability-increasing protein, activated protein C) in relevant pt populations; these therapies are not currently recommended.

- *Prognosis:* Despite the availability of antibiotics and other intensive medical interventions, ~10% of pts die.
  - Necrosis of purpuric lesions leads to scarring and the potential need for skin grafting in ~10% of cases.
  - 5% of pts have hearing loss, 7% of pts have neurologic complications, and ~25% of pts with serogroup B meningococcal disease have psychological disorders.
- *Prevention:* Polysaccharide-based and conjugate vaccines exist for primary prevention; secondary cases can be prevented with antibiotic prophylaxis.
  - Meningococcal polysaccharide vaccines are currently formulated as bivalent (serogroups A and C) or quadrivalent (serogroups A, C, Y, and W) and provide adults with immunity of 2–10 years' duration. Because the B polysaccharide is the same as a polysaccharide expressed in fetuses and is therefore recognized as self, serogroup B strains have not been targeted by polysaccharide vaccines.

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- A variety of meningococcal conjugate vaccines have been developed for administration to infants. A quadrivalent formulation (serogroups A, C, Y, and W) is most common in the United States.
- A combination vaccine that includes outer-membrane vesicles and three recombinant neisserial proteins is effective against serogroup B, is immunogenic in infancy, and has recently been licensed for use.
- Close contacts (i.e., household and kissing contacts) of pts with meningococcal disease should receive prophylaxis with ciprofloxacin, ofloxacin, or ceftriaxone to eradicate nasopharyngeal colonization by *N. meningitidis*.
  - Rifampin fails to eradicate carriage in 15–20% of cases, and emerging resistance has been reported.
  - Pts with meningococcal disease who are treated with an antibiotic that does not clear colonization (e.g., penicillin) should also be given a prophylactic agent at the end of therapy.

## LISTERIAL INFECTIONS

- *Etiology and microbiology: Listeria monocytogenes* is a food-borne pathogen that can cause serious infections, particularly in pregnant women and immunocompromised individuals.
  - The organism is a facultatively anaerobic, nonsporulating, gram-positive rod that demonstrates motility when cultured at low temperatures.
  - After ingestion of food that contains a high bacterial burden, virulence factors expressed by *Listeria* allow internalization into cells, intracellular growth, and cell-to-cell spread.
- *Epidemiology*
  - *Listeria* is commonly found in processed and unprocessed foods such as soft cheeses, delicatessen meats, hot dogs, milk, and cold salads; fresh fruits and vegetables can also transmit the organism.
  - There is no human-to-human transmission (other than vertical transmission from mother to fetus) or waterborne infection.
- *Clinical manifestations: Listeria* causes several clinical syndromes, of which meningitis and septicemia are most common.
  - *Gastroenteritis:* can develop within 48 h after ingestion of contaminated foods containing a large bacterial inoculum
    - Listeriosis should be considered in outbreaks of gastroenteritis when cultures for other likely pathogens are negative.
    - Sporadic cases appear to be uncommon.
  - *Bacteremia:* Pts present with fever, chills, myalgias, and arthralgias. Endocarditis is uncommon and is associated with fatality rates of 35–50%.
  - *Meningitis: Listeria* causes ~5–10% of cases of community-acquired meningitis in adults in the United States, with case–fatality rates of 15–26%.
    - Listerial meningitis differs from meningitis of other bacterial etiologies in that its presentation is often subacute, with meningeal signs and photophobia being less common.
    - The CSF profile usually reveals <1000 WBCs/μL, with a less marked neutrophil predominance than in other meningitides. Low glucose levels and a positive Gram's stain are seen in ~30–40% of cases.
  - *Meningoencephalitis and focal CNS infection: Listeria* can directly invade the brain parenchyma and cause cerebritis or focal abscess.
    - Of CNS infections, ~10% are macroscopic abscesses, which are sometimes misdiagnosed as tumors.
    - Brainstem invasion can cause severe rhombencephalitis, with asymmetric cranial nerve defects, cerebellar signs, and hemiparetic/hemisensory defects.

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- *Infection in pregnant women and neonates:* Listeriosis is a serious infection in pregnancy.
  - Pregnant women are usually bacteremic and present with a nonspecific febrile illness that includes myalgias/arthralgias, backache, and headache; CNS involvement is rare. Infected women usually do well after delivery.
  - Infection develops in 70–90% of fetuses from infected women; almost 50% of infected fetuses die. This risk can be reduced to ~20% with prepartum treatment.
  - Overwhelming listerial fetal infection—*granulomatosis infantiseptica*—is characterized by miliary microabscesses and granulomas, most often in the skin, liver, and spleen.
  - Late-onset neonatal disease develops ~10–30 days after delivery by mothers with asymptomatic infection.

- *Diagnosis:* Timely diagnosis requires that the illness be considered in groups at risk: pregnant women, elderly pts, neonates, immunocompromised pts, and pts with chronic underlying medical conditions (e.g., alcoholism, diabetes).
  - Listeriosis is diagnosed when the organism is cultured from a usually sterile site, such as blood, CSF, or amniotic fluid.
  - Listeriae may be confused with "diphtheroids" or pneumococci in gram-stained CSF or may be gram-variable and confused with *Haemophilus* spp.
  - Serologic tests and PCR assays are not clinically useful at present.

## TREATMENT LISTERIAL INFECTIONS

- Ampicillin (2 g IV q6h) is the drug of choice for the treatment of listerial infections; penicillin is also highly active.
  - Many experts recommend the addition of gentamicin (1.0–1.7 mg/kg IV q8h) for synergy.
  - For penicillin-allergic pts, trimethoprim-sulfamethoxazole (15–20 mg of TMP/kg IV daily in divided doses q6–8h) should be given. Cephalosporins are not effective.
  - Neonates should receive ampicillin and gentamicin, dosed by weight.
- The duration of therapy depends on the syndrome: 2 weeks for bacteremia, 3 weeks for meningitis, 6–8 weeks for brain abscess/encephalitis, and 4–6 weeks for endocarditis. Early-onset neonatal disease can be severe and requires treatment for >2 weeks.

- *Prognosis:* With prompt therapy, many pts recover fully.
  - However, permanent neurologic sequelae are common in pts with brain abscess or rhombencephalitis.
  - Of live-born treated neonates in one series, 60% recovered fully, 24% died, and 13% were left with neurologic or other complications.
- *Prevention:* Pregnant women and other persons at risk for listeriosis should avoid soft cheeses and should avoid or thoroughly reheat ready-to-eat and delicatessen foods, even though the absolute risk posed by these foods is relatively low.

For a more detailed discussion, see Pollard AJ: Meningococcal Infections, Chap. 180, p. 995; Hohmann EL, Portnoy DA: *Listeria monocytogenes* Infections, Chap. 176, p. 982, in HPIM-19.

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# 89 Infections Caused by *Haemophilus, Bordetella, Moraxella*, and HACEK Group Organisms

## *HAEMOPHILUS INFLUENZAE*

### MICROBIOLOGY

*H. influenzae* is a small, gram-negative, pleomorphic coccobacillus that grows both aerobically and anaerobically.

- Six major serotypes (designated *a–f*) have been identified on the basis of antigenically distinct polysaccharide capsules.
- Unencapsulated strains are referred to as nontypable (NTHi).

### EPIDEMIOLOGY

*H. influenzae*, an exclusively human pathogen, is spread by airborne droplets or through direct contact with secretions or fomites.

- Type b (Hib) strains are most important clinically, causing systemic invasive disease, primarily in infants and children <6 years of age.
- Widespread use of Hib conjugate vaccine in industrialized countries has dramatically decreased rates of Hib colonization and invasive disease, but the majority of children worldwide remain unimmunized.
- Both typable and nontypable strains can asymptomatically colonize the nasopharynx.

### PATHOGENESIS

Hib strains cause systemic disease by invasion and systemic spread from the respiratory tract to distant sites (e.g., meninges, bones, joints). In contrast, NTHi strains cause disease by spread from the nasopharynx to contiguous sites (e.g., middle ear, lower respiratory tract).

- The polysaccharide capsule of encapsulated strains is critical for the organism's avoidance of opsonization.
- Levels of maternally derived antibodies to the capsular polysaccharide decline from birth to ~6 months of age and—in the absence of vaccination—remain low until ~2–3 years of age.

### CLINICAL MANIFESTATIONS

- *Hib infection:* The most serious Hib infections are associated with meningitis or epiglottitis.
  - *Meningitis:* primarily affects children <2 years old and presents similarly to meningitis due to other bacterial pathogens
    - Mortality rates are ~5%.
    - Morbidity rates are high: 6% of pts have sensorineural hearing loss; one-fourth have some significant handicap; and one-half have some neurologic sequelae.
  - *Epiglottitis:* occurs in children 2–7 years old and occasionally in adults. It involves cellulitis of the epiglottis and supraglottic tissues that begins with a sore throat and fever and progresses rapidly to dysphagia, drooling, and airway obstruction.
  - *Other infections:* include cellulitis, pneumonia, osteomyelitis, septic arthritis, and bacteremia without an identifiable focus
- *NTHi infection:* NTHi is a common cause of lower respiratory tract disease in adults, particularly those with chronic obstructive pulmonary disease (COPD).

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- *COPD exacerbations:* characterized by increased cough, sputum production, and shortness of breath
- *Pneumonia:* presents similarly to other bacterial pneumonias, including pneumococcal pneumonia
- *Other infections:* NTHi is one of the three most common causes of childhood otitis media and is an important cause of sinusitis (in adults and children) and neonatal bacteremia. It is a less common cause of invasive infections in adults.

### DIAGNOSIS

Recovery of the organism in culture is the most reliable method for diagnosis.

- The presence of gram-negative coccobacilli in gram-stained CSF provides strong evidence for meningitis due to *H. influenzae*.
- Detection of polyribitol ribose phosphate (PRP)—polymers of which form the type b capsule—in CSF allows rapid diagnosis of Hib meningitis before culture results are available.

### TREATMENT *H. INFLUENZAE* INFECTIONS

- Initial therapy for Hib meningitis consists of a third-generation cephalosporin: ceftriaxone (2 g q12h) or cefotaxime (2 g q4–6h) for adults and ceftriaxone (37.5–50 mg/kg q12h) or cefotaxime (50 mg/kg q6h) for children.
  - Children >2 months of age should receive adjunctive dexamethasone (0.15 mg/kg IV q6h for 2 days) to reduce the incidence of neurologic sequelae.
  - Antibiotic therapy should continue for 7–14 days.
- Antibiotic treatment for invasive infections other than meningitis (e.g., epiglottitis) consists of the same antibiotic but at a dosage different from that given for meningitis—e.g., ceftriaxone (2 g q24h) for adults.
  - Treatment duration depends on the clinical response, but a course lasting 1–2 weeks is generally appropriate.
- Most NTHi infections can be treated with oral antibiotics, such as amoxicillin/clavulanate, extended-spectrum cephalosporins, newer macrolides (azithromycin or clarithromycin), and fluoroquinolones (in nonpregnant adults).
  - About 20–35% of NTHi strains produce β-lactamase.
  - The incidence of strains with altered penicillin-binding proteins conferring resistance to ampicillin is increasing in Europe and Japan.

### PREVENTION

Hib vaccine is recommended for all children worldwide; the immunization series should be started at ~2 months of age.

- Secondary attack rates are high among household contacts of pts with Hib disease. All children and adults (except pregnant women) in households with a case of Hib disease and at least one incompletely immunized contact <4 years of age should receive prophylaxis with oral rifampin.
- A vaccine that combines NTHi and pneumococcal antigens is used in many countries outside the United States and has shown partial efficacy in preventing *H. influenzae* otitis media.

## PERTUSSIS

### MICROBIOLOGY AND PATHOGENESIS

*Bordetella pertussis,* the etiologic agent of pertussis, is a fastidious gram-negative pleomorphic aerobic bacillus that attaches to ciliated epithelial cells of the

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nasopharynx, multiplies locally, and produces a wide array of toxins and biologically active products.

- *B. parapertussis* causes a similar, though typically milder, illness. *B. holmesii* causes up to 20% of pertussis-like syndromes.
- The most important toxin in *B. pertussis* is pertussis toxin, which has ADP ribosylating activity. The absence of this toxin in *B. parapertussis* may explain the milder illness.

## EPIDEMIOLOGY

Pertussis is highly communicable. In households, attack rates are 80–100% among unimmunized contacts and 20% among immunized contacts.

- Pertussis remains an important cause of infant morbidity and death in developing countries, with ~195,000 childhood deaths worldwide in 2008.
- In the United States, although the incidence of pertussis has decreased by >95% because of universal childhood vaccination, >40,000 cases were reported in 2012, with increasing rates among adolescents and adults.
- Persistent cough of >2 weeks' duration in an adult may be due to *B. pertussis* in 12–30% of cases.
- Severe morbidity and mortality are restricted to infants <6 months of age.

## CLINICAL MANIFESTATIONS

After an incubation period of 7–10 days, a prolonged coughing illness begins. Symptoms are usually more severe in infants and young children.

- The initial symptoms (the *catarrhal* phase) are similar to those of the common cold (e.g., coryza, lacrimation, mild cough, low-grade fever, malaise) and last 1–2 weeks.
- The *paroxysmal* phase follows and lasts 2–4 weeks. It is characterized by a hallmark cough that occurs in spasmodic fits of 5–10 coughs each. Vomiting or a "whoop" may follow a coughing fit. Apnea and cyanosis can occur during spasms. Most complications occur during this phase.
- During the subsequent *convalescent* phase, coughing episodes resolve gradually over 1–3 months. For 6–12 months, viral infections may induce a recrudescence of paroxysmal cough.
- Disease manifestations are often atypical in adolescents and adults, with paroxysmal cough and the "whoop" being less common. Post-tussive emesis is the best predictor of pertussis as the cause of prolonged cough in adults.
- Lymphocytosis (an absolute lymphocyte count of $>10^5/\mu L$) suggests pertussis in young children, but is not common among affected adolescents and adults.

## DIAGNOSIS

- Cultures of nasopharyngeal secretions—the gold standard for diagnosis—remain positive in untreated cases of pertussis for a mean of 3 weeks after illness onset. Given that the diagnosis often is not considered until the pt is in the paroxysmal phase, there is a small window of opportunity for culture-proven diagnosis.
  - Secretions must be inoculated immediately onto selective media.
  - Results become positive by day 5.
- Compared with culture, PCR of nasopharyngeal specimens is more sensitive and yields positive results longer in both treated and untreated pts.
  - Reporting of pseudo-outbreaks of pertussis based on false-positive PCR results indicates the need for greater standardization.
- Although serology can be useful in pts with symptoms lasting >4 weeks, interpretation of results is complicated by late presentation for medical care and prior immunization.

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**TREATMENT PERTUSSIS**

- Antibiotic therapy does not substantially alter the clinical course unless given early in the catarrhal phase, but is effective at eradicating the organism from the nasopharynx.
  - Macrolides (erythromycin, 1–2 g/d for 1–2 weeks; clarithromycin, 250 mg bid for 1 week; or azithromycin, 500-mg load on day 1, then 250 mg/d for 4 days) are the drugs of choice.
  - Trimethoprim-sulfamethoxazole (TMP-SMX; one double-strength tablet PO bid for 2 weeks) is recommended for macrolide-intolerant pts.
- Cough suppressants are ineffective and have no role in management of pertussis.
- Respiratory isolation is required for hospitalized pts until antibiotics have been given for 5 days.

### PREVENTION

- Chemoprophylaxis with macrolides is recommended for household contacts of pts, especially if there are household members at high risk of severe disease (e.g., children <1 year of age, pregnant women); however, there is no evidence demonstrating that this regimen leads to a decrease in the incidence of clinical disease.
- In addition to the regular childhood immunization schedule, adolescents and adults should receive a one-time booster with an acellular vaccine.

## *MORAXELLA CATARRHALIS*

### MICROBIOLOGY AND EPIDEMIOLOGY

*M. catarrhalis* is an unencapsulated gram-negative diplococcus. Part of the normal flora of the upper airways, *M. catarrhalis* colonizes 33–100% of infants; the prevalence of colonization decreases steadily with age.

### CLINICAL MANIFESTATIONS

- *M. catarrhalis* causes 15–20% of cases of acute otitis media in children. Acute otitis media caused by *M. catarrhalis* or NTHi is clinically milder than cases caused by *Streptococcus pneumoniae*, with less fever and a lower frequency of an erythematous, bulging tympanic membrane.
- *M. catarrhalis* accounts for ~20% of cases of acute bacterial sinusitis in children and for a smaller proportion in adults.
- In adults, *M. catarrhalis* is a common cause of exacerbations of COPD, accounting for ~10% of cases.
- *M. catarrhalis* pneumonia is uncommon, generally affecting elderly pts with underlying cardiopulmonary disease.

### DIAGNOSIS

Invasive procedures are needed to definitively identify the etiology of otitis media or sinusitis and are generally not performed. Isolation of *M. catarrhalis* from sputum samples from pts with COPD is suggestive, but not diagnostic, of *M. catarrhalis* as the cause.

**TREATMENT *M. CATARRHALIS* INFECTIONS**

- Otitis media in children and exacerbations of COPD in adults are generally managed empirically with antibiotics active against *S. pneumoniae, H. influenzae,* and *M. catarrhalis*.

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- Most strains of *M. catarrhalis* are susceptible to amoxicillin/clavulanate, extended-spectrum cephalosporins, newer macrolides (e.g., azithromycin, clarithromycin), TMP-SMX, and fluoroquinolones.
- More than 90% of *M. catarrhalis* strains produce a β-lactamase and are resistant to ampicillin.

## THE HACEK GROUP

### MICROBIOLOGY

The HACEK group consists of fastidious, slow-growing, gram-negative bacteria whose growth requires carbon dioxide. Several *Haemophilus* spp., *Aggregatibacter* (formerly *Actinobacillus*) *actinomycetemcomitans*, *Aggregatibacter* (formerly *Haemophilus*) *aphrophilus*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae* make up this group. Normal residents of the oral cavity, HACEK bacteria can cause both local oral infections and severe systemic disease, particularly endocarditis.

### CLINICAL MANIFESTATIONS

- HACEK organisms caused 0.8–6% of cases of infective endocarditis; most of these cases are due to *Aggregactibacter* spp., *Haemophilus* spp., or *C. hominis*.
- Infection typically occurs in pts with underlying valvular disease, often in the setting of a recent dental procedure or nasopharyngeal infection.
- The aortic and mitral valves are most commonly affected. *Aggregatibacter* and *Haemophilus* spp. cause mitral valve vegetations most often, while *C. hominis* is associated with aortic valve vegetations.
- Embolization is common, with 28–71% of pts affected.
- *H. parainfluenzae* is the most common organism isolated in cases of HACEK endocarditis. Pts usually present within the first 2 months of illness, and 19–50% of pts develop CHF.
- *Aggregatibacter* spp. cause prosthestic valve endocarditis more often than *Haemophilus* spp. *A. actinomycetemcomitans* is isolated from soft tissue infections in association with *Actinomyces israelii*. Pts with *Aggregatibacter* endocarditis often have periodontal disease or have recently had dental work and are sick for several months before diagnosis.
- *C. hominis* typically causes endocarditis in pts with valvular heart disease or prosthetic valves. Long-standing infection with systemic manifestations usually precedes diagnosis. A second species, *C. valvarum*, has now been described in association with endocarditis.
- *E. corrodens* is usually a component of mixed infections and is common in human bite wounds, head and neck soft tissue infections, endocarditis, and infections in IV drug users.
- *K. kingae* is a common cause of skeletal infections in children <3 years old. Inoculation of clinical specimens (e.g., synovial fluid) into aerobic blood-culture bottles enhances recovery of this organism. Infective endocarditis due to *K. kingae* occurs in older children and adults with preexisting valvular disease.

### TREATMENT HACEK GROUP INFECTIONS

- Table 89-1 lists antibiotic regimens used to treat endocarditis and other serious infections caused by HACEK organisms.
- Native-valve endocarditis should be treated for 4 weeks and prosthetic-valve endocarditis for 6 weeks.
- Unlike prosthetic-valve endocarditis caused by other gram-negative organisms, that due to HACEK bacteria can often be cured with antibiotics alone (i.e., without surgery).

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**TABLE 89-1 TREATMENT OF INFECTIONS CAUSED BY HACEK GROUP ORGANISMS**

| Organisms | Preferred Therapy | Alternative Agents | Comments |
|---|---|---|---|
| *Haemophilus* spp.<br>*Aggregatibacter actinomycetemcomitans, A. aphrophilus, A. paraphrophilus*, other species<br>*Cardiobacterium hominis*<br>*Eikenella corrodens*<br>*Kingella kingae* | Ceftriaxone (2 g/d) | Ampicillin/sulbactam (3 g of ampicillin q6h) | Ampicillin/sulbactam resistance has been described in *Haemophilus* and *Aggregatibacter* spp. |
| | | Levofloxacin (500–750 mg/d) | Data on use of levofloxacin for endocarditis therapy are limited. Fluoroquinolones are not recommended for treatment of pts <18 years of age. |
| | | Penicillin (16–18 million units q4h) or ampicillin (2 g q4h) | Penicillin or ampicillin can be used if the organism is susceptible. However, because of the slow growth of HACEK bacteria, antimicrobial testing may be difficult, and β-lactamase production may not be detected. |

For a more detailed discussion, see Murphy TF: *Haemophilus* and *Moraxella* Infections, Chap. 182, p. 1010; Barlam TF, Kasper DL: Infections Due to the HACEK Group and Miscellaneous Gram-Negative Bacteria, Chap. 183e; Top KA, Halperin SA: Pertussis and Other *Bordetella* Infections, Chap. 185, p. 1021, in HPIM-19.

# 90 Diseases Caused by Gram-Negative Enteric Bacteria and *Pseudomonas*

## GRAM-NEGATIVE ENTERIC BACTERIA

### GENERAL CONSIDERATIONS

Gram-negative bacilli (GNB) are normal components of the human colonic flora and/or a number of environmental habitats and can colonize mucosal and skin surfaces, especially in pts in long-term care facilities and hospital settings. GNB cause a wide variety of infections involving diverse anatomic sites in both healthy and compromised hosts; extraintestinal infections due to *Escherichia coli* and, to a lesser degree, *Klebsiella* species are most common. Isolation of GNB from any sterile site

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almost always implies infection, whereas isolation from nonsterile sites requires clinical correlation. Early appropriate antimicrobial therapy improves outcomes. Given worldwide increases in multidrug-resistant GNB (e.g., due to extended-spectrum β-lactamases [ESBLs] and AmpC β-lactamases), combination empirical antimicrobial therapy pending susceptibility results may be appropriate for critically ill pts.

## EXTRAINTESTINAL PATHOGENIC *E. COLI* (EXPEC)

In contrast to intestinal pathogenic *E. coli* (see below), ExPEC strains are often found in the intestinal flora of healthy individuals but cause disease only when they enter a normally sterile extraintestinal site (e.g., the urinary tract, peritoneal cavity, or lungs). Most ExPEC strains have virulence factor profiles distinct from those of other commensal strains and from those of pathogenic strains that cause intestinal infections.

### Clinical Manifestations

The clinical presentation depends in large part on the site of the body infected by ExPEC.

- *UTI:* The urinary tract is the site most frequently infected by ExPEC; see Chap. 144 for more details. *E. coli* causes 80–90% of ~6–8 million episodes of acute uncomplicated UTI in premenopausal women.
- *Abdominal and pelvic infection:* The abdomen and pelvis represent the second most common site of infection by ExPEC, which may be isolated in the setting of a polymicrobial infection; see Chap. 81 for more details. Syndromes include peritonitis, intraabdominal abscesses, and cholangitis.
- *Pneumonia:* ExPEC is generally the third or fourth most commonly isolated GNB in hospital-acquired pneumonia and can be a common cause of pneumonia in pts residing in long-term-care facilities; see Chap. 132 for more details.
- *Meningitis: E. coli* is one of the two leading causes of neonatal meningitis (the other being group B *Streptococcus).* Strains with the K1 capsular serotype are generally involved.
- *Cellulitis/musculoskeletal infection: E. coli* often contributes to infection of decubitus ulcers and diabetic lower-extremity ulcers, cellulitis, and burn-site or surgical-site infections. Hematogenously acquired osteomyelitis, particularly vertebral, is more commonly caused by *E. coli* than is generally appreciated. See Chap. 84 for more details.
- *Bacteremia: E. coli* is one of the two most common blood isolates of clinical significance. *E. coli* bacteremia can arise from primary infection at any site, but originates most commonly from the urinary tract (50–67% of episodes) and next most commonly from the abdomen (25% of episodes). *E. coli* bacteremia is typically associated with sepsis. Endovascular infections are rare but have been described.

### Diagnosis

ExPEC grows readily on standard media under either aerobic or anaerobic conditions. More than 90% of strains ferment lactose and are indole positive.

**TREATMENT EXTRAINTESTINAL INFECTIONS CAUSED BY *E. COLI***

- Rates of resistance to ampicillin, first-generation cephalosporins, trimethoprim-sulfamethoxazole (TMP-SMX), and fluoroquinolones are increasing. ESBLs are increasingly common in *E. coli*.
- Carbapenems and amikacin are the most predictably active agents overall, but carbapenemase-producing strains are on the rise.
- It is important to use the most appropriate narrower-spectrum agent whenever possible and to avoid treating colonized but uninfected pts, thus combating the increase in antibiotic resistance.

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## INTESTINAL PATHOGENIC *E. COLI*

### Microbiology and Clinical Manifestations

At least five distinct pathotypes of intestinal pathogenic *E. coli* exist; see Chap. 82 for more details. As mentioned above, these strains are rarely encountered as part of the commensal flora in healthy individuals.

- *Shiga toxin–producing E. coli (STEC)/enterohemorrhagic E. coli (EHEC)/Shiga toxin–producing enteroaggregregative E. coli (STEAEC):* In addition to diarrhea, STEC/EHEC infection results in the hemolytic–uremic syndrome (HUS) in 2–8% of pts, particularly those who are very young or elderly. STEAEC results in a higher rate of HUS (~20%), with a higher incidence among adults, especially young women.
  - STEC/EHEC/STEAEC is associated with ingestion of contaminated food (e.g., undercooked ground beef, fresh produce) and water; person-to-person transmission (e.g., at day-care centers) is an important route for secondary spread.
  - Disease can be caused by $<10^2$ colony-forming units (CFUs) of STEC/EHEC/STEAEC.
  - In contrast to the other pathotypes, STEC/EHEC/STEAEC (including *E. coli* O157:H7) causes infection more frequently in industrialized countries than in developing countries.
- *Enterotoxigenic E. coli (ETEC):* These strains are a major cause of endemic diarrhea among children residing in tropical and low-income countries and are the most common agent of traveler's diarrhea; $10^6$–$10^{10}$ CFU are needed to cause disease.
- *Enteropathogenic E. coli (EPEC):* EPEC is an important cause of diarrhea among infants in developing countries.
- *Enteroinvasive E. coli (EIEC):* EIEC, an uncommon cause of diarrhea, produces inflammatory colitis (stools containing mucus, blood, and inflammatory cells) similar to that caused by *Shigella* and primarily affects children and travelers in developing countries; $10^8$–$10^{10}$ CFU are needed to cause disease.
- *Enteroaggregative and diffusely adherent E. coli (EAEC):* EAEC was initially described in young children in developing countries. More recent studies indicate that EAEC may be a common cause of prolonged, watery diarrhea in all age groups in industrialized countries.

### Diagnosis

Specific diagnosis is usually unnecessary except when STEC/EHEC/STEAEC is involved. To detect the latter, simultaneous culture (screening for *E. coli* strains that do not ferment sorbitol followed by serotyping for O157) and testing for Shiga toxins or toxin genes is recommended.

**TREATMENT** INTESTINAL INFECTIONS CAUSED BY *E. COLI*

- See Chap. 82 for more details. Replacement of water and electrolytes and avoidance of antibiotics in STEC/EHEC/STEAEC infection (since antibiotic use may increase the incidence of HUS) are indicated.

## *KLEBSIELLA*

### Epidemiology

*K. pneumoniae* colonizes the colon in 5–35% of healthy individuals and, from a medical standpoint, is the most important *Klebsiella* species. *K. oxytoca* primarily causes infections in long-term care and hospital settings. *K. pneumoniae* subspecies *rhinoscleromatis*, which causes rhinoscleroma, and *K. pneumoniae* subspecies *ozaenae*, which causes chronic atrophic rhinitis, infect pts in tropical climates.

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## Clinical Manifestations

As in other GNB infections, the clinical presentation depends on the infected anatomic site.

- *Pneumonia: Klebsiella* is a common cause of pneumonia among residents of long-term care facilities and hospitalized pts. In Asia and South Africa, community-acquired pneumonia due to hypervirulent strains of *K. pneumoniae* is increasingly common, particularly among younger, healthy pts.
  - The presentation is similar to that of pneumonia caused by other enteric GNB, with purulent sputum production and pulmonary infiltrates on CXR.
  - Infection can progress to pulmonary necrosis, pleural effusion, and empyema.
- *UTI: K. pneumoniae* causes 1–2% of cases of uncomplicated cystitis and 5–17% of cases of complicated UTI.
- *Abdominal infections: Klebsiella* causes a spectrum of disease similar to that of *E. coli*, but with less frequent occurrence. Hypervirulent strains have become a common cause of monomicrobial community-acquired liver abscess, spontaneous bacterial peritonitis, and splenic abscess.
- *Bacteremia:* Bacteremia can arise from a primary infection at any site; infections of the urinary tract, respiratory tract, and abdomen (especially hepatic abscess) each account for 15–30% of episodes.
- *Other infections: Klebsiella* cellulitis or soft tissue infection most frequently affects devitalized tissue and immunocompromised hosts. *Klebsiella* can also cause endophthalmitis, nosocomial sinusitis, and osteomyelitis.

## Diagnosis

Klebsiellae usually ferment lactose, although the *K. pneumoniae* subspecies *rhinoscleromatis* and *ozaenae* are nonfermenters and are indole negative.

### TREATMENT *KLEBSIELLA* INFECTIONS

- Klebsiellae are resistant to ampicillin and ticarcillin.
  - The increase in plasmid-encoded ESBLs has led to increasing resistance to third- and fourth-generation cephalosporins, aminoglycosides, tetracyclines, and TMP-SMX.
  - Fluoroquinolone resistance is increasing, especially among ESBL-containing strains.
- Empirical treatment of serious or health care–associated *Klebsiella* infections with amikacin or carbapenems is prudent; however, carbapenemase-producing strains are increasing in frequency. Optimal therapy for carbapenemase strains is unclear, but tigecycline and the polymyxins (e.g., colistin) are used most frequently on the basis of in vitro susceptibility profiles. When resistance to these agents is documented, combination therapy is often used.

# *PROTEUS*

## Epidemiology

*P. mirabilis* is part of the normal flora in 50% of healthy people and causes 90% of *Proteus* infections. *P. vulgaris* and *P. penneri* are isolated primarily from pts in hospitals and long-term care facilities.

## Clinical Manifestations

Most *Proteus* infections arise from the urinary tract. *Proteus* species account for 1–2% of uncomplicated UTIs, 5% of hospital-acquired UTIs, and 10–15% of complicated UTIs (especially those associated with urinary catheters).

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- *Proteus* produces high levels of urease that result in alkalinization of urine and ultimately in formation of struvite and carbonate-apatite calculi.
- Infections at other sites are uncommon but include pneumonia, abdominal infections, soft tissue infections, and bacteremia.

## Diagnosis

*Proteus* strains are typically lactose negative, produce $H_2S$, and exhibit swarming motility on agar plates. *P. mirabilis* and *P. penneri* are indole negative, whereas *P. vulgaris* is indole positive.

**TREATMENT** ***PROTEUS* INFECTIONS**

- *P. mirabilis* is susceptible to most agents except tetracycline, nitrofurantoin, polymyxins, and tigecycline. Resistance to ampicillin, first-generation cephalosporins, and fluoroquinolones is increasing.
- *P. vulgaris* and *P. penneri* are more resistant; induction of variants with stable derepression of chromosomal AmpC β-lactamase may occur with *P. vulgaris* isolates. Carbapenems, fourth-generation cephalosporins, amikacin, TMP-SMX, and fosfomycin exhibit excellent activity: 90–100% of *Proteus* isolates are susceptible.

## OTHER GRAM-NEGATIVE ENTERIC PATHOGENS

- *Enterobacter* (e.g., *E. cloacae*, *E. aerogenes*), *Acinetobacter* (e.g., *A. baumannii*), *Serratia* (e.g., *S. marcescens*), and *Citrobacter* (e.g., *C. freundii*, *C. koseri*) usually cause nosocomial infections. Risk factors include immunosuppression, comorbid disease, prior antibiotic use, and ICU stays.
- Infections caused by *Morganella* (e.g., *M. morganii*) and *Providencia* (e.g., *P. stuartii*, *P. rettgeri*) resemble *Proteus* infections in terms of epidemiology, pathogenicity, and clinical manifestations but occur almost exclusively among persons in long-term care facilities and, to a lesser degree, among hospitalized pts.

## Clinical Manifestations

These organisms generally cause a spectrum of disease similar to that caused by other GNB, including pneumonia (particularly ventilator-associated), UTI (especially catheter-related), intravascular device–related infection, surgical-site infection, and abdominal infections.

- *Citrobacter*, *Morganella*, and *Providencia* infections are generally associated with UTIs.
- *Acinetobacter* has caused soft tissue and bone infections among soldiers with battlefield injuries and is a well-known pathogen in burn units.

**TREATMENT** **INFECTIONS CAUSED BY OTHER GRAM-NEGATIVE ENTERIC PATHOGENS**

- Significant antibiotic resistance among these organisms makes therapy challenging.
  - Many of these organisms (e.g., *Serratia*, *Providencia*, *Acinetobacter*, *Citrobacter*, *Enterobacter*, *Morganella*) have a derepressible AmpC β-lactamase that results in resistance to third-generation cephalosporins, monobactams, and—in many cases—β-lactam/β-lactamase inhibitor combinations.
  - *Morganella* and *Providencia* are inherently resistant to the polymyxins and tigecycline.

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- Carbapenems and amikacin are most reliably active, and fourth-generation cephalosporins are active provided the organism does not express an ESBL. Susceptibility testing is essential. Some isolates may retain susceptibility only to colistin and polymyxin B.

### *AEROMONAS*

*A. hydrophila* causes >85% of *Aeromonas* infections. *Aeromonas* organisms proliferate in potable water, freshwater, and soil and are a putative cause of gastroenteritis. *Aeromonas* causes bacteremia and sepsis in infants and compromised hosts, especially those with cancer, hepatobiliary disease, trauma, or burns. The organisms can produce skin lesions similar to the ecthyma gangrenosum caused by *Pseudomonas aeruginosa*. *Aeromonas* causes nosocomial infections related to catheters, surgical incisions, and use of leeches.

**TREATMENT** *AEROMONAS* INFECTIONS

- *Aeromonas* is usually susceptible to fluoroquinolones (e.g., ciprofloxacin, 500 mg PO q12h or 400 mg IV q12h), third- and fourth-generation cephalosporins, carbapenems, and aminoglycosides.
- Susceptibility testing is critical to guide therapy since *Aeromonas* can produce various β-lactamases, including carbapenemases.

## *PSEUDOMONAS AERUGINOSA* AND RELATED ORGANISMS

The pseudomonads make up a set of gram-negative organisms unable to ferment lactose. This group includes three medically important genera—*Pseudomonas*, *Burkholderia*, and *Stenotrophomonas*—that typically cause opportunistic disease.

### *P. AERUGINOSA*

#### Microbiology

*P. aeruginosa* is a motile gram-negative rod that commonly produces green or bluish pigment and may have a mucoid appearance (which is particularly common in isolates from pts with cystic fibrosis). *P. aeruginosa* differs from enteric GNB in that it has a positive reaction in the oxidase test and does not ferment lactose.

#### Epidemiology

Because *P. aeruginosa* is found in most moist environments (e.g., in soil, in tap water, and on countertops), people routinely come into contact with the organism. The many factors that predispose to *P. aeruginosa* infection include disruption of cutaneous or mucosal barriers (e.g., due to burns or trauma), immunosuppression (e.g., due to neutropenia, AIDS, or diabetes), and disruption of the normal bacterial flora (e.g., due to broad-spectrum antibiotic therapy).

- *P. aeruginosa* is no longer a major cause of life-threatening bacteremia among pts with neutropenia or burn injury.
- *P. aeruginosa* bacteremia is currently most common among pts in the ICU.

#### Clinical Manifestations

*P. aeruginosa* can infect virtually all sites in the body but has a strong predilection for the lungs.

- *Pneumonia: P. aeruginosa* is considered a major cause of ventilator-associated pneumonia, although colonization may be difficult to distinguish from true infection.

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  - Clinically, most pts have a slowly progressive infiltrate, although progression is rapid in some cases. Infiltrates may become necrotic.
  - It is unclear whether an invasive procedure (e.g., bronchoalveolar lavage, protected-brush sampling of distal airways) is superior to tracheal aspiration in obtaining samples for culture.
  - Chronic respiratory infection with *P. aeruginosa* is associated with underlying or predisposing conditions (e.g., cystic fibrosis, bronchiectasis).
- *Bacteremia:* The presentation of *P. aeruginosa* bacteremia resembles that of sepsis in general but may be more severe, with attributable mortality rates of 28–44%.
  - Pathognomonic skin lesions (*ecthyma gangrenosum*) that at first are painful, reddish, and maculopapular and later become black and necrotic may develop in pts with marked neutropenia or HIV infection.
  - Endovascular infections occur mostly in IV drug users and pts with prosthetic valves.
- *Bone and joint infections: P. aeruginosa* is an infrequent cause of bone and joint infections.
  - Injection drug use (associated with sternoclavicular joint infections and vertebral osteomyelitis) and UTIs in the elderly (associated with vertebral osteomyelitis) are risk factors.
  - *Pseudomonas* osteomyelitis of the foot most often follows puncture wounds through sneakers and most commonly affects children.
- *CNS infections:* CNS infections due to *P. aeruginosa* are relatively rare and are almost always secondary to a surgical procedure or head trauma.
- *Eye infections:* Keratitis and corneal ulcers can occur, usually resulting from trauma or surface injury by contact lenses. These infections are rapidly progressing entities that demand immediate therapeutic intervention. *P. aeruginosa* endophthalmitis secondary to bacteremia is a fulminant disease with severe pain, chemosis, decreased visual acuity, anterior uveitis, vitreous involvement, and panophthalmitis.
- *Ear infections:* In addition to mild swimmer's ear, *Pseudomonas* ear infections can result in malignant otitis externa, a life-threatening infection that presents as severe ear pain and decreased hearing.
  - Pts may develop cranial-nerve palsies or cavernous venous sinus thrombosis.
  - Most ear infections due to *P. aeruginosa* occur in elderly diabetic pts.
- *UTIs:* UTIs due to *P. aeruginosa* usually result from a foreign body in the urinary tract, an obstruction in the genitourinary system, or urinary tract instrumentation or surgery.
- *Skin and soft tissue infections: P. aeruginosa* can cause a variety of dermatitides, including pyoderma gangrenosum in neutropenic pts, folliculitis, and other papular or vesicular lesions. Multiple outbreaks have been linked to whirlpools, spas, and swimming pools.
- *Infections in pts with fever and neutropenia: P. aeruginosa* is always targeted in empirical treatment of these pts, given high rates of infection in the past and high associated mortality rates.
- *Infections in pts with AIDS: P. aeruginosa* infections in pts with AIDS can be fatal even though the clinical presentation is not particularly severe.
  - Pneumonia is the most common type of infection, with a high frequency of cavitary disease.
  - Since the advent of antiretroviral therapy, *P. aeruginosa* infection has declined in incidence among these pts but still occurs.

## TREATMENT *P. AERUGINOSA* INFECTIONS

- See Table 90-1 for antibiotic options and schedules.
- Several observational studies indicate that a single modern antipseudomonal β-lactam agent to which the isolate is sensitive is as efficacious as combination

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**TABLE 90-1 ANTIBIOTIC TREATMENT OF INFECTIONS DUE TO *PSEUDOMONAS AERUGINOSA* AND RELATED SPECIES**

| Infection | Antibiotics and Dosages | Other Considerations |
|---|---|---|
| Bacteremia | | |
| Nonneutropenic host | Monotherapy: Ceftazidime (2 g q8h IV) *or* cefepime (2 g q12h IV)<br>Combination therapy: Piperacillin/tazobactam (3.375 g q4h IV) *or* imipenem (500 mg q6h IV) *or* meropenem (1 g q8h IV) *or* doripenem (500 mg q8h IV)<br>***plus***<br>Amikacin (7.5 mg/kg q12h *or* 15 mg/kg q24h IV) | Add an aminoglycoside for patients in shock and in regions or hospitals where rates of resistance to the primary β-lactam agents are high. Tobramycin may be used instead of amikacin (susceptibility permitting). The duration of therapy is 7 days for nonneutropenic patients. Neutropenic patients should be treated until no longer neutropenic. |
| Neutropenic host | Cefepime (2 g q8h IV) *or* all other agents (except doripenem) in above dosages | |
| Endocarditis | Antibiotic regimens as for bacteremia for 6–8 weeks | Resistance during therapy is common. Surgery is required for relapse. |
| Pneumonia | Drugs and dosages as for bacteremia, except that the available carbapenems should not be the sole primary drugs because of high rates of resistance during therapy | IDSA guidelines recommend the addition of an aminoglycoside or ciprofloxacin. The duration of therapy is 10–14 days. |
| Bone infection, malignant otitis externa | Cefepime or ceftazidime at the same dosages as for bacteremia; aminoglycosides not a necessary component of therapy; ciprofloxacin (500–750 mg q12h PO) may be used | Duration of therapy varies with the drug used (e.g., 6 weeks for a β-lactam agent; at least 3 months for oral therapy except in puncture-wound osteomyelitis, for which the duration should be 2–4 weeks). |
| Central nervous system infection | Ceftazidime or cefepime (2 g q8h IV) or meropenem (1 g q8h IV) | Abscesses or other closed-space infections may require drainage. The duration of therapy is ≥2 weeks. |
| Eye infection | | |
| Keratitis/ulcer | Topical therapy with tobramycin/ciprofloxacin/levofloxacin eyedrops | Use maximal strengths available or compounded by pharmacy. Therapy should be administered for 2 weeks or until the resolution of eye lesions, whichever is shorter. |

(*Continued*)

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**TABLE 90-1 ANTIBIOTIC TREATMENT OF INFECTIONS DUE TO *PSEUDOMONAS AERUGINOSA* AND RELATED SPECIES (*CONTINUED*)**

| Infection | Antibiotics and Dosages | Other Considerations |
|---|---|---|
| Endophthalmitis | Ceftazidime or cefepime as for central nervous system infection<br>***plus***<br>Topical therapy | |
| Urinary tract infection | Ciprofloxacin (500 mg q12h PO) *or* levofloxacin (750 mg q24h) *or* any aminoglycoside (total daily dose given once daily) | Relapse may occur if an obstruction or a foreign body is present. The duration of therapy for complicated UTI is 7–10 days (up to 2 weeks for pyelonephritis). |
| Multidrug-resistant *P. aeruginosa* infection | Colistin (100 mg q12h IV) for the shortest possible period to obtain a clinical response | Doses used have varied. Dosage adjustment is required in renal failure. Inhaled colistin may be added for pneumonia (100 mg q12h). |
| *Stenotrophomonas maltophilia* infection | TMP-SMX (1600/320 mg q12h IV) *plus* ticarcillin/clavulanate (3.1 g q4h IV) for 14 days | Resistance to all agents is increasing. Levofloxacin or tigecycline may be alternatives, but there is little published clinical experience with these agents. |
| *Burkholderia cepacia* infection | Meropenem (1 g q8h IV) *or* TMP-SMX (1600/320 mg q12h IV) for 14 days | Resistance to both agents is increasing. Do not use them in combination because of possible antagonism. |
| Melioidosis, glanders | Ceftazidime (2 g q6h) *or* meropenem (1 g q8h) *or* imipenem (500 mg q6h) for 2 weeks<br>***followed by***<br>TMP-SMX (1600/320 mg q12h PO) for 3 months | |

***Abbreviations:*** IDSA, Infectious Diseases Society of America; TMP-SMX, trimethoprim-sulfamethoxazole.

therapy. However, if—in the local environment—the susceptibility rate to first-line agents is <80%, empirical combination therapy should be administered until isolate-specific susceptibility data are available.

## BACTERIA RELATED TO *PSEUDOMONAS* SPECIES

### *Stenotrophomonas maltophilia*

*S. maltophilia* is an opportunistic pathogen. Most infections occur in the setting of prior broad-spectrum antimicrobial therapy that has eradicated the normal flora in immunocompromised pts.

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- *S. maltophilia* causes pneumonia, especially ventilator-associated pneumonia, with or without bacteremia.
- Central venous line infection (most often in cancer pts) and ecthyma gangrenosum in neutropenic pts have been described.

### *Burkholderia cepacia*

This organism can colonize airways during broad-spectrum antimicrobial treatment and is a cause of ventilator-associated pneumonia, catheter-associated infection, and wound infection.

- *B. cepacia* is recognized as an antibiotic-resistant nosocomial pathogen in ICU pts.
- *B. cepacia* can cause a rapidly fatal syndrome of respiratory distress and septicemia (the "cepacia syndrome") in pts with cystic fibrosis.

**TREATMENT** *S. MALTOPHILIA* AND *B. CEPACIA* INFECTIONS

- Intrinsic resistance to many antibiotics limits treatment. See Table 90-1 for recommended antibiotic regimens.

### Miscellaneous Organisms

Melioidosis is endemic to Southeast Asia and northern Australia and is caused by *B. pseudomallei*. Glanders is associated with close contact with horses or other equines and is caused by *B. mallei*. These diseases present as acute or chronic pulmonary or extrapulmonary suppurative illnesses or as acute septicemia.

For a more detailed discussion, see Barlam TF, Kasper DL: Infections Due to the HACEK Group and Miscellaneous Gram-Negative Bacteria, Chap. 183e; Russo TA, Johnson JR: Diseases Caused by Gram-Negative Enteric Bacilli, Chap. 186, p. 1025; Paterson DL, Peleg AY: *Acinetobacter* Infections, Chap. 187, p. 1036; Ramphal R: Infections Due to *Pseudomonas* Species and Related Organisms, Chap. 189, p. 1042, in HPIM-19.

# 91 Infections Caused by Miscellaneous Gram-Negative Bacilli

## BRUCELLOSIS

### Microbiology

Brucellae are small, gram-negative, unencapsulated, nonsporulating, nonmotile rods or coccobacilli that can persist intracellularly. The genus *Brucella* includes four major clinically relevant species: *B. melitensis* (acquired by humans most commonly from

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sheep, goats, and camels), *B. suis* (from swine), *B. abortus* (from cattle or buffalo), and *B. canis* (from dogs).

## Epidemiology

Brucellosis is transmitted via ingestion, inhalation, or mucosal or percutaneous exposure; the disease in humans is usually associated with exposure to infected animals or their products in either occupational settings (e.g., slaughterhouse work, farming) or domestic settings (e.g., consumption of contaminated foods, especially dairy products). The global prevalence of brucellosis is unknown because of difficulties in diagnosis and inadequacies in reporting systems.

## Clinical Manifestations

Regardless of the specific infecting species, brucellosis often presents with one of three patterns: a febrile illness similar to but less severe than typhoid fever; fever and acute monoarthritis, typically of the hip or knee, in a young child (septic arthritis); or long-lasting fever, misery, and low-back or hip pain in an older man (vertebral osteomyelitis).

- An incubation period of 1 week to several months is followed by the development of undulating fever; sweats; increasing apathy and fatigue; and nonspecific symptoms such as anorexia, headache, myalgias, and chills.
- *Brucella* infection can cause lymphadenopathy, hepatosplenomegaly, epididymoorchitis, neurologic involvement, and focal abscess.
- Given the persistent fever and similar symptoms, tuberculosis is the most important differential diagnosis (Table 91-1).

## Diagnosis

Laboratory personnel must be alerted to the potential diagnosis to ensure that they take precautions to prevent occupational exposure.

- The organism is successfully cultured in 50–70% of cases. Cultures using the BACTEC system usually become positive in 7–10 days and can be deemed negative at 3 weeks.
- PCR analysis of blood or tissue samples is more sensitive, faster, and safer than culture.

**TABLE 91-1 RADIOLOGY OF THE SPINE: DIFFERENTIATION OF BRUCELLOSIS FROM TUBERCULOSIS**

| | Brucellosis | Tuberculosis |
|---|---|---|
| Site | Lumbar and others | Dorsolumbar |
| Vertebrae | Multiple or contiguous | Contiguous |
| Diskitis | Late | Early |
| Body | Intact until late | Morphology lost early |
| Canal compression | Rare | Common |
| Epiphysitis | Anterosuperior (Pom's sign) | General: upper and lower disk regions, central, subperiosteal |
| Osteophyte | Anterolateral (parrot beak) | Unusual |
| Deformity | Wedging uncommon | Anterior wedge, gibbus |
| Recovery | Sclerosis, whole-body | Variable |
| Paravertebral abscess | Small, well-localized | Common and discrete loss, transverse process |
| Psoas abscess | Rare | More likely |

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- Agglutination assays for IgM are positive early in infection. Single titers of ≥1:160 and ≥1:320 are diagnostic in nonendemic and endemic areas, respectively.

**TREATMENT BRUCELLOSIS**

- The recommended regimen is streptomycin at a dosage of 0.75–1 g/d IM (or gentamicin at 5–6 mg/kg qd) for 14–21 days plus doxycycline at 100 mg bid for 6 weeks.
  - Rifampin (600–900 mg/d) plus doxycycline (100 mg bid) for 6 weeks constitute an alternative regimen (the current World Health Organization [WHO] recommendation).
  - Significant neurologic disease requires at least 3–6 months of treatment, with ceftriaxone supplementation of a standard regimen.
  - Endocarditis requires a four-drug regimen (an aminoglycoside, rifampin, a tetracycline, and ceftriaxone or a fluoroquinolone) for at least 6 weeks.
  - Relapse rates range from 5% to >20% and depend on the specific antibiotic regimen used; pts should be monitored for at least 2 years.

## TULAREMIA

### Microbiology and Epidemiology

Tularemia is the only disease caused by *Francisella tularensis*, a small, gram-negative, aerobic bacillus that is a potential agent of bioterrorism.

- Human infection occurs via interaction with biting or blood-sucking insects (especially ticks and tabanid flies in the spring and summer), wild or domestic animals (e.g., wild rabbits, squirrels), or the environment.
  - The organism gains entry into the skin or mucous membranes through bites or inapparent abrasions or is acquired via inhalation or ingestion.
  - As few as 10 organisms can result in infection when injected into the skin or inhaled; $>10^8$ organisms are required to produce infection via the oral route.
- More than half of U.S. cases occur in Arkansas, Oklahoma, and Missouri.

### Clinical Manifestations

After an incubation period of 2–10 days, tularemia generally starts with an acute onset of fever, chills, headache, and myalgias. The *ulceroglandular/glandular* forms of tularemia affect 75–85% of pts, but several other syndromes involving systemic manifestations can occur.

- *Ulceroglandular/glandular tularemia:* The hallmark of ulceroglandular tularemia is an indurated, erythematous, nonhealing ulcer lasting 1–3 weeks that begins as a pruritic or tender lesion, ulcerates, has sharply demarcated edges and a yellow exudate, and develops a black base.
  - Inguinal/femoral lymphadenopathy is most common in adults; nodes can become fluctuant and drain spontaneously.
  - In glandular tularemia (5–10% of cases), no primary skin lesion is apparent.
- *Oculoglandular tularemia:* In 1% of pts, infection of the conjunctiva—usually by contact with contaminated fingers—results in purulent conjunctivitis with regional lymphadenopathy and debilitating pain. Painful preauricular lymphadenopathy distinguishes tularemia from other diseases.
- *Oropharyngeal and GI tularemia:* Acquired through oral inoculation (via contaminated foods or fingers), the infection can present as pharyngitis and cervical adenopathy, intestinal ulcerations, mesenteric lymphadenopathy, diarrhea, nausea, vomiting, and abdominal pain.

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- *Pulmonary tularemia:* Infection is acquired via inhalation or via hematogenous spread from ulceroglandular or typhoidal tularemia. Pts present with signs and symptoms similar to those of pneumonia of other etiologies (e.g., nonproductive cough, dyspnea, pleuritic chest pain, CXR with bilateral patchy or lobar infiltrates or cavitary lesions).
- *Typhoidal tularemia:* Due to pharyngeal or GI inoculation or to bacteremic disease, typhoidal tularemia consists of fever and signs of sepsis, generally without skin lesions or lymphadenopathy. This form is the result of a large inoculum or a preexisting compromising condition.

### Diagnosis

The diagnosis of tularemia is most frequently confirmed by serology, although up to 30% of pts infected for 3 weeks have negative results in serologic tests.

- Cultures are positive in only 10% of cases; organisms in culture pose a significant risk to laboratory personnel.
- PCR has been used to detect *F. tularensis* DNA in clinical specimens, mainly for ulceroglandular disease.

**TREATMENT TULAREMIA**

- Gentamicin (2.5 mg/kg IV bid for 7–10 days) is considered the drug of choice; pts who defervesce within the first 48–72 h of treatment may receive a 5- to 7-day course.
  - Streptomycin (1 g IM q12h for 10 days) is also effective, but tobramycin is not.
  - Doxycycline is another alternative, but it must be given for at least 14 days because it is only bacteriostatic against *F. tularensis*.
  - Healing of skin lesions and lymph nodes may take 1–2 weeks. Late lymph-node suppuration can occur, with sterile necrotic tissue.

## PLAGUE

### Epidemiology

*Yersinia pestis* causes plague, a systemic zoonosis that primarily affects small rodents in rural areas of Africa (where 80% of all human cases worldwide occur), Asia, and the Americas. As the rodent population succumbs to disease, fleas (the arthropod vector) search for a new host and can transmit the bacteria to humans.

- In addition to fleabites, direct contact with infected tissues or airborne droplets can cause human infections. Given the possibility of airborne transmission, *Y. pestis* is a potential agent of bioterrorism.
- A mean of seven cases per year occur in the United States, most of them near the "Four Corners" (the junction point of New Mexico, Arizona, Colorado, and Utah) and further west in California, southern Oregon, and western Nevada.

### Clinical Manifestations

Worldwide, bubonic plague accounts for 80–95% of all plague cases, with primary septicemic plague occurring in 10–20% of cases and primary pulmonary plague in only a small minority of cases.

- *Bubonic plague:* After an incubation period of 2–6 days, the onset of bubonic plague is sudden and is characterized by fever (>38°C), malaise, myalgia, dizziness, and increasing pain due to progressive lymphadenitis in the regional lymph nodes near the fleabite or other inoculation site.
  - The tender, swollen lymph node (bubo) has a boggy consistency with an underlying hard core when palpated.

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  - With treatment, fever resolves within 2–5 days, although buboes may remain enlarged for >1 week and can become fluctuant; without treatment, infection can disseminate and cause serious illness (e.g., secondary pneumonic plague, meningitis).
- *Primary septicemic plague:* Pts present with gram-negative septicemia not preceded by lymphadenopathy. Persons >40 years old are at greater risk, although this form of the disease can occur in all age groups. Diabetes and hemochromatosis are additional risk factors.
- *Pneumonic plague:* After a short incubation period averaging a few hours to 3 days, pts experience a sudden onset of fever, nonspecific signs and symptoms (e.g., headache, myalgias, vomiting), and respiratory manifestations (e.g., cough, chest pain, sputum production with hemoptysis).
  - Pneumonitis that is initially segmental can progress to lobar pneumonia and then to bilateral lung involvement.
  - The mortality rate is nearly 100% without treatment and is still >50% with effective treatment.

## Diagnosis

The WHO recommends an initial presumptive diagnosis followed by confirmation in a reference laboratory.

- The appropriate specimens for diagnosis of bubonic, pneumonic, and septicemic plague are bubo aspirate (after injection of 1 mL of normal saline), bronchoalveolar lavage fluid or sputum, and blood, respectively. Gram's, Wayson, or Wright-Giemsa staining of these samples may reveal bipolar gram-negative rods.
- Given the potential risk to laboratory workers, culture of *Y. pestis* should be performed only at reference laboratories, which use direct immunofluorescence, PCR, and/or specific bacteriophage lysis as confirmatory tests for identification. The optimal growth temperature is 25–29°C.
- In the absence of other positive diagnostic testing, a serologic diagnosis can be made.

### TREATMENT PLAGUE

- Streptomycin (1g IM q12h) or gentamicin (5 mg/kg IV q24h) is the drug of choice. Levofloxacin (500 mg PO/IV q24h), doxycycline (200 mg/d PO/IV in 1 or 2 doses), and chloramphenicol (12.5 mg/kg PO/IV q6h) are alternative agents.
- For pts who are hospitalized with pneumonic plague or in whom this disease is suspected, respiratory droplet precautions should be implemented until treatment has been given for at least 48 h.
- Postexposure antimicrobial prophylaxis lasting 7 days is recommended after household, hospital, or other close (<2 m) contact with persons with untreated pneumonic plague. Doxycycline (200 mg/d PO/IV in 1 or 2 doses), levofloxacin (500 mg PO q24h), ciprofloxacin (500 mg PO q12h), or trimethoprim-sulfamethoxazole (320 mg of the trimethoprim component PO q12h) are effective agents for prophylaxis.

## *BARTONELLA* INFECTIONS

- *Bartonella* species are fastidious, facultative intracellular, gram-negative bacteria that cause an array of infectious disease syndromes in humans.
- Most *Bartonella* species have successfully adapted to survival in specific domestic or wild mammals, creating a reservoir for human infection. The exceptions are *B. bacilliformis* and *B. quintana*, which are not zoonotic.
- Clinical presentation generally depends on both the infecting *Bartonella* species and the immune status of the infected individual.
- Therapy for syndromes caused by *Bartonella* is summarized in Table 91-2.

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**TABLE 91-2 ANTIMICROBIAL THERAPY FOR DISEASE CAUSED BY *BARTONELLA* SPECIES IN ADULTS**

| Disease | Antimicrobial Therapy |
|---|---|
| Typical cat-scratch disease | Not routinely indicated; for pts with extensive lymphadenopathy, consider azithromycin (500 mg PO on day 1, then 250 mg PO qd for 4 days) |
| Cat-scratch disease retinitis | Doxycycline (100 mg PO bid) *plus* rifampin (300 mg PO bid) for 4–6 weeks |
| Other atypical cat-scratch disease manifestations[a] | As per retinitis; treatment duration should be individualized |
| Trench fever or chronic bacteremia with *B. quintana* | Gentamicin (3 mg/kg IV qd for 14 days) *plus* doxycycline (200 mg PO qd or 100 mg PO bid for 6 weeks) |
| Suspected *Bartonella* endocarditis | Gentamicin[b] (1 mg/kg IV q8h for ≥14 days) *plus* doxycycline (100 mg PO/IV bid for 6 weeks[c]) *plus* ceftriaxone (2 g IV qd for 6 weeks) |
| Confirmed *Bartonella* endocarditis | As for suspected *Bartonella* endocarditis *minus* ceftriaxone |
| Bacillary angiomatosis | Erythromycin[d] (500 mg PO qid for 3 months)<br>*or*<br>Doxycycline (100 mg PO bid for 3 months) |
| Bacillary peliosis | Erythromycin[d] (500 mg PO qid for 4 months)<br>*or*<br>Doxycycline (100 mg PO bid for 4 months) |
| Carrión's disease | |
| Oroya fever | Chloramphenicol (500 mg PO/IV qid for 14 days) *plus* another antibiotic (β-lactam preferred)<br>*or*<br>Ciprofloxacin (500 mg PO bid for 10 days) |
| Verruga peruana | Rifampin (10 mg/kg PO qd, to a maximum of 600 mg, for 14 days)<br>*or*<br>Streptomycin (15–20 mg/kg IM qd for 10 days) |

[a]Data on treatment efficacy for encephalitis and hepatosplenic cat-scratch disease are lacking. Therapy similar to that given for retinitis is reasonable.
[b]Some experts recommend gentamicin at 3 mg/kg IV qd. If gentamicin is contraindicated, rifampin (300 mg PO bid) can be added to doxycycline for documented *Bartonella* endocarditis.
[c]Some experts recommend extending oral doxycycline therapy for 3–6 months.
[d]Other macrolides are probably effective and may be substituted for erythromycin or doxycycline.
***Source:*** Recommendations are modified from JM Rolain et al: *Antimicrob Agents Chemother* 48:1921, 2004.

## CAT-SCRATCH DISEASE (CSD)

### Microbiology and Epidemiology

*B. henselae* is the principal etiologic agent of CSD, although other *Bartonella* species may rarely be involved. Consistent with the disease's name, contact (being scratched, bitten, or licked) with apparently healthy cats, and especially with kittens, is the primary source of infection. Adults are affected nearly as frequently as children. In the United States, the estimated incidence is ~10 cases per 100,000 population.

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## Clinical Manifestations

Of pts with CSD, 85–90% have typical disease consisting of a localized lesion (papule, vesicle, or nodule) at the site of inoculation with subsequent painful regional lymphadenopathy ≥1–3 weeks after cat contact.

- Axillary and epitrochlear nodes are most commonly involved and suppurate in 10–15% of cases.
- Low-grade fever, malaise, and anorexia develop in ~50% of pts.
- Atypical disease involves extranodal manifestations (e.g., fever of unknown origin, ophthalmologic manifestations, neurologic involvement, osteomyelitis) and occurs in 10–15% of pts.
- In immunocompetent pts, the disease resolves spontaneously without treatment, although its resolution takes weeks or months.

## Diagnosis

Serologic testing is most commonly used but is variably sensitive and specific. It is noteworthy that seroconversion may take a few weeks. *Bartonella* species are difficult to culture, but PCR analysis of lymph node tissue, pus, or the primary inoculation lesion is highly sensitive and specific.

### BACILLARY ANGIOMATOSIS AND PELIOSIS

Bacillary angiomatosis is caused by *B. henselae* and *B. quintana*, while peliosis is caused only by the former species. These diseases occur most often in HIV-infected pts with CD4+ T cell counts of <100/μL.

- Pts with bacillary angiomatosis present with one or more painless skin lesions that may be tan, red, or purple in color. SC masses or nodules, ulcerated plaques, and verrucous growths also occur. Painful osseous lesions, primarily in the long bones, may develop and appear as lytic lesions on radiography.
- Peliosis is an angioproliferative disorder characterized by blood-filled cystic structures that affects primarily the liver but also the spleen and lymph nodes. Hypodense hepatic areas are usually evident on imaging.
- Both diseases are diagnosed on histologic grounds. Blood cultures may be positive.

### TRENCH FEVER

- Trench fever (*5-day fever*) is caused by *B. quintana*, which is spread by the human body louse to its only animal reservoir: humans.
- Much less common today than in the trenches of World War I, the disease now primarily affects homeless people.
- After a usual incubation period of 15–25 days, disease classically ranges from a mild febrile illness to a recurrent or protracted and debilitating disease. Fever is often periodic, with episodes of 4–5 days separated by ~5-day afebrile periods.
- Diagnosis requires identification of *B. quintana* in blood cultures.
- Untreated, the disease usually lasts 4–6 weeks. Death is rare.

### *BARTONELLA* ENDOCARDITIS

*Bartonella* species (typically *B quintana* or *B. henselae*) are an important cause of culture-negative endocarditis. The disease's manifestations are similar to those of subacute endocarditis of any etiology (Chap. 80). Even if incubated for prolonged periods (up to 6 weeks), blood cultures are positive in only ~25% of cases. Serologic or PCR testing for *Bartonella* in cardiac valve tissue can help establish the diagnosis in pts with negative blood cultures.

### CARRIÓN'S DISEASE (OROYA FEVER AND VERRUGA PERUANA)

Carrión's disease is a biphasic disease caused by *B. bacilliformis*, which is transmitted by a sandfly vector found in the Andes valleys of Peru, Ecuador, and Colombia.

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- *Oroya fever* is the initial, bacteremic, systemic form, and *verruga peruana* is its late-onset, eruptive manifestation.
- Oroya fever may present as a nonspecific bacteremic febrile illness without anemia or as acute, severe hemolytic anemia with hepatomegaly and jaundice of rapid onset.
  - In verruga peruana, red, hemangioma-like, cutaneous vascular lesions of various sizes appear either weeks to months after systemic illness or with no previous suggestive history. The lesions persist for months up to 1 year.
- In systemic illness, Giemsa-stained blood films show typical intraerythrocytic bacilli, and blood and bone marrow cultures are positive. Serologic assays may be helpful. Biopsy may be required to confirm the diagnosis of verruga peruana.

For a more detailed discussion, see Beeching NJ, Corbel MJ: Brucellosis, Chap. 194e; Jacobs RF, Schutze GE: Tularemia, Chap. 195, p. 1066; Prentice MB: Plague and Other *Yersinia* Infections, Chap. 196, p. 1070; and Giladi M, Ephros M: *Bartonella* Infections, Including Cat-Scratch Disease, Chap. 197, p. 1078, in HPIM-19.

# 92 Anaerobic Infections

## DEFINITIONS

- *Anaerobic bacteria:* require reduced oxygen tension for growth; do not grow on the surface of solid media in 10% $CO_2$ in air
- *Microaerophilic bacteria:* grow in an atmosphere of 10% $CO_2$ in air or under anaerobic or aerobic conditions, but grow best if only a small amount of atmospheric oxygen is present
- *Facultative bacteria:* grow in the presence or absence of oxygen

## TETANUS

### Microbiology, Epidemiology, and Pathogenesis

Tetanus is characterized by increased muscle tone and spasms caused by tetanospasmin ("tetanus toxin"), a toxin produced by *Clostridium tetani*.

- *C. tetani* is a spore-forming, anaerobic gram-positive rod that is ubiquitous in soil and whose spores are highly resilient.
- Tetanus is a rare disease in the developed world: only 231 cases were reported in the United States between 2001 and 2008. Most cases occur in incompletely vaccinated or unvaccinated individuals.
- After spores contaminate wounds (typically puncture wounds or, in the case of neonates, the umbilical stump) and reach a suitable anaerobic environment (e.g., devitalized tissue), organisms proliferate and release toxin.

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- The toxin blocks release of inhibitory neurotransmitters (glycine and γ-aminobutyric acid) in presynaptic terminals, and rigidity results from an increased resting firing rate of the α-motor neurons.
- A toxin dose as low as 2.5 ng/kg can be fatal.

## Clinical Manifestations

*C. tetani* can cause a usually mild local disease confined to the muscles near the wound or a more severe generalized disease (e.g., neonatal disease).

- If the cranial nerves are involved in localized cephalic tetanus, the pt may aspirate or develop airway obstruction due to pharyngeal or laryngeal muscle spasm. This situation is associated with a poor prognosis.
- The early signs and symptoms of generalized tetanus often include trismus (lockjaw), muscle pain and stiffness, back pain, and difficulty swallowing. As the disease progresses, painful muscle spasms develop and can sometimes be strong enough to cause crush fractures.
  - Without ventilatory support, respiratory failure is the most common cause of death in tetanus.
  - Autonomic disturbance (e.g., labile blood pressure; GI stasis; increased tracheal secretions; acute, high-output renal failure) is maximal during the second week of severe tetanus, and death due to cardiovascular events becomes the major risk.

## Diagnosis

The diagnosis is made on clinical grounds. Culture of *C. tetani* from a wound provides supportive evidence.

### TREATMENT TETANUS

- The mainstays of early treatment are the elimination of ongoing toxin production and the neutralization of circulating toxin.
  - The entry wound should be identified, cleaned, and debrided of necrotic material in order to remove anaerobic foci of infection and prevent further toxin production.
  - Metronidazole (400 mg rectally or 500 mg IV q6h for 7 days) is the preferred antibiotic. Penicillin (100,000–200,000 IU/kg qd) is an alternative but theoretically may increase spasms.
  - Antitoxin should be given as early as possible.
  - Standard treatment consists of a single IM dose of tetanus immune globulin (TIG; 3000–5000 IU) or equine antitoxin (10,000–20,000 IU). However, there is evidence that intrathecal TIG (50–1500 IU) inhibits disease progression and leads to a better outcome than IM-administered TIG.
- TIG is preferred as it is less likely to cause an anaphylactoid reaction.
- Monitoring and supportive care in a calm, quiet environment are important because light and noise can trigger spasms.
  - Spasms are controlled by heavy sedation with benzodiazepines, chlorpromazine, and/or phenobarbital; magnesium sulfate can also be used as a muscle relaxant. The doses required to control spasms also cause respiratory depression; thus, it is difficult to control spasms adequately in settings without mechanical ventilation.
  - Cardiovascular instability in severe tetanus is notoriously difficult to treat; increased sedation (e.g., with magnesium sulfate or morphine) or administration of short-acting agents that work specifically on the cardiovascular system (e.g., esmolol, calcium antagonists, inotropes) may be required.
- Recovery from tetanus may take 4–6 weeks. Because natural disease does not induce immunity, recovering pts should be immunized.

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## Prevention

Vaccination effectively prevents disease.

- "Catch-up" vaccination schedules recommend a three-dose primary course followed by two further doses for unimmunized adolescents. For persons who have received a complete primary course in childhood but no further boosters, two doses at least 4 weeks apart are recommended.
- Individuals sustaining tetanus-prone wounds should be immunized if their vaccination status is incomplete or unknown or if their last booster was given >10 years earlier. Pts sustaining wounds not classified as clean or minor should also undergo passive immunization with TIG.

## Prognosis

A shorter incubation period (time from wound to first symptom) or onset period (time from first symptom to first generalized spasm) is associated with worse outcome.

# BOTULISM

## Microbiology, Epidemiology, and Pathogenesis

Botulism is a paralytic disease caused by neurotoxins elaborated by *Clostridium botulinum*, an anaerobic spore-forming gram-positive bacterium, as well as a few other toxigenic *Clostridium* spp.

- Botulism is caused by the toxin's inhibition of acetylcholine release at the neuromuscular junction through an enzymatic mechanism.
  - *C. botulinum* toxin types A, B, E, and (rarely) F cause human disease, with toxin type A causing the most severe syndrome.
  - Toxin type E is associated with foods of aquatic origin.
- Transmission is usually due to consumption of foods contaminated with botulinum toxin, but contamination of wounds with spores also can result in disease.
  - Most U.S. food-borne cases (average, 23 cases per year) are associated with home-canned food.
  - Infant botulism results from toxigenic clostridial colonization of the intestine of children <1 year of age and is the most common form of the disease in the United States, with ~80–100 cases reported annually.
- Toxin is heat-labile, and spores are heat-resistant; these properties underscore the importance of properly heating foods.
- Botulinum toxin is among the most toxic substances known and thus is of concern as a potential weapon of bioterrorism.

## Clinical Manifestations

Botulism occurs naturally as four syndromes: (1) food-borne illness; (2) wound infection; (3) infant botulism; and (4) adult intestinal toxemia, which is similar to infant botulism. The disease presents as symmetric cranial-nerve palsies (diplopia, dysarthria, dysphonia, ptosis, facial paralysis, and/or impaired gag reflex) followed by symmetric, descending flaccid paralysis that may progress to respiratory failure and death. Constipation due to paralytic ileus is nearly universal, and fever is usually absent.

- *Food-borne botulism* occurs 8–36 h (or up to 10 days, depending on the dose) after ingestion of food contaminated with toxin and ranges in severity from mild to fatal (within 24 h). Nausea, vomiting, and abdominal pain may precede or follow the onset of paralysis.
- *Wound botulism* occurs when spores contaminate wounds and germinate, with an incubation period of 4–17 days.

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- In *infant botulism* and *adult intestinal toxemia*, spores germinate in the intestine and produce toxin, which is absorbed and causes illness. This form in infants has been associated with contaminated honey; thus, honey should not be fed to children <12 months of age. Adult pts typically have some anatomic or functional bowel abnormality or have a bowel flora disrupted by recent antibiotic use.

### Diagnosis

The clinical symptoms suggest the diagnosis. The definitive test is the demonstration of the toxin in clinical specimens (serum, stool, gastric aspirates, wound material) and food samples.

- When results are not readily available, clinical decisions (e.g., to administer botulinum antitoxin) need to be made in their absence.
- This test may yield a negative result even if the pt has botulism, particularly if specimens are collected >7 days after symptom onset; additional tests (e.g., culture of stool or wound material for toxigenic clostridia) may be necessary.

**TREATMENT BOTULISM**

- The mainstays of treatment are meticulous supportive care and immediate administration of botulinum antitoxin—the only specific treatment.
  - Adults are given an equine antitoxin available through the CDC (770-488-7100); infant botulism is treated with a human-origin antitoxin (licensed as BabyBIG®) available through the California Department of Public Health (510-231-7600).
  - In wound botulism, suspect wounds and abscesses should be cleaned, debrided, and drained promptly, and antimicrobial therapy (e.g., with a penicillin) should be guided by clinical judgment, as its clinical efficacy has not been established and may result in increased circulating toxin from lysis of bacteria.

### Prognosis

Botulinum antitoxin limits progression of illness by neutralizing free toxin without affecting paralysis that is already present. Toxin binding is irreversible, but nerve terminals do regenerate.

## OTHER CLOSTRIDIAL INFECTIONS

### Microbiology and Pathogenesis

Clostridia are pleomorphic, gram-positive, spore-forming organisms. Most species are obligate anaerobes; some (e.g., *C. septicum*, *C. tertium*) can grow—but not sporulate—in air.

- In humans, clostridia reside in the GI and female genital tracts and on the oral mucosa.
- Clostridial species produce more protein toxins than any other bacterial genus; the *C. perfringens* epsilon toxin is among the most lethal and is considered a potential agent of bioterrorism.

### Epidemiology and Clinical Manifestations

Life-threatening clostridial infections range from intoxications (e.g., food poisoning, tetanus) to necrotizing enteritis/colitis, bacteremia, myonecrosis, and toxic shock syndrome (TSS).

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- *Clostridial wound contamination:* Of open traumatic wounds, 30–80% are contaminated with clostridial species. Diagnosis and treatment of clostridial infection should be based on clinical signs and symptoms, given that clostridia are isolated with equal frequency from both suppurative and well-healing wounds.
- *Polymicrobial infections involving clostridia:* Clostridial species can be involved in infection throughout the body; 66% of intraabdominal infections related to compromised mucosal integrity involve clostridia (most commonly *C. ramosum*, *C. perfringens*, and *C. bifermentans*).
- *Enteric clostridial infections:* Disease ranges from food-borne illnesses and antibiotic-associated colitis (Chap. 82) to extensive necrosis of the intestine (e.g., *enteritis necroticans* and *necrotizing enterocolitis*, which are due to toxigenic *C. perfringens* type C and type A, respectively).
- *Clostridial bacteremia: C. perfringens* causes 79% of clostridial bacteremias; when associated with myonecrosis, clostridial bacteremia has a grave prognosis.
  - *C. septicum* is also commonly associated with bacteremia (<5% of cases). More than 50% of pts with *C. septicum* bacteremia have a GI anomaly or an underlying malignancy. Neutropenia (of any origin) is also associated with *C. septicum* bacteremia.
    - Pts with clostridial bacteremia—particularly that due to *C. septicum*—require immediate treatment, as infection can metastasize and cause spontaneous myonecrosis.
- *Clostridial skin and soft-tissue infections:* Necrotizing clostridial soft-tissue infections are rapidly progressive and are characterized by marked tissue destruction, gas in the tissues, and shock. Most pts develop severe pain, crepitus, brawny induration with rapid progression to skin sloughing, violaceous bullae, and marked tachycardia.
  - *C. perfringens myonecrosis (gas gangrene)* is accompanied by bacteremia, hypotension, and multiorgan failure and is invariably fatal if untreated.
    - If due to trauma, gas gangrene has an incubation period of 6 h to <4 days. Disease initially presents as excruciating pain at the affected site and the development of a foul-smelling wound containing a thin serosanguineous discharge and gas bubbles.
    - Spontaneous gas gangrene results from hematogenous seeding of normal muscle with toxigenic clostridia from a GI source. Confusion, extreme pain in the absence of trauma, and fever should heighten suspicion.
  - *TSS:* Endometrial clostridial infection (particularly with *C. sordellii*) is usually related to pregnancy or gynecologic procedures and proceeds rapidly to TSS and death.
    - Systemic manifestations, including edema, effusions, profound leukocytosis (50,000–200,000/μL), and hemoconcentration (Hct of 75–80%), are followed by the rapid onset of hypotension and multiple-organ failure.
    - Fever is usually absent.
  - Other clostridial skin and soft-tissue infections include crepitant cellulitis (involving SC or retroperitoneal tissues in diabetic pts), cellulitis and abscess formation due to *C. histolyticum*, and endophthalmitis due to *C. sordellii* or *C. perfringens*.

## Diagnosis

Isolation of clostridia from clinical sites does not in itself indicate severe disease. Clinical findings and presentation must also be taken into account.

## TREATMENT OTHER CLOSTRIDIAL INFECTIONS

- Table 92-1 lists treatment regimens for clostridial infections.

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**TABLE 92-1 TREATMENT OF CLOSTRIDIAL INFECTIONS**

| Condition | Antibiotic Treatment | Penicillin Allergy | Adjunctive Treatment/Note |
|---|---|---|---|
| Wound contamination | None | — | Treatment should be based on clinical signs and symptoms as listed below and not solely on bacteriologic findings. |
| Polymicrobial anaerobic infections involving clostridia (e.g., abdominal wall, gynecologic) | Ampicillin (2 g IV q4h) ***plus*** Clindamycin (600–900 mg IV q6–8h) ***plus*** Ciprofloxacin (400 mg IV q6–8 h) | Vancomycin (1 g IV q12h) ***plus*** Metronidazole (500 mg IV q6h) ***plus*** Ciprofloxacin (400 mg IV q6–8h) | Empirical therapy should be initiated. Therapy should be based on Gram's stain and culture results and on sensitivity data when available. Add gram-negative coverage if indicated (see text). |
| Clostridial sepsis | Penicillin, 3–4 mU IV q4–6h ***plus*** Clindamycin (600–900 mg IV q6–8h) | Clindamycin alone ***or*** Metronidazole (as above) ***or*** Vancomycin (as above) | Transient bacteremia without signs of systemic toxicity may be clinically insignificant. |
| Gas gangrene | Penicillin G (4 mU IV q4–6h) ***plus*** Clindamycin (600–900 mg IV q6–8h) | Cefoxitin (2 g IV q6h) ***plus*** Clindamycin (600–900 mg IV q6–8h) | Emergent surgical exploration and thorough debridement are extremely important. Hyperbaric oxygen therapy may be considered after surgery and antibiotic initiation. |

## MIXED ANAEROBIC INFECTIONS

### Microbiology, Epidemiology, and Pathogenesis

Nonsporulating anaerobic bacteria are important components of the normal flora of mucosal surfaces of the mouth, lower GI tract, skin, and female genital tract and contribute to physiologic, metabolic, and immunologic functions of the host.

- Most clinically relevant anaerobes are relatively aerotolerant and can survive for prolonged periods in the presence of low levels of oxygen.
  - Clinically relevant anaerobes include gram-positive cocci (e.g., *Peptostreptococcus* spp.), gram-positive rods (e.g., spore-forming clostridia and *Propionibacterium acnes*), and gram-negative bacilli (e.g., the *Bacteroides fragilis* group in the intestines, *Fusobacterium* spp. in the oral cavity and GI tract, *Prevotella* spp. in the oral cavity and female genital tract, and *Porphyromonas* spp. in the oral microbiota).

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- Infections caused by anaerobes are typically polymicrobial (including at least one anaerobic organism and sometimes involving microaerophilic and facultative bacteria) and occur when organisms penetrate a previously sterile site that has a reduced oxidation–reduction potential—e.g., from tissue ischemia, trauma, surgery, perforated viscus, shock, or aspiration. Bacterial synergy, bacterial virulence factors, and mechanisms of abscess formation are factors involved in the pathogenesis of anaerobic infections.
- Anaerobes account for 0.5–12% of all cases of bacteremia, with *B. fragilis* isolated in 60–80% of these cases.

## Clinical Manifestations

The clinical presentation of anaerobic infections depends, in part, on the anatomic location affected.

- *Mouth, head, and neck infections:* Odontogenic infections (e.g., dental caries, periodontal disease, gingivitis) are common, can spread locally, and may be life-threatening.
  - Acute necrotizing ulcerative gingivitis (trench mouth, Vincent's stomatitis) is associated with bleeding tender gums, foul breath, and ulceration with gray exudates.
  - Noma (*cancrum oris*) is a necrotizing infection of the oral mucous membranes that rapidly evolves from gingival inflammation to orofacial gangrene with destruction of bone and soft tissue. Noma occurs most frequently in 1- to 4-year-old children with malnutrition or systemic disease, particularly those in sub-Saharan Africa.
  - Acute necrotizing infection of the pharynx is associated with ulcerative gingivitis. Pts have a sore throat, foul breath, fever, a choking sensation, and tonsillar pillars that are swollen, red, ulcerated, and covered with a gray membrane. Aspiration of infected material can lead to a lung abscess.
  - Peripharyngeal infections include peritonsillar abscess (*quinsy*; caused by a mixed flora including anaerobes and group A streptococci) and submandibular space infection (*Ludwig's angina*), which arises from the second and third molars in 80% of cases and is associated with swelling (sometimes leading to respiratory obstruction), pain, trismus, and displacement of the tongue.
  - Chronic sinusitis and otitis (Chap. 58) are commonly due to anaerobes.
  - Complications of anaerobic mouth, head, and neck infections include Lemierre's syndrome, osteomyelitis, CNS infections (e.g., brain abscess, epidural abscess, subdural empyema), mediastinitis, pleuropulmonary infections, and hematogenous dissemination.
    - Lemierre's syndrome, which is typically due to *Fusobacterium necrophorum*, is an acute oropharyngeal infection with secondary septic thrombophlebitis of the internal jugular vein and frequent metastasis, most commonly to the lung. A typical clinical triad includes pharyngitis, a tender/swollen neck, and noncavitating pulmonary infiltrates.
    - Pleuropulmonary infections include aspiration pneumonia (which is difficult to distinguish from chemical pneumonitis due to aspiration of gastric juices), necrotizing pneumonitis, lung abscesses, and empyema. Bacterial aspiration pneumonia is associated with a depressed gag reflex, impaired swallowing, or altered mental status; anaerobic lung abscess usually arises from a dental source.
- *Intraabdominal infections:* See Chap. 81.
- *Pelvic infections:* See Chap. 83 for more details. Anaerobes, typically in combination with coliforms, are isolated from most women with genital tract infections (e.g., pelvic inflammatory disease, pelvic abscess, endometritis, tuboovarian abscess, postoperative or postpartum infections) that are not caused by a sexually transmitted pathogen. The major anaerobic pathogens are *B. fragilis*, *Prevotella* spp. (*bivia*, *disiens*, *melaninogenica*), anaerobic cocci, and *Clostridium* spp.

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- *Skin and soft tissue infections:* See Chap. 84 for more details. These infections most frequently occur at sites prone to contamination with feces or with upper airway secretions.
- *Bone and joint infections:* Anaerobic bone and joint infections usually occur adjacent to soft tissue infections. Actinomycosis is the leading cause of anaerobic bone infections worldwide; *Fusobacterium* spp. are the most common anaerobic cause of septic arthritis.

## Diagnosis

The three critical steps in successfully culturing anaerobic bacteria from clinical samples are (1) proper specimen collection, with avoidance of contamination by the normal microbiota; (2) rapid specimen transport to the microbiology laboratory in anaerobic transport media; and (3) proper specimen handling. A foul odor is often indicative (and nearly pathognomonic) of an anaerobic infection.

## TREATMENT MIXED ANAEROBIC INFECTIONS

- Appropriate treatment requires antibiotic administration (Table 92-2), surgical resection or debridement of devitalized tissues, and drainage.
  - Given that most infections involving anaerobes also include aerobic bacteria, therapeutic regimens should include agents active against both classes of organisms.
  - Infections above the diaphragm usually reflect the orodental microbiota, which includes many organisms that produce β-lactamase. Accordingly, the

**TABLE 92-2 ANTIMICROBIAL THERAPY FOR INFECTIONS INVOLVING COMMONLY ENCOUNTERED ANAEROBIC GRAM-NEGATIVE RODS**

| Category 1 (Nearly Always Active) | Category 2 (Usually Active) | Category 3 (Variable Resistance) | Category 4 (Resistance) |
|---|---|---|---|
| Carbapenems (imipenem, meropenem, doripenem) | Tigecycline | Cephamycins (cefoxitin, cefotetan) | Aminoglycosides |
| Metronidazole[a] | High-dose antipseudomonal penicillins | Clindamycin | Monobactams |
| β-Lactam/β-lactamase inhibitor combinations (ampicillin/sulbactam, ticarcillin/clavulanic acid, piperacillin/tazobactam) | | Penicillins | Trimethoprim-sulfamethoxazole |
| Chloramphenicol[b] | | Cephalosporins | |
| | | Tetracycline | |
| | | Vancomycin | |
| | | Erythromycin | |
| | | Moxifloxacin | |

[a]Usually needs to be given in combination with aerobic bacterial coverage. For infections originating below the diaphragm, aerobic gram-negative coverage is essential. For infections from an oral source, aerobic gram-positive coverage is added. Metronidazole also is not active against *Actinomyces, Propionibacterium*, or other gram-positive non-spore-forming bacilli (e.g., *Eubacterium, Bifidobacterium*) and is unreliable against peptostreptococci.

[b]Despite excellent in vitro activity against all clinically important anaerobes, this drug is less desirable than other active drugs because of documented clinical failures.

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recommended regimens include clindamycin, a β-lactam/β-lactamase inhibitor combination, or metronidazole in combination with a drug active against microaerophilic and aerobic streptococci.

– Infections below the diaphragm must be treated with agents active against *Bacteroides* spp., such as metronidazole, β-lactam/β-lactamase inhibitor combinations, or carbapenems. Treatment should also cover the aerobic gram-negative flora, including enterococci (e.g., ampicillin or vancomycin) when indicated.

- Pts with anaerobic infections that fail to respond to treatment or that relapse should be reassessed, with consideration of additional surgical drainage or debridement. Superinfection with resistant gram-negative facultative or aerobic bacteria should also be considered.

For a more detailed discussion, see Thwaites CL, Yen LM: Tetanus, Chap. 177, p. 984; Maslanka S, Rao AK: Botulism, Chap. 178, p. 987; Bryant AE, Stevens DL: Gas Gangrene and Other Clostridial Infections, Chap. 179, p. 990; and Cohen-Poradosu R, Kasper DL: Infections Due to Mixed Anaerobic Organisms, Chap. 201, p. 1094, in HPIM-19.

# 93 Nocardiosis, Actinomycosis, and Whipple's Disease

## NOCARDIOSIS

### Microbiology

Nocardiae are branching, beaded, gram-positive filaments that usually give positive results with modified acid-fast stains. These saprophytic aerobic actinomycetes are common in soil.

- Nine species or species complexes are most commonly associated with human disease.
- Speciation of nocardiae is precluded in most clinical laboratories because it is nearly impossible without molecular phylogenetic techniques.
- *Nocardia brasiliensis* is most often associated with localized skin lesions.

### Epidemiology

Nocardiosis occurs worldwide and has an incidence of ~0.375 cases per 100,000 persons in Western countries. The risk of disease is greater than usual among persons who have deficient cell-mediated immunity—e.g., that associated with lymphoma, transplantation, glucocorticoid therapy, or HIV infection with <250 CD4+ T cells/μL.

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## Pathogenesis

Pneumonia and disseminated disease follow inhalation of fragmented bacterial mycelia.

- Nocardiosis causes abscesses with neutrophilic infiltration and necrosis.
- Organisms have multiple mechanisms for surviving within phagocytes.

## Clinical Manifestations

- *Respiratory tract disease:* Pneumonia is usually subacute, presenting over days to weeks, but can be acute in immunocompromised pts.
  - A prominent cough productive of small amounts of thick purulent sputum, fever, anorexia, weight loss, and malaise are common; dyspnea, hemoptysis, and pleuritic chest pain are less common.
  - CXR may demonstrate single or multiple nodular infiltrates of varying sizes that tend to cavitate. Empyema is noted in one-quarter of cases.
  - Extrapulmonary disease is documented in >50% of cases.
- *Extrapulmonary disease:* In 20% of cases of disseminated disease, lung disease is absent.
  - Nocardial dissemination manifests as subacute abscesses in the brain (most commonly), skin, kidney, bone, eye, and/or muscle.
  - Brain abscesses are usually supratentorial, are often multiloculated, can be single or multiple, and tend to burrow into ventricles or extend into the subarachnoid space.
  - Meningitis is uncommon, and nocardiae are difficult to recover from CSF.
- *Disease following transcutaneous inoculation:* usually presents as cellulitis, lymphocutaneous disease, or actinomycetoma
  - *Cellulitis* presents 1–3 weeks after a break in the skin (often with contamination by soil).
    - The firm, tender, erythematous, warm, and nonfluctuant lesions may involve underlying structures, but dissemination is rare.
    - *N. brasiliensis* and species in the *N. otitidiscaviarum* complex are most common in cellulitis.
  - *Lymphocutaneous* disease resembles sporotrichosis and presents as a pyodermatous nodule at the inoculation site, with central ulceration and purulent or honey-colored discharge.
    - SC nodules often appear along lymphatics that drain the primary lesion.
  - *Actinomycetoma* progresses from a nodular swelling at the site of local trauma (typically on the feet or hands, although other sites can be affected) to fistula formation; dissemination is rare.
    - The discharge is serous or purulent and can contain granules consisting of masses of mycelia.
    - Lesions, which spread slowly along fascial planes to involve adjacent skin and SC tissue and bone, can cause extensive deformity after months or years.
- *Eye disease:* Endophthalmitis can occur after eye surgery or during disseminated disease.

## Diagnosis

- Sputum or pus should be examined microscopically and by culture for the presence of nocardiae. In pts with nocardial pneumonia, sputum smears are often negative, and bronchoscopy may be needed to obtain adequate specimens.
  - Cultures take 2–4 weeks to yield the organism. To maximize the likelihood of isolation, the laboratory should be alerted if nocardiosis is being considered.
  - Sputum cultures positive for nocardiae should be assumed to reflect disease in immunocompromised hosts, but may represent colonization in immunocompetent pts.

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- Discharge from lesions suspected to constitute an actinomycetoma should be examined for granules, the appearance of which can help differentiate this diagnosis from eumycetoma (cases involving fungi) and botryomycosis (cases involving cocci or bacilli).
  - Granules from actinomycetomas consist of fine filaments (0.5–1 μm wide) radiating from a central core.
  - In contrast, granules from eumycetomas have broader filaments (2–5 μm wide) encased in a matrix, and those from botryomycosis consist of loose masses of bacteria.
- Brain imaging should be considered in pts with pulmonary or disseminated disease.

## TREATMENT NOCARDIOSIS

- Sulfonamides are the empirical drugs of choice, and trimethoprim-sulfamethoxazole (TMP-SMX; 10–20 mg of TMP/kg qd and 50–100 mg of SMX/kg qd initially, with later reduction to 5 and 25 mg/kg qd, respectively) may be more effective than sulfonamides alone.
  - Susceptibility testing, particularly in severe cases or cases failing to improve, can guide alternative treatments and should be performed at reference labs.
  - Alternative oral agents that are often effective include minocycline, linezolid (whose long-term use is complicated by side effects), amoxicillin/clavulanic acid (except for strains in the *N. nova* complex), and fluoroquinolones (with moxifloxacin and gemifloxacin the most active).
  - Effective parenteral agents include amikacin, ceftriaxone, cefotaxime, and imipenem.
- Pts with severe disease are initially treated with a combination of TMP-SMX, amikacin, and either ceftriaxone or imipenem. After definite clinical improvement, the regimen can usually be simplified to a single oral agent.
- Surgical management of nocardial infections is similar to that of other bacterial diseases.
  - Brain abscesses that are large or unresponsive to antibiotic treatment should be aspirated.
  - Medical therapy is generally sufficient for actinomycetomas.
- Relapse is common.
  - Long courses of therapy are required (Table 93-1).
  - Pts should be followed for at least 6 months after therapy completion.

# ACTINOMYCOSIS

## Microbiology

Actinomycosis is caused by anaerobic or microaerophilic bacteria, primarily of the genus *Actinomyces* (e.g., *A. israelii, A. naeslundii*, *A. odontolyticus*), that colonize the mouth, colon, and vagina. Most infections are polymicrobial, but the role of other species in the pathogenesis of the disease is unclear.

## Epidemiology

Actinomycosis is associated with poor dental hygiene, prolonged use of intrauterine contraceptive devices (IUCDs), and treatment with bisphosphonates.

## Pathogenesis

After disruption of the mucosal barrier, resident *Actinomyces* can infect locally and spread contiguously in a slow progressive manner, ignoring tissue planes. The hallmark of actinomycosis is the development of single or multiple indurated lesions with fibrotic walls often described as "wooden." Central necrosis of lesions with neutrophils and sulfur granules is virtually diagnostic of the disease.

**TABLE 93-1 TREATMENT DURATION FOR NOCARDIOSIS**

| Disease | Duration |
|---|---|
| Pulmonary or systemic | |
| Intact host defenses | 6–12 months |
| Deficient host defenses | 12 months[a] |
| CNS disease | 12 months[b] |
| Cellulitis, lymphocutaneous syndrome | 2 months |
| Osteomyelitis, arthritis, laryngitis, sinusitis | 4 months |
| Actinomycetoma | 6–12 months after clinical cure |
| Keratitis | Topical: until apparent cure<br>Systemic: until 2–4 months after apparent cure |

[a]In some pts with AIDS and CD4+ T lymphocyte counts of <200/μL or with chronic granulomatous disease, therapy for pulmonary or systemic disease must be continued indefinitely.
[b]If all apparent CNS disease has been excised, the duration of therapy may be reduced to 6 months.

## Clinical Manifestations

- *Oral-cervicofacial disease:* Infection starts as a soft-tissue swelling, abscess, or mass, often at the angle of the jaw, with occasional contiguous extension to the cranium, cervical spine, or thorax. Pain, fever, and leukocytosis are variable. Radiation therapy and particularly bisphosphonate treatment are associated with actinomycosis of the maxilla and mandible.
- *Thoracic disease:* The pulmonary parenchyma and/or pleural space is usually involved. Chest pain, fever, and weight loss are common.
  - Radiographic studies demonstrate a mass lesion or pneumonia. Cavitary disease or mediastinal or hilar adenopathy may occur, and >50% of pts have pleural thickening, effusion, or empyema.
  - Lesions cross fissures or pleura and may involve the mediastinum, contiguous bone, or the chest wall. In the absence of these findings, the disease is often mistaken for a neoplasm or for pneumonia.
- *Abdominal disease:* The diagnosis is challenging given that abdominal disease may not present clinically until months or years after the initial event (e.g., appendicitis, diverticulitis, bowel surgery) and that any abdominal organ or region can be involved.
  - The disease usually presents as an abscess, mass, or lesion fixed to underlying tissue and is often mistaken for cancer.
  - Sinus tracts to the abdominal wall, perianal region, or other organs may develop and mimic inflammatory bowel disease. Recurrent disease or a wound or fistula that fails to heal suggests actinomycosis.
- *Pelvic disease:* Pelvic actinomycosis is often associated with IUCDs that have been in place for >1 year. The presentation is indolent and may follow removal of the device.
  - Pts have fever, weight loss, abdominal pain, and abnormal vaginal bleeding or discharge. Endometritis progresses to pelvic masses or tuboovarian abscess.
  - When there are no symptoms and *Actinomyces*-like organisms are identified on Papanicolaou-stained specimens, the pt should undergo close follow-up but the IUCD does not have to be removed.
- *Miscellaneous sites:* Actinomycosis can involve musculoskeletal tissue, soft tissue, or (rarely) the CNS. Hematogenous dissemination, most commonly to the lungs and liver, can occur.

## Diagnosis

Actinomycosis should be considered when a chronic progressive process with mass-like features crosses tissue boundaries, a sinus tract develops, and/or the pt has evidence of a refractory or relapsing infection despite short courses of antibiotics.

- Aspirations, biopsies, or surgical excision may be required to obtain material for diagnosis.
- Microscopic identification of sulfur granules (an in vivo matrix of bacteria, calcium phosphate, and host material) in pus or tissues helps establish the diagnosis; however, additional histopathologic and microbiologic studies are required to distinguish actinomycosis from mycetoma and botryomycosis, in both of which sulfur granules develop.
- Anaerobic cultures usually require 5–7 days to become positive but may take 2–4 weeks; even a single antibiotic dose can affect the yield of cultures.

**TREATMENT ACTINOMYCOSIS**

- For serious infection and bulky disease, IV therapy for 2–6 weeks (usually with penicillin, 18–24 million units IV daily) followed by oral therapy for 6–12 months (e.g., with penicillin or ampicillin) is suggested.
  - Less extensive disease, particularly that involving the oral–cervicofacial region, may be cured with a shorter course.
  - If treatment is extended beyond the point of resolution of measurable disease (as quantified by CT or MRI), relapse is minimized.
- Suitable alternative agents include the tetracyclines (e.g., doxycycline or minocycline, 100 mg PO/IV q12h) or clindamycin (900 mg IV q8h or 300–450 mg PO q6h).

# WHIPPLE'S DISEASE

## Microbiology and Epidemiology

Whipple's disease is a chronic multiorgan infection caused by *Tropheryma whipplei*, a weakly staining gram-positive bacillus. Seroprevalence studies indicate that ~50% of people in Western Europe and ~75% of those in rural Senegal have been exposed to *T. whipplei*. The route of transmission is unclear but probably involves fecal–oral spread and possibly droplet and/or airborne transmission.

## Clinical Manifestations

Exposure to *T. whipplei* typically results in asymptomatic carriage but can lead to acute disease or chronic infection (Whipple's disease).

- *Acute infection:* Acquisition of *T. whipplei* can result in fever, acute gastroenteritis, and/or pneumonia.
- *Chronic infection:* "Classic" Whipple's disease typically begins with oligo- or polyarthralgias/seronegative arthritis. GI signs and symptoms (diarrhea, weight loss, abdominal pain) due to involvement of the duodenum and/or jejunum begin, on average, 6–8 years later. Other organ systems (e.g., the CNS and the cardiac, pulmonary, and lymphatic systems) are variably involved.

## Diagnosis

The key to diagnosis is considering *T. whipplei* infection. PCR-based testing of tissue specimens rather than body fluids generally has a higher diagnostic yield. Histologic examination of intestinal biopsy samples remains an important diagnostic procedure, although it is less sensitive than PCR.

**TREATMENT WHIPPLE'S DISEASE**

Although the optimal regimen and duration are not known (and likely depend on the site of infection), ceftriaxone (2 g IV q24h) or meropenem (1 g IV q8h) for 2 weeks followed by TMP-SMX (160/800 mg PO bid) for 3–12 months appears to be efficacious. For CNS or cardiac infection, ceftriaxone (2 g IV q12h) or meropenem (2 g IV q8h) for ≥2 weeks followed by oral doxycycline or minocycline plus hydroxychloroquine or chloroquine for ≥1 year seems prudent.

For a more detailed discussion, see Filice GA: Nocardiosis, Chap. 199, p. 1084; and Russo TA: Actinomycosis and Whipple's Disease, Chap. 200, p. 1088, in HPIM-19.

# 94 Tuberculosis and Other Mycobacterial Infections

## TUBERCULOSIS

### MICROBIOLOGY

Tuberculosis (TB) is caused by organisms of the *Mycobacterium tuberculosis* complex, which includes *M. tuberculosis*, the most common and important agent of human mycobacterial disease, and *M. bovis*, which (like several other mycobacterial species) is acquired via ingestion of unpasteurized milk. *M. tuberculosis* is a thin aerobic bacillus that is neutral on Gram's staining but that, once stained, is acid-fast; i.e., it cannot be decolorized by acid alcohol because of the cell wall's high content of mycolic acids and other lipids.

### EPIDEMIOLOGY

An estimated 9 million new cases of TB occurred worldwide in 2013, with ~1.5 million TB-related deaths—almost entirely in low-income countries. Globally, TB rates are stable or falling.

- In the United States, TB primarily affects HIV-infected adults, immigrants, the elderly, and disadvantaged/marginalized populations.
- Isolates of *M. tuberculosis* that are multidrug-resistant (MDR; resistant to at least isoniazid and rifampin) and extensively drug-resistant (XDR; resistant to isoniazid, rifampin, and fluoroquinolones and to amikacin, kanamycin, or capreomycin) are increasing in frequency; ~480,000 cases of MDR-TB may have emerged in 2013, of which ~10% were probably XDR.
- Disease from a pt with pulmonary TB is spread by droplet nuclei that are aerosolized by coughing, sneezing, or speaking.
  - Droplets <5–10 μm in diameter may be suspended in air for several hours.
  - Transmission is determined by the intimacy and duration of contact with a pt with TB, the degree of infectiousness of the pt, and the shared environment.

  - Pts with cavitary or laryngeal disease are most infectious, with as many as $10^5$–$10^7$ acid-fast bacilli (AFB)/mL of sputum.
- Risk factors for development of active disease after *M. tuberculosis* infection include recent acquisition (i.e., within the preceding 18 months), comorbidity (e.g., HIV disease, diabetes, silicosis, immunosuppression, gastrectomy), malnutrition, tobacco smoking, and presence of fibrotic lesions.

## PATHOGENESIS

AFB that reach alveoli are ingested by macrophages. The bacilli impair phagosome maturation, multiply, lyse the macrophages, and spread to regional lymph nodes, from which they may disseminate throughout the body. These initial stages of infection are generally asymptomatic and induce cellular and humoral immunity.

- About 2–4 weeks after infection, a tissue-damaging response resulting from delayed-type hypersensitivity (the basis for tuberculin skin testing [TST]) destroys nonactivated macrophages that contain multiplying bacilli, and a macrophage-activating response activates cells capable of killing AFB. A granuloma forms at the site of the primary lesion and at sites of dissemination. The lesions can then either heal by fibrosis or undergo further evolution. Despite "healing," viable bacilli can remain dormant within macrophages or in necrotic material for years.
- Cell-mediated immunity confers partial protection against TB. Cytokines secreted by alveolar macrophages contribute to disease manifestations, granuloma formation, and mycobacterial killing.

## CLINICAL MANIFESTATIONS

TB is classified as pulmonary, extrapulmonary, or both. Extrapulmonary TB may occur in 10–40% of pts, with even higher rates among HIV-infected pts.

### Pulmonary TB

Primary disease may cause no or mild signs and symptoms (fever and occasional pleuritic chest pain) in contrast to the prolonged disease course that is common in postprimary or adult-type disease.

- Primary disease is frequently located in the middle and lower lobes. The primary lesion usually heals spontaneously, and a calcified nodule (Ghon focus) remains.
  - Transient hilar and paratracheal lymphadenopathy is common.
  - In immunosuppressed pts and children, primary disease may progress rapidly to significant clinical disease, with cavitation, pleural effusions, and hematogenous dissemination (miliary disease).
- Adult-type disease presents initially with nonspecific and insidious signs and symptoms, such as diurnal fever, night sweats, weight loss, anorexia, malaise, and weakness.
  - As the disease progresses, pts develop cough and purulent sputum production, often with blood streaking. Extensive cavitation may develop, with occasional massive hemoptysis following erosion of a vessel located in the wall of a cavity.
  - Disease is usually localized to the apical and posterior segments of the upper lobes and the superior segments of the lower lobes.

### Extrapulmonary TB

Any site in the body can be involved, but the most commonly affected sites are (in order of frequency) the lymph nodes, pleura, genitourinary tract, bones and joints, meninges, peritoneum, and pericardium. Up to two-thirds of HIV-infected pts with TB have extrapulmonary disease.

- *Lymphadenitis* occurs in 35% of extrapulmonary TB cases, especially among children and HIV-infected pts. Painless swelling of cervical and supraclavicular nodes (scrofula) is typical.

  - Nodes are discrete early on but can develop into a matted nontender mass with a fistulous tract.
  - Fine-needle aspiration or surgical-excision biopsy of the node is required for diagnosis. Cultures are positive in 70–80% of cases.
- *Pleural involvement* is common (~20% of extrapulmonary cases) and results from a hypersensitivity response to mycobacterial antigens or contiguous spread of parenchymal inflammation.
  - Pleural fluid is straw-colored and exudative, with protein levels >50% of those in serum, normal to low glucose levels, a usual pH of ~7.3 (occasionally <7.2), and pleocytosis (500–6000 cells/μL). The pleural concentration of adenosine deaminase, if low, virtually excludes TB.
  - Pleural biopsy is often required for diagnosis, with up to 80% of biopsy cultures and 75% of PCR tests positive. Direct smears, cultures, and PCR of pleural fluid are less sensitive.
  - Empyema is an uncommon complication of pulmonary TB and results from rupture of a cavity with many bacilli into the pleural space. In these cases, direct smears and cultures are often positive, and surgical drainage is usually required in addition to chemotherapy.
- In *genitourinary disease*, local symptoms predominate (e.g., urinary frequency, dysuria, hematuria, abdominal or flank pain), and up to 75% of pts have a CXR demonstrating previous or concomitant pulmonary disease. Disease is occasionally identified only after severe destructive lesions of the kidneys have developed.
  - In 90% of cases, urinalysis shows pyuria and hematuria with negative bacterial cultures.
  - Mycobacterial culture of three morning urine specimens is diagnostic in 90% of cases.
- Weight-bearing joints (spine, hips, and knees) are the most common sites of *skeletal disease*.
  - Spinal TB (Pott's disease) often involves two or more adjacent vertebral bodies; in adults, lower thoracic/upper lumbar vertebrae are usually affected. Disease spreads to adjacent vertebral bodies, later affecting the intervertebral disk and causing collapse of vertebral bodies in advanced disease (kyphosis, gibbus). Paravertebral cold abscesses may form.
- *Meningitis* occurs most often in young children and HIV-seropositive pts. Disease typically evolves over 1–2 weeks and often involves paresis of cranial nerves (particularly of ocular nerves). The ultimate evolution is toward coma, with hydrocephalus and intracranial hypertension.
  - CSF can have a high lymphocyte count, an elevated protein level, and a low glucose concentration. Cultures are positive in 80% of cases. PCR is ~80% sensitive and is the preferred initial diagnostic option.
  - Neurologic sequelae are seen in ~25% of treated pts; adjunctive glucocorticoids enhance survival among pts >14 years of age but do not reduce the frequency of neurologic sequelae.
- *Gastrointestinal disease* can affect any portion of the GI tract (with the terminal ileum and cecum most commonly involved), causing abdominal pain, obstruction, hematochezia, and often a palpable mass. TB peritonitis can follow spread of the organism from ruptured lymph nodes and intraabdominal organs; peritoneal biopsy is usually required for diagnosis.
- *Pericarditis* is characterized by an acute or subacute onset of fever, dull retrosternal pain, and sometimes a friction rub. Effusion is common. Chronic constrictive pericarditis is a potentially fatal complication, even in treated pts. Adjunctive glucocorticoids remain controversial; no conclusive data demonstrate a benefit.
- *Miliary disease* arises from hematogenous spread of *M. tuberculosis* throughout the body. Symptoms are nonspecific, and small (1- to 2-mm) granulomas may develop in many organs. Hepatomegaly, splenomegaly, lymphadenopathy, and choroidal tubercles of the eye may occur.

## HIV-Associated TB

The manifestations of TB vary with the stage of HIV infection. When cell-mediated immunity is only partly compromised, pulmonary TB presents as typical upper-lobe cavitary disease. In late HIV infection, a primary TB-like pattern may be evident, with diffuse interstitial or miliary infiltrates, little or no cavitation, and intrathoracic lymphadenopathy.

- Extrapulmonary disease occurs frequently; common forms include lymphadenitis, meningitis, pleuritis, pericarditis, mycobacteremia, and disseminated disease.
- Immune reconstitution inflammatory syndrome (IRIS), which may occur 1–3 months after initiation of antiretroviral therapy, may exacerbate the signs and symptoms of TB.

## DIAGNOSIS

The key to diagnosis is a high index of suspicion.

- AFB microscopy of diagnostic specimens—i.e., light microscopy of specimens stained with Ziehl-Neelsen basic fuchsin dyes or fluorescence microscopy of samples stained with auramine-rhodamine—can provide a presumptive diagnosis. In suspected pulmonary TB, two or three sputum samples should be examined.
- Definitive diagnosis requires growth of *M. tuberculosis* in culture or identification of the organism's DNA in clinical samples.
  - Liquid media and speciation by molecular methods have decreased the time required for diagnostic confirmation to 2–3 weeks (from 4–8 weeks).
  - Nucleic acid amplification is useful not only for rapid confirmation of TB in AFB-positive specimens but also for diagnosis of AFB-negative pulmonary and extrapulmonary TB.
- Drug susceptibility can be assessed via indirect testing on solid media (which takes ≥8 weeks), direct testing in liquid media (which takes ~3 weeks), or PCR (which can provide results within hours).
- TST is of limited value in active disease because of low sensitivity and specificity but is the most widely used screening test for latent TB infection.
- Interferon γ release assays (IGRAs) measure the release of interferon γ by T cells after stimulation with TB-specific antigens and are more specific for *M. tuberculosis* than is TST.
  - In low-incidence settings, IGRAs may be more sensitive than TST.
  - In high TB- and/or HIV-burden settings, the performance of IGRAs has varied greatly, and these tests are not recommended as a replacement for the TST.

# TREATMENT TUBERCULOSIS

## DRUGS

### First-Line Agents

- *Rifampin:* Rifampin is the most important and potent antituberculous agent. The standard dosage in adults is 600 mg/d.
  - The drug distributes well throughout body tissues, including inflamed meninges. It turns body fluids (e.g., urine, saliva, tears) red-orange and is excreted through bile and the enterohepatic circulation.
  - Rifampin is usually well tolerated; adverse events are infrequent and generally mild.
  - Of note, rifampin is a potent inducer of the hepatic cytochrome P450 system and decreases the half-life of many other drugs.
- *Isoniazid:* Isoniazid is a critical drug for active and latent TB disease. The usual adult dosage is 300 mg/d or 900 mg twice per week.
  - Isoniazid is distributed well throughout the body and infected tissues, including CSF and body cavities.

- The most important toxicities are hepatotoxicity and peripheral neuropathy.
  - Isoniazid-associated hepatitis is idiosyncratic. Its frequency increases with age and alcohol use and in the postpartum period.
  - Because peripheral neuropathy can result from interference with pyridoxine metabolism, pyridoxine (25–50 mg/d) should be given to pts with other risk factors for neuropathy, such as diabetes, alcohol abuse, or malnutrition.

- *Ethambutol:* The least potent first-line agent, ethambutol is synergistic with the other drugs in the standard first-line regimen. Ethambutol is usually given at a dosage of 15 mg/kg daily.
  - The drug is distributed throughout the body but reaches only low levels in CSF.
  - This agent can cause dose-dependent optic neuritis, producing central scotoma and impairing both visual acuity and the ability to see green.
- *Pyrazinamide:* The usual dosage is 15–30 mg/kg daily (maximum, 2 g/d). The drug distributes well throughout the body, including the CSF.
  - Hyperuricemia that can be managed conservatively is common.
  - Clinical gout is rare.

**Other Effective Agents**

- *Streptomycin:* The usual adult dose is 0.75–1.0 g IM daily or 5 times per week. Streptomycin causes ototoxicity (primarily vestibulotoxicity) but is less nephrotoxic than other aminoglycosides.
- *Rifabutin:* Rifabutin has fewer drug interactions than rifampin and is recommended in place of rifampin for HIV-infected pts who are taking protease inhibitors or non-nucleoside reverse transcriptase inhibitors. Rifabutin reaches tissue concentrations 5–10 times higher than those in plasma and has a much longer half-life than rifampin. The drug is well tolerated, and its adverse effects are dose related.
- *Rifapentine:* Rifapentine is similar to rifampin but can be given once or twice weekly. This drug is not approved for treatment in HIV-infected pts because of elevated rates of relapse.

**Second-Line Agents**

- *Fluoroquinolones:* Levofloxacin, gatifloxacin (no longer marketed in the United States because of its severe toxicity), and moxifloxacin have solid, broad antimycobacterial activity. Ciprofloxacin and ofloxacin are no longer recommended for treatment of TB because of poor efficacy.
- Other agents (e.g., capreomycin, clofazimine, linezolid) are used uncommonly but may be needed in disease caused by resistant strains of *M. tuberculosis*.

**REGIMENS** See Table 94-1.

- During the initial phase, the majority of tubercle bacilli are killed, symptoms resolve, and usually the pt becomes noninfectious. The continuation phase is required to eliminate persisting mycobacteria and prevent relapse.
- Nonadherence to the regimen is the most important impediment to cure. Directly observed treatment (especially during the initial 2 months) and fixed drug-combination products should be used if possible.
- Bacteriologic evaluation is the preferred method of monitoring response to treatment.
  - Virtually all pts should have negative sputum cultures after 3 months of treatment. If the culture remains positive, treatment failure and drug resistance should be suspected.
  - With extrapulmonary TB, bacteriologic monitoring may not be feasible. In these cases, the response to treatment must be assessed clinically and radiographically.

**TABLE 94-1 RECOMMENDED ANTITUBERCULOSIS TREATMENT REGIMENS**

| | Initial Phase | | Continuation Phase | |
|---|---|---|---|---|
| **Indication** | **Duration, Months** | **Drugs** | **Duration, Months** | **Drugs** |
| New smear- or culture-positive cases | 2 | HRZE[a,b] | 4 | HR[a,c,d] |
| New culture-negative cases | 2 | HRZE[a] | 4 | HR[a] |
| Pregnancy | 2 | HRE[e] | 7 | HR |
| Relapses and treatment default (pending susceptibility testing) | 3 | HRZES[f] | 5 | HRE |
| Failures[g] | ← Tailored according to drug susceptibility testing → | | | |
| Resistance (or intolerance) to H | Throughout (6–9) | RZE[h] | | |
| Resistance (or intolerance) to R | ← Same as for MDR-TB; see below [i] → | | | |
| MDR-TB (resistance to at least H + R) | Throughout (20 months in most cases) | Q, Inj[j], Eto/Pto, Z, Cs/PAS | | |
| XDR-TB | ← Tailored according to drug susceptibility testing[k] → | | | |
| Intolerance to Z | 2 | HRE | 7 | HR |

(*Continued*)

**TABLE 94-1 RECOMMENDED ANTITUBERCULOSIS TREATMENT REGIMENS (*CONTINUED*)**

| | Initial Phase | | Continuation Phase | |
|---|---|---|---|---|
| **Indication** | **Duration, Months** | **Drugs** | **Duration, Months** | **Drugs** |

[a]All drugs can be given daily or intermittently (three times weekly throughout). A twice-weekly regimen after 2–8 weeks of daily therapy during the initial phase is sometimes used, although it is not recommended by the WHO.
[b]Streptomycin can be used in place of ethambutol but is no longer considered a first-line drug.
[c]Some experts suggest extending the continuation phase to 7 months for patients with cavitary pulmonary tuberculosis who remain sputum culture–positive after the initial phase of treatment. However, treatment in such patients must be guided by drug susceptibility testing to rule out drug-resistant TB.
[d]A clinical trial showed that HIV-negative patients with noncavitary pulmonary tuberculosis who have negative sputum AFB smears after the initial phase of treatment can be given once-weekly rifapentine/isoniazid in the continuation phase.
[e]The 6-month regimen with pyrazinamide can probably be used safely during pregnancy and is recommended by the WHO and the International Union Against Tuberculosis and Lung Disease. If pyrazinamide is not included in the initial treatment regimen, the minimal duration of therapy is 9 months.
[f]Streptomycin should be discontinued after 2 months. Drug susceptibility results will determine the best regimen option.
[g]The availability of rapid molecular methods to identify drug resistance allows initiation of a proper regimen at the start of treatment.
[h]Although normally not recommended, a fluoroquinolone may strengthen the regimen for patients with extensive disease. A later-generation agent (such as levofloxacin, moxifloxacin, or possibly gatifloxacin; see text) is preferred.
[i]Isoniazid is added if susceptibility to this agent is confirmed or presumed.
[j]Amikacin and kanamycin (aminoglycosides) or capreomycin (polypeptide). Any of these injectable agents is recommended for the first 8 months in most patients, but the duration may be modified according to the clinical response to therapy. Continuation of treatment with the injectable drug for at least 4 months after culture conversion is advised.
[k]Aggressive management of cases comprising early drug-susceptibility testing, rational combination of at least five drugs (one of which is an injectable agent), readjustment of the regimen, strict directly observed therapy, monthly bacteriologic monitoring, intensive patient support, and possible adjuvant surgery may result in cure and avert death.
***Abbreviations:*** Cs/PAS, cycloserine or para-aminosalicylic acid; E, ethambutol; Eto/Pto, ethionamide or prothionamide; H, isoniazid; Inj, an injectable agent (the aminoglycosides amikacin and kanamycin or the polypeptide capreomycin); MDR-TB, multidrug-resistant tuberculosis; Q, a quinolone antibiotic; R, rifampin; S, streptomycin; WHO, World Health Organization; XDR-TB, extensively drug-resistant tuberculosis; Z, pyrazinamide.

- Drug resistance may be either primary (i.e., present in a strain prior to therapy) or acquired (i.e., arising during treatment because of an inadequate regimen or noncompliance).
- Close monitoring for drug toxicity should take place during treatment and should include baseline LFTs and monthly questioning about possible hepatitis symptoms. High-risk pts (e.g., older pts, pts who use alcohol daily) should have LFT values monitored during treatment.
- For pts with symptomatic hepatitis and those with marked (five- to sixfold) elevations in serum levels of aspartate aminotransferase, treatment should be stopped and drugs reintroduced one at a time after liver function has returned to normal.
- Three important considerations are relevant to TB treatment in HIV-infected pts: an increased frequency of paradoxical reactions, interactions between antiretroviral agents and rifamycins, and development of rifampin monoresistance with widely spaced intermittent treatments.

**TABLE 94-2 TUBERCULIN REACTION SIZE AND TREATMENT OF LATENT *MYCOBACTERIUM TUBERCULOSIS* INFECTION**

| Risk Group | Tuberculin Reaction Size, mm |
|---|---|
| HIV-infected persons | ≥5 |
| Recent contacts of a patient with TB | ≥5[a] |
| Organ transplant recipients | ≥5 |
| Persons with fibrotic lesions consistent with old TB on chest radiography | ≥5 |
| Persons who are immunosuppressed, e.g., due to the use of glucocorticoids or tumor necrosis factor α inhibitors | ≥5 |
| Persons with high-risk medical conditions[b] | ≥5 |
| Recent immigrants (≤5 years) from high-prevalence countries | ≥10 |
| Injection drug users | ≥10 |
| Mycobacteriology laboratory personnel; residents and employees of high-risk congregate settings[c] | ≥10 |
| Children <5 years of age; children and adolescents exposed to adults in high-risk categories | ≥10 |
| Low-risk persons[d] | ≥15 |

[a]Tuberculin-negative contacts, especially children, should receive prophylaxis for 2–3 months after contact ends and should then undergo repeat TST. Those whose results remain negative should discontinue prophylaxis. HIV-infected contacts should receive a full course of treatment regardless of TST results.
[b]These conditions include silicosis and end-stage renal disease managed by hemodialysis
[c]These settings include correctional facilities, nursing homes, homeless shelters, and hospitals and other health care facilities.
[d]Except for employment purposes where longitudinal TST screening is anticipated, TST is not indicated for these low-risk persons. A decision to treat should be based on individual risk/benefit considerations.
***Source:*** Adapted from Centers for Disease Control and Prevention: TB elimination—treatment options for latent tuberculosis infection (2011). Available at *http://www.cdc.gov/tb/publications/factsheets/testing/skintestresults.pdf.*

**TABLE 94-3 REGIMENS FOR THE TREATMENT OF LATENT TUBERCULOSIS INFECTION (LTBI) IN ADULTS[a]**

| Regimen | Schedule | Duration | Comments |
|---|---|---|---|
| Isoniazid | 300 mg/d (5 mg/kg)<br>Alternative: 900 mg twice weekly (15 mg/kg) | 9 months (6 months acceptable) | Supplement with pyridoxine (25–50 mg daily).<br>Twice-weekly regimens require directly observed therapy. |
| Rifampin | 600 mg/d (10 mg/kg) | 4 months | Broader efficacy studies are needed. |
| Isoniazid plus rifapentine[b] | 900 mg (15 mg/kg) weekly + 900 mg weekly | 12 weeks | Directly observed therapy is recommended for the once-weekly regimen.<br>This regimen may be supplemented with pyridoxine (25–50 mg/d). |

***Source:*** D Menzies et al: *Ann Intern Med* 149:689, 2008; American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: *Am J Respir Crit Care Med* 167:603, 2003; and T Sterling et al: *N Engl J Med* 365:2155, 2011.
[a]Adapted from Table 205e-1 in HPIM-19.
[b]This regimen is not recommended for HIV-infected pts who are receiving antiretroviral therapy or for pregnant women.

### PREVENTION

- *Vaccination:* An attenuated strain of *M. bovis*, bacille Calmette-Guérin (BCG), protects infants and young children from serious forms of TB (e.g., meningitis and miliary disease) and is recommended for routine use in countries with high TB prevalence.
- *Treatment of latent infection:* Candidates for chemoprophylaxis are identified by TST or IGRA. Positive skin tests are determined by reaction size and risk group (Table 94-2). Drug treatment should be considered for pts with evidence of latent infection (Table 94-3). Isoniazid should not be given to persons with active liver disease.

## LEPROSY

### MICROBIOLOGY AND EPIDEMIOLOGY

Leprosy is a nonfatal chronic infectious disease caused by *M. leprae*, an obligate intracellular bacterial species indistinguishable microscopically from other mycobacteria. The organism is confined to humans, armadillos (in some locales), and sphagnum moss.

- *M. leprae* cannot yet be cultured in vitro. The organism has a doubling time in mice of 2 weeks (compared with 20 min for *Escherichia coli* and 1 day for *M. tuberculosis*).
- Leprosy, which is associated with poverty and rural residence, is a disease of the developing world; its global prevalence is difficult to assess and is variously estimated at 0.6–8 million.
  - More than 80% of the world's cases occur in a few countries: India, China, Myanmar, Indonesia, Nepal, Brazil, Nigeria, and Madagascar.

  - In the United States, ~4000 people have leprosy and 100–200 new cases are reported annually.
- The route of transmission is uncertain but may be via nasal droplets, contact with infected soil, or insect vectors.

## CLINICAL MANIFESTATIONS

The spectrum from polar tuberculoid to polar lepromatous disease is associated with an evolution from asymmetric localized macules and plaques to nodular and indurated symmetric generalized skin manifestations, an increasing bacterial load, and loss of *M. leprae*–specific cellular immunity. Prognosis, complications, and intensity of antimicrobial therapy depend on where a pt presents on the clinical spectrum. The incubation period ranges from 2 to 40 years but is usually 5–7 years.

### Tuberculoid (TT) Leprosy

At the less severe end of the disease spectrum, TT leprosy results in symptoms confined to the skin and peripheral nerves.

- One or several hypopigmented macules or plaques with sharp margins that are hypesthetic and have lost sweat glands and hair follicles are present. AFB are few or absent.
- There is asymmetric enlargement of one or several peripheral nerves—most often the ulnar, posterior auricular, peroneal, and posterior tibial nerves—associated with hypesthesia and myopathy.

### Lepromatous (LL) Leprosy

Pts develop symmetrically distributed skin nodules, raised plaques, and diffuse dermal infiltration that can cause leonine facies, loss of eyebrows and lashes, pendulous earlobes, and dry scaling.

- Numerous bacilli are present in skin (up to $10^9$/g), nerves, and all organs except the lungs and CNS.
- Nerve enlargement and damage are usually symmetric and are due to bacillary invasion.

## COMPLICATIONS

- *Reactional states:* These common, immunologically mediated inflammatory states cause considerable morbidity. Erythema nodosum leprosum—characterized by painful erythematous papules that resolve spontaneously in ~1 week—occurs in ~50% of pts near the LL end of the disease spectrum within 2 years of initiation of therapy.
- *Extremities:* Neuropathy results in insensitivity and affects fine touch, pain, and heat receptors. The loss of distal digits in leprosy is a consequence of insensitivity, trauma, secondary infection, and—in lepromatous pts—a poorly understood and sometimes profound osteolytic process.
- *Eyes:* Owing to cranial nerve palsies, lagophthalmos and corneal insensitivity may complicate leprosy, resulting in trauma, secondary infection, and (without treatment) corneal ulcerations and opacities. Leprosy is a major cause of blindness in low-income countries.
- *Nerve abscesses:* Pts with leprosy can develop abscesses of nerves (most commonly the ulnar) and require urgent surgical decompression to prevent irreversible sequelae.

## DIAGNOSIS

In TT leprosy, the advancing edge of a skin lesion should be biopsied. In LL leprosy, biopsy of even normal-appearing skin often yields positive results. Serology, skin testing, and PCR of the skin offer little diagnostic assistance.

## TREATMENT LEPROSY

### DRUGS

- Rifampin (600 mg daily or monthly) is the only agent bactericidal against *M. leprae*. See the preceding section on *M. tuberculosis* for more details on rifampin.
- Monotherapy with dapsone (50–100 mg/d) results in a resistance-related relapse rate of only 2.5%.
  - A decrease in hemoglobin levels of ~1 g/dL is a common adverse effect; the sulfone syndrome (high fever, anemia, exfoliative dermatitis, and a mononucleosis-type blood picture) occurs rarely.
  - G6PD deficiency must be ruled out before therapy to avoid hemolytic anemia.
- Clofazimine (50–100 mg/d, 100 mg 3 times per week, or 300 mg monthly) is a phenazine iminoquinone dye that is weakly active against *M. leprae*. Adverse effects include red-black skin discoloration.

**REGIMENS** Given the unreliability of skin smears and the lack of accessibility to histopathology in many countries in which leprosy is endemic, treatment regimens are based on the number of lesions present.

- *Paucibacillary disease* in adults (<6 skin lesions) is treated with dapsone (100 mg/d) and rifampin (600 mg monthly, supervised) for 6 months or with dapsone (100 mg/d) for 5 years. For a single lesion, a single dose of rifampin (600 mg), ofloxacin (400 mg), and minocycline (100 mg) is recommended.
- *Multibacillary disease* in adults (≥6 skin lesions) is treated with dapsone (100 mg/d) plus clofazimine (50 mg/d)—unsupervised—in addition to rifampin (600 mg monthly) plus clofazimine (300 mg monthly)—supervised—for 1 year.
  - Some experts prefer rifampin (600 mg/d) for 3 years and dapsone (100 mg/d) for life.
  - Relapse can occur years later; prolonged follow-up is needed.
- *Reactional states*
  - Lesions at risk for ulceration or in cosmetically important areas can be treated with glucocorticoids (40–60 mg/d for at least 3 months).
  - If erythema nodosum leprosum is present and persists despite two short courses of steroids (40–60 mg/d for 1–2 weeks), thalidomide (100–300 mg nightly) should be given. Because of thalidomide's teratogenicity, its use is strictly regulated.

## INFECTIONS WITH NONTUBERCULOUS MYCOBACTERIA (NTM)

Mycobacteria other than those of the *M. tuberculosis* complex and *M. leprae* are referred to as *nontuberculous* or *atypical* mycobacteria and are ubiquitous in soil and water.

### MICROBIOLOGY

NTM are broadly differentiated into rapidly and slowly growing forms (<7 days and ≥7 days, respectively). *M. abscessus*, *M. fortuitum*, and *M. chelonae* are examples of rapid growers; species such as *M. avium* and *M. intracellulare* (the *M. avium* complex, or MAC), *M. kansasii, M. ulcerans,* and *M. marinum* are slow growers.

### EPIDEMIOLOGY

Most NTM cause disease in humans only rarely unless some aspect of host defense is impaired (as in bronchiectasis) or breached (as by inoculation—e.g., during liposuction or trauma). The bulk of NTM disease in North America is due to *M. kansasii*, MAC organisms, and *M. abscessus*.

## CLINICAL MANIFESTATIONS

Although there are many NTM species, the clinical presentations they cause can be broadly categorized by the organ system(s) affected.

- *Disseminated disease* is now quite rare; even pts with advanced HIV infection do not often develop disseminated NTM infection, given improved treatment of HIV infection and effective antimycobacterial prophylaxis.
  - Organisms typically spread from the bowel to the bone marrow and bloodstream, but disease is indolent, and it can take weeks or months for the pt to present for medical attention with malaise, fever, weight loss, organomegaly, and lymphadenopathy.
  - A child with involvement of ≥2 organ systems and no iatrogenic cause should be evaluated for defects in the interferon γ/interleukin 12 pathway.
- *Pulmonary disease* represents the most common NTM infection in industrialized countries. MAC organisms are most commonly involved in North America. Pts present with months or years of throat clearing, nagging cough, and slowly progressive fatigue. *M. kansasii* can cause a TB-like syndrome, with hemoptysis, chest pain, and cavitary lung disease.
- Isolated *cervical lymphadenopathy* is the most common NTM infection among young children in North America and is most frequently caused by MAC organisms. The nodes are typically firm and painless and develop in the absence of systemic symptoms.
- *Skin and soft tissue disease* usually requires a break in the skin for introduction of the organism. Different NTM species are associated with specific exposures.
  - *M. fortuitum* is linked to pedicure bath–associated infections, particularly if skin abrasion (e.g., during leg shaving) has immediately preceded the pedicure.
  - Rapidly growing NTM are associated with outbreaks of infection acquired via skin contamination from surgical instruments (especially in cosmetic surgery), injections, and other procedures. These infections are typically accompanied by painful, erythematous, draining SC nodules, usually without associated fever or systemic symptoms.
  - *M. marinum* can be acquired from fish tanks, swimming pools, barnacles, and fish scales. Pts typically develop papules or ulcers ("fish-tank granuloma") that can progress to tendonitis and tender nodules on the arm in a pattern similar to that caused by *Sporothrix schenckii*. Lesions appear days or weeks after acquisition of the organism.
  - *M. ulcerans* is a waterborne organism found primarily in tropical areas, especially in Africa. Skin lesions are typically painless, clean ulcers that slough and can cause osteomyelitis.

## DIAGNOSIS

Similar to *M. tuberculosis*, NTM can be detected on acid-fast or fluorochrome smears of clinical samples and can be cultured on mycobacterial medium. Isolation of NTM from a clinical specimen may reflect colonization and requires an assessment of the organism's clinical significance.

- Isolation of NTM from blood specimens is clear evidence of disease; many NTM species require special media and will not grow in standard blood culture medium.
- The American Thoracic Society has published guidelines for the diagnosis of pulmonary NTM disease that require the growth of NTM from two of three sputum samples, a positive bronchoalveolar lavage sample, or a pulmonary parenchyma biopsy sample with granulomatous inflammation or mycobacteria found on section and NTM in culture. Although these guidelines are specific to MAC, *M. abscessus,* and *M. kansasii*, they probably apply to other NTM as well.
- The only antibiotic susceptibility assessment indicated is testing of MAC organisms for susceptibility to clarithromycin and of *M. kansasii* for susceptibility to rifampin.

**TREATMENT INFECTIONS WITH NTM**

Since NTM disease evolves over a long period, it is rarely necessary to begin treatment on an emergency basis before identifying the infecting species.

- MAC infection requires multidrug therapy with a macrolide (clarithromycin or azithromycin), ethambutol, and a rifamycin (rifampin or rifabutin). Therapy is prolonged, generally continuing for 12 months after culture conversion; typically, a course lasts for at least 18 months.
- *M. kansasii* lung disease is similar to TB in many ways and is also effectively treated with isoniazid (300 mg/d), rifampin (600 mg/d), and ethambutol (15 mg/kg per day). Treatment should continue until cultures have been negative for at least 1 year.
- Extrapulmonary disease due to rapidly growing NTM is often treated successfully with a macrolide and another drug (with the choice based on in vitro susceptibility). Pulmonary disease due to *M. abscessus* is difficult to cure and often requires repeated courses that include a macrolide along with an IV-administered agent such as amikacin, a carbapenem, cefoxitin, or tigecycline.
- *M. marinum* infection is effectively treated with any combination of a macrolide, ethambutol, and a rifamycin for 1–2 months after clinical resolution of isolated soft-tissue disease; tendon and bone involvement may require longer courses in light of clinical evolution.
- Treatment of infections caused by other NTM is less well defined, but macrolides and aminoglycosides are usually effective, with other agents added as indicated.

For a more detailed discussion, see Raviglione MC: Tuberculosis, Chap. 202, p. 1102; Gelber RH: Leprosy, Chap. 203, p. 1122; Holland SM: Nontuberculous Mycobacterial Infections, Chap. 204, p. 1128; and O'Donnell MR, Reddy D, Saukkonen JJ: Antimycobacterial Agents, Chap. 205e, in HPIM-19.

# 95 Lyme Disease and Other Nonsyphilitic Spirochetal Infections

## LYME BORRELIOSIS

### Microbiology and Epidemiology

*Borrelia burgdorferi*, the causative agent of Lyme disease, is a fastidious microaerophilic spirochete. The human infection Lyme borreliosis is caused primarily by three pathogenic genospecies: *B. burgdorferi sensu stricto* (hereafter referred to as *B. burgdorferi*), *Borrelia garinii*, and *Borrelia afzelii*.

- *B. burgdorferi* is the sole cause of Lyme borreliosis in the United States; all three genospecies are found in Europe, and the latter two species occur in Asia.
- Lyme disease is the most common vector-borne illness in the United States, with ~300,000 cases each year.
  - *Ixodes* ticks transmit the disease.
  - *I. scapularis*, which also transmits babesiosis and anaplasmosis, is found in northeastern and midwestern states; *I. pacificus* is found in western states.
- The white-footed mouse is the preferred host for larval and nymphal *I. scapularis*. Adult ticks prefer the white-tailed deer as host.
- Nymphal ticks transmit the disease to humans during the early summer months after feeding for ≥24 h.

## Clinical Manifestations

Lyme disease usually begins with *erythema migrans* (EM; stage 1, localized infection) before disseminating (stage 2) or causing persistent infection (stage 3).

- *Stage 1 (localized infection):* After an incubation period of 3–32 days, EM develops at the site of the tick bite (commonly the thigh, groin, or axilla) in 80% of pts.
  - The classic presentation is a red macule that expands slowly to form an annular lesion with a bright red outer border and central clearing. Central erythema, induration, necrosis, vesicular changes, or many red rings within an outer ring are also possible.
  - Most pts do not remember the preceding tick bite.
- *Stage 2 (disseminated infection):* Given that some pts do not notice EM, many pts present within days or weeks after infection with secondary annular skin lesions, nonspecific systemic signs and symptoms, neurologic deficits, or cardiac manifestations due to hematogenous spread.
  - Nonspecific signs and symptoms include severe headache, mild neck stiffness, fever, chills, migratory musculoskeletal pain, arthralgias, malaise, and fatigue. These manifestations subside within a few weeks, even in untreated pts.
  - Neurologic deficits occur in ~15% of pts and may include meningitis; encephalitis; cranial neuritis, including bilateral facial palsy; motor or sensory radiculoneuropathy; mononeuritis multiplex; ataxia; or myelitis. Lymphocytic pleocytosis (~100 cells/μL) is found in CSF, often along with elevated protein levels and normal or slightly low glucose concentrations.
  - Cardiac involvement occurs in ~8% of pts. Atrioventricular (AV) block of fluctuating degree is most common, but acute myopericarditis is possible. Cardiac involvement usually lasts for only a few weeks but may recur in untreated pts.
- *Stage 3 (persistent infection):* Of untreated pts in the United States, ~60% develop frank arthritis, usually consisting of intermittent attacks of oligoarticular arthritis in large joints (especially the knees) that last for weeks or months.
  - Joint-fluid cell counts range from 500 to 110,000/μL (average, 25,000/μL); the majority of the cells are neutrophils.
  - Arthritis can persist despite eradication of spirochetes, potentially due to infection-induced autoimmunity or retained spirochetal antigens.
  - Chronic neurologic involvement (e.g., subtle encephalopathy affecting memory, mood, or sleep; peripheral neuropathy) is less common. In Europe, severe encephalomyelitis is seen with *B. garinii* infection.
  - Acrodermatitis chronica atrophicans, a late skin manifestation, is seen in Europe and Asia and is associated with *B. afzelii* infection.
- *Post-Lyme syndrome:* For months or years afterward, ~10% of pts have subjective pain, neurocognitive manifestations, or fatigue symptoms—a syndrome indistinguishable from chronic fatigue syndrome and fibromyalgia. There is no evidence that these symptoms are caused by active infection.

## Diagnosis

Serologic evidence combined with a compatible clinical picture is the usual basis for diagnosis.

- Only 20–30% of pts have positive serologic results in acute-phase samples, whereas 70–80% have positive results in convalescent-phase samples obtained 2–4 weeks later. Of note, serologic tests do not discriminate between active and past disease as both IgM and IgG may persist for years after treatment.
  - Serologic analysis consisting of a two-step approach (ELISA screening with western blot confirmation for cases with positive or equivocal results) is recommended only for pts with at least an intermediate pretest likelihood of having Lyme disease.
  - IgM and IgG testing should be done in the first 2 months of illness, after which IgG testing alone is adequate.
  - CDC-adopted criteria dictate that the IgM western blot must show at least 2 of 3 defined bands and that the IgG western blot must show at least 5 of 10 defined bands to be considered positive.
- PCR is most useful for joint fluid, is less sensitive for CSF, and has little or no utility for plasma or urine.
- Although culture of the organism is possible, it is reserved primarily for research settings.

### TREATMENT LYME BORRELIOSIS

- Doxycycline (100 mg bid) is the agent of choice for men and nonpregnant women with localized or disseminated infection and is also effective against anaplasmosis (Chap. 96).
  - Amoxicillin (500 mg tid), cefuroxime (500 mg bid), erythromycin (250 mg qid), and newer macrolides—preferred in that order—are alternative agents.
  - Except in cases of neurologic disease and third-degree AV block, the drug can usually be taken by mouth.
  - A 14-day course of treatment for localized infection or a 21-day course for disseminated infection is generally sufficient.
  - Approximately 15% of pts experience a Jarisch-Herxheimer-like reaction during the first 24 h of treatment.
- For pts with objective neurologic abnormalities (with the possible exception of isolated facial palsy), IV treatment with ceftriaxone for 14–28 days should be given. Cefotaxime or penicillin is an alternative.
- Pts with high-degree AV block (PR interval, >0.3 s) should receive IV treatment for at least part of the course; cardiac monitoring is recommended.
- Pts with Lyme arthritis should be treated with 30 days of oral doxycycline or amoxicillin.
  - For pts who do not respond to oral agents, re-treatment with IV ceftriaxone for 28 days is appropriate.
  - If joint inflammation persists for months after both oral and IV antibiotics, anti-inflammatory agents, disease-modifying antirheumatic drugs, or synovectomy may be successful.
- For pts diagnosed with chronic Lyme disease, no data demonstrate that additional antibiotic therapy is helpful.

## Prophylaxis

The risk of infection with *B. burgdorferi* after a recognized tick bite is so low that antibiotic prophylaxis is not routinely indicated. However, if an attached, engorged *I. scapularis* nymph is found or if follow-up will be difficult, a single 200-mg dose of doxycycline, given within 72 h of the tick bite, effectively prevents the disease.

### Prognosis

Early treatment results in an excellent prognosis. Most pts recover with minimal or no residual deficits.

## ENDEMIC TREPONEMATOSES

### Microbiology and Epidemiology

The endemic treponematoses—yaws (*Treponema pallidum* subspecies *pertenue*), endemic syphilis (*T. pallidum* subspecies *endemicum*), and pinta (*T. carateum*)—are nonvenereal chronic diseases acquired during childhood and caused by organisms closely related to the agent of syphilis, *T. pallidum* subspecies *pallidum*.

- Disease is transmitted by direct contact.
- The most recent WHO estimate (1995) suggested that there are 460,000 new cases per year and a prevalence of 2.5 million infected persons.
- Disease is limited to people in rural areas of developing nations and recent émigrés from these regions.

### Clinical Manifestations

The major clinical distinctions made between venereal syphilis and the nonvenereal treponematoses are the apparent lack of congenital transmission and of CNS involvement in the nonvenereal infections. However, these distinctions may not be entirely accurate.

- *Yaws* is characterized by the development of one or more primary lesions ("mother yaw") followed by multiple disseminated skin lesions.
  - At 3–4 weeks after acquisition of the organism, the pt develops a papule that ultimately enlarges, is associated with regional lymphadenopathy, and heals spontaneously within 6 months.
  - Late gummatous lesions of the skin and long bones affect 10% of untreated persons and are similar to the destructive lesions of leprosy and leishmaniasis.
- *Endemic syphilis* is initially localized to mucocutaneous and mucosal surfaces. Pts develop an intraoral papule, which is followed by mucous patches on the oral mucosa and mucocutaneous lesions resembling the condylomata lata of secondary syphilis. Destructive gummas, osteitis, and gangosa (destruction of the nose, maxilla, palate, and pharynx) are more common in endemic syphilis than in yaws.
- *Pinta* is the most benign of the treponemal infections in that it does not cause destructive lesions or involve tissues other than the skin. The disease has three stages that are characterized by marked changes in skin color.

### Diagnosis

The diagnosis is based on clinical presentation, dark-field microscopy of scrapings from lesions, and serologic testing (as for venereal syphilis).

**TREATMENT ENDEMIC TREPONEMATOSES**

Benzathine penicillin (1.2 million units for adults, 600,000 units for children <10 years of age) is the treatment of choice. A single dose of azithromycin (30 mg/kg; maximum, 2 g) is also effective, and doxycycline is probably an effective alternative.

## LEPTOSPIROSIS

### Microbiology and Epidemiology

Leptospires are spirochetal organisms that cause an important zoonosis with a broad spectrum of clinical manifestations.

- Rodents, particularly rats, are the most important reservoir, but leptospirosis affects almost all mammalian species. Transmission can occur during contact with urine, blood, or tissue from infected animals or, more commonly, during exposure to contaminated environments (e.g., during recreational water activities).
- Globally, there are ~1 million severe cases each year, with a mean case–fatality rate of ~10%.

### Clinical Manifestations

After an average incubation period of 1–2 weeks, infection by *Leptospira* results in a subclinical infection, an undifferentiated febrile illness, or Weil's disease (the most severe form).

- Leptospirosis is a biphasic illness. The initial *leptospiremic* phase lasts 3–10 days and is characterized by fever; organisms can be cultured from blood during this phase. After another 3–10 days (the *immune* phase), symptoms resolve, and leptospires can be cultured from urine.
  - Nonspecific physical findings may include conjunctival suffusion, nonexudative pharyngeal injection, muscle tenderness, lymphadenopathy, crackles on lung auscultation, jaundice, hepatosplenomegaly, and a transient rash.
- Severe leptospirosis, often referred to as *Weil's syndrome*, encompasses the triad of hemorrhage, jaundice, and acute renal injury. Up to 50% of pts die of septic shock with multiorgan failure and/or severe bleeding in the lungs, GI and urogenital tracts, and skin.

### Diagnosis

An appropriate exposure history combined with any of the protean manifestations of leptospirosis suggests the clinical diagnosis and guides confirmatory testing.

- Definitive diagnosis rests on demonstration of the organism by culture isolation (which takes weeks or months), on a positive PCR result, or on seroconversion or a ≥4-fold rise in antibody titer.
  - Leptospires can be cultured from blood and CSF during the first 7–10 days of illness.
  - Urine cultures are positive in the second week of illness.

**TREATMENT LEPTOSPIROSIS**

- Prompt initiation of antibiotics probably shortens the course of severe leptospirosis and prevents the progression of mild disease.
- For mild disease, oral treatment with doxycycline, azithromycin, ampicillin, or amoxicillin is recommended. In regions where rickettsial diseases are co-endemic, doxycycline or azithromycin is the drug of choice.
- For severe disease, parenteral treatment with penicillin, ceftriaxone, cefotaxime, or doxycycline should be given. From a pragmatic viewpoint, severe leptospiral disease frequently requires empirical initiation of broad-spectrum parenteral therapy before the diagnosis is confirmed.

## RELAPSING FEVER

### Microbiology

*Borrelia recurrentis* causes louse-borne relapsing fever (LBRF) and is transmitted from person to person by the body louse. Spirochetes are introduced not from the bite itself but from rubbing of the insect's feces into the bite site in response to

irritation. Tick-borne relapsing fever (TBRF), a zoonosis usually transmitted via the bite of various *Ornithodoros* ticks, is caused by multiple *Borrelia* species. *B. miyamotoi* can cause relapsing fever but is transmitted to humans from other mammals by hard ticks (e.g., *Ixodes scapularis*) that also transmit *B. burgdorferi* and other tick-borne illnesses.

## Epidemiology

LBRF transmission is currently limited to Ethiopia and adjacent countries, with epidemics occurring during famine, natural disaster, and war. TBRF occurs worldwide, with Africa most affected. In North America, most cases are due to *B. hermsii* and *B. turicatae* and occur in the western United States and Canada.

## Clinical Manifestations

- Both TBRF and LBRF present with a sudden onset of discrete febrile periods separated by afebrile periods of a few days.
  - In LBRF, the first episode of fever persists for 3–6 days and is followed by a single milder episode.
  - In TBRF, multiple febrile periods last 1–3 days each.
  - In both forms, the duration of an afebrile period ranges from 4 to 14 days.
- In addition to fever, pts commonly develop headaches, myalgias, nausea, abdominal pain (due to hepatosplenomegaly), and arthralgias.
  - Petechiae, ecchymoses, and epistaxis are common in LBRF but not in TBRF.
  - Localizing neurologic findings (e.g., Bell's palsy, deafness, visual impairment) are more common in TBRF.

## Diagnosis

In pts with a compatible history (i.e., a characteristic fever pattern and exposure to body lice or soft-bodied ticks 1–2 weeks prior to illness onset), laboratory confirmation is made by the detection or isolation of spirochetes from blood during a febrile episode. Microscopic examination of Wright- or Giemsa-stained thin blood smears usually yields positive results if the concentration of spirochetes is $\geq 10^5$/mL.

- PCR techniques may reveal spirochetes between febrile episodes.
- Serologic confirmation of infection is limited by false-positive results and poor sensitivity.

### TREATMENT RELAPSING FEVER

- One dose of doxycycline (200 mg PO), tetracycline (500 mg PO), or penicillin G (400,000–800,000 units IM) is effective for LBRF. A 10-day course of tetracycline (500 mg q6h) or doxycycline (100 mg bid) is preferred for TBRF; erythromycin (500 mg q6h) is an alternative when tetracyclines are contraindicated. The Jarisch-Herxheimer reaction, which has an incidence of ~80% in LBRF and ~50% in TBRF, presents as rigors, fevers, and hypotension within 2–3 h of initiation of antibiotic therapy. Given that some cases are fatal, pts should be monitored for several hours following the first dose of antibiotics.
- Little is known about treatment for *B. miyamotoi* infections, but the guidelines for Lyme disease are probably sufficient.

## Prognosis

The mortality rates for untreated LBRF and TBRF are 10–70% and 4–10%, respectively. With treatment, the mortality rate is 2–5% for LBRF and <2% for TBRF.

For a more detailed discussion, see Lukehart SA: Endemic Treponematoses, Chap. 207e; Hartskeerl RA, Wagenaar JFP: Leptospirosis, Chap. 208, p. 1140; Barbour AG: Relapsing Fever, Chap. 209, p. 1146; and Steere AC: Lyme Borreliosis, Chap. 210, p. 1149, in HPIM-19. For a discussion of syphilis, see Chap. 83 in this manual.

# 96 Rickettsial Diseases

## Microbiology

Rickettsiae are obligate intracellular gram-negative coccobacilli and short bacilli usually transmitted by tick, mite, flea, or louse vectors. Except in the case of louse-borne typhus, humans are incidental hosts.

## Clinical Manifestations

The clinical manifestations of all the acute rickettsial presentations are similar during the first 5 days and consist of nonspecific signs and symptoms: fever, headache, and myalgias with or without nausea, vomiting, and cough. As the course progresses, clinical manifestations—including occurrence of a macular, maculopapular, or vesicular rash; eschar; pneumonitis; and meningoencephalitis—vary from one disease to another. (See Table 96-1 and details below.)

## TICK- AND MITE-BORNE SPOTTED FEVERS

### ROCKY MOUNTAIN SPOTTED FEVER (RMSF)

#### Epidemiology

Caused by *R. rickettsii*, RMSF has the highest case–fatality rate of all rickettsial diseases.

- In the United States, the prevalence is highest in the south-central and southeastern states. Most cases occur between May and September.
- A rare presentation of fulminant RMSF is seen most often in male black pts with G6PD deficiency.
- RMSF is transmitted by different ticks in different geographic areas—e.g., the American dog tick (*Dermacentor variabilis*) transmits RMSF in the eastern two-thirds of the United States and in California, and the Rocky Mountain wood tick (*D. andersoni*) transmits RMSF in the western United States.

#### Pathogenesis

Rickettsiae are inoculated by the tick after ≥6 h of feeding, spread lymphohematogenously, and infect numerous foci of contiguous endothelial cells. Increased vascular permeability, with edema, hypovolemia, and ischemia, causes tissue and organ injury.

**TABLE 96-1 FEATURES OF SELECTED RICKETTSIAL INFECTIONS**

| Disease | Organism | Transmission | Geographic Range | Incubation Period, Days | Duration, Days | Rash, % | Eschar, % | Lymphadenopathy[a] |
|---|---|---|---|---|---|---|---|---|
| Rocky Mountain spotted fever | *Rickettsia rickettsii* | Tick bite: *Dermacentor andersoni*, *D. variabilis* | United States | 2–14 | 10–20 | 90 | <1 | + |
| | | *Amblyomma cajennense*, *A. aureolatum* | Central/South America | | | | | |
| | | *Rhipicephalus sanguineus* | Mexico, Brazil, United States | | | | | |
| Mediterranean spotted fever | *R. conorii* | Tick bite: *R. sanguineus*, *Rhipicephalus pumilio* | Southern Europe, Africa, Middle East, Central Asia | 5–7 | 7–14 | 97 | 50 | + |
| African tick-bite fever | *R. africae* | Tick bite: *A. hebraeum*, *A. variegatum* | Sub-Saharan Africa, West Indies | 4–10 | 4–19 | 50 | 90 | ++++ |
| Maculatum disease | *R. parkeri* | Tick bite: *A. maculatum* | United States, South America | 2–10 | 6–16 | 88 | 94 | ++ |
| Rickettsialpox | *R. akari* | Mite bite: *Liponyssoides sanguineus* | United States, Ukraine, Turkey, Mexico, Croatia | 10–17 | 3–11 | 100 | 90 | +++ |
| Tick-borne lymphadenopathy | *R. slovaca* | Tick bite: *D. marginatus*, *D. reticularis* | Europe | 7–9 | 17–180 | 5 | 100 | ++++ |
| Flea-borne spotted fever | *R. felis* | Flea (mechanism undetermined): *Ctenocephalides felis* | Worldwide | 8–16 | 8–16 | 80 | 15 | — |

*(Continued)*

**TABLE 96-1 FEATURES OF SELECTED RICKETTSIAL INFECTIONS (*CONTINUED*)**

| Disease | Organism | Transmission | Geographic Range | Incubation Period, Days | Duration, Days | Rash, % | Eschar, % | Lymphadenopathy[a] |
|---|---|---|---|---|---|---|---|---|
| Epidemic typhus | *R. prowazekii* | Louse feces: *Pediculus humanus corporis*, fleas and lice of flying squirrels, or recrudescence | Worldwide | 7–14 | 10–18 | 80 | None | — |
| Murine typhus | *R. typhi* | Flea feces: *Xenopsylla cheopis*, *C. felis*, others | Worldwide | 8–16 | 9–18 | 80 | None | — |
| Human monocytotropic ehrlichiosis | *Ehrlichia chaffeensis* | Tick bite: *A. americanum*, *D. variabilis* | United States | 1–21 | 3–21 | 26 | None | ++ |
| Ewingii ehrlichiosis | *E. ewingii* | Tick bite: *A. americanum* | United States | 1–21 | 4–21 | 0 | None | |
| Unnamed ehrlichiosis | *E. muris*–like agent | Tick bite: *Ixodes scapularis* | United States | Unknown | 3–14 | None | None | |
| Human granulocytotropic anaplasmosis | *Anaplasma phagocytophilum* | Tick bite: *I. scapularis*, *I. ricinus*, *I. pacificus*, *I. persulcatus* | United States, Europe, Asia | 4–8 | 3–14 | Rare | None | — |
| Unnamed disease | *Candidatus* Neoehrlichia mikurensis | Tick bite: *I. ricinus*, *I. persulcatus*, *Haemaphysalis concinna* | Europe, China | ≥8 | 11–75 | 10 | None | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Scrub typhus | *Orientia tsutsugamushi* | Mite bite: *Leptotrombidium deliense*, others | Asia, Australia, Pacific and Indian Ocean islands | 9–18 | 6–21 | 50 | 35 | +++ |
| Q fever | *Coxiella burnetii* | Inhalation of aerosols of infected parturition material (goats, sheep, cattle, cats, others), ingestion of infected milk or milk products | Worldwide except New Zealand, Antarctica | 3–30 | 5–57 | <1 | None | — |

[a]++++, severe; +++, marked; ++, moderate; +, present in a small proportion of cases; —, not a noted feature.

## Clinical Manifestations

The incubation period is ~1 week (range, 2–14 days). After 3 days of nonspecific symptoms, half of pts have a rash characterized by macules appearing on the wrists and ankles and subsequently spreading to the rest of the extremities and the trunk.

- Lesions ultimately become petechial in 41–59% of pts, appearing on or after day 6 of illness in ~74% of all cases that include a rash. The palms and soles become involved after day 5 in 43% of pts but do not become involved at all in 18–64%.
- Pts may develop hypovolemia, prerenal azotemia, hypotension, noncardiogenic pulmonary edema, renal failure, hepatic injury, and cardiac involvement with dysrhythmias. Bleeding is a rare but potentially life-threatening consequence of severe vascular damage.
- CNS involvement—manifesting as encephalitis, focal neurologic deficits, or meningoencephalitis—is an important determinant of outcome. In meningoencephalitis, CSF findings are notable for pleocytosis with a mononuclear cell or neutrophil predominance, increased protein levels, and normal glucose levels.
- Laboratory findings may include increased plasma levels of acute-phase reactants such as C-reactive protein, hypoalbuminemia, hyponatremia, and elevated levels of creatine kinase.

## Prognosis

Without treatment, the pt usually dies in 8–15 days; fulminant RMSF can result in death within 5 days. The mortality rate is 3–5% despite the availability of effective antibiotics, mostly because of delayed diagnosis. Survivors of RMSF usually return to their previous state of health.

## Diagnosis

Within the first 3 days, diagnosis is difficult, since only 3% of pts have the classic triad of fever, rash, and known history of tick exposure. When the rash appears, RMSF should be considered.

- Immunohistologic examination of a cutaneous biopsy sample from a rash lesion is the only useful diagnostic test during acute illness, with a sensitivity of 70% and a specificity of 100%.
- Serology, most commonly the indirect immunofluorescence assay (IFA), is usually positive 7–10 days after disease onset, and a diagnostic titer of ≥1:64 is usually documented.

### TREATMENT ROCKY MOUNTAIN SPOTTED FEVER

- Doxycycline (100 mg bid PO or IV) is the agent of choice for both children and adults but not for pregnant women and pts allergic to this drug, who should receive chloramphenicol.
- Treatment is given until the pt is afebrile and has been improving for 2 or 3 days.

## OTHER TICK-BORNE SPOTTED FEVERS

- *R. conorii* causes disease in southern Europe, Africa, and Asia. The name for *R. conorii* infection varies by region (e.g., Mediterranean spotted fever, Kenya tick typhus).
  - Disease is characterized by high fever, rash, and—in most locales—an inoculation eschar (*tâche noire*) at the site of the tick bite.
  - A severe form of disease with a mortality rate of ~50% occurs in pts with diabetes, alcoholism, or heart failure.
- *R. africae* causes African tick-bite fever, which occurs in sub-Saharan Africa and the Caribbean and is a mild illness consisting of headache, fever, eschar, and regional lymphadenopathy.

- Tick-borne spotted fever is diagnosed on the basis of clinical and epidemiologic findings; the diagnosis is confirmed by serology or detection of rickettsiae.

**TREATMENT OTHER TICK-BORNE SPOTTED FEVERS**

Doxycycline (100 mg PO bid for 1–5 days) or chloramphenicol (500 mg qid PO for 7–10 days) is effective for treatment. Pregnant pts may be treated with josamycin (3 g/d PO for 5 days).

## RICKETTSIALPOX

### Epidemiology

Rickettsialpox is caused by *R. akari* and is maintained by mice and their mites. Recognized principally in New York City, rickettsialpox has been reported in other urban and rural locations in the United States as well as in Ukraine, Croatia, Mexico, and Turkey.

### Clinical Manifestations

A papule forms at the site of the mite bite and develops a central vesicle that becomes a painless black-crusted eschar surrounded by an erythematous halo. Lymph nodes draining the region of the eschar enlarge.

- After an incubation period of 10–17 days, malaise, chills, fever, headache, and myalgia mark disease onset.
- A macular rash appears on day 2–6 of illness and evolves sequentially into papules, vesicles, and crusts that heal without scarring.
- If untreated, fever lasts 6–10 days.

**TREATMENT RICKETTSIALPOX**

Doxycycline is the drug of choice for treatment.

# FLEA- AND LOUSE-BORNE TYPHUS GROUP RICKETTSIOSES

## ENDEMIC MURINE TYPHUS (FLEA-BORNE)

### Etiology and Epidemiology

Caused by *R. typhi*, endemic murine typhus has a rat reservoir and is transmitted by fleas.

- Humans become infected when *Rickettsia*-laden flea feces are scratched into pruritic bite lesions; less often, the flea bite itself transmits the organisms or aerosolized rickettsiae from flea feces are inhaled.
- In the United States, endemic typhus occurs mainly in southern Texas and southern California; globally, it occurs in warm (often coastal) areas throughout the tropics and subtropics.
- Flea bites often are not recalled by pts, but exposure to animals such as cats, opossums, raccoons, skunks, and rats is reported by ~40%.
- Risk factors for severe disease include older age, underlying disease, and treatment with a sulfonamide drug.

### Clinical Manifestations

Prodromal symptoms 1–3 days before the abrupt onset of chills and fever include headache, myalgia, arthralgia, nausea, and malaise; nausea and vomiting are nearly universal early in illness.

- Rash is apparent at presentation (usually ~4 days after symptom onset) in 13% of pts; 2 days later, half of the remaining pts develop a maculopapular rash that involves the trunk more than the extremities, is seldom petechial, and rarely involves the face, palms, or soles.
- Pulmonary disease is common, causing a hacking, nonproductive cough in 35% of pts. Almost one-fourth of pts who undergo CXR have pulmonary densities due to interstitial pneumonia, pulmonary edema, and pleural effusions.
- Laboratory abnormalities include anemia, leukopenia early in the course, leukocytosis late in the course, thrombocytopenia, hyponatremia, hypoalbuminemia, mildly increased hepatic aminotransferase levels, and prerenal azotemia.
- Complications may include respiratory failure, hematemesis, cerebral hemorrhage, and hemolysis.
- The duration of untreated disease averages 12 days (range, 9–18 days).

## Diagnosis

The diagnosis can be based on culture, PCR, serologic studies of acute- and convalescent-phase sera, or immunohistology, but most pts are treated empirically.

**TREATMENT ENDEMIC MURINE TYPHUS (FLEA-BORNE)**

Doxycycline (100 mg PO bid for 7–15 days) is effective. Ciprofloxacin provides an alternative if doxycycline is contraindicated.

# EPIDEMIC TYPHUS (LOUSE-BORNE)

## Etiology and Epidemiology

Epidemic typhus is caused by *R. prowazekii* and is transmitted by the human body louse. Eastern flying squirrels and their lice and fleas maintain *R. prowazekii* in a zoonotic cycle.

- The louse lives in clothing under poor hygienic conditions, particularly in colder climates and classically at times of war or natural disaster.
- Lice feed on pts with epidemic typhus and then defecate the organism on their subsequent host during their next meal. The pt autoinoculates the organism while scratching.
- *Brill-Zinsser disease* is a recrudescent form of epidemic typhus whose occurrence years after acute illness suggests that *R. prowazekii* remains dormant in the host, with reactivation when immunity wanes.

## Clinical Manifestations

Epidemic typhus presents abruptly with the onset of high fevers, prostration, severe headache, cough, and severe myalgias. Photophobia with conjunctival injection and eye pain is also common.

- A rash appears on the upper trunk around the fifth day of illness and spreads to involve all body-surface areas except the face, palms, and soles.
- Confusion and coma, skin necrosis, and gangrene of the digits are noted in severe cases.
- Untreated, the disease is fatal in 7–40% of cases. Pts develop renal failure, multiorgan involvement, and prominent neurologic manifestations.

## Diagnosis

Epidemic typhus is sometimes misdiagnosed as typhoid fever. The diagnosis can be based on serology, immunohistochemistry, or detection of the organism in a louse found on a pt.

**TREATMENT EPIDEMIC TYPHUS (LOUSE-BORNE)**

Doxycycline (100 mg bid) is given until 2 or 3 days after the pt has defervesced, although a one-time dose of 200 mg has proved effective under epidemic conditions.

## SCRUB TYPHUS

- *Orientia tsutsugamushi*, the agent of scrub typhus, is transmitted by larval mites or chiggers in environments with heavy scrub vegetation.
- Disease occurs during the wet season. It is endemic in eastern and southern Asia, northern Australia, and the Pacific islands.
- The classic case description includes signs rarely seen in indigenous pts: an eschar at the site of chigger feeding, regional lymphadenopathy, and maculopapular rash. Westerners commonly do not present with all three findings. Severe cases include encephalitis and interstitial pneumonia.
- Scrub typhus can be diagnosed by serologic assays (IFA, indirect immunoperoxidase, and enzyme immunoassays); PCR analysis of eschars and blood is also effective.

**TREATMENT SCRUB TYPHUS**

A 7- to 15-day course of doxycycline (100 mg bid) or chloramphenicol (500 mg qid) or a 3-day course of azithromycin (500 mg qd) is effective.

## EHRLICHIOSES AND ANAPLASMOSIS

Two distinct *Ehrlichia* species and one *Anaplasma* species—all obligately intracellular organisms—are transmitted by ticks to humans and cause infections that can be severe and prevalent.

### HUMAN MONOCYTOTROPIC EHRLICHIOSIS (HME)

#### Etiology and Epidemiology

HME is caused by *Ehrlichia chaffeensis* and, in the United States, generally occurs in southeastern, south-central, and mid-Atlantic states from May to July. The incidence can be as high as 414 cases per 100,000 population.

- *E. chaffeensis* is transmitted by the Lone Star tick (*Amblyomma americanum*), and white-tailed deer are the major reservoir.
- The median age of pts is 52 years; 60% of pts are male.
- *E. ewingii* and an *E. muris*–like agent cause an illness similar to, but less severe than, that due to *E. chaffeensis*.

#### Clinical Manifestations

Clinical findings are nonspecific and include fever (96%), headache (72%), myalgia (68%), and malaise (77%). Nausea, vomiting, diarrhea, cough, rash, and confusion may be noted.

- The median incubation period is 8 days.
- Disease can be severe: up to 49% of pts are hospitalized and ~2% die. Complications include a toxic shock–like syndrome, respiratory distress, cardiac failure, hepatitis, meningoencephalitis, fulminant infection, and hemorrhage.
- Leukopenia (61%), thrombocytopenia (73%), and elevated serum aminotransferase levels (84%) are common.

## Diagnosis

Because HME can be fatal, empirical antibiotic therapy based on clinical diagnosis is required. PCR testing before initiation of antibiotic therapy or retrospective serodiagnosis to detect increased antibody titers can be performed. Morulae are seen in <10% of peripheral-blood smears.

**TREATMENT HUMAN MONOCYTOTROPIC EHRLICHIOSIS**

Doxycycline (100 mg PO/IV bid) or tetracycline (250–500 mg PO q6h) is effective and should be continued for 3–5 days after defervescence.

# HUMAN GRANULOCYTOTROPIC ANAPLASMOSIS (HGA)

## Etiology and Epidemiology

HGA is caused by *Anaplasma phagocytophilum* and, in the United States, occurs mainly in northeastern and upper midwestern states.

- The geographic distribution is similar to that of Lyme disease and *Babesia microti* infection, given the shared *Ixodes scapularis* tick vector.
- HGA incidence peaks in May through July, but the disease can occur year-round.
- The epidemiology of HGA is similar to that of HME, with males (59%) and older persons (median age, 51 years) more often affected.

## Clinical Manifestations

Given high seroprevalence rates in endemic areas, it appears that most people develop subclinical infections.

- After an incubation period of 4–8 days, pts develop fever (75–100%), myalgia (77%), headache (82%), and malaise (97%).
- Severe complications—respiratory distress, a toxic shock–like syndrome, and opportunistic infections—occur most often in elderly pts.
- On laboratory examination, pts are found to have leukopenia (55%), thrombocytopenia (75%), and elevated serum aminotransferase levels (83%).

## Diagnosis

HGA should be considered in pts with influenza-like illness during May through December and in pts with atypical severe presentations of Lyme disease.

- Peripheral-blood films may reveal morulae in neutrophils in 20–75% of infections.
- PCR testing before antibiotic therapy or retrospective serologic testing demonstrating a ≥4-fold rise in antibody titer can confirm the diagnosis.

**TREATMENT HUMAN GRANULOCYTOTROPIC ANAPLASMOSIS**

Doxycycline (100 mg PO bid) is effective, and most pts defervesce within 24–48 h. Pregnant women and children <8 years old may be treated with rifampin.

## Prevention

HME and HGA are prevented by avoidance of ticks in endemic areas, use of protective clothing and tick repellents, careful tick searches after exposures, and prompt removal of attached ticks.

## Q FEVER

### Microbiology

*Coxiella burnetii*—the etiologic agent of Q fever—is a small, pleomorphic coccobacillus that has a gram-negative cell wall and is located intracellularly.

### Epidemiology and Pathogenesis

A worldwide disease, Q fever is a zoonosis. Cattle, sheep, and goats are responsible for most cases of human infection; many other animals can serve as vectors of transmission or as reservoirs of disease.

- *C. burnetii* localizes to the uterus and mammary glands of infected female mammals. It is reactivated in pregnancy and is found at high concentrations in the placenta. At parturition, the organism is dispersed as an aerosol, and infection usually follows inhalation.
- Abattoir workers, veterinarians, farmers, and other persons who have contact with infected animals, particularly with newborn animals or infected products of conception, are at risk.
- In the United States, there are 28–54 cases per year; in Australia, there are 30 cases per 1 million population per year.

### Clinical Manifestations

The specific presentation of acute Q fever differs geographically (e.g., pneumonia in Nova Scotia and granulomatous hepatitis in Marseille), potentially reflecting differences in routes of infection or infecting strains; chronic Q fever almost always implies endocarditis.

- *Acute Q fever:* After an incubation period of 3–30 days, pts may present with flu-like syndromes, prolonged fever, pneumonia, hepatitis, pericarditis, myocarditis, meningoencephalitis, and infection during pregnancy.
  - Signs and symptoms are often nonspecific (e.g., fever, fatigue, headache, chills, sweats, nausea, vomiting, diarrhea, cough, and occasionally rash).
  - Multiple rounded opacities on CXR in pts in endemic areas are highly suggestive of Q fever pneumonia.
  - The WBC count is usually normal, but thrombocytopenia occurs. During recovery, reactive thrombocytosis can develop.
  - Prolonged fatigue, along with a constellation of nonspecific symptoms (e.g., headaches, myalgias, arthralgias), can follow Q fever (post–Q fever fatigue syndrome).
- *Chronic Q fever:* Pts with *C. burnetii* endocarditis typically have prior valvular heart disease, immunosuppression, or chronic renal failure.
  - Fever is absent or low grade; pts may be ill for >1 year before diagnosis.
  - Valvular vegetations are seen in 21–50% of cases with transesophageal echocardiography but in only 12% with transthoracic echocardiography. The vegetations differ from those in bacterial endocarditis of other etiologies and manifest as endothelium-covered nodules on the valve.
  - The disease should be suspected in all pts with culture-negative endocarditis.
  - Although *C. burnetii* can be isolated by a shell-vial technique, most laboratories are not permitted to attempt isolation because of the organism's highly contagious nature. PCR testing of tissue or biopsy specimens can be used, but serology is the most common diagnostic tool; IFA is the method of choice.

**TREATMENT Q FEVER**

- Acute Q fever is treated with doxycycline (100 mg bid for 14 days).
  - Quinolones are also efficacious.
  - If Q fever is diagnosed during pregnancy, trimethoprim-sulfamethoxazole should be administered up to term.

- The currently recommended treatment for chronic Q fever is doxycycline (100 mg bid) and hydroxychloroquine (200 mg tid; plasma concentrations maintained at 0.8–1.2 μg/mL) for 18 months.
  - In vitro, hydroxychloroquine renders doxycycline bactericidal against *C. burnetii*.
  - The minimal inhibitory concentration (MIC) of doxycycline for the pt's isolate should be determined and serum levels monitored, with a goal of a serum level–to–doxycycline MIC ratio of ≥1.
  - Pts should be advised about photosensitivity and retinal toxicity risks with treatment.
  - Pts who cannot receive doxycycline–hydroxychloroquine should be treated with at least two agents active against *C. burnetii*. The combination of rifampin (300 mg once daily) plus doxycycline (100 mg bid) or ciprofloxacin (750 mg bid) has been used with success.
    - This alternative regimen should be discontinued when IgG antibody levels have decreased by fourfold at 1 year, IgM antibody to phase II has disappeared, and the pt is clinically stable.

For a more detailed discussion, see Walker DH, Dumler JS, Marrie T: Rickettsial Diseases, Chap. 211, p. 1154, in HPIM-19.

# 97 *Mycoplasma pneumoniae*, *Legionella* Species, and *Chlamydia pneumoniae*

*Mycoplasma pneumoniae*, *Legionella* species, and *Chlamydia pneumoniae* are often grouped together as the most important causes of "atypical" community-acquired pneumonia. (For a discussion of urogenital mycoplasmas, see Chap. 83.)

## *MYCOPLASMA PNEUMONIAE*

With a size of only 150–350 nm, mycoplasmas are the smallest free-living organisms. Genome sequence data from many different *Mycoplasma* species have helped define the minimal set of genes necessary for cellular life. Lacking a cell wall and bounded only by a plasma membrane, mycoplasmas colonize mucosal surfaces of the respiratory and urogenital tracts.

### Epidemiology

*M. pneumoniae* occurs worldwide with no seasonal pattern. Infection causes upper respiratory tract disease ~20 times more frequently than pneumonia.

- Infection is acquired by inhalation of aerosols, with an incubation period of 2–4 weeks.
- *M. pneumoniae* accounts for ~23% of cases of community-acquired pneumonia in adults.

## Clinical Manifestations

The clinical presentation does not help distinguish *M. pneumoniae* pneumonia from that of any other bacterial etiology.

- Acute *M. pneumoniae* infection manifests as a nonspecific upper respiratory syndrome with pharyngitis, tracheobronchitis, and/or wheezing.
- Pneumonia develops in 3–13% of infected pts. The most common presenting symptom is a nonproductive cough. Headache, malaise, chills, and fever are common.
- On physical examination, ~80% of pts have wheezes or rales.
- Symptoms usually resolve in 2–3 weeks, and appropriate antimicrobial therapy significantly shortens the duration of clinical illness.
- Infection uncommonly results in critical illness and rarely causes death.
- Extrapulmonary manifestations of *M. pneumoniae* infection are relatively uncommon but include skin eruptions (e.g., erythema multiforme major, rashes), neurologic manifestations (e.g., encephalitis, Guillain-Barré syndrome, acute demyelinating encephalomyelitis), septic arthritis (particularly in pts with hypogammaglobulinemia), and hematologic manifestations (e.g., hemolytic anemia, coagulopathies).

## Diagnosis

Clinical findings, nonmicrobiologic laboratory tests, and CXR are not useful in distinguishing *M. pneumoniae* pneumonia from pneumonia of other etiologies.

- Acute *M. pneumoniae* infection can be diagnosed by PCR analysis of respiratory tract secretions, which is 65–90% sensitive and 90–100% specific.
- *M. pneumoniae* culture (which requires special medium) is not recommended for routine diagnosis because its sensitivity is ≤60% and growth of the organism can take weeks.
- Serologic testing for IgM and IgG antibodies to *M. pneumoniae* requires acute- and convalescent-phase samples and is therefore less useful for diagnosis of active infections. Moreover, IgM antibodies to *M. pneumoniae* can persist for up to 1 year after acute infection.
- Measurement of cold agglutinin titers is no longer recommended for the diagnosis of *M. pneumoniae* infection because the findings are nonspecific.

### TREATMENT *M. PNEUMONIAE* INFECTIONS

- Antibiotic options include macrolides (azithromycin, 500 mg PO for 1 day followed by 250 mg for 4 days), tetracyclines (doxycycline, 100 mg PO bid for 10–14 days), and respiratory fluoroquinolones (levofloxacin, 500–750 mg PO qd for 10–14 days).
- Ciprofloxacin and ofloxacin are *not* recommended because of their high minimal inhibitory concentrations against *M. pneumoniae*.

# *LEGIONELLA* SPECIES

## Microbiology

Legionellaceae are intracellular aerobic gram-negative bacilli that grow on buffered charcoal yeast extract (BCYE) agar. *L. pneumophila* causes 80–90% of cases of human *Legionella* disease and includes 16 serogroups; serogroups 1, 4, and 6 are most common.

## Epidemiology

- *Legionella* is found in fresh water and human-constructed water sources. Outbreaks have been traced to drinking water systems and rarely to cooling towers.

- The organisms are transmitted to individuals primarily via aspiration, but can also be transmitted by aerosolization and direct instillation into the lungs during respiratory tract manipulations.
- *Legionella* is the fourth most common cause of community-acquired pneumonia, accounting for 2–13% of cases. It causes 10–50% of cases of nosocomial pneumonia if the hospital's water system is colonized with the organism.
- Pts who have chronic lung disease, who smoke, and/or who are elderly, immunosuppressed, or recently discharged from the hospital are at particularly high risk for disease.

## Clinical Manifestations

Legionellosis manifests as either an acute, febrile, self-limited illness (Pontiac fever) or pneumonia (Legionnaires' disease).

- Pontiac fever is a flulike illness with a 24- to 48-h incubation period. Malaise, fatigue, and myalgias occur in 97% of cases. Fever, chills, and headaches are also very common, but pneumonia does not develop. The disease is self-limited and does not require antimicrobial treatment. Recovery takes place in a few days.
- Legionnaires' disease is more severe than other atypical pneumonias and is more likely to result in ICU admission.
  - After a usual incubation period of 2–10 days, nonspecific symptoms (e.g., fever, malaise, fatigue, headache, anorexia) develop and are followed by a cough that is usually mild and only slightly productive. Chest pain and GI difficulties can be prominent.
  - Radiologic findings are nonspecific, but pleural effusions are present in 28–63% of pts on hospital admission.
  - Legionnaires' disease is not readily distinguishable from pneumonia of other etiologies based on clinical manifestations, but diarrhea, confusion, temperatures >39°C (102.2°F), hyponatremia, increased aminotransferase levels, hematuria, hypophosphatemia, and elevated creatine phosphokinase levels are documented more frequently than in other pneumonias.
  - Extrapulmonary infection results from hematogenous dissemination and most commonly affects the heart (e.g., myocarditis, pericarditis).

## Diagnosis

The use of *Legionella* testing—especially the *Legionella* urinary antigen test—is recommended for all pts with community-acquired pneumonia.

- Sputum or bronchoscopy specimens can be subjected to direct fluorescent antibody (DFA) staining and culture.
  - DFA testing is rapid and specific but is less sensitive than culture.
  - Cultures on BCYE medium (with antibiotics to suppress competing flora) require 3–5 days to become positive.
- Serologic confirmation requires comparison of acute- and convalescent-phase samples. Detection of the necessary fourfold rise in titers often requires 12 weeks, but a single titer of 1:256 is presumptive evidence for Legionnaires' disease.
- Urinary antigen testing is rapid, inexpensive, easy to perform, second only to culture in terms of sensitivity, and highly specific. It is useful only for *L. pneumophila* serogroup 1, which causes 80% of disease cases.
  - Urinary antigen is detectable 3 days after disease onset and generally disappears over 2 months, although positivity can be prolonged if the pt is receiving glucocorticoid therapy.
  - The test is not affected by antibiotic administration.

## TREATMENT *LEGIONELLA* INFECTIONS

- Newer macrolides (e.g., azithromycin at 500 mg/d PO, with doubling of the first dose considered; or clarithromycin at 500 mg bid IV or PO) or fluoroquinolones

(e.g., levofloxacin at 750 mg/d IV or 500 mg/d PO or moxifloxacin at 400 mg/d PO) are most effective.
  - Rifampin (300–600 mg bid) combined with either class of drug is recommended in severe cases.
  - Tetracyclines (doxycycline at 100 mg bid IV or PO) are alternatives.
- Immunocompetent hosts should receive 10–14 days of therapy, but immunocompromised hosts and pts with advanced disease should receive a 3-week course.
  - A 5- to 10-day course of azithromycin is adequate because of this drug's long half-life.
  - A clinical response usually occurs within 3–5 days after the initiation of parenteral therapy, at which point oral therapy can be substituted.

## Prognosis

Mortality rates approach 80% among immunocompromised pts who do not receive timely therapy. Among immunocompetent hosts, mortality can approach 31% without treatment but ranges from 0 to 11% with appropriate and timely therapy. Fatigue, weakness, and neurologic symptoms can persist for >1 year.

# *CHLAMYDIA PNEUMONIAE*

## Epidemiology

*C. pneumoniae* is a common cause of human respiratory diseases, primarily in young adults.

- Seroprevalence rates of 40–70% demonstrate that *C. pneumoniae* is widespread worldwide. Seropositivity is first detected at school age and then increases by ~10% per decade.
- The role of *C. pneumoniae* in atherosclerotic disease has long been discussed, but large-scale treatment studies have cast doubts on the etiologic role of this organism in this disease.

## Clinical Manifestations

The clinical spectrum of *C. pneumoniae* infection includes acute pharyngitis, sinusitis, bronchitis, and pneumonia.

- Pneumonia due to *C. pneumoniae* resembles that due to *M. pneumoniae*. Pts have antecedent upper respiratory tract symptoms, fever, nonproductive cough, minimal findings on auscultation, small segmental infiltrates on CXR, and no leukocytosis.
  - Primary infection is more severe than reinfection.
  - Elderly pts can have severe disease.

## Diagnosis

Serology is the most clinically useful means for diagnosing *C. pneumoniae* infection.

- The diagnosis of acute *C. pneumoniae* infection requires demonstration of a fourfold rise in titer between acute- and convalescent-phase serum samples.
- Culture of the organism is difficult and is not routinely attempted. PCR assays for *C. pneumoniae* are currently available only for research purposes.

## TREATMENT *C. PNEUMONIAE* INFECTIONS

- Erythromycin or tetracycline (2 g/d for 10–14 days) is recommended.
- Other macrolides (e.g., azithromycin) or quinolones (e.g., levofloxacin) are alternative agents.

For a more detailed discussion, see Yu VL, Pedro-Botet ML, Lin YE: *Legionella* Infections, Chap. 184, p. 1014; Hardy RD: Infections Due to Mycoplasmas, Chap. 212, p. 1163; Gaydos CA, Quinn TC: Chlamydial Infections, Chap. 213, p. 1165, in HPIM-19.

# 98 *Chlamydia trachomatis* and *C. psittaci*

## MICROBIOLOGY

- Chlamydiae are obligate intracellular bacteria, possess both DNA and RNA (a characteristic that distinguishes them from viruses), and have a cell wall similar to that of gram-negative bacteria.
- These organisms have a complex reproductive cycle and exist in two forms.
  - The *elementary body* (the infective form) is adapted for extracellular survival, while the *reticulate body* is adapted for intracellular survival and multiplication.
  - Within 18–24 h after infection of the cell, reticulate bodies have replicated and begin to condense into elementary bodies that are released to infect other cells or people.
- Three chlamydial species infect humans: *Chlamydia trachomatis*, *C. psittaci*, and *C. pneumoniae*.
  - CF tests and enzyme immunoassays that detect lipopolysaccharide identify chlamydiae only to the genus level.
  - The microimmunofluorescence (MIF) test can differentiate among the three species.
  - For a discussion of *C. pneumoniae*, see Chap. 97.

## *C. TRACHOMATIS* INFECTIONS

### GENITAL INFECTIONS, INCLUDING LYMPHOGRANULOMA VENEREUM

See Chap. 83.

### TRACHOMA AND ADULT INCLUSION CONJUNCTIVITIS (AIC)

#### Etiology

- Trachoma is a chronic conjunctivitis caused by *C. trachomatis* serovars A, B, Ba, and C. Transmission occurs through contact with ocular discharge from infected pts, which is sometimes transferred by flies.
- AIC is an acute eye infection occurring in adults exposed to infected genital secretions and in their newborns. This infection is caused by sexually transmitted *C. trachomatis* strains, usually serovars D–K.

## Epidemiology

Trachoma is a leading cause of preventable infectious blindness, with ~6 million pts having been affected. In the hyperendemic regions of northern and sub-Saharan Africa, the Middle East, and parts of Asia, the prevalence of trachoma is ~100% by the third year of life. Reinfection and persistent infection are common.

## Clinical Manifestations

Both trachoma and AIC present clinically as conjunctivitis characterized by small lymphoid follicles in the conjunctiva, although trachoma usually starts insidiously before 2 years of age.

- With progression of trachoma, there is inflammatory leukocytic infiltration and superficial vascularization (pannus formation) of the cornea.
  - Scarring eventually distorts the eyelids, turning lashes inward and abrading the eyeball (trichiasis and entropion).
  - The corneal epithelium eventually ulcerates, with subsequent scarring and blindness.
  - Destruction of goblet cells, lacrimal ducts, and glands causes dry-eye syndrome (xerosis), with resultant corneal opacity and secondary bacterial corneal ulcers.
- AIC is an acute unilateral follicular conjunctivitis with preauricular lymphadenopathy and presents similarly to acute conjunctivitis due to adenovirus or HSV.
  - Corneal inflammation is evidenced by discrete opacities, punctate epithelial erosions, and superficial corneal vascularization.
  - Left untreated, the disease may persist for 6 weeks to 2 years.

## Diagnosis

Clinical diagnosis of trachoma is based on the presence of two of the following signs: lymphoid follicles on the upper tarsal conjunctiva, typical conjunctival scarring, vascular pannus, or limbal follicles.

- Intracytoplasmic chlamydial inclusions are found in 10–60% of Giemsa-stained conjunctival smears from children with severe inflammation.
- However, chlamydial nucleic acid amplification tests are more sensitive in detecting infection.

**TREATMENT TRACHOMA/AIC**

- AIC responds to azithromycin (a single 1-g oral dose) or doxycycline (100 mg PO bid for 7 days). Treatment of sexual partners is needed to prevent ocular reinfection and chlamydial genital disease.

# *C. PSITTACI* INFECTIONS

## Etiology and Epidemiology

Most avian species can harbor *C. psittaci*, but psittacine birds (e.g., parrots, parakeets) are most often infected. Human infections are uncommon and occur only as a zoonosis.

- Exposure is greatest in poultry workers and in owners of pet birds.
- Present in nasal secretions, excreta, tissues, and feathers of infected birds, *C. psittaci* is transmitted to humans by direct contact with infected birds or by inhalation of aerosols. Transmission from person to person has never been documented.

- As a result of quarantine of imported birds and improved veterinary-hygienic measures, outbreaks and sporadic cases of psittacosis are now rare, with fewer than 50 confirmed cases reported in the United States each year.

### Clinical Manifestations

Psittacosis in humans can range in severity from asymptomatic or mild infections to acute primary atypical pneumonia (which can be fatal in 10% of untreated cases) to severe chronic pneumonia.

- After an incubation period of >5–19 days, pts present with fever, chills, muscular aches and pains, severe headaches, hepatomegaly and/or splenomegaly, and GI symptoms.
- Cardiac complications may include endocarditis and myocarditis.

### Diagnosis

This diagnosis is confirmed by serologic studies.

- The gold standard is the MIF test.
- Any antibody titer >1:16 or a fourfold rise between paired acute- and convalescent-phase serum samples, in combination with a clinically compatible syndrome, can be used to diagnose psittacosis.

**TREATMENT** *C. PSITTACI* INFECTIONS

- Tetracycline (250 mg PO qid for 3 weeks) is the antibiotic of choice.
- Erythromycin (500 mg PO qid) is an alternative agent.

For a more detailed discussion, see Gaydos CA, Quinn TC: Chlamydial Infections, Chap. 213, p. 1165, in HPIM-19.

# 99 Herpesvirus Infections

## HERPES SIMPLEX VIRUSES

### MICROBIOLOGY AND PATHOGENESIS

The herpes simplex viruses HSV-1 and HSV-2 are linear, double-stranded DNA viruses that share ~50% sequence homology. Exposure to HSV at mucosal surfaces or abraded skin sites permits viral entry and replication in cells of the epidermis and dermis prior to infection of neuronal cells and development of a latent infection in ganglia.

- Reactivation occurs when normal viral gene expression resumes, with reappearance of the virus on mucosal surfaces.

- Both antibody-mediated and cell-mediated immunity (including type-specific immunity) are clinically important.

## EPIDEMIOLOGY

HSV-1 is acquired more frequently and at an earlier age than HSV-2. More than 90% of adults have antibodies to HSV-1 by the fifth decade of life. Antibodies to HSV-2 usually are not detected until adolescence and correlate with sexual activity. The seroprevalence of HSV-2 is higher in the developing than in the developed world; up to 60% of pregnant women in sub-Saharan Africa are seropositive.

- HSV is transmitted by contact with active lesions or with virus shed from mucocutaneous surfaces by asymptomatic persons.
- HSV reactivation is very common: HSV DNA can be detected on 20–30% of days by PCR, with most genital reactivation episodes lasting <6 h.
- The large reservoir of unidentified carriers and the frequent asymptomatic reactivation of HSV-2 have fostered the continued spread of HSV throughout the world.
- HSV-2 infection is associated with a two- to fourfold increase in HIV-1 acquisition; in fact, 33–50% of HIV-1 infections may be attributable to HSV-2 in men who have sex with men and in populations of sub-Saharan Africa.

## CLINICAL MANIFESTATIONS

Both viral subtypes can cause indistinguishable genital and oral–facial infections. Overall, genital HSV-2 is twice as likely to reactivate as genital HSV-1, and HSV-2 infection recurs 8–10 times more often. In contrast, oral–labial HSV-1 infection recurs more frequently than oral–labial HSV-2 infection. The incubation period for primary infection with either virus is 1–26 days (median, 6–8 days).

### Oral–Facial Infections

Primary HSV-1 infection results in gingivostomatitis, pharyngitis, and up to 2 weeks of fever, malaise, myalgia, inability to eat, and cervical adenopathy, with lesions on the palate, gingiva, tongue, lip, face, posterior pharynx, and/or tonsillar pillars and occasional exudative pharyngitis.

- Reactivation of HSV from the trigeminal ganglia is associated with asymptomatic viral excretion in the saliva, intraoral mucosal ulcerations, or ulcers on the vermilion border of the lip or external facial skin.
  - Approximately 50–70% of pts undergoing trigeminal nerve-root decompression and 10–15% of pts undergoing dental extraction develop oral–labial herpes a median of 3 days after the procedure.
  - Reactivation of HSV-1 or VZV in the mandibular portion of the facial nerve causes flaccid paralysis (Bell's palsy).
- Immunosuppressed pts can have a severe infection that extends into the mucosa and skin, causing friability, necrosis, bleeding, pain, and inability to eat or drink.
- Pts with atopic dermatitis may also develop severe oral–facial HSV infection (eczema herpeticum), with extensive skin lesions and occasional visceral dissemination.
- HSV infection is the precipitating event in ~75% of cases of erythema multiforme.

### Genital Infections (See Chap. 83)

First-episode primary genital herpes is characterized by fever, headache, malaise, and myalgias. Pain, itching, dysuria, vaginal and urethral discharge, and tender inguinal lymphadenopathy are the predominant local symptoms.

- Pts with prior HSV-1 infection have milder cases.
- Reactivation infections are often subclinical or can cause genital lesions or urethritis with dysuria.

- Even without a history of rectal intercourse, perianal lesions can occur as a result of latency established in the sacral dermatome from prior genital tract infection.

## Whitlow

In HSV infection of the finger, pts experience an abrupt onset of edema, erythema, pain, and vesicular or pustular lesions of the fingertips that are often confused with the lesions of pyogenic bacterial infection. Fever, lymphadenitis, and epitrochlear and axillary lymphadenopathy are common.

## Herpes Gladiatorum

HSV infection caused by trauma to the skin during wrestling can occur anywhere on the body but commonly affects the thorax, ears, face, and hands.

## Eye Infections

HSV is the most frequent cause of corneal blindness in the United States.

- HSV keratitis presents as acute onset of pain, blurred vision, chemosis, conjunctivitis, and dendritic corneal lesions. Topical glucocorticoids may exacerbate disease. Recurrences are common.
- Other manifestations include chorioretinitis and acute necrotizing retinitis.

## Central and Peripheral Nervous System Infections

In the United States, HSV causes 10–20% of all cases of sporadic viral encephalitis, and 95% of these cases are due to HSV-1 (either primary or reactivated infection). The estimated annual incidence is 2.3 cases per 1 million persons.

- Pts present with an acute onset of fever and focal neurologic symptoms and signs, especially in the temporal lobe. In severe cases, RBCs can be found in the CSF as a result of hemorrhagic necrosis.
- Given the potential severity of infection, antiviral treatment should be started empirically until the diagnosis is confirmed or an alternative diagnosis is made.
- HSV meningitis, which is usually seen in association with primary genital HSV infection, is an acute self-limited disease manifested by headache, fever, and mild photophobia and lasting 2–7 days.
  - Of cases of aseptic meningitis, 3–15% are due to HSV.
  - HSV is the most common cause of recurrent lymphocytic meningitis (Mollaret's meningitis).
- Autonomic dysfunction caused by either HSV or VZV most commonly affects the sacral region, resulting in numbness, tingling of the buttocks or perineal areas, urinary retention, constipation, and impotence.
  - Symptoms take days or weeks to resolve.
  - In rare instances, transverse myelitis or Guillain-Barré syndrome follows HSV infection.

## Visceral Infections

HSV infection of visceral organs usually results from viremia; multiple-organ involvement is common, but occasionally only the esophagus, lung, or liver is affected.

- In HSV esophagitis, pts present with odynophagia, dysphagia, substernal pain, weight loss, and multiple oval ulcerations on an erythematous base. Detection of HSV is necessary to distinguish this entity from esophagitis of other etiologies (e.g., *Candida* esophagitis).
- HSV pneumonitis is rare except among severely immunocompromised pts and results in focal necrotizing pneumonitis with a mortality rate of >80%.
- Hepatic HSV infection occurs primarily in immunocompromised pts and is associated with fever, abrupt elevations of bilirubin and serum aminotransferase levels, and leukopenia (<4000 WBCs/μL).

## Neonatal Infections

The frequency of visceral and/or CNS infection is highest among HSV-infected infants <6 weeks of age; the mortality rate without therapy is 65%.

- Infection is usually acquired perinatally from contact with infected genital secretions during delivery.
- Approximately 50–70% of cases are due to HSV-2. The risk is elevated 10-fold for infants born to a mother who has recently acquired HSV.

### DIAGNOSIS

Microscopic evaluation, viral culture, serology, and PCR are all clinically useful for diagnosing HSV infection.

- Regardless of the detection method, the sensitivity is greater for vesicular rather than ulcerative mucosal lesions, in primary rather than recurrent disease, and in immunocompromised rather than immunocompetent pts.
- PCR is most sensitive for detection of HSV and should be used whenever possible.
- A Tzanck smear (Giemsa-stained scrapings from the base of lesions) to detect giant cells or intranuclear inclusions characteristic of both HSV and VZV infections has a low level of sensitivity; its use requires clinicians skilled in this technique.
- Serologic tests can be used to demonstrate prior exposure to HSV; no reliable IgM detection method for defining acute HSV infection is available.

### TREATMENT INFECTIONS WITH HERPES SIMPLEX VIRUSES

- Table 99-1 details antiviral chemotherapy for HSV infection.
  - All antiviral agents licensed for use against HSV inhibit the viral DNA polymerase.
  - Acyclovir can crystallize in the renal parenchyma, causing transient renal insufficiency; this drug should be given over the course of 1 h to a well-hydrated pt.
  - Acyclovir-resistant strains of HSV are rare but have been identified, primarily in immunocompromised pts. In general, these isolates are also resistant to valacyclovir and famciclovir, which have similar mechanisms of action.

### PREVENTION

The use of barrier forms of contraception, especially condoms, decreases the likelihood of HSV transmission, particularly during asymptomatic viral excretion. Chronic daily therapy with valacyclovir can also be partially effective in reducing acquisition of HSV-2, particularly by susceptible women.

## VARICELLA-ZOSTER VIRUS

### MICROBIOLOGY AND PATHOGENESIS

VZV—a double-stranded DNA virus in the family Herpesviridae—has a pathogenic cycle similar to that of HSV. Primary infection is transmitted by the respiratory route. The virus replicates and causes viremia, which is reflected by the diffuse and scattered skin lesions in varicella; it then establishes latency in the dorsal root ganglia and can reactivate through unknown mechanisms at a later time.

### EPIDEMIOLOGY AND CLINICAL MANIFESTATIONS

VZV causes two distinct entities: primary infection (varicella or chickenpox) and reactivation infection (herpes zoster or shingles). Humans are the only known reservoir for VZV.

**TABLE 99-1 ANTIVIRAL CHEMOTHERAPY FOR HERPES SIMPLEX VIRUS (HSV) INFECTION**

**I. Mucocutaneous HSV infections**

A. *Infections in immunosuppressed pts*

1. *Acute symptomatic first or recurrent episodes:* IV acyclovir (5 mg/kg q8h) or oral acyclovir (400 mg qid), famciclovir (500 mg bid or tid), or valacyclovir (500 mg bid) is effective. Treatment duration may vary from 7 to 14 days.
2. *Suppression of reactivation disease (genital or oral-labial):* IV acyclovir (5 mg/kg q8h) or oral valacyclovir (500 mg bid) or acyclovir (400–800 mg three to five times per day) prevents recurrences during the 30-day period immediately after transplantation. Longer-term HSV suppression is often used for persons with continued immunosuppression. In bone marrow and renal transplant recipients, oral valacyclovir (2 g/d) is also effective in reducing cytomegalovirus infection. Oral valacyclovir at a dose of 4 g/d has been associated with thrombotic thrombocytopenic purpura after extended use in HIV-positive persons. In HIV-infected persons, oral acyclovir (400–800 mg bid), valacyclovir (500 mg bid), or famciclovir (500 mg bid) is effective in reducing clinical and subclinical reactivations of HSV-1 and HSV-2.

B. *Infections in immunocompetent pts*

1. *Genital herpes*
   a. *First episodes:* Oral acyclovir (200 mg five times per day or 400 mg tid), valacyclovir (1 g bid), or famciclovir (250 mg bid) for 7–14 days is effective. IV acyclovir (5 mg/kg q8h for 5 days) is given for severe disease or neurologic complications such as aseptic meningitis.
   b. *Symptomatic recurrent genital herpes:* Short-course (1- to 3-days) regimens are preferred because of low cost, likelihood of adherence, and convenience. Oral acyclovir (800 mg tid for 2 days), valacyclovir (500 mg bid for 3 days), or famciclovir (750 or 1000 mg bid for 1 day, a 1500-mg single dose, or 500 mg stat followed by 250 mg q12h for 3 days) effectively shortens lesion duration. Other options include oral acyclovir (200 mg five times per day), valacyclovir (500 mg bid), and famciclovir (125 mg bid for 5 days).
   c. *Suppression of recurrent genital herpes:* Oral acyclovir (400–800 mg bid) or valacyclovir (500 mg daily) is given. Pts with more than nine episodes per year should take oral valacyclovir (1 g daily or 500 mg bid) or famciclovir (250 mg bid or 500 mg bid).

2. *Oral–labial HSV infections*

   a. *First episode:* Oral acyclovir is given (200 mg five times per day or 400 mg tid); an oral acyclovir suspension can be used (600 mg/m$^2$ qid). Oral famciclovir (250 mg bid) or valacyclovir (1 g bid) has been used clinically. The duration of therapy is 5–10 days.

   b. *Recurrent episodes:* If initiated at the onset of the prodrome, single-dose or 1-day therapy effectively reduces pain and speeds healing. Regimens include oral famciclovir (a 1500-mg single dose or 750 mg bid for 1 day) or valacyclovir (a 2-g single dose or 2 g bid for 1 day). Self-initiated therapy with six times daily topical penciclovir cream effectively speeds healing of oral–labial HSV. Topical acyclovir cream has also been shown to speed healing.

   c. *Suppression of reactivation of oral–labial HSV:* If started before exposure and continued for the duration of exposure (usually 5–10 days), oral acyclovir (400 *mg* bid) prevents reactivation of recurrent oral–labial HSV infection associated with severe sun exposure.

3. *Surgical prophylaxis of oral or genital HSV infection:* Several surgical procedures, such as laser skin resurfacing, trigeminal nerve-root decompression, and lumbar disk surgery, have been associated with HSV reactivation. IV acyclovir (3–5 mg/kg q8h) or oral acyclovir (800 mg bid), valacyclovir (500 mg bid), or famciclovir (250 mg bid) effectively reduces reactivation. Therapy should be initiated 48 h before surgery and continued for 3–7 days.

4. *Herpetic whitlow:* Oral acyclovir (200 mg) is given five times daily (alternative: 400 mg tid) for 7–10 days.

5. *HSV proctitis:* Oral acyclovir (400 mg five times per day) is useful in shortening the course of infection. In immunosuppressed pts or in pts with severe infection, IV acyclovir (5 mg/kg q8h) may be useful.

6. *Herpetic eye infections:* In acute keratitis, topical trifluorothymidine, vidarabine, idoxuridine, acyclovir, penciclovir, and interferon are all beneficial. Debridement may be required. Topical steroids may worsen disease.

**II. Central nervous system HSV infections**

A. *HSV encephalitis:* IV acyclovir (10 mg/kg q8h; 30 mg/kg per day) is given for 10 days or until HSV DNA is no longer detected in cerebrospinal fluid.

B. *HSV aseptic meningitis:* No studies of systemic antiviral chemotherapy exist. If therapy is to be given, IV acyclovir (15–30 mg/kg per day) should be used.

C. *Autonomic radiculopathy:* No studies are available. Most authorities recommend a trial of IV acyclovir.

(*Continued*)

**TABLE 99-1 ANTIVIRAL CHEMOTHERAPY FOR HERPES SIMPLEX VIRUS (HSV) INFECTION (*CONTINUED*)**

**III. Neonatal HSV infections:** Oral acyclovir (60 mg/kg per day, divided into three doses) is given. The recommended duration of IV treatment is 21 days. Monitoring for relapse should be undertaken. Continued suppression with oral acyclovir suspension should be given for 3–4 months.

**IV. Visceral HSV infections**

A. *HSV esophagitis:* IV acyclovir (15 mg/kg per day) is given. In some pts with milder forms of immunosuppression, oral therapy with valacyclovir or famciclovir is effective.

B. *HSV pneumonitis:* No controlled studies exist. IV acyclovir (15 mg/kg per day) should be considered.

**V. Disseminated HSV infections:** No controlled studies exist. IV acyclovir (5 mg/kg q8h) should be tried. Adjustments for renal insufficiency may be needed. No definite evidence indicates that therapy will decrease the risk of death.

**VI. Erythema multiforme associated with HSV:** Anecdotal observations suggest that oral acyclovir (400 mg bid or tid) or valacyclovir (500 mg bid) will suppress erythema multiforme.

**VII. Infections due to acyclovir-resistant HSV:** IV foscarnet (40 mg/kg IV q8h) should be given until lesions heal. The optimal duration of therapy and the usefulness of its continuation to suppress lesions are unclear. Some pts may benefit from cutaneous application of trifluorothymidine or 5% cidofovir gel.

## Chickenpox

Pts present with fever, malaise, and rash characterized by maculopapules, vesicles, and scabs in various stages of evolution. The skin lesions are small, with an erythematous base of 5–10 mm, and appear in successive crops over 2–4 days. Severity varies from person to person, but older pts tend to have more severe disease.

- In immunocompetent hosts, the disease is benign and lasts 3–5 days. In contrast, immunocompromised pts have numerous slower-healing lesions (often with a hemorrhagic base) and are more likely to develop visceral complications that, if not treated, are fatal in 15% of cases.
- The incubation period ranges from 10 to 21 days but is usually 14–17 days. Pts are infectious for 48 h before onset of rash and remain infectious until all vesicles have crusted.
- The virus is highly contagious, with an attack rate of 90% among susceptible persons. Historically, children 5–9 years old accounted for half of all cases; vaccination has dramatically changed the epidemiology of infection and has caused a significant decrease in the annualized incidence of chickenpox.
- Complications of varicella include bacterial superinfection of the skin, CNS involvement, pneumonia, myocarditis, and hepatic involvement.
  - Bacterial superinfection is usually caused by *Streptococcus pyogenes* or *Staphylococcus aureus*.
  - CNS involvement, usually manifesting as acute cerebellar ataxia and meningeal irritation ~21 days after the onset of rash, runs a benign course. Aseptic meningitis, encephalitis, transverse myelitis, Guillain-Barré syndrome, or Reye's syndrome (which mandates the avoidance of aspirin administration to children) can occur. There is no specific therapy other than supportive care.
  - VZV pneumonia is the most serious complication and develops more frequently among adults (occurring in up to 20% of cases) than among children. The onset comes 3–5 days into illness, with tachypnea, cough, dyspnea, fever, cyanosis, pleuritic chest pain, and hemoptysis. CXR shows nodular infiltrates and interstitial pneumonitis. Resolution of pneumonitis parallels improvement of the skin rash.

## Herpes Zoster (Shingles)

Herpes zoster represents a reactivation of VZV from dorsal root ganglia and usually manifests as a unilateral vesicular eruption within a dermatome, often associated with severe pain.

- Dermatomal pain may precede lesions by 48–72 h, and dermatomes T3 to L3 are most frequently involved.
- The usual duration of disease is 7–10 days, but it may take as long as 2–4 weeks for the skin to return to normal.
- With ~1.2 million cases each year in the United States, the incidence is highest among pts ≥50 years of age.
- Pts with herpes zoster can transmit infection to seronegative individuals, with consequent chickenpox.
- Complications include zoster ophthalmicus (which can lead to blindness), Ramsay Hunt syndrome (characterized by pain and vesicles in the external auditory canal, loss of taste in the anterior two-thirds of the tongue, and ipsilateral facial palsy), and postherpetic neuralgia (pain persisting for months after resolution of cutaneous disease).
- Immunocompromised pts—particularly those with Hodgkin's disease and non-Hodgkin's lymphoma—are at greatest risk for severe zoster and progressive disease. Cutaneous dissemination occurs in 40% of these pts and increases the risk for other complications (pneumonitis, meningoencephalitis, hepatitis).

## DIAGNOSIS

Definitive diagnosis requires isolation of VZV in culture, detection of VZV by molecular means (PCR, immunofluorescent staining of cells from the lesion base), or serology (seroconversion or a ≥4-fold rise in antibody titer between convalescent- and acute-phase serum specimens).

## TREATMENT VARICELLA-ZOSTER VIRUS INFECTIONS

- *Chickenpox:* Antiviral therapy can be helpful if started within 24 h of symptom onset.
  - For children <12 years of age, acyclovir (20 mg/kg PO q6h) is recommended.
  - For adolescents and adults, acyclovir (800 mg PO five times daily), valacyclovir (1 g PO tid), or famciclovir (250 mg PO tid) for 5–7 days is recommended.
  - Good hygiene, meticulous skin care, and antipruritic drugs are important to relieve symptoms and prevent bacterial superinfection of skin lesions.
- *Zoster:* Lesions heal more quickly with antiviral treatment.
  - Famciclovir (500 mg PO tid for 7 days) or valacyclovir (1 g PO tid for 5–7 days) is preferred over acyclovir (800 mg PO five times daily for 7–10 days), given superior pharmacokinetics and pharmacodynamics.
- *VZV infection in severely immunocompromised pts:* Severely immunocompromised pts should receive parenteral acyclovir, at least at the outset (10 mg/kg IV q8h for 7 days), for chickenpox and herpes zoster to reduce the risk of visceral complications, although this regimen does not speed the healing or relieve the pain of skin lesions.
  - Low-risk immunocompromised pts can be treated with oral valacyclovir or famciclovir.
  - If feasible, immunosuppression should be decreased during concomitant acyclovir administration.
- *Zoster ophthalmicus:* Antiviral treatment, analgesics for severe pain, and immediate consultation with an ophthalmologist are required.
- *Postherpetic neuralgia:* Gabapentin, pregabalin, amitriptyline, lidocaine patches, and fluphenazine may relieve pain and can be given along with routine analgesic agents. Prednisone (given along with antiviral therapy at 60 mg/d for the first week of zoster and then at a dose tapered by 50% weekly over the next 2 weeks) can accelerate quality-of-life improvements, including a return to usual activity; prednisone treatment is indicated only for healthy elderly persons with moderate or severe pain at presentation.

## PREVENTION

Three methods are used for the prevention of VZV infections.

- *Active immunization:* For all children and seronegative adults, two doses of a live attenuated varicella vaccine are recommended. Irrespective of serologic status, pts >50 years old should receive a vaccine with 18 times the viral content of varicella vaccine; zoster vaccine reduces the incidence of zoster and postherpetic neuralgia.
- *Passive immunization:* Varicella-zoster immune globulin (VZIg) can be given to VZV-susceptible hosts within 10 days (ideally within 96 h) of a significant exposure if the risk of complications from varicella is high (e.g., immunocompromised pts, susceptible pregnant women, premature infants, neonates whose mothers had chickenpox onset within 5 days before or 2 days after delivery).
- *Antiviral treatment:* Seven days after intense exposure, antiviral prophylaxis can be given to high-risk pts who are ineligible for vaccine or for whom the 96-h window after direct contact has passed. This intervention may lessen illness severity.

## HUMAN HERPESVIRUS (HHV) TYPES 6, 7, AND 8

- HHV-6 causes exanthem subitum (roseola infantum, a common childhood febrile illness with rash) and 10–20% of febrile seizures without rash in infancy.
  - In older age groups, HHV-6 has been associated with mononucleosis syndromes and (in immunocompromised hosts) encephalitis, pneumonitis, syncytial giant-cell hepatitis, and disseminated disease.
  - More than 80% of adults are seropositive for HHV-6.
- HHV-7 is frequently acquired during childhood, and infections typically manifest as fever and seizures. The virus is commonly present in saliva.
- HHV-8 infection in healthy children can present as fever and rash; in immunocompromised pts, primary infection may present as fever, splenomegaly, pancytopenia, and rapid-onset Kaposi's sarcoma.
  - HHV-8 is associated with Kaposi's sarcoma, body cavity–based lymphoma in AIDS pts, and multicentric Castleman's disease.
  - Unlike other herpesvirus infections, HHV-8 infection is much more common in some geographic areas (e.g., central and southern Africa) than in others (North America, Asia, northern Europe).
  - The virus appears to be sexually spread and may also be transmitted in saliva, by organ transplantation, and through IV drug use.

For a more detailed discussion, see Baden LR, Dolin R: Antiviral Chemotherapy, Excluding Antiretroviral Drugs, Chap. 215e; Corey L: Herpes Simplex Virus Infections, Chap. 216, p. 1175; Whitley RJ: Varicella-Zoster Virus Infections, Chap. 217, p. 1183; Kotton CN, Hirsch MS: Cytomegalovirus and Human Herpesvirus Types 6, 7, and 8, Chap. 219, p. 1190, in HPIM-19.

# 100 Cytomegalovirus and Epstein-Barr Virus Infections

## CYTOMEGALOVIRUS

### MICROBIOLOGY

CMV is a herpesvirus, has double-stranded DNA, and renders infected cells 2–4 times the size of surrounding cells. These cytomegalic cells contain an eccentrically placed intranuclear inclusion surrounded by a clear halo, with an "owl's-eye" appearance.

### EPIDEMIOLOGY

CMV disease is found worldwide. In many regions, the vast majority of adults are seropositive, as are ~50% of adults in the United States and Canada. Perinatal and early childhood infections are common; ~1% of U.S. newborns are infected.

- The virus can be spread in breast milk, saliva, feces, and urine.
- Transmission requires repeated or prolonged contact as opposed to casual contact. Sexual transmission is common among adolescents and adults, and CMV has been identified in semen and cervical secretions.
- Latent CMV infection persists throughout life unless reactivation is triggered by depressed cell-mediated immunity (e.g., in transplant recipients or HIV-infected pts).

## PATHOGENESIS

Primary CMV infection is associated with a vigorous T lymphocyte response; activated CD8+ T cells predominate among atypical lymphocytes.

- Latent infection occurs in multiple cell types and various organs. Chronic antigen stimulation in the presence of immunosuppression (e.g., in the transplantation setting) and certain immunosuppressive agents (e.g., antithymocyte globulin) promote CMV reactivation.
- CMV disease increases the risk of infection with opportunistic pathogens by depressing T lymphocyte responsiveness.

## CLINICAL MANIFESTATIONS

The most common presentation is CMV mononucleosis in immunocompetent pts, but disease can be more severe in immunocompromised pts (including newborns).

### Congenital CMV Infection

Cytomegalic inclusion disease occurs in ~5% of infected fetuses in the setting of primary maternal CMV infection in pregnancy.

- Petechiae, hepatosplenomegaly, and jaundice are present in 60–80% of cases; microcephaly with or without cerebral calcifications, intrauterine growth retardation, prematurity, and chorioretinitis are less common.
- Laboratory findings include elevated values in LFTs, thrombocytopenia, conjugated hyperbilirubinemia, hemolysis, and increased CSF protein levels.
- The mortality rate is 20–30% among infants with severe disease; survivors have intellectual or hearing difficulties.

### Perinatal CMV Infection

Perinatal infection with CMV is acquired by breast-feeding or contact with infected maternal secretions (e.g., in the birth canal). Although most pts are asymptomatic, disease similar to—but less severe than—congenital CMV disease can occur.

### CMV Mononucleosis

Signs and symptoms last 2–6 weeks and include high fevers, profound fatigue and malaise, myalgias, headache, and splenomegaly. In contrast to EBV infection, exudative pharyngitis and cervical lymphadenopathy are rare in CMV infection.

- Laboratory findings include relative lymphocytosis with >10% atypical lymphocytes, transaminitis, and immunologic abnormalities (e.g., the presence of cryoglobulins, rheumatoid factor, or cold agglutinins).
- The incubation period ranges from 20 to 60 days.
- Recovery is generally complete, but postviral asthenia can persist for months.

### CMV Infection in Immunocompromised Pts

CMV is the most common viral pathogen complicating organ transplantation, with the greatest risk of infection 1–4 months after transplantation. HIV-infected pts with CD4+ T cell counts of <50–100/μL also are at risk for severe CMV disease.

- Primary CMV infection (including reinfection with a new, donor-derived strain) is more likely than reactivation to cause severe disease with high viral loads.
  - Reactivation infection is common but less important clinically.
  - The transplanted organ is at particular risk; e.g., CMV pneumonitis tends to follow lung transplantation.
  - The risk of severe disease is reduced by antiviral prophylaxis or preemptive therapy.
- Pts present initially with prolonged fever, malaise, anorexia, fatigue, night sweats, and arthralgias or myalgias but can ultimately have multiorgan involvement.
  - Respiratory involvement is evidenced by tachypnea, hypoxia, unproductive cough, and chest radiographs demonstrating bilateral interstitial or reticulonodular infiltrates.
  - GI involvement often includes hepatitis and ulcer formation. Colitis is the most common manifestation in organ transplant recipients.
  - CMV encephalitis, particularly in HIV-infected pts, can occur as either progressive dementia or ventriculoencephalitis characterized by cranial nerve deficits, disorientation, and lethargy.
  - CMV retinitis is an important cause of blindness in pts with advanced AIDS.

## DIAGNOSIS

Diagnosis requires isolation of CMV or detection of its antigens or DNA in appropriate clinical specimens in conjunction with a compatible clinical syndrome. Immunofluorescence assays for CMV antigens (pp65), PCR, viral culture, and serology are all useful means of detection.

## TREATMENT CYTOMEGALOVIRUS INFECTIONS

- When possible, seronegative donors should be used for seronegative transplant recipients.
- Ganciclovir (5 mg/kg IV bid for 14–21 days followed by 5 mg/kg IV qd) or valganciclovir (the oral prodrug of ganciclovir; 900 mg PO bid for 14–21 days followed by 900 mg PO qd) produces response rates of 70–90% among HIV-infected pts with CMV retinitis or colitis.
  - In severe infections, ganciclovir is often combined with CMV immune globulin.
  - Neutropenia is an adverse reaction to ganciclovir treatment that may require administration of colony-stimulating factors.
  - Prophylactic or suppressive treatment can be given to high-risk transplant recipients (those who are seropositive before transplantation or culture positive without symptoms afterward).
  - Resistance to ganciclovir is common among pts treated for >3 months and is usually related to mutations in the CMV *UL97* gene.
  - For CMV retinitis, ganciclovir can be administered via a slow-release pellet sutured into the eye, but this intervention does not provide treatment for the contralateral eye or for systemic disease.
- Foscarnet (180 mg/kg qd divided into 2 or 3 doses for 2 weeks, followed by 90–120 mg/kg IV qd) inhibits CMV DNA polymerase and is active against most ganciclovir-resistant CMV isolates. The primary adverse events include electrolyte disturbances and renal dysfunction.
- Cidofovir (5 mg/kg IV per week for 2 weeks followed by 3–5 mg/kg IV every 2 weeks) is a nucleotide analogue that is also effective against ganciclovir-resistant CMV; however, it can cause severe nephrotoxicity by proximal tubular cell injury. The use of saline hydration and probenecid reduces this adverse effect.
- CMV immune or hyperimmune globulin may reduce the risk of CMV disease in seronegative renal transplant recipients and prevent congenital CMV infection in infants born to women with primary CMV infection during pregnancy.

## EPSTEIN-BARR VIRUS

### EPIDEMIOLOGY

EBV is a DNA virus in the family Herpesviridae that infects >90% of persons by adulthood.

- Infectious mononucleosis (IM) is a disease of young adults and is more common in areas with higher standards of hygiene; infection occurs at a younger age in areas with deficient standards of hygiene.
- EBV is spread by contact with oral secretions (e.g., by transfer of saliva during kissing) and is shed in oropharyngeal secretions by >90% of asymptomatic seropositive individuals.

### PATHOGENESIS

EBV infects the epithelium of the oropharynx and salivary glands as well as B cells in tonsillar crypts prior to a period of viremia.

- B cells undergo polyclonal activation, and memory B cells form the reservoir for EBV. Reactive T cells proliferate, with up to 40% of CD8+ T cells directed against EBV antigens during acute infection.
- Cellular immunity is more important than humoral immunity in controlling infection. If T cell immunity is compromised, EBV-infected B cells may proliferate—a step toward neoplastic transformation.

### CLINICAL MANIFESTATIONS

The nature of EBV disease depends on the pt's age and immune status: young children typically develop asymptomatic infections or mild pharyngitis, adolescents and adults develop an IM syndrome, and immunocompromised pts can develop lymphoproliferative disease.

- In IM, a prodrome of fatigue, malaise, and myalgia may last for 1–2 weeks before the onset of fever, exudative pharyngitis, and lymphadenopathy with tender, symmetric, and movable nodes; splenomegaly is more prominent in the second or third week.
  - The incubation period is ~4–6 weeks.
  - Most pts treated with ampicillin develop a rash that does not represent a true penicillin allergy.
  - Illness lasts for 2–4 weeks, but ~10% of pts have fatigue that persists for ≥6 months. EBV is not, however, a cause of chronic fatigue syndrome.
  - Lymphocytosis occurs in the second or third week, with >10% atypical lymphocytes (enlarged cells with abundant cytoplasm and vacuoles); abnormal liver function is common.
  - Complications include CNS disease (e.g., meningitis, encephalitis), Coombs-positive autoimmune hemolytic anemia, splenic rupture, and upper airway obstruction due to hypertrophy of lymphoid tissue.
- Lymphoproliferative disease—i.e., infiltration of lymph nodes and multiple organs by proliferating EBV-infected B cells—occurs in pts with deficient cellular immunity (e.g., pts with AIDS, those with severe combined immunodeficiency, and those receiving immunosuppressive medications). Pts develop fever and lymphadenopathy or GI symptoms.
- Oral hairy leukoplakia—raised, white, corrugated, EBV DNA–containing lesions on the tongue—is an early manifestation of infection with HIV in adults.
- EBV-associated malignancies include Burkitt's lymphoma (~90% of cases in Africa and ~15% of cases in the United States), anaplastic nasopharyngeal carcinoma in southern China, gastric cancer (with ~9% of these tumors positive for EBV),

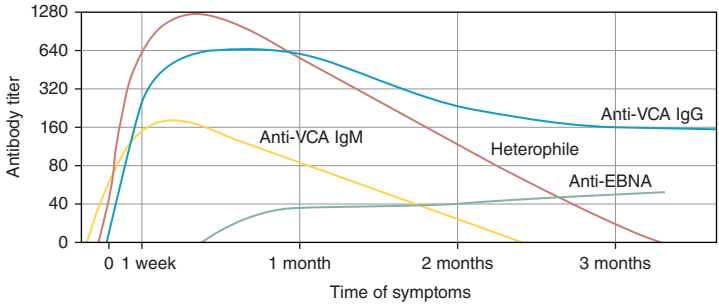


**FIGURE 100-1** Pattern of Epstein-Barr virus (EBV) serology during acute infection. EBNA, Epstein-Barr nuclear antigen; VCA, viral capsid antigen. *(From JI Cohen, in NS Young et al [eds]: Clinical Hematology. Philadelphia, Mosby, 2006.)*

Hodgkin's disease (especially the mixed-cellularity type), and CNS lymphoma (especially HIV-related).

## DIAGNOSIS

Serologic testing is the mainstay of diagnostic assessment. PCR analysis can be useful in monitoring EBV DNA levels in blood from pts with lymphoproliferative disease.

- Heterophile antibodies (Figure 100-1) form the basis of most rapid testing, which assesses the ability of serum to agglutinate sheep, horse, or cow erythrocytes after adsorption with guinea pig kidney.
  - The antibodies can persist for up to 1 year after infection.
  - The monospot test for heterophile antibodies is ~75% sensitive and ~90% specific in comparison with EBV-specific serologies.
  - Pts <5 years old and elderly pts usually do not develop heterophile antibodies.
- EBV-specific antibody testing can be used in heterophile-negative pts and in pts with atypical disease. Antibodies to viral capsid antigen occur in >90% of cases, with elevated IgM titers present only during the first 2–3 months of disease.
- Antibodies to Epstein-Barr nuclear antigen are not detected until 3–6 weeks after symptom onset and then persist for life.

## TREATMENT EPSTEIN-BARR VIRUS INFECTIONS

- IM is treated with supportive measures, including rest and analgesia.
  - Excessive physical activity should be avoided in the first month of illness to reduce the possibility of splenic rupture, which necessitates splenectomy.
  - Administration of glucocorticoids may be indicated for some complications of IM; e.g., these agents may be given to prevent airway obstruction or to treat autoimmune hemolytic anemia, hemophagocytic lymphohistiocytosis, or severe thrombocytopenia.
  - Antiviral therapy (e.g., with acyclovir) is generally not effective for IM but is effective for oral hairy leukoplakia.
- Treatment of posttransplantation EBV lymphoproliferative syndrome is generally directed toward reduction of immunosuppression, although other treatments—e.g., with interferon α, antibody to CD20 (rituximab), and donor lymphocyte infusions—have been used with varying success.

For a more detailed discussion, see Baden LR, Dolin R: Antiviral Chemotherapy, Excluding Antiretroviral Drugs, Chap. 215e; Cohen JI: Epstein-Barr Virus Infections, Including Infectious Mononucleosis, Chap. 218, p. 1186; and Kotton CN, Hirsch MS: Cytomegalovirus and Human Herpesvirus Types 6, 7, and 8, Chap. 219, p. 1190, in HPIM-19.

# 101 Influenza and Other Viral Respiratory Diseases

## INFLUENZA

### Microbiology and Pathogenesis

Influenza A, B, and C viruses are RNA viruses and members of the family Orthomyxoviridae that have different nucleoprotein (NP) and matrix (M) protein antigens. Influenza A and B viruses are major human pathogens and are morphologically similar; influenza B infection is associated with less severe disease than influenza A infection, and influenza C virus causes subclinical disease.

- Influenza A viruses are subtyped by surface hemagglutinin (H) and neuraminidase (N) antigens.
  - Virus attaches to sialic acid cell receptors via the hemagglutinin. Neuraminidase degrades the receptor and plays a role in the release of virus from infected cells after replication.
  - Antibodies to the H antigen are the major determinants of immunity, while antibodies to the N antigen limit viral spread and contribute to reduction of the infection.
- Influenza is acquired from aerosolized respiratory secretions of acutely ill individuals and possibly by hand-to-hand contact or other personal or fomite contact. Viral shedding usually stops 2–5 days after disease onset.

### Epidemiology

Influenza outbreaks occur each year but vary in extent and severity. Influenza A epidemics occur almost exclusively during the winter months in temperate climates but take place year-round in the tropics. These epidemics begin abruptly, peak over 2–3 weeks, last 2–3 months, and then subside rapidly.

- Global pandemics (the most recent of which took place in 2009 and was due to an A/H1N1 virus) occur, by definition, at multiple locations; they carry high attack rates (10–20% of the general population), extend beyond normal seasonality patterns, and are due in part to the propensity of the H and N antigens to undergo periodic antigenic variation.
  - Major changes (which are restricted to influenza A viruses) are called *antigenic shifts* and are associated with pandemics.
  - Minor variations are called *antigenic drifts*.

- Avian influenza viruses (e.g., A/H5N1) cause sporadic human cases, but sustained human-to-human transmission has not been observed; infection is linked to direct contact with infected poultry.
- Swine can sustain simultaneous infection with swine, human, and avian influenza viruses; these multiple-virus infections facilitate reassortment of genetic segments of different viruses. For example, the pandemic A/H1N1 virus of 2009–2010 represented a quadruple reassortment among swine, avian, and human influenza viruses.
- Interpandemic outbreaks of influenza are associated with an average of 226,000 hospitalizations and 23,000 excess deaths per year in the United States. Chronic cardiopulmonary disease and old age are the most prominent risk factors for severe illness.

## Clinical Manifestations

Influenza has a wide spectrum of clinical presentations, ranging from a mild illness resembling the common cold to severe prostration with relatively few respiratory symptoms. The classic description involves the abrupt onset of headache, fever, chills, myalgia, and malaise in the setting of respiratory symptoms (e.g., cough, sore throat).

- Pts typically defervesce within 2–3 days, but respiratory symptoms accompanied by substernal pain can persist for ≥1 week. Postinfluenzal asthenia may persist for weeks, particularly in the elderly.
- Complications of influenza (pneumonia and extrapulmonary manifestations) are more common among pts <5 and >65 years old, pregnant women, and pts with chronic disorders (e.g., cardiopulmonary disease, diabetes, renal diseases, hemoglobinopathies, or immunosuppression).
  - *Pneumonia:* Primary influenza pneumonia is the least common but most severe of the pneumonic complications, most often affecting pts with mitral stenosis and pregnant women. Pts have progressive pulmonary disease and high titers of virus in respiratory secretions.
    - *Secondary bacterial pneumonia* is usually due to *Streptococcus pneumoniae*, *Staphylococcus aureus*, or *Haemophilus influenzae* and presents as the reappearance of fever and respiratory symptoms after 2–3 days of clinical improvement.
    - The most common pneumonic complication involves aspects of viral and bacterial pneumonia.
  - *Extrapulmonary complications:* Reye's syndrome, myositis, rhabdomyolysis, myoglobinuria, and CNS disease (e.g., encephalitis, transverse myelitis, Guillain-Barré syndrome) can occur as complications of influenza infection.
    - Reye's syndrome is a serious complication in children that is associated with influenza B virus (and less commonly with influenza A virus), varicella-zoster virus, and aspirin therapy for the antecedent viral infection.

## Laboratory Findings

Reverse-transcription PCR of respiratory samples (e.g., throat swabs, nasopharyngeal washes, sputum) is the most sensitive and specific technique for detecting influenza.

- Rapid tests that detect viral antigens yield results quickly, can sometimes distinguish influenza A and B viruses, and are relatively specific but variably sensitive.
- Serologic testing requires the availability of acute- and convalescent-phase sera and is useful only retrospectively.

## TREATMENT INFLUENZA

- See Table 101-1 for specific treatment of influenza.
  - Antiviral agents have been tested in young adults with uncomplicated influenza but not in the treatment or prevention of complications associated with influenza.
  - If started within 2 days of illness due to a susceptible virus (with possible efficacy up to 5 days after onset of symptoms), the neuraminidase inhibitors

**TABLE 101-1 ANTIVIRAL MEDICATIONS FOR TREATMENT AND PROPHYLAXIS OF INFLUENZA**

| | Age Group (Years) | | |
|---|---|---|---|
| **Antiviral Drug** | **Children (≤12)** | **13–64** | **≥65** |
| **Oseltamivir** | | | |
| Treatment, influenza A and B | Age 1–12, dose varies by weight[a] | 75 mg PO bid | 75 mg PO bid |
| Prophylaxis, influenza A and B | Age 1–12, dose varies by weight[b] | 75 mg PO qd | 75 mg PO qd |
| **Zanamivir** | | | |
| Treatment, influenza A and B | Age 7–12, 10 mg bid by inhalation | 10 mg bid by inhalation | 10 mg bid by inhalation |
| Prophylaxis, influenza A and B | Age 5–12, 10 mg qd by inhalation | 10 mg qd by inhalation | 10 mg qd by inhalation |
| **Amantadine[c]** | | | |
| Treatment, influenza A | Age 1–9, 5 mg/kg in 2 divided doses, up to 150 mg/d | Age ≥10, 100 mg PO bid | ≤100 mg/d |
| Prophylaxis, influenza A | Age 1–9, 5 mg/kg in 2 divided doses, up to 150 mg/d | Age ≥10, 100 mg PO bid | ≤100 mg/d |
| **Rimantadine[c]** | | | |
| Treatment, influenza A | Not approved | 100 mg PO bid | 100–200 mg/d |
| Prophylaxis, influenza A | Age 1–9, 5 mg/kg in 2 divided doses, up to 150 mg/d | Age ≥10, 100 mg PO bid | 100–200 mg/d |

[a]<15 kg: 30 mg bid; >15–23 kg: 45 mg bid; >23–40 kg: 60 mg bid; >40 kg: 75 mg bid. For children <1 year of age, see *www.cdc.gov/h1n1flu/recommendations.htm*.
[b]<15 kg: 30 mg qd; >15–23 kg: 45 mg qd; >23–40 kg: 60 mg qd; >40 kg: 75 mg qd. For children <1 year of age, see *www.cdc.gov/h1n1flu/recommendations.htm*.
[c] Amantadine and rimantadine are not currently recommended (2013–2014) because of widespread resistance in influenza A viruses. Their use may be reconsidered if viral susceptibility is reestablished.

(oseltamivir and zanamivir) and the adamantane agents (amantadine and rimantadine) reduce the duration of signs and symptoms by 1–1.5 days and ~50%, respectively.

– An IV formulation of peramivir, a neuraminidase inhibitor, has recently been approved by the FDA; an IV formulation of zanamivir is in clinical trials.

– Zanamivir may exacerbate bronchospasm in asthmatic pts, while oseltamivir has been associated with nausea and vomiting (reactions whose incidence is reduced if the drug is given with food) and with neuropsychiatric side effects in children.

– Amantadine causes mild CNS side effects (e.g., jitteriness, anxiety, insomnia, difficulty concentrating) in ~5–10% of pts; rimantadine has fewer CNS side effects.

- For uncomplicated influenza in individuals at low risk for complications, symptom-based rather than antiviral therapy may be considered.

### Prophylaxis

Annual vaccination with either an inactivated or a live attenuated vaccine is the main public health measure for prevention of influenza.

- Vaccine strains are generated from influenza A and B viruses that have circulated during the previous influenza season and whose circulation during the upcoming season is predicted.
  - For inactivated vaccines, 50–80% protection against influenza is expected if the vaccine virus and the currently circulating viruses are closely related.
  - Influenza vaccination is currently recommended for all individuals >6 months of age.
- Chemoprophylaxis against influenza (Table 101-1) should be reserved for individuals at high risk of complications who have had close contact with a pt sick with influenza. Chemoprophylaxis can be administered simultaneously with inactivated—but not with live—vaccine.

## OTHER COMMON VIRAL RESPIRATORY INFECTIONS

Acute viral respiratory illnesses account for ≥50% of all acute illnesses; adults have 3–4 cases per person per year. The clinical presentations of viral infections generally are not specific enough to allow an etiologic diagnosis, and viral illnesses are typically grouped into clinical syndromes (e.g., the "common cold," pharyngitis, tracheitis, pneumonia). This section will cover the six major groups of respiratory viruses; see Table 101-2 for an overview and Chap. 58 for additional details on viral respiratory infections.

### RHINOVIRUSES

#### Microbiology

Rhinoviruses are nonenveloped, single-stranded RNA viruses in the family Picornaviridae that together are the major cause of the "common cold" (up to 50% of cases).

#### Epidemiology

Rhinoviruses are spread by direct contact with infected secretions, usually respiratory droplets.

#### Clinical Manifestations

After an incubation period of 1–2 days, pts develop rhinorrhea, sneezing, nasal congestion, and sore throat that last for 4–9 days. Fever and other systemic signs and symptoms are unusual in adults.

- Severe disease, including fatal pneumonia, is rare but has been described in immunocompromised pts, particularly bone marrow transplant recipients.

#### Diagnosis

An etiologic diagnosis usually is not attempted, given that the disease is generally mild and self-limited. PCR and tissue culture methods are available.

#### Treatment

Treatment is limited to symptom relief (e.g., with antihistamines, decongestants).

### CORONAVIRUSES

#### Microbiology

Coronaviruses are pleomorphic, single-stranded RNA viruses.

**TABLE 101-2 ILLNESSES ASSOCIATED WITH RESPIRATORY VIRUSES**

| | Frequency of Respiratory Syndromes | | |
|---|---|---|---|
| **Virus** | **Most Frequent** | **Occasional** | **Infrequent** |
| Rhinoviruses | Common cold | Exacerbation of chronic bronchitis and asthma | Pneumonia in children |
| Coronaviruses[a,b] | Common cold | Exacerbation of chronic bronchitis and asthma | Pneumonia and bronchiolitis |
| Human respiratory syncytial virus | Pneumonia and bronchiolitis in young children | Common cold in adults | Pneumonia in elderly and immunosuppressed pts |
| Parainfluenza viruses | Croup and lower respiratory tract disease in young children | Pharyngitis and common cold | Tracheobronchitis in adults; lower respiratory tract disease in immunosuppressed pts |
| Adenoviruses | Common cold and pharyngitis in children | Outbreaks of acute respiratory disease in military recruits[c] | Pneumonia in children; lower respiratory tract and disseminated disease in immunosuppressed pts |
| Influenza A viruses | Influenza[d] | Pneumonia and excess mortality in high-risk pts | Pneumonia in healthy individuals |
| Influenza B viruses | Influenza[d] | Rhinitis or pharyngitis alone | Pneumonia |
| Enteroviruses | Acute undifferentiated febrile illnesses[e] | Rhinitis or pharyngitis alone | Pneumonia |
| Herpes simplex viruses | Gingivostomatitis in children; pharyngotonsillitis in adults | Tracheitis and pneumonia in immunocompromised pts | Disseminated infection in immunocompromised pts |
| Human metapneumoviruses | Upper and lower respiratory tract disease in children | Upper respiratory tract illness in adults | Pneumonia in elderly and immunosuppressed pts |

[a]Severe acute respiratory syndrome–associated coronavirus (SARS-CoV) caused epidemics of pneumonia from November 2002 to July 2003 (see text).
[b]Middle East respiratory syndrome coronavirus (MERS-CoV) has caused severe respiratory illnesses from 2012 to the time of this writing (2015); see text.
[c]Serotypes 4 and 7 most commonly; also serotypes 14 and 21.
[d]Fever, cough, myalgia, malaise.
[e]May or may not have a respiratory component.

## Epidemiology and Clinical Manifestations

Coronaviruses often result in the common cold (accounting for 10–35% of cases), with symptoms similar to those caused by rhinoviruses.

- Compared with that for rhinoviruses, the incubation period for coronaviruses is slightly longer (3 days) and the duration of illness is slightly shorter (6–7 days).
- In 2002–2003, a coronavirus-induced severe acute respiratory syndrome (SARS) developed in >8000 pts in 28 countries (with 90% of cases in China and Hong Kong) and was associated with a ~9.5% case–fatality rate; no cases were reported after 2004.
  - SARS has an incubation period of 2–7 days, after which pts develop fever, malaise, headache, myalgias, and then (1–2 days later) a nonproductive cough and dyspnea.
  - Pts can develop ARDS and multiorgan dysfunction in the second week of illness.
- The Middle East respiratory syndrome coronavirus (MERS-CoV) was first identified in 2012 and has caused more than 1600 cases, with a 36% case–fatality rate. All cases have been associated with contact or travel to the Arabian Peninsula.
  - After an incubation period of ~5 days, pts develop cough and fever that progress to respiratory failure within a week.

## Diagnosis

Laboratory diagnosis of coronavirus-induced colds is rarely required, but ELISA, immunofluorescence, and reverse-transcription PCR (RT-PCR) assays can detect the virus in clinical specimens.

- The coronavirus associated with SARS (SARS-CoV) and MERS-CoV can be detected by RT-PCR or viral culture of respiratory samples.

**TREATMENT CORONAVIRUSES**

- For the common cold, no treatment beyond symptom relief is generally needed.
- For SARS and MERS, aggressive supportive care is most important. No specific therapy (e.g., with ribavirin, glucocorticoids) has been established as efficacious.

# HUMAN RESPIRATORY SYNCYTIAL VIRUS (HRSV)

## Microbiology

HRSV is an enveloped, single-stranded RNA virus and a member of the family Paramyxoviridae.

## Epidemiology

With an attack rate approaching 100% among susceptible individuals, HRSV is a major respiratory pathogen among young children (particularly those 2–3 months of age) and the foremost cause of lower respiratory disease among infants.

- HRSV accounts for 20–25% of hospital admissions of young children for pneumonia and for up to 75% of cases of bronchiolitis in this age group.
- The virus is transmitted efficiently via contact with contaminated fingers or fomites and by spread of coarse aerosols. The incubation period is ~4–6 days.

## Clinical Manifestations

Infants typically develop rhinorrhea, low-grade fever, cough, and wheezing; 25–40% of infections result in lower tract disease, including pneumonia, bronchiolitis, and tracheobronchitis.

- In adults, HRSV typically presents as the common cold, but it can cause lower respiratory tract disease with fever, including severe pneumonia in pts who are elderly or immunosuppressed or who have cardiopulmonary disease. HRSV pneumonia has a case–fatality rate of 20–80% among transplant pts.

## Diagnosis

Rapid viral diagnosis is available by immunofluorescence, ELISA, or RT-PCR of nasopharyngeal washes, aspirates, or (less satisfactorily) swabs.

**TREATMENT HUMAN RESPIRATORY SYNCYTIAL VIRUS**

- Treatment is symptom-based for upper tract disease and mild lower tract disease.
- For severe lower tract disease, intubation and ventilatory assistance should be given as needed.
  - Aerosolized ribavirin has a demonstrated modest beneficial effect for infants with severe HRSV pneumonia, but its efficacy in older children and adults (including immunocompromised pts) has not been established.
  - No benefit has been found in any pt population for IV immunoglobulin (IVIg), immunoglobulin with high titers of antibody to HRSV (RSVIg), or a monoclonal IgG antibody to HRSV (palivizumab).

## Prevention

Monthly administration of palivizumab is approved for prophylaxis in children <2 years of age who have bronchopulmonary dysplasia or cyanotic heart disease or who were born prematurely. In settings with high transmission rates (e.g., pediatric wards), contact precautions are useful to limit spread of the virus.

# HUMAN METAPNEUMOVIRUS

## Microbiology

Human metapneumovirus is a pleomorphic, single-stranded RNA virus of the family Paramyxoviridae.

## Epidemiology

Human metapneumovirus accounts for 1–5% of childhood upper respiratory tract infections and for 2–4% of acute respiratory illnesses in ambulatory adults.

## Clinical Manifestations

Disease manifestations are similar to those caused by HRSV.

## Diagnosis

The diagnosis is made by immunofluorescence, PCR, or tissue culture of nasal aspirates or respiratory secretions.

## Treatment

Treatment is primarily supportive and symptom-based.

# PARAINFLUENZA VIRUS

## Microbiology and Epidemiology

This enveloped, single-stranded RNA virus of the family Paramyxoviridae ranks second only to HRSV as a cause of lower respiratory tract disease among young children and is the most common cause of croup (laryngotracheobronchitis).

## Clinical Manifestations

Infections are milder among older children and adults, but severe, prolonged, and fatal infection has been reported among pts with severe immunosuppression, including transplant recipients.

## Diagnosis

Tissue culture, rapid testing with immunofluorescence or ELISA (both of which are less sensitive), or PCR of respiratory tract secretions, throat swabs, or nasopharyngeal washings can detect the virus.

### TREATMENT PARAINFLUENZA VIRUS

Treatment of upper respiratory tract disease is symptom-based. Humidified air may be helpful for mild cases of croup.

- For cases of croup with respiratory distress, intermittent racemic epinephrine and glucocorticoids are beneficial.
- Anecdotal reports describe the use of ribavirin (particularly in immunosuppressed pts), but its clinical utility is still unclear.

# ADENOVIRUSES

## Microbiology and Epidemiology

Adenoviruses are double-stranded DNA viruses that cause ~10% of acute respiratory infections among children and <2% of respiratory illnesses among civilian adults. Some serotypes are associated with outbreaks among military recruits. Transmission takes place primarily from fall to spring via inhalation of aerosolized virus, through inoculation of the conjunctival sacs, and probably via the fecal–oral route.

## Clinical Manifestations

In children, adenovirus causes acute upper and lower respiratory tract infections and outbreaks of pharyngoconjunctival fever (a syndrome of fever, bilateral conjunctivitis, sore throat, and cervical adenopathy typically due to types 3 and 7).

- In adults (particularly military recruits), adenovirus types 4 and 7 cause an acute respiratory disease consisting of a prominent sore throat, fever on the second or third day of illness, cough, coryza, and regional adenopathy. Pharyngeal edema and tonsillar hypertrophy with little or no exudate may be seen.
- In addition to respiratory disease, adenovirus can cause diarrheal illness, hemorrhagic cystitis, and epidemic keratoconjunctivitis. In pts who have received a solid-organ transplant, adenovirus can affect the transplanted organ and disseminate to other organs.

## Diagnosis

Definitive diagnosis can be made by isolation of the virus in tissue culture; by rapid testing (immunofluorescence or ELISA) of nasopharyngeal aspirates, conjunctival or respiratory secretions, urine, or stool; or by PCR testing (the diagnostic standard).

## Treatment

Treatment is supportive. Ribavirin and cidofovir exhibit in vitro activity against adenovirus and therefore are used occasionally in disseminated adenovirus infections, but definitive efficacy data are not available.

For a more detailed discussion, see Baden LR, Dolin R: Antiviral Chemotherapy, Excluding Antiretroviral Drugs, Chap. 215e; Dolin R: Common Viral Respiratory Infections, Chap. 223, p. 1202; and Cohen YZ, Dolin R: Influenza, Chap. 224, p. 1209, in HPIM-19.

# 102 Rubeola, Rubella, Mumps, and Parvovirus Infections

## MEASLES (RUBEOLA)

### Definition and Microbiology

Measles is a highly contagious disease that is characterized by a prodromal illness of fever, cough, coryza, and conjunctivitis followed by a generalized maculopapular rash. Measles is caused by a nonsegmented, single-stranded, negative-sense RNA virus of the genus *Morbillivirus* and the family Paramyxoviridae.

### Epidemiology

Humans are the only reservoir for measles virus; unvaccinated infants who have lost maternal antibodies account for the bulk of susceptible individuals. However, as measles vaccine coverage increases, the age distribution of the disease shifts upward: in the United States, adolescents and adults are the most likely age groups to acquire measles.

- Routine administration of the measles vaccine has markedly reduced worldwide mortality due to measles; in 2008, there were ~164,000 deaths.
- Pts are contagious for several days before and after the rash appears. The virus is spread primarily via respiratory droplets over short distances. Secondary attack rates among susceptible contacts are >90%.

### Clinical Manifestations

Approximately 10 days after infection with measles virus, pts develop fever and malaise, followed by cough, coryza, and conjunctivitis; the characteristic rash occurs 14 days after infection.

- An erythematous, nonpruritic, maculopapular rash begins at the hairline and behind the ears, spreads down the trunk and limbs to include the palms and soles, can become confluent, and begins to fade (in the same order of progression) by day 4.
- Koplik's spots are pathognomonic for measles and consist of bluish-white dots ~1 mm in diameter surrounded by erythema. They appear on the buccal mucosa ~2 days before the rash appears and fade with the onset of rash.
- Pts with impaired cellular immunity may not develop a rash and have a higher case–fatality rate than those with intact immunity.
- Complications include giant-cell pneumonitis, secondary bacterial infection of the respiratory tract (e.g., otitis media, bronchopneumonia), and CNS disorders.
  - Postmeasles encephalitis occurs within 2 weeks of rash onset in ~1 in 1000 cases and is characterized by fever, seizures, and a variety of neurologic abnormalities.
  - Measles inclusion-body encephalitis (MIBE) and subacute sclerosing panencephalitis (SSPE) occur months to years after acute infection and are caused by persistent measles virus infection.
    - MIBE is a fatal complication that primarily affects pts with defects in cellular immunity.
    - SSPE is a progressive disease characterized by seizures and deterioration of cognitive and motor functions, with death occurring 5–15 years after measles virus infection.

## Diagnosis

The characteristic rash and pathognomonic Koplik's spots permit a clinical diagnosis.

- Serologic testing is the most common method of laboratory diagnosis. Measles-specific IgM is usually detectable within 1–3 days of rash onset.
- Viral culture and reverse-transcription PCR analysis of clinical specimens are used occasionally to detect measles.

**TREATMENT MEASLES**

- Supportive care is the mainstay of treatment, as there is no specific antiviral therapy for measles. Prompt antibiotic therapy for pts with secondary bacterial infections helps reduce morbidity and mortality risks.
- Vitamin A (for children ≥12 months: 200,000 IU/d for 2 days) is recommended by the World Health Organization (WHO) for all children with measles.

## Prevention

In the United States, children are routinely immunized with two doses of a live attenuated vaccine containing measles, mumps, and rubella (MMR) antigens.

- Vaccine-induced immunity lasts for at least several decades; rates of secondary vaccine failure 10–15 years after immunization are ~5%. In contrast, natural infection leads to life-long immunity.
- Administration of immunoglobulin within 6 days of exposure, which can prevent or modify the disease in immunocompetent persons, is recommended for children <1 year old, immunocompromised pts, and pregnant women. A dose of 0.25 mL/kg is given to healthy pts and a dose of 0.5 mL/kg to immunocompromised hosts, with a maximal dose of 15 mL.

# RUBELLA (GERMAN MEASLES)

## Microbiology and Epidemiology

Rubella is a contagious infectious disease caused by a single-stranded, enveloped RNA virus in the family Togaviridae and the genus *Rubivirus*.

- In 2012, there were 94,030 cases of rubella worldwide, although this figure is probably an underestimate because of poor reporting. Since 2004, rubella has not been an endemic disease in the United States.
- Virus is spread via respiratory droplets, and primary implantation and replication occur in the nasopharynx. Placental infection can lead to chronic infection of virtually all fetal organs, which sometimes persists for up to 1 year after birth.

## Clinical Manifestations

While acquired rubella infection is generally benign, congenital rubella infection can be more severe.

- *Acquired infection:* With an incubation period of 14 days, acquired rubella is characterized by a generalized maculopapular rash that lasts ≤3 days; ~50% of infections are subclinical or without rash.
  - Occipital and/or postauricular lymphadenopathy may occur during the second week after exposure.
  - In older children and adults, the rash may be preceded by a 1- to 5-day prodrome consisting of low-grade fever, malaise, and upper respiratory symptoms.
  - Arthralgias and arthritis are common among adults, particularly women.
- *Congenital infection:* Congenital rubella infection can lead to a number of physical defects, usually involving the eyes (e.g., cataracts), ears (e.g., deafness), and heart (e.g., pulmonary arterial stenosis).

– Up to 90% of women infected with rubella virus during the first 11 weeks of pregnancy will deliver an infant with congenital rubella.
– The congenital rubella rate is 20% for maternal infections acquired during the first 20 weeks of pregnancy.

## Diagnosis

Given the difficulty of diagnosing rubella clinically, serologic testing (for the presence of IgM or a ≥4-fold rise in IgG titer) is generally used for diagnosis.

- If the IgM sample taken within the first 4 days of rash is negative but clinical suspicion remains, testing should be repeated; IgM antibody titers are generally positive for up to 6 weeks.
- Congenital rubella can be diagnosed by detection of IgM antibodies, although titers may be negative during the first month; by isolation of the virus from throat swabs, urine, or CSF; and/or by an IgG titer that does not decline at the expected rate of a twofold dilution per month.
- In the United States, screening of pregnant women for rubella IgG antibodies is part of routine prenatal care; seronegative women should be vaccinated postpartum.

## Treatment

Symptom-based treatment for various manifestations, such as fever and arthralgia, is appropriate. No rubella-specific therapies are available.

## Prevention

As of 2012, 69% of countries holding membership in the WHO had recommended inclusion of a rubella-containing vaccine in the routine childhood vaccination schedule. One dose induces seroconversion in ≥95% of persons ≥1 year of age and provides long-term (potentially life-long) immunity.

- Pregnant women should not receive the vaccine, and pregnancy should be avoided for at least 28 days after vaccination.
- Immunoglobulin does not prevent rubella virus infection after exposure and therefore is not recommended as routine postexposure prophylaxis.

# MUMPS

## Definition and Microbiology

Mumps is an acute systemic communicable viral infection whose most distinctive feature is swelling of one or both parotid glands. It is caused by mumps virus, a negative-strand nonsegmented RNA paramyxovirus.

## Epidemiology

The estimated annual global incidence of mumps is 100–1000 cases per 100,000 population in countries without national mumps vaccination programs. In the United States, there were <300 cases in 2001 because levels of childhood vaccination are high, although occasional outbreaks—particularly among college students—continue to occur because of inadequate coverage in focal areas and waning of vaccine immunity with time.

- The incubation period of mumps is ~19 days, and humans are the only natural hosts.
- Mumps virus is transmitted by respiratory secretions and fomites. Pts are contagious from 1 week before to 1 week after symptom onset and are most contagious 1–2 days before symptom onset.

## Clinical Manifestations

Up to half of infections are asymptomatic or lead to nonspecific respiratory symptoms. Unilateral or bilateral parotitis lasting >2 days is present in 70–90% of symptomatic infections.

- A prodrome involving low-grade fever, malaise, myalgia, headache, and anorexia may precede the development of parotitis and last for 1–7 days.
  - Pts with parotitis typically have difficulty eating, swallowing, and/or talking and may have an earache.
  - Glandular swelling disappears within 1 week.
- Epididymo-orchitis is the second most common manifestation of mumps, developing in 15–30% of cases in postpubertal males.
  - Orchitis, characterized by a painful, tender, and enlarged testis, is bilateral in 10–30% of cases and resolves within 1 week.
  - Oophoritis (manifested by lower abdominal pain and vomiting) occurs in ~5% of women with mumps.
  - Sterility after mumps is rare.
- Symptomatic CNS disease (e.g., aseptic meningitis) occurs in <10% of pts and is usually self-limited.
  - In CSF pleocytosis, neutrophils often predominate in the first 24 h before being replaced by lymphocytes on the second day.
  - Cranial nerve palsies occasionally lead to permanent sequelae, particularly deafness.
- Less common manifestations include pancreatitis, myocarditis, thyroiditis, nephritis, and arthritis. Mumps in pregnancy does not appear to lead to premature birth, low birth weight, or fetal malformations.

### Diagnosis

Laboratory diagnosis is generally based on detection of viral RNA in clinical samples (e.g., buccal or throat swab, CSF, urine, seminal fluid) via reverse-transcription PCR or serology. Serologic assays are of limited utility since IgM may not be detectable <3 days or >6 weeks after symptom onset and IgG titers often exhibit little fluctuation between acute- and convalescent-phase samples.

### Treatment

Mumps is generally a benign, self-resolving illness in which symptom-based and supportive therapies are most helpful.

### Prevention

Current United States recommendations are for a two-dose vaccination schedule, with the first dose at ≥1 year old and the second dose at least 28 days after the first. Outbreaks, such as those occurring in 2006 in the United States, the United Kingdom, and Canada, demonstrate that vaccine-induced immunity is not life-long.

## PARVOVIRUS INFECTION

### Microbiology

Parvovirus B19 (B19V), a nonenveloped single-stranded DNA virus of the family Parvoviridae, is the only member of this family shown definitively to cause significant human disease.

### Epidemiology

B19V exclusively infects humans, is endemic worldwide, and is transmitted via the respiratory route. By the age of 15 years, ≥50% of children are seropositive. Of elderly pts, >90% have detectable antibody.

### Pathogenesis

B19V replicates in erythroid progenitors, which are among the few cells that express the B19V receptor, blood group P antigen (globoside). Infection leads to high-titer viremia and arrest of erythropoiesis. When an IgM and IgG antibody response is mounted, normal erythropoiesis resumes.

## Clinical Manifestations

Most B19V infections are asymptomatic or are associated with only a mild nonspecific illness.

- *Erythema infectiosum (fifth disease):* The main manifestation of symptomatic B19V disease, erythema infectiosum presents as a low-grade fever ~7–10 days after exposure and a facial "slapped-cheek" rash (more common among children) a few days later. Two or three days after the facial rash develops, a lacy, reticular macular rash may spread to the extremities.
- *Polyarthropathy syndrome:* Arthralgias, typically symmetric and affecting the small joints of the hands and occasionally the ankles, knees, and wrists, occur in ~50% of adults (more commonly women). Most cases resolve in a few weeks, but some persist for months.
- *Transient aplastic crisis (TAC):* Pts with chronic hemolytic conditions (e.g., hemoglobinopathies, autoimmune hemolytic anemia) can develop aplastic crisis with B19V infection that can be life-threatening. Pts display symptoms associated with severe anemia.
- *Pure red-cell aplasia/chronic anemia:* Immunosuppressed pts can develop persistent anemia with reticulocytopenia, high levels of B19V DNA in serum, and absent or low levels of B19V IgG. B19V occasionally causes a hemophagocytic syndrome.
- *Hydrops fetalis:* B19V infection during pregnancy can lead to hydrops fetalis and/or fetal loss. The risk of transplacental fetal infection is ~30%, and the risk of fetal loss (which occurs predominantly early in the second trimester) is ~9%. The risk of congenital infection is <1%.

## Diagnosis

Diagnosis in immunocompetent pts generally relies on detection of B19V-specific IgM antibodies, which can be detected coincident with the rash in erythema infectiosum or by day 3 of TAC.

- B19V-specific IgG is detectable by the seventh day of illness and persists for life.
- Detection of B19V DNA via quantitative PCR should be used to diagnose early TAC or chronic anemia. In acute infection, the viremia load can be $>10^{12}$ B19V DNA IU/mL of serum; pts with TAC or chronic anemia generally have $>10^{5}$ B19V IU/mL.

## TREATMENT PARVOVIRUS INFECTION

- Treatment of B19V infection is generally supportive as no specific therapy exists. TAC should be treated with transfusions as needed.
- In pts receiving immunosuppressive agents, treatment should be reduced to the extent feasible to allow an immune response. IV immunoglobulin (400 mg/kg daily for 5–10 days) may cure or ameliorate persistent B19V infection in immunosuppressed pts.

For a more detailed discussion, see Brown KE: Parvovirus Infections, Chap. 221, p. 1195; Rainwater-Lovett K, Moss WJ: Measles (Rubeola), Chap. 229, p. 1295; Zimmerman LA, Reef SE: Rubella (German Measles), Chap. 230e; and Rubin SA, Carbone KM: Mumps, Chap. 231e, in HPIM-19.

# 103 Enteroviral Infections

## MICROBIOLOGY

- Enteroviruses are so named because of their ability to multiply in the GI tract, but they do not typically cause gastroenteritis.
- Enteroviruses are members of the family Picornaviridae and encompass >100 human serotypes: 3 serotypes of poliovirus, 21 serotypes of coxsackievirus A, 6 serotypes of coxsackievirus B, 28 serotypes of echovirus, enteroviruses 68–71, and multiple enteroviruses (beginning with enterovirus 73) recently identified by molecular techniques. In the United States, coxsackievirus B1 and echoviruses 18, 9, and 6 account for ~50% of all enteroviral infections.

## PATHOGENESIS

- Studies of poliovirus infection form the basis of our understanding of enteroviral pathogenesis.
- After ingestion, poliovirus infects GI tract mucosal epithelial cells, spreads to regional lymph nodes, causes viremia, and replicates in the reticuloendothelial system; in some cases, a second round of viremia occurs.
- Virus gains access to the CNS either via the bloodstream or via direct spread from neural pathways.
- Virus is present in blood for 3–5 days. It is shed from the oropharynx for up to 3 weeks and from the GI tract for up to 12 weeks after infection; hypogammaglobulinemic pts can shed virus for >20 years.
- Infection is controlled by humoral and secretory immunity in the GI tract.

## EPIDEMIOLOGY

- Enteroviruses cause disease worldwide, especially in areas with crowded conditions and poor hygiene.
- Infants and young children are most often infected and are the most frequent shedders.
- Transmission takes place mainly by the fecal–oral route, but airborne transmission and placental transmission have been described.
- The incubation period ranges from 2 to 14 days but usually is <1 week in duration. Pts are most infectious shortly before and after the onset of symptoms.

## CLINICAL MANIFESTATIONS

### Poliovirus

After an incubation period of 3–6 days, ~5% of pts present with a minor illness (abortive poliomyelitis), characterized by fever, malaise, sore throat, myalgias, and headache, that usually resolves within 3 days.

- *Asymptomatic infection*: >90% of all infections
- *Aseptic meningitis (nonparalytic poliomyelitis):* occurs in ~1% of pts. Examination of CSF reveals normal glucose and protein concentrations and lymphocytic pleocytosis (with PMNs sometimes predominating early).
- *Paralytic disease:* the least common form; presents ≥1 day after aseptic meningitis as severe back, neck, and muscle pain as well as gradually developing motor weakness
  - The weakness is usually asymmetric and proximal and is most common in the legs. The arms and the abdominal, thoracic, and bulbar muscles are also frequently involved.

  - Paralysis generally occurs only during the febrile phase.
  - Physical examination reveals weakness, fasciculations, decreased muscle tone, and reduced or absent reflexes in affected areas; hyperreflexia may precede the loss of reflexes. Bulbar paralysis is associated with dysphagia, difficulty handling secretions, or dysphonia.
  - Respiratory insufficiency due to aspiration or neurologic involvement may develop. Severe medullary infection may lead to circulatory collapse.
  - Most pts recover some function, but around two-thirds have residual neurologic sequelae.
- *Vaccine-associated poliomyelitis:* The risk of acquiring poliomyelitis after vaccination with the live oral vaccine is estimated to be 1 case per 2.5 million doses and is ~2000 times higher among immunodeficient persons, especially pts with hypo- or agammaglobulinemia.
- *Postpolio syndrome:* new weakness 20–40 years after poliomyelitis. Onset is insidious, progression is slow, and plateau periods can last 1–10 years.

## Other Enteroviruses

In the United States, 5–10 million cases of symptomatic enteroviral disease other than poliomyelitis occur each year. More than 50% of nonpoliovirus enteroviral infections are subclinical.

- *Nonspecific febrile illness (summer grippe)*: Pts present with acute-onset fever, malaise, and headache, with occasional upper respiratory symptoms.
  - Disease resolves within a week.
  - Disease frequently occurs during the summer and early fall.
- *Generalized disease of the newborn*: Neonates, typically within the first week of life, present with an illness resembling bacterial sepsis, with fever, irritability, and lethargy.
  - Myocarditis, hypotension, hepatitis, DIC, meningitis, and pneumonia are complications.
  - A history of a recent flu-like illness in the mother should prompt consideration of this disease.
- *Aseptic meningitis and encephalitis*: Enteroviruses cause 90% of cases of aseptic meningitis among children and young adults in which an etiologic agent can be identified; 10–35% of viral encephalitis cases are due to enteroviruses.
  - Pts have an acute onset of fever, chills, headache, photophobia, nausea, and vomiting, with meningismus on examination. Diarrhea, rashes, myalgias, pleurodynia, myocarditis, and herpangina may occur. Encephalitis is much less common and is usually mild, with an excellent prognosis in healthy hosts.
  - CSF examination reveals pleocytosis, with PMNs sometimes predominating early but a shift to lymphocyte predominance within 24 h. Total cell counts usually do not exceed 1000/μL. CSF glucose and protein levels are typically normal.
  - Symptoms resolve within 1 week, but CSF abnormalities persist longer.
- *Pleurodynia (Bornholm disease):* Pts have an acute onset of fever associated with spasms of pleuritic chest pain (more common among adults) or upper abdominal pain (more common among children) that typically last 15–30 min. Fever subsides when pain resolves.
  - Coxsackievirus B is the most common cause.
  - Disease lasts for a few days and can be treated with NSAIDs and heat application to the affected muscles.
- *Myocarditis and pericarditis:* Enteroviruses (e.g., coxsackievirus B) cause up to one-third of cases of acute myocarditis. Pts have upper respiratory symptoms followed by fever, chest pain, dyspnea, arrhythmias, and occasionally heart failure.
  - Disease occurs most often in newborns (who are most severely ill), adolescents, and young adults.

  - A pericardial friction rub, ST-segment and T-wave abnormalities on electrocardiography, and elevated serum levels of myocardial enzymes can be present.
  - Up to 10% of pts develop chronic dilated cardiomyopathy.
- *Exanthems*: Enteroviral infection is the leading cause of exanthems among children in the summer and fall. Echoviruses 9 and 16 are common causes.
- *Hand-foot-and-mouth disease:* generally due to coxsackievirus A16 and enterovirus 71. Pts present with fever, anorexia, and malaise, which are followed by sore throat and vesicles on the buccal mucosa, tongue, and dorsum or palms of the hands and occasionally on the palate, uvula, tonsillar pillars, or feet.
  - The disease is highly infectious, with attack rates of almost 100% among young children. Symptoms resolve within a week.
  - Epidemics of enterovirus 71 infection occurred in Taiwan in 1998 and in China in 2008–2010; the latter resulted in ~500,000 infections and 126 deaths. These epidemics were associated with CNS disease (e.g., brain-stem encephalitis, seizures), myocarditis, and pulmonary hemorrhage. Deaths occurred primarily among children ≤5 years old.
- *Herpangina:* usually caused by coxsackievirus A infection. Pts develop fever, sore throat, odynophagia, and grayish-white papulovesicular lesions on an erythematous base that ulcerate and are concentrated in the posterior portion of the mouth.
  - Lesions can persist for weeks.
  - In contrast to herpes simplex stomatitis, enteroviral herpangina is not associated with gingivitis.
- *Acute hemorrhagic conjunctivitis:* associated with enterovirus 70 and coxsackievirus A24. Pts experience an acute onset of severe eye pain, blurred vision, photophobia, and watery eye discharge; edema, chemosis, and subconjunctival hemorrhage are evident. Symptoms resolve within 10 days.

## DIAGNOSIS

- Enterovirus can be isolated from throat or rectal swabs, stool, and/or normally sterile body fluids.
  - Positive results for normally sterile body fluids, such as CSF and serum, reflect disease.
  - In contrast, positive stool and throat cultures may simply reflect colonization.
- In general, serotyping is not clinically useful outside of epidemiologic studies.
- PCR detects all serotypes that infect humans, with high sensitivity (70–100%) and specificity (>80%).
  - PCR of CSF is less likely to be positive if pts present ≥3 days after meningitis onset or with enterovirus 71 infection.
  - PCR of serum is also useful in disseminated disease.

## TREATMENT ENTEROVIRAL INFECTIONS

- Most enteroviral illness resolves spontaneously, but immunoglobulin may be helpful in pts with γ globulin defects and chronic infection.
- Glucocorticoids are contraindicated.

## PREVENTION AND ERADICATION

- Hand hygiene, use of gowns and gloves, and enteric precautions (for 7 days after disease onset) prevent nosocomial transmission of enteroviruses during epidemics.
- The availability of poliovirus vaccines and the implementation of polio eradication programs have largely eliminated disease due to wild-type poliovirus; of 293 cases in 2012, 85% were from Nigeria, Pakistan, and Afghanistan—the only countries where polio remains endemic. Outbreaks and sporadic disease due to vaccine-derived poliovirus occur.

- Both oral poliovirus vaccine (OPV) and inactivated poliovirus vaccine (IPV) induce IgG and IgA antibodies that persist for at least 5 years.
- Most developing countries, particularly those with persistent wild-type poliomyelitis, use OPV because of its lower cost and ease of administration. The suboptimal seroconversion rate among children in low-income countries, even after multiple OPV doses, contributes to difficulties in eradication.
- Most industrialized countries have adopted all-IPV childhood vaccination programs.
  - Unvaccinated adults in the United States do not need routine poliovirus vaccination but should receive three doses of IPV (the second dose 1–2 months after the first and the final dose 6–12 months later) if they are traveling to polio-endemic areas or might be exposed to wild-type poliovirus in their communities or workplaces.
  - Adults at increased risk of exposure who have received their primary vaccination series should receive a single dose of IPV.

For a more detailed discussion, see Cohen JI: Enterovirus, Parechovirus, and Reovirus Infections, Chap. 228, p. 1289, in HPIM-19.

# 104 Insect- and Animal-Borne Viral Infections

## RABIES

### Microbiology

Rabies is a zoonosis generally transmitted to humans by the bite of a rabid animal and caused by rabies virus—a nonsegmented, negative sense, single-stranded RNA virus in the family Rhabdoviridae. Each animal reservoir harbors distinct rabies virus variants.

### Epidemiology

Worldwide, canine rabies causes ~55,000 human deaths each year, most of them affecting rural populations and children in Asia and Africa.

- Endemic canine rabies has been eliminated in the United States and most other resource-rich countries but persists in bats, raccoons, skunks, and foxes. In 2012, there were 6162 confirmed animal cases of rabies in the United States.
- Bats (especially silver-haired and tricolored bats) cause most human cases in North America, although there may be no known history of a bat bite or other bat exposure.

### Pathogenesis

The incubation period can range from a few days to >1 year but is usually 20–90 days. During most of this period, rabies virus is present at or close to the site of the bite.

- The virus binds to postsynaptic nicotinic acetylcholine receptors and spreads centripetally along peripheral nerves toward the CNS at a rate of up to ~250 mm/d. Establishment of CNS infection is followed by centrifugal spread along peripheral nerves to other tissues, including salivary glands—hence the excretion of virus in the saliva of rabid animals.
- The most characteristic pathologic CNS finding is the *Negri body*—an eosinophilic cytoplasmic inclusion that is composed of rabies virus proteins and viral RNA and is found primarily within Purkinje cells of the cerebellum and in pyramidal neurons of the hippocampus.

## Clinical Manifestations

Rabies usually presents as atypical encephalitis with preservation of consciousness; the disease may be difficult to recognize after the onset of coma. This disease, which usually leads to death despite aggressive therapy, has three phases.

- *Prodrome:* Pts have fever, headache, malaise, nausea, vomiting, and anxiety or agitation lasting 2–10 days. Paresthesias, pain, or pruritus near the site of exposure (which has usually healed at this point) is found in 50–80% of cases and strongly suggests rabies.
- *Acute neurologic phase:* Pts present with the encephalitic (furious) form of rabies in 80% of cases and with the paralytic form in 20%.
  - *Encephalitic form:* Pts develop signs and symptoms common to other viral encephalitides (e.g., fever, confusion, hallucinations, combativeness, and seizures) that last 2–10 days. Autonomic dysfunction is common and includes hypersalivation, gooseflesh, cardiac arrhythmia, and/or priapism.
    - A distinguishing feature of rabies is prominent early brainstem dysfunction resulting in hydrophobia and aerophobia (involuntary, painful contraction of the diaphragm and the accessory respiratory, laryngeal, and pharyngeal muscles in response to swallowing liquid or exposure to a draft of air).
    - Hypersalivation and pharyngeal dysfunction produce characteristic foaming at the mouth.
    - Death usually occurs within days of brainstem involvement. With aggressive supportive care, late complications include cardiopulmonary failure, disturbances of water balance (syndrome of inappropriate antidiuretic hormone secretion or diabetes insipidus), and GI hemorrhage.
  - *Paralytic form:* For unknown reasons, muscle weakness predominates but cardinal features of rabies encephalitis (hyperexcitability, hydrophobia, aerophobia) are lacking. Muscle weakness usually begins in the bitten extremity and proceeds to quadriparesis.
- *Coma and death:* Even with aggressive supportive measures, recovery is rare. Death usually occurs within 2 weeks.

## Diagnosis

In North America, the diagnosis is often considered relatively late in the clinical course. Rabies should be considered for pts with acute atypical encephalitis or acute flaccid paralysis (including those in whom Guillain-Barré syndrome is suspected).

- Most routine laboratory tests in rabies are normal or nonspecific; it is important to test for alternative, potentially treatable diagnoses.
- Negative antemortem rabies-specific laboratory tests never exclude a diagnosis of rabies, and tests may need to be repeated after an interval for diagnostic confirmation.
  - In a previously unimmunized pt, serum neutralizing antibodies to rabies virus are diagnostic, but these antibodies may not be present until late in the disease course. The presence of rabies virus–specific antibodies in CSF suggests rabies encephalitis, regardless of immunization status.
  - Reverse-transcription PCR (RT-PCR) can detect virus in fresh saliva samples, CSF, and skin and brain tissues.

- Direct fluorescent antibody testing is highly sensitive and specific and can be applied to brain tissue or skin biopsy samples from the nape of the neck (where virus is found in cutaneous nerves at the base of hair follicles).

**TREATMENT RABIES**

Management is palliative and supportive. There is no established treatment for rabies.

## Prevention

Rabies is almost uniformly fatal but is nearly always preventable with appropriate postexposure prophylaxis during the incubation period. Only seven pts have survived infection with rabies virus, and only one of these pts had not received rabies vaccine before disease onset.

- An algorithm for rabies postexposure prophylaxis is depicted in Fig. 104-1.
  - Local wound care (e.g., thorough washing, debridement of devitalized tissue) can greatly reduce the risk of rabies.
  - All previously unvaccinated pts should receive human rabies immune globulin (RIG, 20 IU/kg; 40 IU/kg for equine RIG) no later than 7 days after the first vaccine dose. The entire dose should be infiltrated at the site of the bite; if not anatomically feasible, the residual RIG should be given IM at a distant site.
  - Inactivated rabies vaccine should be given as soon as possible (1 mL IM in the deltoid region), with doses repeated on days 3, 7, and 14 for previously unvaccinated pts; previously vaccinated pts require booster doses only on days 0 and 3.
- Preexposure prophylaxis is occasionally given to persons at high risk (including certain travelers to rabies-endemic areas). A primary vaccine schedule is given on days 0, 7, and 21 or 28.

# INFECTIONS CAUSED BY ARTHROPOD- AND RODENT-BORNE VIRUSES

## Microbiology and Pathogenesis

Most zoonotic viruses only incidentally infect and produce disease in humans; only a few agents are regularly spread among humans by arthropods.

- The major families of arthropod- and rodent-borne viruses include the Arenaviridae, Bunyaviridae, Flaviviridae, Orthomyxoviridae, Reoviridae, Rhabdoviridae, and Togaviridae—all RNA viruses.
- Arthropod-borne viruses infect the vector after a blood meal from a viremic vertebrate (usually nonhuman); after spreading throughout the vector and ultimately reaching the salivary glands, the viruses can be transmitted to another vertebrate during a blood meal.
- Humans become infected with rodent-borne viruses by inhalation of aerosols containing the viruses and through close contact with chronically infected rodents and their excreta.

## Clinical Manifestations

Infection is usually subclinical; when disease does occur, it generally does so in one of five occasionally overlapping clinical syndromes: fever and myalgia, encephalitis, arthritis and rash, pulmonary disease, or viral hemorrhagic fever (HF).

**Fever and Myalgia** This is the most common syndrome associated with zoonotic viruses. Typically, pts have an acute onset of fever, chills, severe myalgia, malaise, and headache; true arthritis is not found. Complete recovery after 2–5 days of illness is usual. Important examples include the following:

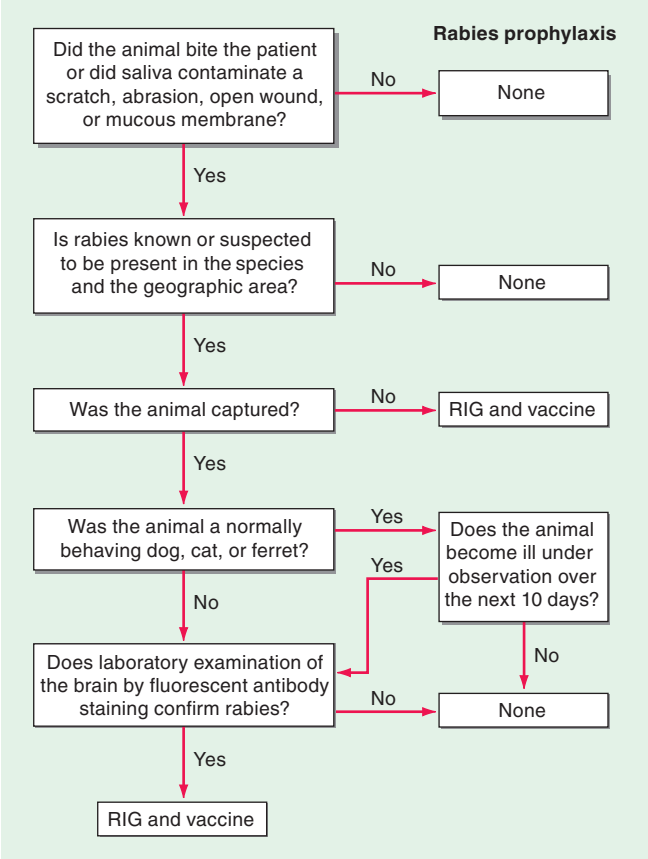


**FIGURE 104-1** Algorithm for rabies postexposure prophylaxis. RIG, rabies immune globulin. *(From L Corey, in* Harrison's Principles of Internal Medicine, *15th ed. E Braunwald et al [eds]: New York, McGraw-Hill, 2001, adapted with permission.)*

- *Lymphocytic choriomeningitis (LCM):* This infection is transmitted from chronically infected mice and pet hamsters via aerosols of excreta and secreta. About one-fourth of infected pts have a 3- to 6-day febrile phase, a brief remission, and then recurrent fever, severe headache, nausea, vomiting, and meningeal signs lasting ~1 week.
  - Other manifestations include transient alopecia, arthritis, pharyngitis, cough, maculopapular rash, and orchitis.
  - Pregnant women can have mild infection yet pass on the virus to the fetus, who can develop hydrocephalus and chorioretinitis.
  - The diagnosis should be considered when an adult has aseptic meningitis and any of the following applies: autumn seasonality, a well-marked febrile prodrome, a low CSF glucose level, or CSF mononuclear cell counts >1000/μL.
  - LCM viremia is most likely in the initial febrile phase of illness. LCM can also be diagnosed by IgM-capture ELISA of serum or CSF or by RT-PCR of CSF.

- *Dengue:* With 50–100 million cases annually, dengue is probably the most important arthropod-borne viral disease worldwide. The four serotypes of dengue viruses are all transmitted by the mosquito *Aedes aegypti*, which is also a vector for yellow fever. After an incubation period of 4–7 days, pts experience the sudden onset of fever, frontal headache, retroorbital pain, back pain, severe myalgia (*break-bone fever*), adenopathy, palatal vesicles, and scleral injection.
  - The illness usually lasts 1 week, and a maculopapular rash often appears near the time of defervescence (usually day 3–5).
  - A second infection with a different dengue serotype can lead to severe dengue (previously called *dengue hemorrhagic fever*; see "Hemorrhagic Fever," below).
  - The diagnosis is made by IgM ELISA or paired serologic tests during recovery or by antigen-detection ELISA or RT-PCR during the acute phase. Virus is easily isolated from blood during the acute phase by inoculation of mosquitoes or mosquito cell culture. Leukopenia, thrombocytopenia, and increased serum aminotransferase levels may be documented.

**Encephalitis** Depending on the causative virus, the ratio of clinical to subclinical disease, the mortality rate, and residua vary widely. The pt usually presents with a prodrome of nonspecific signs and symptoms (e.g., fever, abdominal pain, sore throat, respiratory signs) that is followed quickly by headache, meningeal signs, photophobia, and vomiting; involvement of deeper structures leads to lethargy, cognitive deficits, focal neurologic signs, and coma. Acute encephalitis usually lasts from a few days to 2–3 weeks, and recovery may be slow and incomplete. Treatable causes of encephalitis (e.g., HSV) should be ruled out promptly. Some important examples of arboviral encephalitides follow.

- *Japanese encephalitis:* This infection is present throughout Asia and the western Pacific islands. A Parkinsonian presentation and seizures are typical in severe cases. An effective vaccine (ideally given on days 0 and 28, with the second dose administered ≥1 week prior to travel) is available and is indicated for summer travelers to rural Asia, where the risk can be as high as 1 case per 5000 travelers per week.
- *West Nile encephalitis:* Present throughout the Western Hemisphere and now the leading cause of arboviral encephalitis in the United States, West Nile virus is a common cause of febrile disease without CNS infection, but it occasionally causes aseptic meningitis or encephalitis. Encephalitis, serious sequelae, and death are more common among elderly pts, diabetic and hypertensive pts, and pts with previous CNS disease. Unusual clinical features include chorioretinitis, flaccid paralysis, and initial presentation with focal neurologic deficits.
- *Eastern equine encephalitis (EEE):* EEE occurs primarily within endemic swampy foci along the eastern coast of the United States during the summer and early fall. EEE is one of the most severe arboviral diseases and is characterized by rapid onset, rapid progression, high mortality risk (50–75%), and frequent residua. PMN-predominant pleocytosis of the CSF within the first 1–3 days of disease is an indication of severity.

**Arthritis and Rash** Alphaviruses are common causes of arthritis accompanied by a febrile illness and maculopapular rash, usually during the summer in temperate climates. Examples include the following:

- *Sindbis virus:* Found in northern Europe and southern Africa, this virus, which has an incubation period of <1 week, causes a maculopapular rash that often vesiculates on the trunk and extremities. The arthritis of this condition is multiarticular, migratory, and incapacitating, with resolution of the acute phase in a few days; joint pains may persist for months or years.
- *Chikungunya virus:* Found primarily in Africa, Asia, and the Caribbean, this virus has an incubation period of 2–10 days and results in the abrupt onset of fever, severe arthralgias, migratory polyarthritis mainly affecting small joints, and a rash that begins coincident with defervescence at day 2–3 of illness.

- *Barmah Forest and Ross River viruses:* As causes of epidemic polyarthritis in Australia and the eastern Pacific Islands, these viruses produce a rash and disabling symmetrical joint pain, typically in the absence of other prominent constitutional symptoms, after an incubation period of 7–9 days. Because of joint pain, only ~50% and 90% of pts can resume normal activities at 4 weeks and 3 months, respectively.

**Pulmonary Disease** After a prodrome (e.g., fever, malaise, myalgias, GI disturbances) of ~3–4 days, pts with hantavirus pulmonary syndrome (HPS) enter a cardiopulmonary phase marked by tachycardia, tachypnea, and mild hypotension. Over the next few hours, the illness may rapidly progress to severe hypoxemia and respiratory failure; the mortality rate is ~30–40% with good management. Pts surviving the first 2 days of hospitalization usually recover with no residua.

- The disease is linked to rodent exposure. Sin Nombre virus infects the deer mouse and is the most important virus causing HPS in the United States.
- Thrombocytopenia (an important early clue), hemoconcentration, proteinuria, and hypoalbuminemia are typical.
- IgM testing of acute-phase serum may give positive results, even during the prodromal stage, and can confirm the diagnosis. RT-PCR of blood clots or tissue usually gives a positive result in the first 7–9 days of illness.
- Treatment is nonspecific and requires intensive respiratory management and other supportive measures.

**Viral Hemorrhagic Fever (VHF)** The VHF syndrome is a constellation of findings based on vascular instability and decreased vascular integrity. All VHF syndromes begin with the abrupt onset of fever and myalgia and can progress to severe prostration, headache, dizziness, photophobia, abdominal and/or chest pain, anorexia, and GI disturbances. On initial physical examination, there is conjunctival suffusion, muscular or abdominal tenderness to palpation, hypotension, petechiae, and periorbital edema. Laboratory examination usually reveals elevated serum aminotransferase levels, proteinuria, and hemoconcentration. Shock, multifocal bleeding, and CNS involvement (encephalopathy, coma, convulsions) are poor prognostic signs. Early recognition is important; appropriate supportive measures and, in some cases, virus-specific therapy can be instituted.

- *Lassa fever:* Endemic and epidemic in West Africa, Lassa fever has a more gradual onset than other VHF syndromes. Bleeding is evident in 15–30% of cases. A maculopapular rash is often noted in light-skinned pts with Lassa fever.
  - Pregnant women have higher mortality rates, and the fetal death rate is ~90%.
  - Pts with high-level viremia or a serum aspartate aminotransferase level of >150 IU/mL are at an elevated risk of death, and the administration of ribavirin (32 mg/kg IV × 1 dose, followed by 16 mg/kg q6h for 4 days and then 8 mg/kg q8h for 6 days), which appears to reduce this risk, should be considered.
- *Junin/Argentinian and Machupo/Bolivian HF syndromes:* These syndromes resemble Lassa fever; however, thrombocytopenia, bleeding, and CNS dysfunction (e.g., confusion, cerebellar signs) are common.
  - Passive antibody treatment for Junin/Argentinian HF is effective, and an effective vaccine exists.
  - Ribavirin at the doses recommended for Lassa fever is likely to be effective in all South American VHF syndromes.
- *Rift Valley fever:* Although Rift Valley fever virus typically causes fever and myalgia, VHF can occur with prominent liver involvement, renal failure, and probably DIC.
  - Retinal vasculitis can occur in ~10% of otherwise mild infections, and pts' vision can be permanently impaired.
  - There is no proven therapy for Rift Valley fever. A live attenuated vaccine is in trials.

- *HF with renal syndrome (HFRS):* This entity is most often caused in Europe by Puumala virus, in the Balkans by Dobrava-Belgrade virus, and in eastern Asia by Hantaan virus.
  - Severe cases of HFRS evolve in identifiable stages: the *febrile* stage with myalgia, lasting 3 or 4 days; the *hypotensive* stage, often associated with shock and lasting from a few hours to 48 h; the *oliguric* stage with renal failure, lasting 3–10 days; and the *polyuric* stage with diuresis and hyposthenuria.
  - Infections with Puumala virus result in a much-attenuated picture but the same general presentation.
  - IgM-capture ELISA is positive within 2 days of admission and confirms the diagnosis.
  - The mainstay of therapy is expectant management of shock and renal failure. Ribavirin may reduce rates of mortality and morbidity in severe cases if treatment is begun within the first 4 days of illness.
- *Yellow fever:* A former cause of major epidemics, yellow fever causes a typical VHF syndrome with prominent hepatic necrosis, most commonly in urban South America and Africa. Pts are viremic for 3–4 days and can have jaundice, hemorrhage, black vomit, anuria, and terminal delirium. Vaccination of visitors to endemic areas and control of the mosquito vector *A. aegypti* prevent disease.
- *Severe dengue:* Previous infection with a heterologous dengue virus serotype may elicit nonprotective antibodies and exacerbate disease if pts are reinfected. In mild cases, lethargy, thrombocytopenia, and hemoconcentration occur 2–5 days after typical dengue fever, usually at the time of defervescence. In severe cases, frank shock occurs, with cyanosis, hepatomegaly, ascites and pleural effusions, and GI bleeding. The period of shock lasts 1–2 days.
  - The risk decreases considerably after age 12. Severe dengue is more common among females than among males, among whites than among blacks, and among well-nourished than among malnourished persons; it is also more common if dengue virus 1—as opposed to dengue virus 4—precedes infection with dengue virus 2.
  - With good care, the overall mortality rate is as low as 1%. Control of *A. aegypti*, the mosquito vector, is the key to control of the disease.

## EBOLA AND MARBURG VIRUS INFECTIONS

### Microbiology

The family Filoviridae contains two genera, *Marburgvirus* and *Ebolavirus*, that consist of negative-sense, single-stranded RNA viruses capable of infecting humans. *Ebolavirus* has five species named for their original site of recognition, and *Marburgvirus* has two species.

- Both Marburg virus and Ebola virus are biosafety level 4 pathogens because of high mortality rates (except for Reston virus, an Ebola virus, which is nonpathogenic for humans) and aerosol infectivity.

### Epidemiology

- Filoviruses pathogenic for humans are exclusively endemic to Equatorial Africa.
- As of February 2016, there had been ~31,000 human filovirus infections and ~13,000 deaths (mortality rate, ~40%), the overwhelming majority of which occurred during an outbreak in 2014–2015.
- Since the discovery of filoviruses in 1967, there have been ~50 natural host-to-human spillover events. Bats are thought to be the reservoir for Marburg and Ebola viruses.
- Human-to-human transmission occurs through direct contact or exposure to infected bodily fluids and tissues; there is no evidence of such transmission by aerosol or respiratory droplets.

## Pathogenesis

The pathogenic hallmarks of filovirus infection include pronounced suppression of the immune system, severe disturbance of the clotting system, and impairment of vascular integrity. Although petechiae, ecchymoses, and other hemorrhagic signs are detected in internal organs, mucous membranes, and skin, actual severe blood loss is a rare event.

## Clinical Manifestations

After a 3- to 25-day incubation period, pts develop a biphasic syndrome with a 1- to 2-day relative remission separating the two phases.

- The first phase lasts 5–7 days and is characterized by an abrupt onset of fever, chills, severe headache, cough, myalgia, pharyngitis, and arthralgia and the development of a maculopapular rash.
- The second phase involves the GI tract (e.g., abdominal pain, vomiting, diarrhea), respiratory tract (e.g., chest pain, cough), vascular system (e.g., postural hypotension, edema), CNS (e.g., confusion, headache, coma), and hemorrhagic manifestations.
- Early leukopenia followed by leukocytosis with a left shift, thrombocytopenia, elevated levels of liver enzymes, and prolonged coagulation is common.
- Pts typically die 4–14 days after infection. Survivors may have prolonged and incapacitating sequelae (e.g., arthralgia, asthenia, iridocyclitis, hearing loss, psychosis, transverse myelitis).
- Filoviruses can persist in the liver, eyes, or testicles of survivors for months after convalescence and can be reactivated (causing recurrent disease) or transmitted sexually.

## Diagnosis

High concentrations of virus in blood can be documented by antigen-capture ELISA, virus isolation, or RT-PCR. Other diagnoses that must be excluded (as they closely mimic infection with Ebola or Marburg virus) include other VHF (particularly yellow fever), falciparum malaria, typhoid fever, and gram-negative septicemia.

### TREATMENT EBOLA AND MARBURG VIRUS INFECTIONS

- Any treatment must be administered under increased safety precautions by experienced specialists using appropriate personal protective equipment (e.g., gowns, gloves, shoe covers, face shields) to prevent further transmission.
- Treatment of filovirus infections is entirely supportive as no efficacious virus-specific therapy is available.
- Several experimental therapies, including vaccines, are currently being evaluated and have demonstrated some promise in small-scale studies.

For a more detailed discussion, see Jackson AC: Rabies and Other Rhabdovirus Infections, Chap. 232, p. 1299; Kuhn JH, Peters CJ: Arthropod-Borne and Rodent-Borne Virus Infections, Chap. 233, p. 1304; and Kuhn JH: Ebolavirus and Marburgvirus Infections, Chap. 234, p. 1323, in HPIM-19.

# 105 HIV Infection and AIDS

## DEFINITION

AIDS was originally defined empirically by the Centers for Disease Control and Prevention (CDC) as "the presence of a reliably diagnosed disease that is at least moderately indicative of an underlying defect in cell-mediated immunity in the absence of any known cause for such a defect." Following the recognition of the causative virus, HIV, and the development of sensitive and specific tests for HIV infection, the definition of AIDS has undergone substantial revision. The current surveillance definition categorizes HIV-infected persons on the basis of clinical conditions associated with HIV infection and CD4+ T lymphocyte counts (Tables 226-1, and 226-2, pp. 1215 and 1216, in HPIM-19). From a practical standpoint, the clinician should view HIV disease as a spectrum of disorders ranging from primary infection, with or without the acute HIV syndrome, to the asymptomatic infected state, to advanced disease characterized by opportunisitic infections and neoplasms.

## ETIOLOGY AND TRANSMISSION

AIDS is caused by infection with the human retroviruses HIV-1 or 2. HIV-1 is the most common cause worldwide. These viruses are passed through sexual contact; through transfusion of contaminated blood or blood products; through sharing of contaminated needles and syringes among injection drug users; intrapartum or perinatally from mother to infant; or via breast milk. There is no evidence that the virus can be passed through casual or family contact or by insects such as mosquitoes. There is a definite, though small, occupational risk of infection for health care workers and laboratory personnel who work with HIV-infected specimens. The risk of transmission of HIV from an infected health care worker to his or her pts through invasive procedures is extremely low.

## EPIDEMIOLOGY

As of January 1, 2014, an estimated 1,194,039 cumulative cases of AIDS had been diagnosed in the United States; approximately 660,000 people with an AIDS diagnosis have died. However, the death rate from AIDS has decreased substantially over the past two decades, primarily due to the increased use of effective antiretroviral drugs. Currently, an estimated 1.2 million people are living with HIV infection in the United States; approximately 13% of these individuals are unaware that they are infected. An estimated 50,000 individuals are newly infected each year in the United States; this figure has remained stable for at least 15 years. Among adults and adolescents newly diagnosed with HIV infection in 2013, ~80% were men and ~20% were women. Of new HIV/AIDS diagnoses among men, ~81% were due to male-to-male sexual contact, ~10% to heterosexual contact, and ~5% to injection drug use. Among women, ~87% were due to heterosexual contact and ~12% to injection drug use. HIV infection/AIDS is a global pandemic, especially in developing countries. At the end of 2014, the estimated number of cases of HIV infection worldwide was ~36.9 million, more than two-thirds of which were in sub-Saharan Africa; ~47% of cases were in women and 2.6 million were in children. In 2014, there were 2 million new HIV infections worldwide and 1.2 million deaths.

## PATHOPHYSIOLOGY AND IMMUNOPATHOGENESIS

The hallmark of HIV disease is a profound immunodeficiency resulting from a progressive quantitative and qualitative deficiency of the subset of T lymphocytes referred to as *helper T cells* that are defined phenotypically by the expression on the

cell surface of the CD4 molecule, which serves as the primary cellular receptor for HIV. A co-receptor must be present with CD4 for efficient entry of HIV-1 into target cells. The two major co-receptors for HIV-1 are the chemokine receptors CCR5 and CXCR4. The CD4+ T lymphocyte and cells of monocyte lineage are the principal cellular targets of HIV.

## Primary Infection

Following initial transmission, the virus infects CD4+ cells, probably T lymphocytes, monocytes, or bone marrow–derived dendritic cells. Both during this initial stage and later in infection, the lymphoid system is a major site for the establishment and propagation of HIV infection. The gut-associated lymphoid tissue (GALT) plays a role in the establishment of infection and in the early depletion of memory CD4+ T cells.

Essentially all pts undergo a viremic stage during primary infection; in some pts this is associated with the "acute retroviral syndrome," a mononucleosis-like illness (see below). This phase is important in disseminating virus to lymphoid and other organs throughout the body, and it is ultimately contained only partially by the development of an HIV-specific immune response.

## Establishment of Chronic and Persistent Infection

Despite the robust immune response that is mounted following primary infection, the virus is not cleared from the body. Instead, a chronic infection develops that persists for a median time of 10 years before the untreated pt becomes clinically ill. During this period of clinical latency, the number of CD4+ T cells gradually declines, but few, if any, clinical signs and symptoms may be evident. However, active viral replication can almost always be detected by as plasma viremia and the demonstration of virus replication in lymphoid tissue. The level of steady-state viremia (referred to as the *viral set point*) at ~6 months to 1 year postinfection has important prognostic implications for the progression of HIV disease; individuals with a low viral set point at 6 months to 1 year after infection progress to AIDS more slowly than do those whose set point is very high at this time (Fig. 226-22, p. 1231, in HPIM-19).

## Advanced HIV Disease

In untreated pts or in pts in whom therapy has not controlled viral replication (see below), after some period of time (often years), CD4+ T cell counts will fall below a critical level (~200/μL) and pts become highly susceptible to opportunistic diseases. The presence of a CD4+ T cell count of <200/μL or an AIDS-defining opportunistic disease establishes a diagnosis of AIDS. Control of plasma viremia by effective antiretroviral therapy, particularly maintaining the plasma viral load consistently at <50 copies of RNA per mL, even in individuals with low CD4+ T cell counts, has dramatically increased survival in these pts, including those whose CD4+ T cell counts may not increase significantly as a result of therapy.

### IMMUNE ABNORMALITIES IN HIV DISEASE

A broad range of immune abnormalities has been documented in HIV-infected pts, resulting in varying degrees of immunodeficiency. These include both quantitative and qualitative defects in lymphocytes, and qualitative defects in monocyte/macrophage and natural killer (NK) cell function. Autoimmune phenomena also have been observed in HIV-infected individuals.

### IMMUNE RESPONSE TO HIV INFECTION

Both humoral and cellular immune responses to HIV develop soon after primary infection (see summary in Table 226-7 and Fig. 226-26, p. 1243, in HPIM-19). Humoral responses include antibodies with HIV binding and neutralizing activity, as well as antibodies participating in antibody-dependent cellular cytotoxicity

(ADCC). Cellular immune responses include the generation of HIV-specific CD4+ and CD8+ T lymphocytes, as well as NK cells and mononuclear cells mediating ADCC. CD8+ T lymphocytes may also suppress HIV replication in a noncytolytic, non-MHC-restricted manner. This effect is mediated by soluble factors such as the CC-chemokines RANTES, MIP-1α, and MIP-1β. For the most part, the natural immune response to HIV is not adequate. Broadly reacting neutralizing antibodies against HIV are not easily generated in infected individuals, and eradication of the virus from infected individuals by naturally occurring immune responses has not been reported.

## DIAGNOSIS OF HIV INFECTION

Laboratory diagnosis of HIV infection depends on the demonstration of anti-HIV antibodies and/or the detection of HIV or one of its components.

The standard screening test for HIV infection is the detection of anti-HIV antibodies using an enzyme immunoassay (EIA). This test is highly sensitive (>99.5%) and is quite specific. Most commercial EIA kits are able to detect antibodies to both HIV-1 and 2 and many also detect the HIV core antigen p24. The Western blot detects antibodies to HIV antigens of specific molecular weights. Antibodies to HIV begin to appear within 2 weeks of infection, and the period of time between initial infection and the development of detectable antibodies is rarely >3 months. Plasma p24 antigen levels rise during the first few weeks following infection, prior to the appearance of anti-HIV antibodies. A guideline for the use of these serologic tests in the diagnosis of HIV infection is depicted in Fig. 105-1.

HIV can be cultured directly from tissue, peripheral blood cells, or plasma, but this is most commonly done in a research setting. HIV genetic material can be detected using reverse transcriptase PCR (RT-PCR), branched DNA (bDNA), or nucleic acid sequence–based assay (NASBA). These tests are useful in pts with a

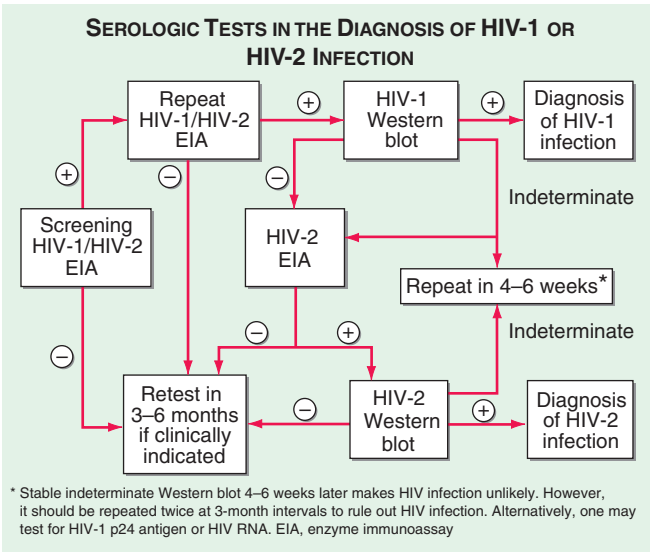


**FIGURE 105-1** Algorithm for the use of serologic tests in the diagnosis of HIV-1 or HIV-2 infection.

positive or indeterminate EIA and an indeterminate Western blot. They turn positive early in infection and will usually be positive in pts in whom serologic testing may be unreliable (such as those with hypogammaglobulinemia).

## LABORATORY MONITORING OF PTS WITH HIV INFECTION

Measurement of the CD4+ T cell count and level of plasma HIV RNA are important parts of the routine evaluation and monitoring of HIV-infected individuals. The CD4+ T cell count is a generally accepted indicator of the immunologic competence of the pt with HIV infection, and there is a close relationship between the CD4+ T cell count and the clinical manifestations of AIDS (Fig. 226-31, p. 1248, in HPIM-19). Pts with CD4+ T cell counts <200/μL are at higher risk of infection with *Pneumocystis jiroveci*. Once the count declines to <50/μL, pts are also at higher risk for developing CMV disease and infection with *Mycobacterium avium intracellulare*. Pts should have their CD4+ T cell count measured at the time of diagnosis and every 3–6 months thereafter. (Measurements may be done more frequently in pts with declining counts.) While the CD4+ T cell count provides information on the current immunologic status of the pt, the HIV RNA level predicts what will happen to the CD4+ T cell count in the near future. Measurements of plasma HIV RNA levels should be made at the time of HIV diagnosis and every 3–4 months thereafter in the untreated pt. Measurement of plasma HIV RNA is also useful in making therapeutic decisions about antiretroviral therapy (see below). Following the initiation of therapy or any change in therapy, HIV RNA levels should be monitored approximately every 4 weeks until the effectiveness of the therapeutic regimen is determined by the development of a new steady-state level of HIV RNA. During therapy, levels of HIV RNA should be monitored every 3–6 months to evaluate the continuing effectiveness of therapy.

The sensitivity of an individual's HIV virus(es) to different antiretroviral agents can be tested by either genotypic or phenotypic assays. In the hands of experts, the use of resistance testing to select a new antiretroviral regimen in pts failing their current regimen leads to a ~0.5-log greater decline in viral load compared with the efficacy of regimens selected solely on the basis of drug history. HIV resistance testing may also be of value in selecting an initial treatment regimen in geographic areas with a high prevalence of baseline resistance.

## CLINICAL MANIFESTATIONS OF HIV INFECTION

A complete discussion is beyond the scope of this chapter. The major clinical features of the various stages of HIV infection are summarized below (see also Chap. 226, HPIM-19).

### Acute HIV (Retroviral) Syndrome

Approximately 50–70% of infected individuals experience an acute syndrome following primary infection. The acute syndrome follows infection by 3–6 weeks. It can have multiple clinical features (Table 105-1), lasts 1–2 weeks, and resolves spontaneously as an immune response to HIV develops and the viral load diminishes from its peak levels. Most pts will then enter a phase of clinical latency, although an occasional pt will experience rapidly progressive immunologic and clinical deterioration.

### Asymptomatic Infection

The length of time between HIV infection and development of disease in untreated individuals varies greatly, but the median is estimated to be 10 years. HIV disease with active viral replication usually progresses during this asymptomatic period, and, in the absence of combination antiretroviral therapy (cART) CD4+ T cell counts fall. The rate of disease progression is directly correlated with plasma HIV RNA levels. Pts with high levels of HIV RNA progress to symptomatic disease faster than to those with low levels of HIV RNA.

**TABLE 105-1 CLINICAL FINDINGS IN THE ACUTE HIV SYNDROME**

| General | Neurologic |
|---|---|
| Fever | Meningitis |
| Pharyngitis | Encephalitis |
| Lymphadenopathy | Peripheral neuropathy |
| Headache/retroorbital pain | Myelopathy |
| Arthralgias/myalgias | Dermatologic |
| Lethargy/malaise | Erythematous maculopapular rash |
| Anorexia/weight loss | Mucocutaneous ulceration |
| Nausea/vomiting/diarrhea | |

***Source:*** From B Tindall, DA Cooper: *AIDS* 5:1, 1991.

## Symptomatic Disease

Symptoms of HIV disease can develop at any time during the course of HIV infection. In general, the spectrum of illness changes as the CD4+ T cell count declines. The more severe and life-threatening complications of HIV infection occur in pts with CD4+ T cell counts <200/μL. Overall, the clinical spectrum of HIV disease is constantly changing as pts live longer and new and better approaches to treatment and prophylaxis of opportunistic infections are developed. In addition, a variety of neurologic, cardiovascular, renal, metabolic, and hepatic problems are increasingly seen in pts with HIV infection and may be a direct consequence of HIV infection. The key element to treating symptomatic complications of HIV disease, whether primary or secondary, is achieving good control of HIV replication through the use of cARTand instituting primary and secondary prophylaxis as indicated. Major clinical syndromes seen in the symptomatic stage of HIV infection are summarized below.

- *Persistent generalized lymphadenopathy:* Palpable adenopathy at two or more extrainguinal sites that persists for >3 months without explanation other than HIV infection. Many pts will go on to disease progression.
- *Constitutional symptoms:* Fever persisting for >1 month, involuntary weight loss of >10% of baseline, diarrhea for >1 month in absence of explainable cause.
- *Neurologic disease:* Most common is HIV-associated neurocognitive disease (HAND); other neurologic complications include opportunistic infections such as toxoplasmosis and cryptococcal menigitis, primary CNS lymphoma, CNS Kaposi's sarcoma, aseptic meningitis, myelopathy, peripheral neuropathy, and myopathy.
- *Secondary infectious diseases:* Common secondary infectious agents include *P. jiroveci* (pneumonia), CMV (chorioretinitis, colitis, pneumonitis, adrenalitis), *Candida albicans* (oral thrush, esophagitis), *M. avium intracellulare* (localized or disseminated infection), *M. tuberculosis* (pulmonary or disseminated), *Cryptococcus neoformans* (meningitis, disseminated disease), *Toxoplasma gondii* (encephalitis, intracerebral mass lesion), herpes simplex virus (severe mucocutaneous lesions, esophagitis), *Cryptosporidium* spp. or *Isospora belli* (diarrhea), JC virus (progressive multifocal leukoencephalopathy), bacterial pathogens (pneumonia, sinusitis, skin).
- *Secondary neoplasms:* Kaposi's sarcoma (cutaneous and visceral, more fulminant course than in non-HIV-infected pts), lymphoma (primarily B cell, may be CNS or systemic). Kaposi's sarcoma, body cavity lymphomas and multicentric Castleman's disease are associated witih HHV-8 infection while the B cell lymphomas are often associated with EBV.
- *Other diseases:* A variety of organ-specific syndromes can be seen in HIV-infected pts, either as primary manifestations of the HIV infection or as complications of treatment. Diseases commonly associated with aging are also seen with an increased frequency in pts with HIV infection.

## TREATMENT HIV INFECTION (SEE ALSO CHAP. 226, HPIM-19)

General principles of pt management include counseling, psychosocial support, and screening for infections and other conditions and require comprehensive knowledge of the disease processes associated with HIV infection.

**ANTIRETROVIRAL THERAPY (SEE TABLE 105-2)** The cornerstone of medical management of HIV infection is combination antiretroviral therapy, or cART. Suppression of HIV replication is an important component in prolonging life as well as in improving the quality of life of pts with HIV infection. Data from observational studies and randomized controlled trials have demonstrated that cART is of benefit to the pt at any stage of HIV infection and is also associated with a decreased risk of transmitting infection to an uninfected partner. However, several important questions related to the treatment of HIV disease lack definitive answers. Among them are what is the best initial cART regimen, when should a given regimen be changed, and which drugs in a regimen should be changed when a change is made. The drugs that are currently licensed for the treatment of HIV infection are listed in Table 105-2. These drugs fall into four main categories: those that inhibit the viral reverse transcriptase enzyme, those that inhibit the viral protease enzyme, those that inhibit viral entry, and those that inhibit the viral integrase. In addition, more than a dozen combination drugs that combine 2 or more agents have been licensed (Table 105-2A ). There are numerous drug–drug interactions that must be taken into consideration when using antiretroviral medications.

**Nucleoside/Nucleotide Analogues** These agents act by causing premature DNA-chain termination during the reverse transcription of viral RNA to proviral DNA and should be used in combination with other antiretroviral agents. The most common usage is together with another nucleoside/nucleotide analogue and a nonnucleoside reverse transcriptase inhibitor or a protease inhibitor (see below).

**Nonnucleoside Reverse Transcriptase Inhibitors** These agents interfere with the function of HIV-1 reverse transcriptase by binding to regions outside the active site and causing conformational changes in the enzyme that render it inactive. These agents are very potent; however, when they are used as monotherapy, they result in the rapid emergence of drug-resistant mutants. Five members of this class, *nevirapine*, *delavirdine*, *efavirenz*, *etravirine*, *and rilpivirine* are currently available for clinical use. These drugs are licensed for use in combination with other antiretrovirals.

**Protease Inhibitors** These drugs are potent and selective inhibitors of the HIV-1 protease enzyme and are active in the nanomolar range. Unfortunately, as in the case of the nonnucleoside reverse transcriptase inhibitors, this potency is accompanied by the rapid emergence of resistant isolates when these drugs are used as monotherapy. Thus, the protease inhibitors should be used only in combination with other antiretroviral drugs.

**HIV Entry Inhibitors** These agents act by interfering with the binding of HIV to its receptor or co-receptor or by interfering with the process of fusion. A variety of small molecules that bind to HIV-1 co-receptors are currently in clinical trials. The first drugs in this class to be licensed are the fusion inhibitor *enfuvirtide* and the entry inhibitor *maraviroc*.

**HIV Integrase Inhibitors** These drugs interfere with the integration of proviral DNA into the host cell genome. The first agent in this class, *raltegravir*, was approved in 2007 for use in treatment-experienced pts. Two other integrase inhibitors, dolutegravir and elvitegravir, are also licensed.

**Choice of Antiretroviral Treatment Strategy** The large number of available antiretroviral agents makes the subject of antiretroviral therapy one of the more complicated in the management of HIV-infected pts.

**TABLE 105-2 ANTIRETROVIRAL DRUGS USED IN THE TREATMENT OF HIV INFECTION**

| Drug | Status | Indication | Dose in Combination | Supporting Data | Toxicity |
|---|---|---|---|---|---|
| Nucleoside or Nucleotide Reverse Transcriptase Inhibitors | | | | | |
| Zidovudine (AZT, azidothymidine, Retrovir, 3′azido-3′-deoxythymidine) | Licensed | Treatment of HIV infection in combination with other antiretroviral agents | 200 mg q8h or 300 mg bid | 19 vs 1 death in original placebo-controlled trial in 281 patients with AIDS or ARC | Anemia, granulocytopenia, myopathy, lactic acidosis, hepatomegaly with steatosis, headache, nausea, nail pigmentation, lipid abnormalities, lipoatrophy, hyperglycemia |
| | | Prevention of maternal-fetal HIV transmission | | In pregnant women with CD4+ T cell count ≥200/μL, AZT PO beginning at weeks 14–34 of gestation plus IV drug during labor and delivery plus PO AZT to infant for 6 weeks decreased transmission of HIV by 67.5% (from 25.5% to 8.3%), *n* = 363 | |
| Lamivudine (Epivir, 2′3′-dideoxy-3′-thiacytidine, 3TC) | Licensed | In combination with other antiretroviral agents for the treatment of HIV infection | 150 mg bid<br>300 mg qd | In combination with AZT superior to AZT alone with respect to changes in CD4+ T cell counts in 495 patients who were zidovudine-naïve and 477 patients who were zidovudine-experienced; overall CD4+ T cell counts for the zidovudine group were at baseline by 24 weeks, while in the group treated with zidovudine plus lamivudine, they were 10–50 cells/μL above baseline; 54% decrease in progression to AIDS/death compared with AZT alone | Flare of hepatitis in HBV-co-infected patients who discontinue drug |

| | | | | | |
|---|---|---|---|---|---|
| Emtricitabine (FTC, Emtriva) | Licensed | In combination with other antiretroviral agents for the treatment of HIV infection | 200 mg qd | Comparable to stavudine in combination with didanosine and efavirenz in 571 treatment-naïve patients; similar to 3TC in combination with AZT or stavudine + NNRTI or PI in 440 patients doing well for ≥12 weeks on a 3TC regimen | Hepatotoxicity in HBV-co-infected patients who discontinue drug, skin discoloration |
| Abacavir (Ziagen) | Licensed | For treatment of HIV infection in combination with other antiretroviral agents | 300 mg bid | Abacavir + AZT + 3TC equivalent to indinavir + AZT + 3TC with regard to viral load suppression (~60% in each group with <400 HIV RNA copies/mL plasma) and CD4+ T cell increase (~100/μL in each group) at 24 weeks | Hypersensitivity reaction In HLA-B5701+ individuals (can be fatal); fever, rash, nausea, vomiting, malaise or fatigue, and loss of appetite |
| Tenofovir (Viread) | Licensed | For use in combination with other antiretroviral agents when treatment is indicated | 300 mg qd | Reduction of ~0.6 log in HIV-1 RNA levels when added to background regimen in treatment-experienced patients | Renal, osteomalacia, flare of hepatitis in HBV-co-infected patients who discontinue drug |
| Non-Nucleoside Reverse Transcriptase Inhibitors | | | | | |
| Nevirapine (Viramune) | Licensed | In combination with other antiretroviral agents for treatment of progressive HIV infection | 200 mg/d × 14 days then 200 mg bid<br>*or*<br>400 mg extended release qd | Increase in CD4+ T cell count, decrease in HIV RNA when used in combination with nucleosides | Skin rash, hepatotoxicity |

(*Continued*)

**TABLE 105-2 ANTIRETROVIRAL DRUGS USED IN THE TREATMENT OF HIV INFECTION (*CONTINUED*)**

| Drug | Status | Indication | Dose in Combination | Supporting Data | Toxicity |
|---|---|---|---|---|---|
| Efavirenz (Sustiva) | Licensed | For treatment of HIV infection in combination with other antiretroviral agents | 600 mg qhs | Efavirenz + AZT + 3TC comparable to indinavir + AZT + 3TC with regard to viral load suppression (a higher percentage of the efavirenz group achieved viral load <50 copies/mL, but the discontinuation rate in the indinavir group was unexpectedly high, accounting for most treatment "failures"); CD4 cell increase (~140/μL in each group) at 24 weeks | Rash, dysphoria, elevated liver function tests, drowsiness, abnormal dreams, depression, lipid abnormalities, potentially teratogenic |
| Etravirine (Intelence) | Licensed | In combination with other antiretroviral agents in treatment-experienced patients whose HIV is resistant to nonnucleoside reverse transcriptase inhibitors and other antiretroviral medications | 200 mg bid | Higher rates of HIV RNA suppression to <50 copies/mL (56% vs 39%); greater increases in CD4+ T cell count (89 vs 64 cells) compared to placebo when given in combination with an optimized background regimen | Rash, nausea, hypersensitivity reactions |

| | | | | | |
|---|---|---|---|---|---|
| Rilpivirine (Edurant) | Licensed | In combination with other drugs in previously untreated patients when treatment is indicated. | 25 mg qd | Noninferior to efavirenz with respect to suppression at week 48 in 1368 treatment-naive individuals except in patients with pretherapy HIV RNA levels >100,000 where it was inferior | Nausea, dizziness, somnolence, vertigo, less CNS toxicity and rash than Efavirenz |
| Protease Inhibitors | | | | | |
| Ritonavir (Norvir) | Licensed | In combination with other antiretroviral agents for treatment of HIV infection when treatment is warranted | 600 mg bid (also used in lower doses as pharmacokinetic booster) | Reduction in the cumulative incidence of clinical progression or death from 34% to 17% in patients with CD4+ T cell count <100/μL treated for a median of 6 months | Nausea, abdominal pain, hyperglycemia, fat redistribution, lipid abnormalities, may alter levels of many other drugs, paresthesias, hepatitis |
| Atazanavir (Reyataz) | Licensed | For treatment of HIV infection in combination with other antiretroviral agents | 400 mg qd or300 mg qd + ritonavir100 mg qd when given with efavirenz | Comparable to efavirenz when given in combination with AZT + 3TC in a study of 810 treatment-naïve patients; comparable to nelfinavir when given in combination with stavudine + 3TC in a study of 467 treatment-naïve patients | Hyperbilirubinemia, PR prolongation, nausea, vomiting, hyperglycemia, fat maldistribution, rash transaminase elevations, renal stones |
| Darunavir (Prezista) | Licensed | In combination with 100 mg ritonavir for combination therapy in treatment-experienced adults | 600 mg + 100 mg ritonavir twice daily with food | At 24 weeks, patients with prior extensive exposure to antiretrovirals treated with a new combination including darunavir showed a −1.89-log change in HIV RNA levels and a 92-cell increase in CD4+ T cells compared with −0.48 log and 17 cells in the control arm | Diarrhea, nausea, headache, skin rash, hepatotoxicity, hyperlipidemia, hyperglycemia |

(*Continued*)

**TABLE 105-2 ANTIRETROVIRAL DRUGS USED IN THE TREATMENT OF HIV INFECTION (*CONTINUED*)**

| Drug | Status | Indication | Dose in Combination | Supporting Data | Toxicity |
|---|---|---|---|---|---|
| Entry Inhibitors | | | | | |
| Enfuvirtide (Fuzeon) | Licensed | In combination with other agents in treatment-experienced patients with evidence of HIV-1 replication despite ongoing anti-retroviral therapy | 90 mg SC bid | In treatment of experienced patients, superior to placebo when added to new optimized background (37% vs 16% with <400 HIV RNA copies/mL at 24 weeks; + 71 vs + 35 CD4+ T cells at 24 weeks) | Local injection reactions, hypersensitivity reactions, increased rate of bacterial pneumonia |
| Maraviroc (Selzentry) | Licensed | In combination with other antiretroviral agents in adults infected with only CCR5-tropic HIV-1 | 150–600 mg bid depending on concomitant medications (see text) | At 24 weeks, among 635 patients with CCR5-tropic virus and HIV-1 RNA >5000 copies/mL despite at least 6 months of prior therapy with at least 1 agent from 3 of the 4 antiretroviral drug classes, 61% of patients randomized to maraviroc achieved HIV RNA levels <400 copies/mL compared with 28% of patients randomized to placebo | Hepatotoxicity, nasopharyngitis, fever, cough, rash, abdominal pain, dizziness, musculoskeletal symptoms |
| Integrase Inhibitor | | | | | |
| Raltegravir (Isentress) | Licensed | In combination with other antiretroviral agents | 400 mg bid | At 24 weeks, among 436 patients with 3-class drug resistance, 76% of patients randomized to receive raltegravir achieved HIV RNA levels <400 copies/mL compared with 41% of patients randomized to receive placebo | Nausea, headache, diarrhea, CPK elevation, muscle weakness, rhabdomyolysis |

| | | | | | |
|---|---|---|---|---|---|
| Elvitegravir | Licensed | In combination with other antiretroviral agents | 1 tablet daily | Noninferior to raltegravir or atazanavir/ritonavir in treatment-experienced patients. | Diarrhea, nausea, upper respiratory infections, headache |
| Dolutegravir (Tivicay) | Licensed | In combination with other antiretroviral agents | 50 mg daily for treatment-naïve patients; 50 mg twice daily for treatment-experienced patients or those also receiving efavirenz or rifampin | Noninferior to raltegravir, superior to efavirenz or darunavir/ritonavir | Insomnia, headache, hypersensitivity reactions, hepatotoxicity |

***Abbreviations:*** ARC, AIDS-related complex; NRTIs, nonnucleoside reverse transcriptase inhibitors.

**TABLE 105-2A COMBINATION ANTIRETROVIRAL DRUGS USED IN THE TREATMENT OF HIV INFECTION**

| Drug Name | Components | Drug Name | Components |
|---|---|---|---|
| Atripla | Efavireniz, tenofovir DF (TDF), emtricitabine | Odefsey | Rilpivirine, TAF, emtricitabine |
| Combivir | Zidovudine, lamivudine | Prezcobix | Darunavir–cobicistat |
| Complera | Rilpivirine, TDF, emtricitabine | Stribild | Elvitegravir-cobicistat, TDF, emtricitabine |
| Epzicom | Abacavir, lamivudine | Triumeq | Dolutegravir, abacavir, lamivudine |
| Evotaz | Atazanavir–cobicistat | Trizivir | Abacavir, zidovudine, lamivudine |
| Genvoya | Elvitegravir-cobicistat, tenofovir alafenamide (TAF), emtricitabine | Truvada | TDF, emtricitabine |
| Kaletra | Lopinavir–ritonavir | | |

***Source:*** AIDSinfo Drug Database, https://aidsinfo.nih.gov/drugs.

**TABLE 105-3 PRINCIPLES OF THERAPY OF HIV INFECTION**

1. Ongoing HIV replication leads to immune system damage and progression to AIDS.
2. Plasma HIV RNA levels indicate the magnitude of HIV replication and the rate of CD4+ T cell destruction. CD4+ T cell counts indicate the current level of competence of the immune system.
3. Rates of disease progression differ among individuals, and treatment decisions should be individualized based on plasma HIV RNA levels and CD4+ T cell counts.
4. Maximal suppression of viral replication is a goal of therapy; the greater the suppression the less likely the appearance of drug-resistant quasispecies.
5. The most effective therapeutic strategies involve the simultaneous initiation of combinations of effective anti-HIV drugs with which the pt has not been previously treated and that are not cross-resistant with antiretroviral agents that the pt has already received.
6. The antiretroviral drugs used in combination regimens should be used according to optimum schedules and dosages.
7. The number of available drugs is limited. Any decisions on antiretroviral therapy have a long-term impact on future options for the pt.
8. Women should receive optimal antiretroviral therapy regardless of pregnancy status.
9. The same principles apply to children and adults. The treatment of HIV-infected children involves unique pharmacologic, virologic, and immunologic considerations.
10. Compliance is an important part of ensuring maximal effect from a given regimen. The simpler the regimen, the easier it is for the pt to be compliant.

***Source:*** Modified from *Principles of Therapy of HIV Infection*, USPHS, and the Henry J. Kaiser Family Foundation.

The principles of therapy for HIV infection have been articulated by a panel sponsored by the U.S. Department of Health and Human Services (Table 105-3). Treatment decisions must take into account the fact that one is dealing with a chronic infection and that complete eradication of HIV infection has not been achieved with currently available cART regimens. Thus, therapeutic decisions must take into account the balance between risks and benefits. At present most guidelines recommend cART for anyone with a diagnosis of HIV infection. In addition, one may wish to administer a 4-week course of therapy to uninfected individuals immediately following a high-risk exposure to HIV (see below).

When the decision to initiate therapy is made, the physician must decide which drugs to use in the initial regimen. The options for initial therapy most commonly in use today are (1) two nucleoside/nucleotide analogues (one of which is usually tenofovir or abacavir, and the other of which is usually lamivudine or emtricitabine) combined with an integrase inhibitor; (2) two nucleoside/nucleotide analogues and a protease inhibitor; or (3) two nucleoside/nucleotide analogues and a nonnucleoside reverse transcriptase inhibitor. There are no clear data at present on which to base a distinction between these approaches.

Following the initiation of therapy, one should expect a 1-log (tenfold) reduction in plasma HIV RNA within 1–2 months; eventually a decline in plasma HIV RNA to <50 copies/mL; and a rise in CD4+ T cell count of 100–150/μL during the first year. Failure to achieve and maintain an HIV RNA level <50 copies/mL is an

**TABLE 105-4 INDICATIONS FOR CHANGING ANTIRETROVIRAL THERAPY IN PTS WITH HIV INFECTION[a]**

| |
|---|
| Less than a 1-log drop in plasma HIV RNA by 4 weeks following the initiation of therapy |
| A reproducible significant increase (defined as threefold or greater) from the nadir of plasma HIV RNA level not attributable to intercurrent infection, vaccination, or test methodology |
| Persistently declining CD4+ T cell numbers |
| Clinical deterioration |
| Side effects |

[a]Generally speaking, a change should involve the initiation of at least two drugs felt to be effective in the given pt. The exception to this is when change is being made to manage toxicity, in which case a single substitution is reasonable.
***Source:*** *Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents,* USPHS.

indication to consider a change in therapy. Other reasons for changing therapy are listed in Table 105-4. When changing therapy because of treatment failure, it is important to attempt to provide a regimen with at least two new drugs. In the pt in whom a change is made for reasons of drug toxicity, a simple replacement of one drug is reasonable.

**Treatment of Secondary Infections and Neoplasms** Specific for each infection and neoplasm (see Chap. 226, in HPIM-19).

## Prophylaxis against Secondary Infections

(See also Table 226-11, pp. 1251–1253, in HPIM-19)

Primary prophylaxis is clearly indicated for *P. jiroveci* pneumonia (especially when CD4+ T cell counts fall to <200 cells/μL), for *M. avium* complex infections in pts with CD4+ T cell counts <50 cells/μL, and for *M. tuberculosis* infections in pts with a positive PPD or anergy if at high risk of TB. Vaccination with the influenza and pneumococcal polysaccharide vaccines is generally recommended for all pts and may need to be repeated in pts with CD4+ T cell counts <200/μL when their counts increase to >200/μL. Secondary prophylaxis, when available, is indicated for virtually every infection experienced by HIV-infected pts until they have significant immunologic recovery.

### HIV AND THE HEALTH CARE WORKER

There is a small but definite risk to health care workers of acquiring HIV infection via needle stick exposures, large mucosal surface exposures, or exposure of open wounds to HIV-infected secretions or blood products. The risk of HIV transmission after a skin puncture by an object contaminated with blood from a person with documented HIV infection is ~0.3%, compared with a 20–30% risk for hepatitis B infection from a similar incident. Postexposure prophylaxis may be effective in decreasing the likelihood of acquisition of infection through accidental exposure in the health care setting. In this regard, a U.S. Public Health Service working group has recommended that chemoprophylaxis be given as soon as possible after occupational exposure. While the precise regimen remains a subject of debate, the U.S. Public Health Service guidelines recommend a combination of two nucleoside analogue reverse transcriptase inhibitors plus a third drug given for 4 weeks for high-risk or otherwise complicated exposures. Regardless of which regimen is used, treatment should be initiated as soon as possible after exposure and take into count any available resistance data on the infecting virus.

Prevention of exposure is the best strategy and includes following universal precautions and proper handling of needles and other potentially contaminated objects.

Transmission of TB is another potential risk for all health care workers, including those dealing with HIV-infected pts. All workers should know their PPD status, which should be checked yearly.

### VACCINES

A clinical trial conducted in Thailand demonstrated moderate (31% effective) protection against acquisition of HIV infection. However, this modest degree of efficacy does not justify deployment of the vaccine; active investigation continues in the pursuit of a safe and effective vaccine against HIV, including focusing on the induction of broadly neutralizing antibodies to HIV.

### PREVENTION

Education, counseling, and behavior modification along with the consistent and correct use of condoms in risk situations remain the cornerstones of HIV prevention efforts. Avoidance of shared needle use by injection drug users (IDUs) is critical. If possible, breast-feeding should be avoided by HIV-positive women, as the virus can be transmitted to infants via this route. In societies where withholding of breast-feeding is not feasible, treatment of the mother, if possible, greatly decreases the chances of transmission. Recent studies have demonstrated the important role of medically supervised adult male circumcision in the prevention of acquisition of heterosexually transmitted HIV infection in men. In addition, pre-exposure prophylaxis with cART in men who have sex with men and in heterosexual men and women engaging in risk behaviors, has proven to be an effective means of prevention. Finally, treatment of the HIV-infected partner in heterosexual discordant couples has proved highly effective in preventing transmission of HIV to the uninfected partner.

For a more detailed discussion, see Fauci AS, Lane HC: Human Immunodeficiency Virus Disease: AIDS and Related Disorders, Chap. 226, p. 1215, in HPIM-19.

# 106 Fungal Infections

### GENERAL CONSIDERATIONS

- *Yeasts* (e.g., *Candida*, *Cryptococcus*) appear microscopically as round, budding forms; *molds* (e.g., *Aspergillus*, *Rhizopus*) appear as filamentous forms called *hyphae*; and *dimorphic fungi* (e.g., *Histoplasma*) are spherical in tissue but appear as molds in the environment.
  - *Endemic* fungi (e.g., *Coccidioides*) are not part of the normal human microbiota and infect hosts preferentially by inhalation.
  - *Opportunistic* fungi (e.g., *Candida* and *Aspergillus*) invade the host from normal sites of colonization (e.g., mucous membranes or the GI tract).

- Definitive diagnosis of any fungal infection requires histopathologic identification of the fungus invading tissue and accompanying evidence of an inflammatory response.

## ANTIFUNGAL AGENTS

### Amphotericin B (AmB)

AmB is the broadest-spectrum antifungal agent but has significant toxicities, including nephrotoxicity, fever, chills, and nausea.

- AmB has fungicidal activity and is available only for parenteral administration.
- Lipid formulations lack nephrotoxicity and infusion reactions; whether there is a clinically significant difference in efficacy between the deoxycholate and lipid formulations remains controversial.

### Azoles

The azoles' mechanism of action is inhibition of ergosterol synthesis in the fungal cell wall, resulting in fungistatic activity. Azoles cause little or no nephrotoxicity and are available in oral preparations.

- *Fluconazole:* Fluconazole is available in both oral and IV formulations, has a long half-life, and penetrates into most body fluids, including ocular fluids and CSF.
  - Toxicity is minimal but includes (usually reversible) hepatotoxicity and—at high doses—alopecia, muscle weakness, dry mouth, and metallic taste.
  - Fluconazole is useful for coccidioidal and cryptococcal meningitis and for candidemia, but it is notably ineffective against aspergillosis or mucormycosis.
  - It is effective as fungal prophylaxis in bone-marrow and high-risk liver transplant recipients.
- *Voriconazole:* Available in oral and IV formulations, voriconazole is considered the first-line agent against *Aspergillus* and has a broader spectrum than fluconazole against *Candida* species (including *C. glabrata* and *C. krusei*). It is also active against *Scedosporium* and *Fusarium*.
  - Disadvantages of voriconazole (compared to fluconazole) include multiple drug interactions, hepatotoxicity, skin rashes (including photosensitivity), visual disturbances, and the need to monitor drug levels.
  - As it is metabolized completely by the liver, dose adjustments are required in pts with liver failure. Dose adjustments for renal insufficiency are not required, but the parenteral formulation should be avoided in pts with severe renal insufficiency given the presence of cyclodextrin.
- *Itraconazole:* Available in oral and IV formulations, itraconazole is the drug of choice for mild to moderate blastomycosis and histoplasmosis. It is approved by the FDA for use in febrile neutropenic pts. Disadvantages of itraconazole include its poor penetration into CSF, the use of cyclodextrin in both the oral suspension and the IV preparation, the variable absorption of the drug in capsule form, and the need for monitoring of blood levels in pts taking capsules for disseminated mycoses.
- *Posaconazole:* Approved for prophylaxis of aspergillosis and candidiasis in high-risk immunocompromised pts, posaconazole is also effective against fluconazole-resistant *Candida* isolates and may be useful as salvage therapy for some other fungal infections.

### Echinocandins

The echinocandins, including caspofungin, anidulafungin, and micafungin, act by inhibiting the β-1,3-glucan synthase that is necessary for fungal cell wall synthesis. These agents are considered fungicidal for *Candida* and fungistatic for *Aspergillus*.

- Among the safest antifungal agents, echinocandins offer broad-spectrum fungicidal activity against all *Candida* species, and caspofungin has been efficacious as salvage therapy for aspergillosis.

- If anidulafungin or micafungin is used in combination with cyclosporine, no dose adjustment is needed for either drug.

## Flucytosine

Flucytosine has excellent CSF penetration, but development of resistance has led to its almost always being used in combination with AmB (e.g., for cryptococcal meningitis). Adverse effects include bone marrow suppression.

## Griseofulvin and Terbinafine

Griseofulvin is used primarily for ringworm infection. Terbinafine is used for onychomycosis and ringworm and is as effective as itraconazole.

## Topical Agents

Many drug classes are used for topical treatment of common fungal skin infections: azoles (e.g., clotrimazole, miconazole), polyene agents (e.g., nystatin), and other classes (e.g., ciclopirox olamine, terbinafine).

# CANDIDIASIS

## Microbiology and Epidemiology

*Candida* is a small, thin-walled, ovoid yeast that reproduces by budding and occurs in three forms in tissue: blastospores, pseudohyphae, and hyphae.

- *Candida* is ubiquitous in nature and inhabits the GI tract, the female genital tract, and the skin. Dissemination probably results from fungal entry into the bloodstream from mucosal surfaces after the organisms have multiplied to large numbers as a result of bacterial suppression by antibacterial drugs.
- *C. albicans* is common, but non-*albicans* species (e.g., *C. glabrata*, *C. krusei*, *C. parapsilosis*, *C. tropicalis*) now cause ~50% of all cases of candidemia and disseminated candidiasis.
  - *Candida* spp. represent the fourth most common blood-culture isolate from hospitalized pts in the United States.
  - Pts with a compromised immune system, pts with indwelling catheters, pts with severe burns, and neonates of low birth weight are at risk for hematogenous dissemination.

## Clinical Manifestations

The severity of candidal infections ranges from mild to life threatening, with deep organ infections being at the more severe end of the spectrum.

- *Mucocutaneous candidiasis: Thrush* is characterized by white, adherent, painless, discrete or confluent patches in the mouth, on the tongue, or in the esophagus.
  - *Vulvovaginal candidiasis* presents as pruritus, pain, and a vaginal discharge that may contain whitish "curds."
  - Other cutaneous infections include paronychia, balanitis, and intertrigo (erythematous irritation with pustules in skin folds).
  - *Chronic mucocutaneous candidiasis* is a heterogeneous infection of hair, nails, skin, and mucous membranes that persists despite therapy and is associated with a dysfunctional immune system.
- *Deeply invasive candidiasis:* These infections are most commonly due to hematogenous seeding of organs during candidemia, but they can also be due to contiguous spread of organisms after disruption of normal anatomic barriers (e.g., kidney infection associated with an indwelling urinary catheter).
  - Nearly any organ can be infected, but the brain, chorioretina, heart, and kidneys are most commonly involved. Except in neutropenic pts, the liver and spleen are less often infected.
  - Skin involvement manifests as macronodular lesions.

– Chorioretinal or skin involvement predicts a high probability of abscess formation in deep organs from generalized hematogenous seeding.

## Diagnosis

The most challenging aspect of diagnosis is determining which pts have hematogenously disseminated disease; recovery of *Candida* from sputum, urine, or peritoneal catheters may reflect colonization rather than deep infection.

- The diagnosis of *Candida* infection is established by visualization of pseudohyphae or hyphae in the presence of inflammation in appropriate clinical samples.
- The β-glucan test has a negative predictive value of ~90% and can help exclude disseminated disease.

### TREATMENT CANDIDIASIS

- *Mucocutaneous candidiasis:* Azoles are preferred; nystatin is an alternative.
  - Topical applications are appropriate when possible.
  - Oral therapy can be used for vulvovaginal infections (fluconazole, 150 mg PO as a single dose) and esophageal infections (fluconazole, 100–200 mg/d; or itraconazole, 200 mg/d).
- *Candidemia and suspected disseminated candidiasis:* All pts with candidemia should be treated with a systemic antifungal agent for at least 2 weeks after the last positive blood culture.
  - Lipid formulations of AmB, echinocandins, and fluconazole or voriconazole are all effective; no agent within a given class is clearly superior to the others.
  - The choice of antifungal drug depends on local epidemiology and susceptibility profiles.
  - Neutropenic or hemodynamically unstable pts should be treated with broader-spectrum agents (e.g., AmB, echinocandins) until the pathogen is specifically identified and a clinical response assessed.
  - Fluconazole is preferred for nonneutropenic, hemodynamically stable pts when azole resistance is not considered likely.
  - When possible, foreign materials (e.g., catheters) should be removed or replaced.
  - All pts with candidemia should undergo an ophthalmologic examination because of high rates of *Candida* endophthalmitis, which may require partial vitrectomy.
  - *Candida* endocarditis should be treated with valve removal and long-term antifungal administration (see Chap. 80).
  - *Candida* meningitis is often treated with a polyene plus flucytosine (25 mg/kg qid).
  - Successful treatment of *Candida*-infected prosthetic material (e.g., an artificial joint) nearly always requires removal of the infected material followed by long-term antifungal therapy.

## Prevention

Allogeneic stem cell and high-risk liver transplant recipients typically receive prophylaxis with fluconazole (400 mg/d). Some centers also use antifungal prophylaxis for neutropenic pts.

# ASPERGILLOSIS

## Microbiology and Epidemiology

*Aspergillus*, a mold with septate hyphae branching at 45° angles, has vast numbers of conidia (spores). It has a worldwide distribution and typically grows in decomposing

plant materials and in bedding. *A. fumigatus* is responsible for most cases of invasive aspergillosis, almost all cases of chronic aspergillosis, and most allergic syndromes.

- Inhalation is common; only intense exposures cause disease in healthy, immunocompetent individuals.
- The primary risk factors for invasive aspergillosis are profound neutropenia, glucocorticoid use, therapy with immune modulators (e.g., TNF-α inhibitors, daclizumab, rituximab), and severe liver disease.
- Pts with chronic pulmonary aspergillosis have a wide spectrum of underlying pulmonary diseases (e.g., tuberculosis, sarcoidosis).

## Clinical Manifestations

More than 80% of invasive disease cases involve the lungs; in pts who are significantly immunocompromised, virtually any organ can be affected.

- *Invasive pulmonary aspergillosis:* Pts can be asymptomatic or can present with fever, cough, chest discomfort, hemoptysis, and shortness of breath.
  - Acute and subacute forms have courses of ≤1 month and 1–3 months, respectively.
  - Early diagnosis requires a high index of suspicion, screening for circulating antigen (in leukemia), and urgent CT of the chest.
- *Invasive sinusitis:* Pts have fever, nasal or facial discomfort, and nasal discharge. The sinuses are involved in 5–10% of cases of invasive aspergillosis; sinus involvement is especially likely in leukemic pts and hematopoietic stem cell transplant recipients.
- *Disseminated aspergillosis: Aspergillus* disseminates from lung to brain, skin, thyroid, bone, and other organs, after which pts develop skin lesions and deteriorate clinically over 1–3 days, with fever and signs of mild sepsis. Blood cultures are usually negative.
  - *Cerebral aspergillosis:* Single or multiple lesions, hemorrhagic infarction, and cerebral abscess are common. The presentation can be acute or subacute, with mood changes, focal signs, seizures, and a decline in mental status. MRI is the most useful investigation.
  - *Cutaneous aspergillosis:* Dissemination of *Aspergillus* occasionally results in cutaneous features, usually an erythematous or purplish nontender area that develops into a necrotic eschar.
- *Chronic pulmonary aspergillosis:* Pts develop one or more cavities that expand over months or years, with pulmonary symptoms, fatigue, and weight loss. Pericavitary infiltrates and multiple cavities are typical. Without treatment, pulmonary fibrosis can develop.
- *Aspergilloma:* A fungal ball occurs in up to 20% of residual chest cavities ≥2.5 cm in diameter. Life-threatening hemoptysis may occur.
- *Chronic sinusitis:* Pts develop one of three presentations: a fungal ball in the maxillary sinus; chronic invasive sinusitis that is slowly destructive; or chronic granulomatous sinusitis, which is most common in the Middle East and India and is often caused by *A. flavus*.
- *Allergic bronchopulmonary aspergillosis (ABPA):* A hypersensitivity reaction leads to bronchial plugging, coughing fits, and dyspnea, primarily affecting asthmatics and pts with cystic fibrosis. Total IgE levels are usually >1000 IU/mL.

## Diagnosis

Culture, molecular testing, antigen detection, and histopathology usually confirm the diagnosis; ~40% of cases of invasive aspergillosis are diagnosed only at autopsy.

- Culture may be falsely positive (e.g., in pts with airway colonization) or falsely negative; only 10–30% of pts with invasive *Aspergillus* have a positive culture at any time.

- Galactomannan antigen testing of serum from high-risk pts is best done prospectively, as positive results precede clinical disease; false-positive results can occur (in association, for example, with certain β-lactam/β-lactamase inhibitor antibiotic combinations).
- A *halo sign* on high-resolution thoracic CT scan (a localized ground-glass appearance representing hemorrhagic infarction surrounding a nodule) suggests the diagnosis.

**TREATMENT ASPERGILLOSIS**

- See Table 106-1 for recommended treatments and doses.
  - The duration of treatment for pts with invasive aspergillosis varies from ~3 months to years, depending on the host and the response.
  - Chronic cavitary pulmonary aspergillosis probably requires treatment for life.
- Surgical treatment is important for some forms of aspergillosis (e.g., maxillary sinus fungal ball; single aspergilloma; invasive disease of bone, heart valve, brain, or sinuses).

### Outcome

Invasive aspergillosis is curable if immune reconstitution occurs, whereas allergic and chronic forms are not. The overall mortality rate is ~50% with treatment, but the disease is uniformly fatal without therapy.

## CRYPTOCOCCOSIS

### Microbiology and Epidemiology

*Cryptococcus* is a yeast-like fungus. *C. neoformans* and *C. gattii* are pathogenic for humans and can cause cryptococcosis; most clinical laboratories do not routinely distinguish between these species.

- Worldwide, there are ~1 million cases of cryptococcosis, with >600,000 deaths annually. Most cases are in pts with AIDS.
- Cryptococcosis due to *C. neoformans* is rare in the absence of impaired immunity; in contrast, *C. gattii*–related disease often occurs in immunocompetent pts.
- *C. neoformans* is found in soil contaminated with pigeon droppings, whereas *C. gattii* is associated with eucalyptus trees. Most cases are acquired via inhalation, which results in pulmonary infection.

### Clinical Manifestations

The clinical manifestations of cryptococcosis reflect the site of fungal infection, usually involving the CNS and/or the lungs.

- CNS involvement most commonly presents as chronic meningoencephalitis, with headache, fever, lethargy, sensory and memory deficits, cranial nerve paresis, visual deficits, and meningismus (absent in some cases) lasting for weeks.
- Pulmonary cryptococcosis is generally asymptomatic but can present as cough, increased sputum production, and chest pain. *Cryptococcomas* are granulomatous pulmonary masses associated with *C. gattii* infections.
- Skin lesions are common in pts with disseminated cryptococcosis and can be highly variable, including papules, plaques, purpura, vesicles, tumor-like lesions, and rashes.

### Diagnosis

Diagnosis requires the demonstration of *C. neoformans* in normally sterile tissue (e.g., positive cultures of CSF or blood).

**TABLE 106-1 TREATMENT OF ASPERGILLOSIS[a]**

| Indication | Primary Treatment | Evidence Level[b] | Precautions | Secondary Treatment | Comments |
|---|---|---|---|---|---|
| Invasive[c] | Voriconazole | AI | Drug interactions (especially with rifampin), renal failure (IV only) | AmB, caspofungin, posaconazole, micafungin | As primary therapy, voriconazole carries 20% more responses than AmB. Consider initial combination therapy with an echinocandin in non-neutropenic pts. |
| Prophylaxis | Posaconazole, itraconazole solution | AI | Diarrhea and vomiting with itraconazole, vincristine interaction | Micafungin, aerosolized AmB | Some centers monitor plasma levels of itraconazole and posaconazole. |
| Single aspergilloma | Surgery | BII | Multicavity disease: poor outcome of surgery, medical therapy preferable | Itraconazole, voriconazole, intracavity AmB | Single large cavities with an aspergilloma are best resected. |
| Chronic pulmonary[c] | Itraconazole, voriconazole | BII | Poor absorption of itraconazole capsules with proton pump inhibitors or $H_2$ blockers | Posaconazole, IV AmB, IV micafungin | Resistance may emerge during treatment, especially if plasma drug levels are subtherapeutic. |
| ABPA/SAFS | Itraconazole | AI | Some glucocorticoid interactions, including with inhaled formulations | Voriconazole, posaconazole | Long-term therapy is helpful in most cases. No evidence indicates whether therapy modifies progression to bronchiectasis/fibrosis. |

[a]For information on duration of therapy, see text.
[b]Evidence levels are those used in treatment guidelines (TJ Walsh et al: Treatment of aspergillosis: Clinical practice guidelines of the Infectious Diseases Society of America [IDSA]. Clin Infect Dis 46:327, 2008).
[c]An infectious disease consultation is appropriate for these pts.
***Note:*** The oral dose is usually 200 mg bid for voriconazole and itraconazole and 400 mg bid for posaconazole suspension. The IV dose of voriconazole for adults is 6 mg/kg twice at 12-h intervals (loading doses) followed by 4 mg/kg q12h; a larger dose is required for children and teenagers. Plasma monitoring is helpful in optimizing the dosage. Caspofungin is given as a single loading dose of 70 mg and then at 50 mg/d; some authorities use 70 mg/d for pts weighing >80 kg, and lower doses are required with hepatic dysfunction. Micafungin is given as 50 mg/d for prophylaxis and as at least 150 mg/d for treatment; this drug has not yet been approved by the FDA for this indication. AmB deoxycholate is given at a daily dose of 1 mg/kg if tolerated. Several strategies are available for minimizing renal dysfunction. Lipid-associated AmB is given at 3 mg/kg (AmBisome) or 5 mg/kg (Abelcet). Different regimens are available for aerosolized AmB, but none is FDA approved. Other considerations that may alter dose selection or route include age; concomitant medications; renal, hepatic, or intestinal dysfunction; and drug tolerability.
***Abbreviations:*** ABPA, allergic bronchopulmonary aspergillosis; AmB, amphotericin B; SAFS, severe asthma with fungal sensitization.

- India ink smear of CSF is a useful rapid diagnostic technique but may yield negative results in pts with a low fungal burden.
- Cryptococcal antigen testing of CSF and/or serum provides strong presumptive evidence for cryptococcosis; such testing often yields negative results in pulmonary cryptococcosis and is of limited utility in monitoring response to therapy.

## TREATMENT CRYPTOCOCCOSIS

- Immunocompetent pts
  - Pulmonary cryptococcosis is treated with fluconazole (200–400 mg/d) for 3–6 months.
  - Severe extrapulmonary cryptococcosis may initially require AmB (0.5–1.0 mg/kg daily for 4–6 weeks).
  - CNS disease is treated with an induction phase of AmB (0.5–1.0 mg/kg qd) followed by prolonged consolidation therapy with fluconazole (400 mg/d).
  - Meningoencephalitis is treated with AmB (0.5–1.0 mg/kg) plus flucytosine (100 mg/kg) daily for 6–10 weeks or with the same drugs at the same dosages for 2 weeks followed by fluconazole (400 mg/d) for ≥10 weeks.
- Immunosuppressed pts are treated with the same initial regimens except that maintenance therapy with fluconazole is given for a prolonged period (sometimes throughout life) to prevent relapse.
  - HIV-infected pts with CNS involvement are typically treated with AmB (0.7–1.0 mg/kg daily) plus flucytosine (100 mg/kg qd) for at least 2 weeks followed by fluconazole (400 mg/d) for 10 weeks and then by lifelong maintenance therapy with fluconazole (200 mg/d).
  - An alternative regimen involves fluconazole (400–800 mg/d) plus flucytosine (100 mg/kg qd) for 6–10 weeks followed by fluconazole (200 mg/d) as maintenance therapy.
- Newer triazoles (e.g., voriconazole, posaconazole) appear effective, but clinical experience is still limited.

# MUCORMYCOSIS

## Microbiology and Epidemiology

Mucormycosis is caused by fungi of the order Mucorales, most commonly *Rhizopus oryzae*; despite the name of the disease, *Mucor* species are only rarely the cause.

- Mucorales have characteristic wide (≥6- to 30-μm), thick-walled, ribbon-like, aseptate hyphal elements that branch at right angles.
- These ubiquitous environmental fungi primarily affect pts with diabetes, solid organ or hematopoietic stem cell transplants, prolonged neutropenia, malignancy, and deferoxamine treatment for iron overload syndromes.

## Clinical Manifestations

Mucormycosis is highly invasive and relentlessly progressive, with a mortality rate of >40%. The disease is usually categorized by the anatomic site involved.

- *Rhinocerebral mucormycosis:* In this, the most common form of the disease, pts initially have nonspecific symptoms that include eye or facial pain and facial numbness followed by the onset of conjunctival suffusion, blurry vision, and soft tissue swelling.
  - If untreated, the infection can spread from the ethmoid sinus to the orbit, affecting extraocular muscle function and being associated with proptosis and chemosis.
  - The visual appearance of infected tissue may progress from normal to erythematous to violaceous to a black necrotic eschar.

- *Pulmonary mucormycosis:* In this second most common manifestation, pts typically present with fever, dyspnea, cough, and chest pain. Angioinvasion results in necrosis, cavitation, and/or hemoptysis. Differentiation from aspergillosis is critical as treatment regimens differ; the presence of ≥10 pulmonary nodules, pleural effusion, or concomitant sinusitis makes mucormycosis more likely.
- *Cutaneous mucormycosis:* Caused by external implantation or hematogenous dissemination, necrotizing fasciitis due to mucormycosis has a mortality rate of ~80%.
- *Hematogenously disseminated mucormycosis:* Infection can disseminate from any primary site of infection to any organ but most commonly metastasizes to the brain (with a mortality rate of ~100%).

## Diagnosis

Although definitive diagnosis requires a positive culture from a sterile site, a positive culture from a nonsterile site (e.g., sputum or bronchoalveolar lavage [BAL] fluid) in a pt with a consistent clinical history should prompt treatment pending confirmation of the diagnosis.

- The fact that only ~50% of pts have positive cultures is due, in part, to the organisms' being killed by the tissue homogenization required for preparation of culture.
- The laboratory should be notified that mucormycosis is being considered so that tissue sections instead of tissue homogenates can be cultured.

### TREATMENT MUCORMYCOSIS

- The successful treatment of mucormycosis requires four steps: (1) early diagnosis; (2) reversal of underlying predisposing risk factors, if possible; (3) surgical debridement; and (4) prompt antifungal therapy.
- AmB (AmB deoxycholate, 1–1.5 mg/kg qd; or liposomal AmB, 5–10 mg/kg qd) is preferred.
  - Limited retrospective data suggest that combinations of echinocandins and liposomal AmB may be more effective.
  - Although posaconazole has in vitro activity against Mucorales, few clinical data support its use.
  - Initial clinical trials suggest that liposomal AmB combined with deferasirox (an iron chelator that is fungicidal for clinical isolates of Mucorales; 20 mg/kg PO qd for 2–4 weeks) results in improved survival rates.
  - Treatment should be continued until (1) resolution of clinical signs and symptoms of infection, (2) resolution or stabilization of residual radiographic signs of disease on serial imaging, and (3) resolution of underlying immunosuppression.

# HISTOPLASMOSIS

## Microbiology and Epidemiology

*Histoplasma capsulatum*, a dimorphic fungus, causes histoplasmosis.

- Mycelia are infectious and have microconidial and macroconidial forms. Microconidia are inhaled, reach the alveoli, and are transformed into yeasts with occasional narrow budding. A granulomatous reaction results; in pts with impaired cellular immunity, infection may disseminate.
- Histoplasmosis is the most prevalent endemic mycosis in North America and is also found in Central and South America, Africa, and Asia. In the United States, histoplasmosis is endemic in the Ohio and Mississippi river valleys.
- The fungus is found in soil, particularly that enriched by droppings of birds and bats.

## Clinical Manifestations

Depending on the intensity of exposure, the immune status of the exposed individual, and the underlying lung architecture of the host, disease can range from asymptomatic to life-threatening.

- Immunocompetent pts usually have asymptomatic or mild and self-limited disease.
  - Approximately 1–4 weeks after exposure, some pts develop a flu-like illness with fever, chills, sweats, headache, myalgia, anorexia, cough, dyspnea, and chest pain. 5–10% of pts with acute histoplasmosis develop arthralgia or arthritis, often associated with erythema nodosum.
  - Hilar or mediastinal lymphadenopathy may occur and can cause vascular or tracheoesophageal compression.
- Immunocompromised pts, who are more likely to develop progressive disseminated histoplasmosis (PDH), account for ~70% of cases.
  - The clinical spectrum ranges from a rapidly fatal course with diffuse interstitial or reticulonodular lung infiltrates, shock, and multiorgan failure to a subacute course with focal organ involvement, hepatosplenomegaly, fever, and weight loss.
  - Meningitis, oral mucosal ulcerations, GI ulcerations, and adrenal insufficiency can occur.
- Chronic cavitary histoplasmosis most often affects smokers with structural lung disease (e.g., emphysema) and presents as productive cough, dyspnea, low-grade fever, night sweats, and weight loss.

## Diagnosis

Fungal culture remains the gold standard, but cultures are often negative in less severe cases and may take up to 1 month to become positive.

- In PDH, the culture yield is highest for BAL fluid, bone marrow aspirate, and blood; cultures of sputum or bronchial washings are usually positive in chronic pulmonary histoplasmosis.
- Fungal stains of cytopathology or biopsy materials may be helpful in diagnosing PDH.
- *Histoplasma* antigen assay of body fluids (e.g., blood, urine, CSF, BAL fluid) is useful in diagnosing PDH or acute disease and in monitoring the response to treatment.
- Serology can be helpful in diagnosis but requires ≥1 month for antibody production.

### TREATMENT HISTOPLASMOSIS

- See Table 106-2 for treatment recommendations.
- Fibrosing mediastinitis, which represents a chronic fibrotic reaction to past mediastinal histoplasmosis rather than an active infection, does not respond to antifungal therapy.

# COCCIDIOIDOMYCOSIS

## Microbiology and Epidemiology

Coccidioidomycosis is caused by the two species of the dimorphic soil-dwelling fungus *Coccidioides*: *C. immitis* and *C. posadasii*. These organisms exist as branching, filamentous molds.

- Coccidioidomycosis is confined to the Western Hemisphere between the latitudes of 40°N and 40°S. The disease is highly endemic in California, Arizona, and other areas of the southwestern United States, with ~43 cases per 100,000 residents in 2011; northern Mexico and localized regions in Central and South America also account for cases of infection.

**TABLE 106-2 RECOMMENDATIONS FOR THE TREATMENT OF HISTOPLASMOSIS**

| Type of Histoplasmosis | Treatment Recommendations | Comments |
|---|---|---|
| Acute pulmonary, moderate to severe illness with diffuse infiltrates and/or hypoxemia | Lipid AmB (3–5 mg/kg per day) ± glucocorticoids for 1–2 weeks; then itraconazole (200 mg bid) for 12 weeks. Monitor renal and hepatic function. | Pts with mild cases usually recover without therapy, but itraconazole should be considered if the pt's condition has not improved after 1 month. |
| Chronic/cavitary pulmonary | Itraconazole (200 mg qd or bid) for at least 12 months. Monitor hepatic function. | Continue treatment until radiographic findings show no further improvement. Monitor for relapse after treatment is stopped. |
| Progressive disseminated | Lipid AmB (3–5 mg/kg per day) for 1–2 weeks; then itraconazole (200 mg bid) for at least 12 months. Monitor renal and hepatic function. | Liposomal AmB is preferred, but the AmB lipid complex may be used because of cost. Chronic maintenance therapy may be necessary if the degree of immunosuppression cannot be reduced. |
| Central nervous system | Liposomal AmB (5 mg/kg per day) for 4–6 weeks; then itraconazole (200 mg bid or tid) for at least 12 months. Monitor renal and hepatic function. | A longer course of lipid AmB is recommended because of the high risk of relapse. Itraconazole should be continued until cerebrospinal fluid or CT abnormalities clear. |

***Abbreviation:*** AmB, amphotericin B.

- Direct exposure to soil harboring *Coccidioides* increases risk, but infection, which results from inhalation of airborne arthroconidia, can occur without overt soil exposure and may be related to other climatic factors (e.g., periods of dryness after rainy seasons).

## Clinical Manifestations

Approximately 60% of infected pts are asymptomatic; the remaining 40% have primarily pulmonary disease characterized by fever, cough, and pleuritic chest pain.

- Primary pulmonary infection is sometimes associated with erythema nodosum, erythema multiforme, arthralgias, and arthritis.
  - A history of night sweats, profound fatigue, eosinophilia, and hilar or mediastinal lymphadenopathy suggests the disease.
  - Pneumonic complications include pulmonary nodules (resembling pulmonary malignancies) and pulmonary cavities (a thin-walled lesion in a bronchus that is associated with cough, hemoptysis, and pleuritic chest pain).
- Disseminated infection affects <1% of infected pts, most commonly pts with depressed cellular immunity and pregnant women.
  - Common sites for dissemination include bone, skin, joint, soft tissue, and meninges.
  - Pts with meningitis present with persistent headache, lethargy, confusion, mild to moderate nuchal rigidity, and CSF with lymphocytic pleocytosis and profound hypoglycorrhachia. The mortality rate is ~100% without treatment.

## Diagnosis

Clinical findings that suggest coccidioidomycosis include eosinophilia, hilar or mediastinal adenopathy on radiographic imaging, marked fatigue, and failure to improve with antibiotic therapy. Serology and culture are the primary means of diagnosis. Alert the laboratory of the possible diagnosis to avoid exposure.

- Tube-precipitin (TP) and complement-fixation (CF) assays, immunodiffusion, and an enzyme immunoassay (EIA) are available to detect IgM and IgG antibodies.
  - TP antibody does not gauge disease progression and is not found in CSF.
  - Rising CF titers in serum are associated with clinical progression, and CF antibody in CSF indicates meningitis.
  - EIA frequently yields false-positive results.
- Examination of sputum or other respiratory fluids after Papanicolaou or Gomori methenamine silver staining reveals spherules in many pts with pulmonary disease.

### TREATMENT COCCIDIOIDOMYCOSIS

- The vast majority of pts with coccidioidomycosis do not require treatment. Exceptions include the following:
  - Pts with focal primary pneumonia *and* underlying cellular immunodeficiency or prolonged symptoms (i.e., symptoms persisting for ≥2 months, night sweats occurring for >3 weeks, weight loss of >10%, a serum CF antibody titer of >1:16, and extensive pulmonary involvement apparent on CXR) should be treated with fluconazole (≥400 mg/d) or itraconazole (400–600 mg/d).
  - Pts with diffuse pulmonary disease are often treated initially with AmB (deoxycholate, 0.7–1 mg/kg IV qd; liposomal, 5 mg/kg IV qd), with a switch to prolonged therapy with an oral triazole once clinical improvement occurs.
  - Pts with chronic pulmonary disease or disseminated infection are treated with a triazole for ≥1 year. Relapse occurs in 15–30% of individuals once therapy is discontinued.
  - Pts with meningitis require lifelong triazole therapy; fluconazole is the drug of choice. If triazole therapy fails, intrathecal or intraventricular AmB may be used. Relapse occurs in 80% of pts when therapy is stopped.

# BLASTOMYCOSIS

## Microbiology and Epidemiology

*Blastomyces dermatitidis* is a dimorphic fungus that is found in the southeastern and south-central states bordering the Mississippi and Ohio river basins, in areas of the United States and Canada bordering the Great Lakes and the St. Lawrence River, and sporadically in Africa, the Middle East, and India. Infection is caused by inhalation of *Blastomyces* from moist soil rich in organic debris.

## Clinical Manifestations

Acute pulmonary infection can present as abrupt-onset fever, chills, pleuritic chest pain, myalgias, and arthralgias. However, most pts with pulmonary blastomycosis have chronic indolent pneumonia with fever, weight loss, productive cough, and hemoptysis. Skin disease is common and can present as verrucous (more common) or ulcerative lesions. Blastomycosis can include osteomyelitis in one-fourth of infections and CNS disease in ~40% of pts with AIDS.

## Diagnosis

Smears of clinical samples or cultures of sputum, bronchial washings, pus, or tissue are required for diagnosis. Antigen detection in urine and serum may help diagnose infection and monitor pts during therapy.

**TREATMENT BLASTOMYCOSIS**

- Every pt should be treated because of the high risk of dissemination.
  - For immunocompetent pts with nonsevere disease that does not involve the CNS, itraconazole (200–400 mg/d for 6–12 months) is recommended.
  - Immunocompetent pts with severe disease or CNS manifestations should be treated initially with AmB (deoxycholate, 0.7–1 mg/kg IV qd; liposomal, 3–5 mg/kg IV qd); once their clinical condition improves, therapy can be switched to itraconazole (or, for those with CNS disease, fluconazole, 800 mg/d).
  - Immunocompromised pts with any form of infection should be treated initially with AmB, with a switch to a triazole, as above, once clinical improvement has occurred.

## *MALASSEZIA* INFECTION

*Malassezia* species are components of the normal skin flora and can cause tinea (pityriasis) versicolor, round scaly patches of hypo- or hyperpigmented skin on the neck, chest, or upper arms. *M. furfur* causes catheter-related fungemia in premature neonates receiving IV lipids by central venous catheter. Topical creams and lotions for 2 weeks are effective in treating superficial *Malassezia* infections; fungemia caused by *Malassezia* species is treated with AmB or fluconazole, prompt removal of the catheter, and discontinuation of the lipid infusion.

## SPOROTRICHOSIS

### Microbiology and Epidemiology

*Sporothrix schenckii* is a dimorphic fungus found worldwide in soil, on plants, and on animals. Infection, which results from inoculation of the organism into the skin, is most common among people who participate in landscaping, gardening, or tree farming.

### Clinical Manifestations

Lymphocutaneous sporotrichosis involves secondary lesions (papules that are not very painful and often ulcerate) developing along lymphatic channels proximally from the initial site of inoculation. Other presentations include a fixed lesion (verrucous or ulcerative) at the initial site of inoculation without lymphatic spread, osteoarticular disease (chronic synovitis or septic arthritis in alcoholics), pulmonary disease (most common among pts with chronic obstructive pulmonary disease), and disseminated disease (numerous skin lesions with occasional spread to visceral organs in immunocompromised pts).

### Diagnosis

Culture of material from a skin lesion or histopathologic examination of a skin biopsy sample can confirm the diagnosis.

**TREATMENT SPOROTRICHOSIS**

- Cutaneous and lymphocutaneous sporotrichosis is treated with itraconazole (200 mg/d) until 2–4 weeks *after* lesions resolve, usually for a total of 3–6 months.
- For extracutaneous disease, itraconazole (200 mg bid for ≥12 months) can be given, but initial therapy with liposomal AmB (3–5 mg/kg qd) is more effective for life-threatening pulmonary disease or disseminated infection.

## PARACOCCIDIOIDOMYCOSIS

Paracoccidioidomycosis (South American blastomycosis) is caused by *Paracoccidioides brasiliensis*, a dimorphic fungus acquired by inhalation from environmental

sources. Acute infection occurs in young or immunocompromised pts and manifests as disseminated infection of the reticuloendothelial system. Chronic infection accounts for 90% of cases and presents primarily as progressive pulmonary disease with occasional ulcerative and nodular mucocutaneous lesions in the nose and mouth. Diagnosis relies on culture of the organism. Itraconazole (100–200 mg/d for 6–12 months) is effective, but AmB may be required for seriously ill pts.

## PENICILLIOSIS

*Penicillium marneffei* is a leading cause of opportunistic infection in pts with immunocompromise (e.g., due to AIDS) in Southeast Asia and is acquired by spore inhalation. Clinical manifestations are similar to those of disseminated histoplasmosis, with fever, fatigue, weight loss, lymphadenopathy, hepatomegaly, and skin lesions resembling molluscum contagiosum. The organism grows readily in culture and produces a distinctive red pigment. AmB is the initial treatment of choice for severely ill pts; less severe disease may be treated with itraconazole (200 mg bid for 12 weeks). Suppressive therapy with itraconazole (200 mg/d) may be indicated for pts with HIV infection or AIDS.

## FUSARIOSIS

*Fusarium* species are found worldwide in soil and on plants; inhalation, ingestion, and direct inoculation of spores can cause disease, particularly disseminated disease in immunocompromised pts. Fusariosis is angioinvasive and has clinical manifestations similar to those of aspergillosis. One difference is that painful nodular or necrotic skin lesions are extremely common with disseminated fusariosis. Blood cultures are positive in 50% of cases; the organism is difficult to differentiate from *Aspergillus* in tissue. *Fusarium* species are often resistant to antifungal agents; liposomal AmB (≥5 mg/kg qd), voriconazole (200–400 mg bid), or posaconazole (300 mg/d) is recommended. Even with treatment, mortality rates are ~50%.

## SCEDOSPORIOSIS

*Pseudallescheria boydii*, *Scedosporium apiospermum*, and *S. prolificans* are molds that are angioinvasive, causing pneumonia and widespread dissemination with abscesses (including brain abscess) in immunocompromised hosts. Most disseminated infections are fatal. These organisms are resistant to AmB, echinocandins, and some azoles, but some infections have been cured with voriconazole.

## DERMATOPHYTOSIS

See Chap. 60.

For a more detailed discussion, see Edwards JE Jr: Diagnosis and Treatment of Fungal Infections, Chap. 235, p. 1329; Hage CA, Wheat LJ: Histoplasmosis, Chap. 236, p. 1332; Ampel NM: Coccidioidomycosis, Chap. 237, p. 1334; Sullivan DC, Nolan RL III: Blastomycosis, Chap. 238, p. 1337; Casadevall A: Cryptococcosis, Chap. 239, p. 1339; Edwards JE Jr: Candidiasis, Chap. 240, p. 1342; Denning DW: Aspergillosis, Chap. 241, p. 1345; Spellberg B, Ibrahim AS: Mucormycosis, Chap. 242, p. 1350; Kauffman CA: Superficial Mycoses and Less Common Systemic Mycoses, Chap. 243, p. 1353, in HPIM-19.

# 107 *Pneumocystis* Infections

*Pneumocystis*, an opportunistic fungal pulmonary pathogen, is an important cause of pneumonia in immunocompromised hosts.

## MICROBIOLOGY

- *P. jirovecii* infects humans, whereas *P. carinii*—the original species described—infects rodents.
- Developmental stages include the small trophic form, the cyst, and the intermediate precyst stage.

## EPIDEMIOLOGY

- *Pneumocystis* is found worldwide, and most people are exposed to the organism early in life.
- Infections resulting from environmental sources and person-to-person transmission have been demonstrated; the role of airborne transmission is unclear.
- Defects in cellular and humoral immunity (e.g., due to HIV infection, malignancy, transplantation, immunosuppressive medications) predispose to *Pneumocystis* pneumonia (PCP). The incidence among HIV-infected pts is inversely related to the CD4+ T-cell count: ≥80% of cases occur at counts <200 cells/μL, and most cases develop at counts <100/μL.

## PATHOGENESIS

- The organisms are inhaled into the alveolar space, where they proliferate, provoking a mononuclear cell response. Alveoli become filled with and are damaged by proteinaceous material, with consequently increased alveolar–capillary injury and surfactant abnormalities.
- On histology, alveoli are seen to be filled with foamy, vacuolated exudates.

## CLINICAL MANIFESTATIONS

- Pts develop dyspnea, fever, and nonproductive cough.
  - HIV-infected pts often have an indolent course that presents as mild exercise intolerance or chest tightness without fever or cough. Over days to months, these pts develop the more typical symptoms of PCP.
  - Some pts with HIV infection and most pts with other types of immunosuppression have more acute disease that progresses over a few days to respiratory failure.
- Physical examination findings are nonspecific and invariably include hypoxemia. Pts may initially have a normal chest examination but later, without treatment, develop diffuse rales and signs of consolidation.
- Serum levels of LDH may be elevated because of pulmonary damage, but this finding is neither sensitive nor specific.
- CXR classically reveals bilateral diffuse interstitial infiltrates that are perihilar and symmetrical, although this finding is not specific for PCP. Cysts and pneumothoraces are common CXR findings. Chest CT shows diffuse ground-glass opacities in virtually all pts with PCP, and a normal chest CT essentially rules out the diagnosis.
- Rare cases of disseminated infection have been described, generally involving lymph nodes, spleen, and liver.

## DIAGNOSIS

- Histopathologic staining makes the definitive diagnosis.
  - Cell-wall stains (e.g., methenamine silver) are used for *Pneumocystis* cysts and Wright-Giemsa stains for the nuclei of all developmental stages.
  - Immunofluorescence with monoclonal antibodies increases diagnostic sensitivity.
- The demonstration of organisms in bronchoalveolar lavage fluid is almost 100% sensitive and specific for PCP in immunocompromised pts.
- While detection of organisms in expectorated sputum or throat swabs has very low sensitivity, detection in an induced sputum sample can be—depending on the experience of the center conducting the test—highly sensitive (up to 90%) and specific.
- DNA amplification by PCR is most sensitive but may not distinguish colonization from infection.

## TREATMENT *PNEUMOCYSTIS* INFECTIONS

- Trimethoprim-sulfamethoxazole (TMP-SMX) for 14–21 days is the regimen of choice for all pts. For doses and adverse effects of TMP-SMX and alternative regimens, see Table 107-1.
- For HIV-infected (and likely all) pts with moderate to severe cases (a room air $Pa_{O_2}$ ≤70 mmHg or a $PA_{O_2} - Pa_{O_2}$ gradient ≥35 mmHg), adjunctive glucocorticoids improve the survival rate.

**TABLE 107-1 TREATMENT OF PNEUMOCYSTOSIS (14–21 DAYS)**

| Drug(s) | Dose, Route | Adverse Effects |
|---|---|---|
| **First-Choice Agent** | | |
| TMP-SMX | TMP (5 mg/kg) plus SMX (25 mg/kg) q6–8h PO or IV (two double-strength tablets tid or qid) | Fever, rash, cytopenias, hepatitis, hyperkalemia |
| **Alternative Agents** | | |
| TMP | 5 mg/kg q6–8h PO | Hemolysis (G6PD deficiency), methemoglobinemia, rash, fever, gastrointestinal disturbances |
| ***plus*** | | |
| Dapsone | 100 mg qd PO | |
| Atovaquone | 750 mg bid PO | Rash, fever, hepatitis |
| Clindamycin | 300–450 mg q6h PO or 600 mg q6–8h IV | Hemolysis (G6PD deficiency), methemoglobinemia, neutropenia, rash |
| ***plus*** | | |
| Primaquine | 15–30 mg qd PO | |
| Pentamidine | 3–4 mg/kg qd IV | Hypotension, azotemia, cardiac arrhythmias (torsades des pointes), pancreatitis, dysglycemias, hypocalcemia, neutropenia, hepatitis |
| **Adjunctive Agent** | | |
| Prednisone or methylprednisolone | 40 mg bid × 5 d, 40 mg qd × 5 d, 20 mg qd × 11 d; PO or IV | Peptic ulcer disease, hyperglycemia, mood alteration, hypertension |

***Abbreviations:*** TMP-SMX, trimethoprim-sulfamethoxazole.

- For pts with HIV infection who present with PCP before the initiation of antiretroviral therapy (ART), ART should usually be started within the first 2 weeks of therapy for PCP.
- Pts typically do not respond to therapy for 4–8 days. Pts whose condition continues to deteriorate after 3–4 days or has not improved after 7–10 days should be reevaluated for other infectious processes and for noninfectious processes (e.g., CHF, pulmonary emboli) that may be causing pulmonary dysfunction.

## PROGNOSIS

- Factors that influence mortality risk include advanced age, high degree of immunosuppression, preexisting lung disease, low serum albumin level, need for mechanical ventilation, and development of a pneumothorax.

## PREVENTION

- The most effective method for preventing PCP is to eliminate the cause of immunosuppression (e.g., withdraw immunosuppressive therapy, treat HIV infection).
- Prophylaxis is indicated for HIV-infected pts with CD4+ T-cell counts <200/μL or a history of oropharyngeal candidiasis and for any pt with a history of PCP. Guidelines for other compromised hosts are less clear, but prophylaxis should be considered for pts receiving >20 mg of prednisone daily (or its equivalent) for ≥30 days.
- For prophylactic regimens, see Table 107-2. TMP-SMX is the drug of choice.

**TABLE 107-2 PROPHYLAXIS OF PNEUMOCYSTOSIS**

| Drug(s) | Dose, Route | Comments |
|---|---|---|
| **First-Choice Agent** | | |
| TMP-SMX | One tablet (double- or single-strength) qd PO | Incidence of hypersensitivity is high. Rechallenge for non-life-threatening hypersensitivity; consider dose-escalation protocol. |
| **Alternative Agents** | | |
| Dapsone | 50 mg bid or 100 mg qd PO | Hemolysis is associated with G6PD deficiency. |
| Dapsone *plus* Pyrimethamine *plus* Leucovorin | 50 mg qd PO; 50 mg weekly PO; 25 mg weekly PO | Leucovorin ameliorates cytopenias due to pyrimethamine. |
| Dapsone *plus* Pyrimethamine *plus* Leucovorin | 200 mg weekly PO; 75 mg weekly PO; 25 mg weekly PO | Leucovorin ameliorates cytopenias due to pyrimethamine. |
| Pentamidine | 300 mg monthly via Respirgard II nebulizer | Aerosol may cause bronchospasm. Pentamidine is probably less effective than TMP-SMX or dapsone regimens. |
| Atovaquone | 1500 mg qd PO | Requires fatty meal for optimal absorption. |

***Abbreviations:*** TMP-SMX, trimethoprim-sulfamethoxazole.

For a more detailed discussion, see Masur H, Morris A: *Pneumocystis* Infections, Chap. 244, p. 1358, in HPIM-19.

# 108 Protozoal Infections

## MALARIA

### Microbiology and Epidemiology

Six major species of *Plasmodium* cause nearly all cases of human disease: *P. falciparum*, *P. vivax*, two morphologically identical sympatric species of *P. ovale*, *P. malariae*, and *P. knowlesi*.

- *P. falciparum*, the cause of most cases of severe disease and most deaths, predominates in Africa, New Guinea, and Hispaniola.
- *P. vivax* is more common in Central America.
- *P. falciparum* and *P. vivax* are equally prevalent in South America, the Indian subcontinent, eastern Asia, and Oceania.
- *P. ovale* makes up <1% of isolates outside Africa.
- *P. malariae* is found in most areas (especially throughout sub-Saharan Africa) but is less common.
- *P. knowlesi* (the monkey malaria parasite) can reliably be identified only by molecular techniques and is present in Borneo and Southeast Asia.
- Malaria is the most important parasitic disease in humans, causing ~2000 deaths each day.

### Pathogenesis

After introduction of *sporozoites* into the bloodstream by female anopheline mosquitoes, the parasite travels to the liver and reproduces asexually to form *merozoites* that infect RBCs. The merozoites transform into *trophozoites*, feed on intracellular proteins (principally hemoglobin), multiply 6- to 20-fold every 48 h (*P. knowlesi*, 24 h; *P. malariae*, 72 h), and cause the RBCs to rupture, releasing daughter merozoites. The process then repeats.

- Some parasites develop into long-lived sexual forms called *gametocytes*, whose uptake by another female anopheline mosquito allows transmission.
- In *P. vivax* or *P. ovale* infection, dormant forms called *hypnozoites* remain in liver cells and may cause disease 3 weeks to >1 year later.
- RBCs infected with *P. falciparum* may exhibit *cytoadherence* (attachment to venular and capillary endothelium), *rosetting* (adherence to uninfected RBCs), and *agglutination* (adherence to other infected RBCs). The result is sequestration of *P. falciparum* in vital organs, with consequent underestimation (through parasitemia determinations) of parasite numbers in the body. Sequestration is central to the pathogenesis of falciparum malaria but is not evident in the other human malarias.
- In nonimmune individuals, infection triggers nonspecific host defense mechanisms such as increased splenic filtration.

- With repeated exposure to malaria, pts develop resistance to high-level parasitemia and disease but not to infection.
- Hemoglobinopathies (e.g., sickle cell disease, ovalocytosis, thalassemia) and G6PD deficiency are more common in endemic areas and protect against death from malaria.

## Clinical Manifestations

Pts initially develop nonspecific symptoms (e.g., headache, fatigue, myalgias) that are followed by fever.

- Febrile paroxysms at regular intervals are unusual and suggest infection with *P. vivax* or *P. ovale*.
- Splenomegaly, hepatomegaly, mild anemia, and jaundice may develop.
- The diagnosis of severe falciparum malaria requires one or more of the following: impaired consciousness/coma, severe normocytic anemia, renal failure, pulmonary edema, ARDS, circulatory shock, DIC, spontaneous bleeding, acidosis, hemoglobinuria, jaundice, repeated generalized convulsions, and a parasitemia level of >5%.
  - Cerebral malaria manifests as diffuse symmetric encephalopathy, typically without focal neurologic signs.
  - Coma is an ominous sign associated with mortality rates of ~20%.
- Pregnant women have unusually severe illness. Premature labor, fetal distress, stillbirth, and delivery of low-birth-weight infants are common.
- Tropical splenomegaly (hyperreactive malarial splenomegaly) may result as a chronic complication of malaria and is characterized by massive splenomegaly, hepatomegaly, and an abnormal immunologic response to infection.

## Diagnosis

Although antibody-based diagnostic tests are being used with increasing frequency, demonstration of asexual forms of the parasite on peripheral-blood smears is required for diagnosis.

- Thick and thin smears should be examined; thick smears and the less sensitive thin smears detect parasitemia levels as low as 0.001% and <0.05%, respectively.
- If the level of clinical suspicion is high and smears are initially negative, they should be repeated q12–24h for 2 days.
- Other laboratory findings generally include normochromic, normocytic anemia; elevated inflammatory markers; and thrombocytopenia (~$10^5$/μL).

## TREATMENT MALARIA

- See Table 108-1 for treatment regimens. IV artesunate is approved by the US Food and Drug Administration for emergency use against severe malaria through the Centers for Disease Control and Prevention (CDC) (Malaria Hotline: 855-856-4713; Emergency Operations Center [after hours]: 770-488-7100).
- Pts receiving quinidine should undergo cardiac monitoring; a total plasma level of >8 μg/mL, increased QT intervals (>0.6 s), or QRS widening by >25% is an indication for slowing the infusion rate.
- Exchange transfusions can be considered for severely ill pts, although indications for their use are not yet agreed upon.
- All pts with severe malaria should receive a continuous infusion of dextrose. Unconscious pts should have blood glucose levels measured q4–6h.
- Parasite counts and hematocrits for pts with severe malaria and pts with uncomplicated disease should be measured q6–12h and q24h, respectively.
- Primaquine (0.5 mg of base/kg for 14 days) eradicates persistent liver stages and prevents relapse in *P. vivax* or *P. ovale* infection. G6PD deficiency must be ruled out before treatment.

**TABLE 108-1 REGIMENS FOR THE TREATMENT OF MALARIA[a]**

| Type of Disease or Treatment | Regimen(s) |
|---|---|
| **Uncomplicated Malaria** | |
| Known chloroquine-sensitive strains of *Plasmodium vivax*, *P. malariae*, *P. ovale*, *P. knowlesi*, *P. falciparum*[b] | Chloroquine (10 mg of base/kg stat followed by 5 mg/kg at 12, 24, and 36 h or by 10 mg/kg at 24 h and 5 mg/kg at 48 h)<br>***or***<br>Amodiaquine (10–12 mg of base/kg qd for 3 days) |
| Radical treatment for *P. vivax or P. ovale* infection | In addition to chloroquine or amodiaquine as detailed above, primaquine (0.5 mg of base/kg qd in tropical regions and 0.25 mg/kg for temperate-origin *P. vivax*) should be given for 14 days to prevent relapse. In mild G6PD deficiency, 0.75 mg of base/kg should be given once weekly for 8 weeks. Primaquine should not be given in severe G6PD deficiency. |
| Sensitive *P. falciparum* malaria[c] | Artesunate[d] (4 mg/kg qd for 3 days) *plus* sulfadoxine (25 mg/kg)/pyrimethamine (1.25 mg/kg) as a single dose<br>***or***<br>Artesunate[d] (4 mg/kg qd for 3 days) *plus* amodiaquine (10 mg of base/kg qd for 3 days)[e] |
| Multidrug-resistant *P. falciparum* malaria | Either artemether-lumefantrine[d] (1.5/9 mg/kg bid for 3 days with food)<br>***or***<br>Artesunate[d] (4 mg/kg qd for 3 days) *plus* mefloquine (24–25 mg of base/kg—either 8 mg/kg qd for 3 days or 15 mg/kg on day 2 and then 10 mg/kg on day 3)[e]<br>***or***<br>Dihydroartemisinin-piperaquine[d] (2.5/20 mg/kg qd for 3 days) |
| Second-line treatment/ treatment of imported malaria | Either artesunate[d] (2 mg/kg qd for 7 days) or quinine (10 mg of salt/kg tid for 7 days) *plus 1 of the following 3:*<br>1. Tetracycline[f] (4 mg/kg qid for 7 days)<br>2. Doxycycline[f] (3 mg/kg qd for 7 days)<br>3. Clindamycin (10 mg/kg bid for 7 days)<br>***or***<br>Atovaquone-proguanil (20/8 mg/kg qd for 3 days with food) |
| **Severe Falciparum Malaria**[g] | |
| | Artesunate[d] (2.4 mg/kg stat IV followed by 2.4 mg/kg at 12 and 24 h and then daily if necessary)[h]<br>***or, if unavailable,***<br>Artemether[d] (3.2 mg/kg stat IM followed by 1.6 mg/kg qd)<br>***or, if unavailable,*** |

(*Continued*)

**TABLE 108-1 REGIMENS FOR THE TREATMENT OF MALARIA[a] (*CONTINUED*)**

| Type of Disease or Treatment | Regimen(s) |
|---|---|
| | Quinine dihydrochloride (20 mg of salt/kg[i] infused over 4 h, followed by 10 mg of salt/kg infused over 2–8 h q8h[j])<br>***or, if unavailable,***<br>Quinidine (10 mg of base/kg[i] infused over 1–2 h, followed by 1.2 mg of base/kg per hour[j] with electrocardiographic monitoring) |

[a]In endemic areas, except in pregnant women and infants, a single dose of primaquine (0.25 mg of base/kg) should be added as a gametocytocide to all falciparum malaria treatments to prevent transmission. This addition is considered safe even in G6PD deficiency.
[b]Very few areas now have chloroquine-sensitive *P. falciparum* malaria (Fig. 248-2 in HPIM-19).
[c]In areas where the partner drug to artesunate is known to be effective.
[d]Artemisinin derivatives are not readily available in some temperate countries.
[e]Fixed-dose coformulated combinations are available. The World Health Organization now recommends artemisinin combination regimens as first-line therapy for falciparum malaria in all tropical countries and advocates use of fixed-dose combinations.
[f]Tetracycline and doxycycline should not be given to pregnant women or to children <8 years of age.
[g]Oral treatment should be substituted as soon as the pt recovers sufficiently to take fluids by mouth.
[h]Artesunate is the drug of choice when available. The doses in children weighing <20 kg should be 3 mg/kg. The data from large studies in Southeast Asia showed a 35% lower mortality rate than with quinine, and very large studies in Africa showed a 22.5% reduction in mortality rate compared with quinine.
[i]A loading dose should not be given if therapeutic doses of quinine or quinidine have definitely been administered in the previous 24 h. Some authorities recommend a lower dose of quinidine.
[j]Infusions can be given in 0.9% saline and 5–10% dextrose in water. Infusion rates for quinine and quinidine should be carefully controlled.

## Personal Protection Measures

Measures that can protect persons against infection include avoidance of mosquito exposure, with particular caution at peak feeding times (dusk to dawn); use of insect repellents containing DEET (10–35%) or (if DEET is unacceptable) picaridin (7%); suitable clothing; and insecticide-impregnated bed nets.

## Chemoprophylaxis

See Table 108-2 for prophylaxis options.

- Mefloquine is the only drug advised for pregnant women traveling to areas with drug-resistant malaria and is generally considered safe in the second and third trimesters; data regarding use in the first trimester, although limited, are reassuring.

**TABLE 108-2 DRUGS USED IN THE PROPHYLAXIS OF MALARIA**

| Drug | Usage | Adult Dose | Pediatric Dose | Comments |
|---|---|---|---|---|
| Atovaquone-proguanil (Malarone) | Prophylaxis in areas with chloroquine- or mefloquine-resistant *Plasmodium falciparum* | One adult tablet PO[a] | 5–8 kg: ½ pediatric tablet[b] daily<br>≥8–10 kg: ¾ pediatric tablet daily<br>≥10–20 kg: One pediatric tablet daily<br>≥20–30 kg: Two pediatric tablets daily<br>≥30–40 kg: Three pediatric tablets daily<br>≥40 kg: One adult tablet daily | Begin 1–2 days before travel to malarious areas. Take daily at the same time each day while in the malarious areas and for 7 days after leaving such areas. Atovaquone-proguanil is contraindicated in persons with severe renal impairment (creatinine clearance rate <30 mL/min). In the absence of data, it is not recommended for children weighing <5 kg, pregnant women, or women breast-feeding infants weighing <5 kg. Atovaquone-proguanil should be taken with food or a milky drink. |
| Chloroquine phosphate (Aralen and generic) | Prophylaxis only in areas with chloroquine-sensitive *P. falciparum*[c] or areas with *P. vivax* only | 300 mg of base (500 mg of salt) PO once weekly | 5 mg/kg of base (8.3 mg of salt/kg) PO once weekly, up to maximum adult dose of 300 mg of base | Begin 1–2 weeks before travel to malarious areas. Take weekly on the same day of the week while in the malarious areas and for 4 weeks after leaving such areas. Chloroquine phosphate may exacerbate psoriasis. |
| Doxycycline (many brand names and generic) | Prophylaxis in areas with chloroquine- or mefloquine-resistant *P. falciparum*[c] | 100 mg PO qd (except in pregnant women; see Comments) | ≥8 years of age: 2 mg/kg, up to adult dose | Begin 1–2 days before travel to malarious areas. Take daily at the same time each day while in the malarious areas and for 4 weeks after leaving such areas. Doxycycline is contraindicated in children <8 years of age and in pregnant women. |
| Hydroxychloroquine sulfate (Plaquenil) | An alternative to chloroquine for primary prophylaxis only in areas with chloroquine-sensitive *P. falciparum*[c] or areas with *P. vivax* only | 310 mg of base (400 mg of salt) PO once weekly | 5 mg of base/kg (6.5 mg of salt/kg) PO once weekly, up to maximum adult dose of 310 mg of base | Begin 1–2 weeks before travel to malarious areas. Take weekly on the same day of the week while in the malarious areas and for 4 weeks after leaving such areas. Hydroxychloroquine may exacerbate psoriasis. |

| | | | | |
|---|---|---|---|---|
| Mefloquine (Lariam and generic) | Prophylaxis in areas with chloroquine-resistant *P. falciparum*[c] | 228 mg of base (250 mg of salt) PO once weekly | ≤9 kg: 4.6 mg of base/kg (5 mg of salt/kg) PO once weekly<br>10–19 kg: ¼ tablet once weekly<br>20–30 kg: ½ tablet once weekly<br>31–45 kg: ¾ tablet once weekly<br>≥46 kg: 1 tablet once weekly | Begin 1–2 weeks before travel to malarious areas. Take weekly on the same day of the week while in the malarious areas and for 4 weeks after leaving such areas. Mefloquine is contraindicated in persons allergic to this drug or related compounds (e.g., quinine and quinidine) and in persons with active or recent depression, generalized anxiety disorder, psychosis, schizophrenia, other major psychiatric disorders, or seizures. Use with caution in persons with psychiatric disturbances or a history of depression. Mefloquine is not recommended for persons with cardiac conduction abnormalities. |
| Primaquine | For prevention of malaria in areas with mainly *P. vivax* | 30 mg of base (52.6 mg of salt) PO qd | 0.5 mg of base/kg (0.8 mg of salt/kg) PO qd, up to adult dose; should be taken with food | Begin 1–2 days before travel to malarious areas. Take daily at the same time each day while in the malarious areas and for 7 days after leaving such areas. Primaquine is contraindicated in persons with G6PD deficiency. It is also contraindicated during pregnancy and in lactation unless the infant being breast-fed has a documented normal G6PD level. |
| | Used for presumptive antirelapse therapy (terminal prophylaxis) to decrease risk of relapses of *P. vivax* and *P. ovale* | 30 mg of base (52.6 mg of salt) PO qd for 14 days after departure from the malarious area | 0.5 mg of base/kg (0.8 mg of salt/kg), up to adult dose, PO qd for 14 days after departure from the malarious area | This therapy is indicated for persons who have had prolonged exposure to *P. vivax* and/or *P. ovale*. It is contraindicated in persons with G6PD deficiency as well as during pregnancy and in lactation unless the infant being breast-fed has a documented normal G6PD level. |

[a]An adult tablet contains 250 mg of atovaquone and 100 mg of proguanil hydrochloride.
[b]A pediatric tablet contains 62.5 mg of atovaquone and 25 mg of proguanil hydrochloride.
[c]Very few areas now have chloroquine-sensitive malaria (Fig. 248-2 in HPIM-19).
***Source:*** CDC: *www.cdc.gov/malaria/travelers/drugs.html.*

# BABESIOSIS

## Microbiology

Babesiosis is caused by intraerythrocytic protozoa of the genus *Babesia*. *B. microti*, the cause of most cases, is the etiologic agent in the northeastern and upper midwestern United States, and *B. duncani* is responsible for disease on the West Coast. *B. divergens* causes disease in Europe. The deer tick (*Ixodes scapularis*) transmits *B. microti*.

## Epidemiology

In the United States, infections occur most frequently in the Northeast and upper Midwest. In 2011, >1100 cases were reported in the United States, with ~75% of cases presenting in July and August; this number is probably an underestimate, given that most pts experience a mild and self-limiting disease and may not seek medical attention.

## Clinical Manifestations

Most pts develop a mild illness, but immunosuppressed pts may have more severe disease.

- After an incubation period of 1–4 weeks, pts gradually develop fevers, fatigue, and weakness. Other symptoms may include chills, sweats, myalgias, arthralgias, headache, and—less often—photophobia, shortness of breath, and abdominal pain.
- Severe babesiosis is associated with parasitemia levels of >4%.
  - Risk factors include an age of >50 years, male gender, asplenia, HIV infection/AIDS, malignancy, hemoglobinopathy, and immunosuppression.
  - Complications include ARDS, DIC, CHF, renal failure, and splenic infarcts and rupture.
  - The fatality rate is 5–9% among all hospitalized pts and 20% among immunocompromised pts.

## Diagnosis

Giemsa-stained thin smears identify intraerythrocytic *Babesia* parasites, which appear round, pear-shaped, or ameboid.

- Ring forms resembling *P. falciparum* but without pigment are most common.
- Tetrads ("Maltese crosses")—formed by four budding merozoites—are pathognomonic for *B. microti* and other small *Babesia* species.
- PCR and serology can also be used for diagnostic purposes.

## TREATMENT BABESIOSIS

- Mild to moderate illness should be treated with atovaquone (750 mg PO q12h) plus azithromycin (500 mg PO on day 1 followed by 250 mg/d PO) for 7–10 days.
  - Clindamycin plus quinine is equally effective but not as well tolerated.
- Severe disease should be treated with clindamycin (300–600 mg q6h IV or 600 mg q8h PO) plus quinine (650 mg q6–8h PO) for 7–10 days.
  - High-dose azithromycin (600–1000 mg/d) plus atovaquone is an alternative.
  - Consider exchange transfusion in pts with high-level parasitemia (>10%); hemoglobin levels of ≤10 g/dL; or pulmonary, hepatic, or renal compromise.
  - Immunocompromised pts generally need longer courses of treatment (e.g., 6 weeks), with at least 2 weeks of therapy after parasites are no longer detected on blood smear.
- *B. duncani* and *B. divergens* infections can be treated with IV clindamycin and quinine for 7–10 days.

# LEISHMANIASIS

## Microbiology

*Leishmania* species are extracellular, flagellated promastigotes while dwelling in their sandfly vector, but are obligate intracellular, nonflagellated amastigotes while living in vertebrate hosts, including humans.

- Organisms of the *L. donovani* complex usually cause visceral leishmaniasis and are present in Asia, the Middle East, the horn of Africa, the Mediterranean, and Central and South America.
- *L. tropica*, *L. major*, and *L. aethiopica* cause Old World cutaneous leishmaniasis and are present in Asia and in northern and sub-Saharan Africa.
- The *L. mexicana* complex causes New World cutaneous leishmaniasis and is present in Central America and northern South America.

## Epidemiology

More than 1.5 million cases of leishmaniasis occur annually worldwide, of which 0.7–1.2 million are cutaneous and 200,000–400,000 are visceral.

## Clinical Manifestations

*Visceral leishmaniasis (kala-azar):* Pts most commonly present with an abrupt onset of moderate- to high-grade fever associated with rigor and chills.

- Splenomegaly, hepatomegaly, and (except in the Indian subcontinent) lymphadenopathy are common.
- Leukopenia, anemia, thrombocytopenia, a polyclonal increase in serum immunoglobulins, and hepatic transaminitis are common.
- Up to 50% of pts in India, East Africa, and the Sudan may develop hypopigmented skin lesions (post–kala-azar dermal leishmaniasis) concurrent with or after cure of visceral leishmaniasis. In some cases, these pts may require unusually long treatment courses.

*Cutaneous leishmaniasis:* After an incubation period of days or weeks, papular lesions progress to nodules that ulcerate over weeks or months. Lesions usually heal spontaneously after 2–15 months.

- The margins of the ulcer are raised and indurated, and the base of the ulcer is usually painless.
- Disease due to *L. tropica* may involve *leishmaniasis recidivans*: development of new scaly, erythematous papules in the area of a healed sore.

*Mucosal leishmaniasis:* This disfiguring sequela of New World cutaneous leishmaniasis results from dissemination of parasites from the skin to the naso-oropharyngeal mucosa.

- Disease may occur 1–5 years after the initial cutaneous episode.
- Persistent nasal congestion and bleeding are followed by progressive ulcerative destruction.
- These lesions do not resolve spontaneously.

## Diagnosis

- *Visceral leishmaniasis:* Identification of amastigotes in smears of tissue aspirates is the gold standard for diagnosis.
  - The sensitivity of splenic smears is >95%, but splenic aspiration may be very dangerous; smears of bone marrow and lymph node aspirates have sensitivities of 60–85% and 50%, respectively.

- Several serologic techniques, including a rapid test, are available and offer good sensitivity and specificity.

- *Cutaneous and mucosal leishmaniasis:* Diagnosis is made by microscopy, culture, or PCR examination of aspirates and biopsy specimens from skin lesions and lymph nodes.

**TREATMENT LEISHMANIASIS**

- *Visceral leishmaniasis:* The pentavalent antimonial ($Sb^V$) compounds sodium stibogluconate and meglumine antimoniate (20 mg/kg per day IV or IM for 28–30 days) are the first-line therapeutic agents and provide cure rates >90%.
  - Amphotericin B (AmB; either deoxycholate or a lipid formulation) is recommended in areas with $Sb^V$ resistance (e.g., northeastern India) or if initial $Sb^V$ therapy fails.
  - Paromomycin and the oral agent miltefosine have been approved for the treatment of visceral leishmaniasis in India.
  - Liposomal AmB is the drug of choice for HIV-infected pts.
- *Cutaneous leishmaniasis:* Although lesions generally resolve spontaneously, treatment may be needed if lesions spread or persist.
  - Topical agents can be effective for a few small lesions. Systemic treatment is needed for multiple lesions; lesions on the face, hands, or joints; and lesions of New World cutaneous leishmaniasis.
  - Administration of $Sb^V$ (20 mg/kg daily for 20 days) constitutes the most effective treatment. Exceptions include disease due to *L. guyanensis* (pentamidine isethionate preferred) or *L. aethiopica* (paromomycin preferred).
- *Mucosal leishmaniasis:* $Sb^V$ (20 mg/kg for 30 days) is recommended.
  - Pts require long-term follow-up, and neither relapse nor failure of therapy is uncommon.
  - AmB and potentially miltefosine can be used in cases of relapse or therapy failure.

## TRYPANOSOMIASIS

### CHAGAS DISEASE

#### Microbiology and Pathology

*Trypanosoma cruzi* causes Chagas disease (American trypanosomiasis) and is transmitted among mammalian hosts by hematophagous reduviid bugs. Organisms disseminate through the lymphatics and the bloodstream, often parasitizing muscles particularly heavily.

#### Epidemiology

*T. cruzi* is found exclusively in the Americas and causes disease mostly among the poor in rural areas of Mexico and Central and South America. An estimated 8 million people are chronically infected, with 14,000 deaths annually.

#### Clinical Manifestations

An indurated area of erythema and swelling (the *chagoma*) with local lymphadenopathy develops ≥1 week after parasite invasion and generally precedes malaise, fever, anorexia, and edema of the face and lower extremities.

- *Romaña's sign*—unilateral painless edema of the palpebrae and periocular tissues—occurs when the conjunctiva is the portal of entry.
- Acute disease resolves spontaneously within 4–8 weeks, and pts enter an asymptomatic phase of chronic infection.

- Symptomatic chronic disease becomes apparent years or even decades after initial infection.
  - Cardiac symptoms are common and include rhythm disturbances, segmental or dilated cardiomyopathy, and thromboembolism.
  - Pts can develop megaesophagus and suffer from dysphagia, odynophagia, chest pain, and regurgitation.
  - Megacolon may develop, leading to abdominal pain, chronic constipation, fecaloma formation, obstruction, and volvulus.

## Diagnosis

Microscopic examination of fresh anticoagulated blood, the buffy coat, or blood smears may reveal organisms in cases of acute Chagas disease. Serology has no major diagnostic role in acute disease, but PCR assays can be helpful. Chronic Chagas disease is diagnosed by detection of specific IgG antibodies. Given the frequency of false-positive results, a positive result should be confirmed by at least two additional assays.

### TREATMENT CHAGAS DISEASE

- Only two drugs—nifurtimox and benznidazole—are available to treat Chagas disease; neither is entirely effective.
  - Nifurtimox (8–10 mg/kg qd in four divided oral doses for 90–120 days) reduces symptom duration, parasitemia level, and mortality rate but offers a parasitologic cure in only ~70% of cases.
  - Benznidazole (5 mg/kg qd in two or three divided doses for 60 days) is the drug of choice in Latin America and may provide parasitologic cure rates >90%.
  - Both drugs have a number of side effects.
- Treatment of chronic Chagas disease is controversial; no adequate studies demonstrate efficacy. However, a panel of experts convened by the CDC recommends that pts <50 years old with presumably long-standing *T. cruzi* infection be offered treatment.

# SLEEPING SICKNESS

## Microbiology and Epidemiology

Sleeping sickness (human African trypanosomiasis, HAT) is caused by parasites of the *T. brucei* complex and is transmitted via tsetse flies.

- *T. b. rhodesiense* causes the East African form and *T. b. gambiense* the West African form; these two forms are epidemiologically and clinically distinct illnesses.
- Humans are the only reservoir for *T. b. gambiense*; infection occurs primarily in rural populations and rarely develops in tourists. *T. b. rhodesiense* has reservoirs in antelope and cattle; tourists can be infected when visiting areas where infected game and vectors are present.
- HAT was nearly eradicated in the mid-1960s, resurged in the 1990s, and is now decreasing in incidence because of renewed control activities. Fewer than 10,000 cases were reported to the World Health Organization in 2009.

## Clinical Manifestations

A trypanosomal chancre develops ~1 week after the bite of an infected tsetse fly. A systemic febrile illness without involvement of the CNS (stage 1 disease) then evolves as the parasites disseminate through the bloodstream and lymphatics.

- Bouts of high-grade fever lasting several days are separated by afebrile periods. Malaise, headache, arthralgias, hepatosplenomegaly, and other nonspecific manifestations can develop.

- Lymphadenopathy with discrete, rubbery, nontender nodes is prominent in *T. b. gambiense* disease. Enlargement of nodes of the posterior cervical triangle (*Winterbottom's sign*) is a classic manifestation.
- With CNS invasion (stage 2 disease), pts develop progressive indifference and daytime somnolence, a state that sometimes alternates with restlessness and insomnia. Extrapyramidal signs may include choreiform movements, tremors, and fasciculations; ataxia is common.
- Disease due to *T. b. rhodesiense* is more acute and, if untreated, can lead to death in weeks to months; in contrast, disease due to *T. b. gambiense* can smolder for months or years.

### Diagnosis

Examination of fluid from the chancre, thin or thick blood smears, buffy coats, lymph node aspirates, bone marrow biopsy specimens, or CSF can reveal the parasite.

- Parasitemia is more likely in stage 1 than in stage 2 disease and in pts infected with *T. b. rhodesiense* rather than *T. b. gambiense.*
- CSF should be examined whenever the diagnosis is being considered. Increased opening pressure, increased protein level, and increased mononuclear cell counts are common.

**TREATMENT SLEEPING SICKNESS**

Stage 1 disease

- *T. b. rhodesiense:* suramin (a test dose of 100–200 mg followed by 20 mg/kg IV on days 1, 5, 12, 18, and 26)
  - Hypersensitivity reactions and renal damage are the most important adverse effects.
  - A urinalysis should be done before each dose. Treatment should be discontinued if hematuria or increasing proteinuria is found or if casts are present in the sediment.
- *T. b. gambiense:* pentamidine (4 mg/kg daily IM or IV for 10 days)
  - Serious adverse reactions include nephrotoxicity, abnormal liver function, neutropenia, hypoglycemia, and sterile abscesses.
  - Suramin is an alternative agent.

Stage 2 disease

- *T. b. rhodesiense:* melarsoprol (2.2 mg/kg IV daily for 10 days). To reduce reactive encephalopathy, administer prednisolone (1 mg/kg) with each dose of melarsoprol.
- *T. b. gambiense:* Eflornithine (100 mg/kg IV qid for 2 weeks) is the first-line agent. Either melarsoprol (2.2 mg/kg qd IV for 10 days) or nifurtimox (5 mg/kg PO tid for 7 days) plus eflornithine (100 mg/kg IV bid for 7 days) is an alternative.

## TOXOPLASMOSIS

### Microbiology and Epidemiology

Toxoplasmosis is caused by the intracellular parasite *Toxoplasma gondii*; cats and their prey are the definitive hosts. The primary route of transmission to humans is ingestion of tissue cysts from soil, food (e.g., undercooked meat), or water contaminated by cat feces.

- Roughly one-third of women who contract *T. gondii* during pregnancy transmit the parasite to the fetus, with a 65% risk of transmission if maternal infection is acquired in the third trimester.

- In the United States and most European countries, seroconversion rates increase with age and exposure; 10–67% of persons >50 years old are seropositive.

## Pathogenesis

Both humoral and cellular immunity are important, but subclinical infection commonly persists for the pt's lifetime. Immunocompromised hosts lack factors required to control infection; the consequences are progressive focal destruction and organ failure.

## Clinical Manifestations

Disease in immunocompetent hosts is usually asymptomatic (80–90% of cases) and self-limited and does not require therapy. In contrast, immunocompromised pts, including newborns, can develop severe infections typically involving the CNS.

- In the minority of immunocompetent pts who develop symptoms of acute infection, cervical lymphadenopathy is the most common finding; nodes are nontender and discrete. Generalized lymphadenopathy, fever <40°C (104°F), headache, malaise, and fatigue occur in 20–40% of pts. Clinical disease usually resolves within several weeks, although lymphadenopathy may persist for several months.
- Immunocompromised pts develop acute toxoplasmosis through reactivation of latent infection in 95% of cases; the remainder of cases are due to new acquisition of parasites.
  - CNS findings include encephalopathy, meningoencephalitis, and mass lesions. Pts may develop changes in mental status (75%), fever (10–72%), seizures (33%), headaches (56%), and focal neurologic findings (60%). The brainstem, basal ganglia, pituitary gland, and corticomedullary junction are most often involved.
- Multiple organs (e.g., lungs, GI tract, skin, eyes, heart, liver) can be affected.
  - *Toxoplasma* pneumonia is often confused with *Pneumocystis* pneumonia because of an overlapping pt population and similar clinical presentations (i.e., fever, dyspnea, and nonproductive cough rapidly progressing to respiratory failure).
- Congenital infection, which affects 400–4000 infants each year in the United States, may initially be asymptomatic but can result in reactivation and clinical disease (e.g., chorioretinitis) decades later.
- *Toxoplasma* causes ~35% of all cases of chorioretinitis in the United States and Europe. Blurred vision, macular involvement with loss of central vision, scotoma, photophobia, and eye pain are manifestations of infection. On examination, yellow-white cotton-like patches with indistinct margins of hyperemia are seen. Older lesions appear as white plaques with distinct borders and black spots.

## Diagnosis

Culture of the parasite is difficult and can be done only at specialized laboratories. Serology is the primary method of diagnosis.

- Results of IgM, IgG, and antibody avidity levels can be combined to help determine when infection may have occurred. (Of note, IgM can persist for >1 year.) These tests, along with a more extensive panel of serologic tests, can be performed at the *Toxoplasma* Serology Laboratory at the Palo Alto Medical Foundation (www.pamf.org/serology/clinicianguide.html).
- In immunocompromised pts, a presumptive clinical diagnosis can be based on clinical presentation, history of exposure (e.g., a positive IgG result), and radiologic evaluation. Radiologic studies demonstrate bilateral contrast-enhancing lesions, typically in the basal ganglia and corticomedullary junction. These lesions can be difficult to distinguish from CNS lymphoma, although the latter more frequently consists of only a single lesion. A brain biopsy may be required for definitive diagnosis.

- Congenital toxoplasmosis is diagnosed by PCR of amniotic fluid (to detect the B1 gene of the parasite) and by the persistence of IgG antibody or a positive IgM titer after the first week of life; IgG antibody determinations should be repeated every 2 months.
- Ocular toxoplasmosis is diagnosed by the detection of typical lesions on ophthalmologic examination and the demonstration of a positive IgG titer in serum.

## TREATMENT TOXOPLASMOSIS

- Immunocompetent pts with only lymphadenopathy do not require treatment unless they have persistent, severe symptoms.
- Immunocompromised pts should receive pyrimethamine plus sulfadiazine.
  - In resource-poor settings, trimethoprim-sulfamethoxazole (TMP-SMX; one double-strength tablet daily) is an effective alternative.
  - Either dapsone plus pyrimethamine or atovaquone with or without pyrimethamine is an alternative for pts who cannot take TMP-SMX.
- Congenital infection is treated daily for 1 year with oral pyrimethamine (1 mg/kg), sulfadiazine (100 mg/kg), and folinic acid.
- Ocular toxoplasmosis is treated with pyrimethamine and either sulfadiazine or clindamycin (and sometimes with prednisone) for 1 month.

### Chemoprophylaxis

The risk of disease is very high among AIDS pts who are seropositive for *T. gondii* and have a CD4+ T lymphocyte count of <100/μL. TMP-SMX (one double-strength tablet daily) should be given to these pts as prophylaxis against both *Pneumocystis* pneumonia and toxoplasmosis. Primary or secondary prophylaxis can be stopped if, after institution of antiretroviral treatment, the CD4+ T lymphocyte count remains >200/μL for 3 months.

### Personal Protection Measures

*Toxoplasma* infection can be prevented by the avoidance of undercooked meats and oocyst-contaminated materials (e.g., a cat's litter box).

For a more detailed discussion, see Reed SL, Davis CE: Laboratory Diagnosis of Parasitic Infections, Chap. 245e; Moore TA: Agents Used to Treat Parasitic Infections, Chap. 246e; White NJ, Breman JG: Malaria, Chap. 248, p. 1368; Vannier EG, Krause PJ: Babesiosis, Chap. 249, p. 1384; White NJ, Breman JG: Atlas of Blood Smears of Malaria and Babesiosis, Chap. 250e; Sundar S: Leishmaniasis, Chap. 251, p. 1387; Kirchhoff LV, Rassi A Jr: Chagas Disease and Trypanosomiasis, Chap. 252, p. 1394; Kim K, Kasper LH: *Toxoplasma* Infections, Chap. 253, p. 1398, in HPIM-19.

# 109 Helminthic Infections and Ectoparasite Infestations

## HELMINTHS

### NEMATODES

The nematodes, or roundworms, that are of medical significance can be broadly classified as either tissue or intestinal parasites.

### Tissue Nematode Infections

With the exception of trichinellosis, these infections are due to invasive larval stages that do not reach maturity in humans.

#### Trichinellosis

***Microbiology and Epidemiology*** Eight species of *Trichinella* cause human infection; two—*T. spiralis* and *T. pseudospiralis*—are found worldwide.

- Infection results when humans ingest meat (usually pork) that contains encysted *Trichinella* larvae.
  - The larvae invade the small-bowel mucosa.
  - After 1 week, female worms release new larvae that migrate to striated muscle via the circulation and encyst.
- The host immune response has few deleterious effects on muscle-dwelling larvae.
- About 12 cases of trichinellosis are reported annually in the United States.

***Clinical Manifestations*** Most light infections (<10 larvae per gram of muscle) are asymptomatic. A burden of >50 larvae per gram can cause fatal disease.

- In the first week of infection, large numbers of parasites invading the gut usually cause diarrhea, abdominal pain, constipation, nausea, and/or vomiting.
- In the second week of infection, pts develop symptoms related to larval migration and muscle invasion: hypersensitivity reactions with fever and hypereosinophilia; periorbital and facial edema; and hemorrhages in conjunctivae, retina, and nail beds. Deaths are usually due to myocarditis with arrhythmias or heart failure.
- Approximately 2–3 weeks after infection, larval encystment in muscle causes myositis, myalgias, muscle edema, and weakness (especially in extraocular muscles; the biceps; and muscles of the jaw, neck, lower back, and diaphragm).
- Symptoms peak at 3 weeks; convalescence is prolonged.

***Diagnosis*** Eosinophilia develops in >90% of pts, peaking at a level of >50% at 2–4 weeks after infection.

- An increase in parasite-specific antibody titers after the third week of infection confirms the diagnosis.
- Detection of larvae by microscopic examination of ≥1 g of fresh muscle tissue (i.e., not routine histopathologic sections) also confirms the diagnosis. Yields are highest near tendon insertions.

**TREATMENT TRICHINELLOSIS**

- Mebendazole (200–400 mg tid for 3 days; then 400 mg tid for 8–14 days) or albendazole (400 mg bid for 8–14 days) is active against enteric-stage parasites; the efficacy of these drugs against encysted larvae is inconclusive.

- Glucocorticoids (e.g., prednisone at 1 mg/kg daily for 5 days) may reduce severe myositis and myocarditis.

***Prevention***
Cooking pork until it is no longer pink or freezing it at –15°C (5°F) for 3 weeks kills larvae and prevents infection by most *Trichinella* spp.

**Visceral and Ocular Larva Migrans**
***Microbiology and Epidemiology*** Humans are incidental hosts for nematodes that cause visceral larva migrans. Most cases are caused by the canine ascarid *Toxocara canis*. Infection results when humans—most often preschool children—ingest soil contaminated by puppy feces that contain infective *T. canis* eggs. Larvae penetrate the intestinal mucosa and disseminate hematogenously to a wide variety of organs (e.g., liver, lungs, CNS), provoking intense eosinophilic granulomatous responses.

***Clinical Manifestations*** Symptomatic infections result in fever, malaise, anorexia, weight loss, cough, wheezing, rashes, hepatosplenomegaly, and occasional profound eosinophilia (up to 90%). Ocular disease usually develops in older children or young adults and includes an eosinophilic mass that mimics retinoblastoma, endophthalmitis, uveitis, and/or chorioretinitis.

***Diagnosis*** The clinical diagnosis can be confirmed by an ELISA for toxocaral antibodies. Stool examination for eggs is ineffective because larvae do not develop into adult worms in humans.

**TREATMENT VISCERAL AND OCULAR LARVA MIGRANS**

- The vast majority of *Toxocara* infections are self-limited and resolve without specific therapy.
- For pts with severe disease, glucocorticoids can reduce inflammatory complications.
- Anthelmintic drugs, including mebendazole and albendazole, have not been shown to alter the course of larva migrans.
- Ocular disease can be treated with albendazole (800 mg bid) and glucocorticoids for 5–20 days.

**Cutaneous Larva Migrans** This disease is caused by larvae of animal hookworms, usually the dog and cat hookworm *Ancylostoma braziliense*. Larvae in contaminated soil penetrate human skin; intensely pruritic, erythematous lesions form along the tracks of larval migration and advance several centimeters each day. Ivermectin (a single dose of 200 μg/kg) or albendazole (200 mg bid for 3 days) can relieve the symptoms of this self-limited infestation.

## Intestinal Nematode Infections

Intestinal nematodes infect >1 billion persons worldwide, most commonly in regions with poor sanitation and particularly in developing countries in the tropics or subtropics. Because most helminthic parasites do not self-replicate, clinical disease (as opposed to asymptomatic infection) generally develops only with prolonged residence in an endemic area and is typically related to infection intensity.

**Ascariasis**
***Microbiology*** Ascariasis is caused by *Ascaris lumbricoides*, the largest intestinal nematode, which reaches lengths up to 40 cm.

- Humans—primarily younger children—are infected by ingestion of fecally contaminated soil that contains ascarid eggs.

- Larvae hatch in the intestine, invade the mucosa, migrate to the lungs, break into the alveoli, ascend the bronchial tree, are swallowed, mature in the small intestine, and produce up to 240,000 eggs per day that pass in the feces.

***Clinical Manifestations*** Most infections have a low worm burden and are asymptomatic. During lung migration of the parasite (~9–12 days after egg ingestion), pts may develop a cough and substernal discomfort, occasionally with dyspnea or blood-tinged sputum, fever, and eosinophilia.

- Eosinophilic pneumonitis (Löffler's syndrome) may be evident.
- Heavy infections with numerous entangled worms can occasionally cause pain, small-bowel obstruction, perforation, volvulus, biliary obstruction and colic, or pancreatitis.

***Laboratory Findings*** Ascaris eggs (65 by 45 μm) can be found in fecal samples. Adult worms can pass in the stool or, much less commonly, through the mouth or nose.

**TREATMENT ASCARIASIS**

A single dose of albendazole (400 mg), mebendazole (500 mg), or ivermectin (150–200 μg/kg) is effective; these medications are contraindicated in pregnancy.

### Hookworm

***Microbiology*** Two hookworm species, *Ancylostoma duodenale* and *Necator americanus*, cause human infections. Infectious larvae present in soil penetrate the skin, reach the lungs via the bloodstream, invade the alveoli, ascend the airways, are swallowed, reach the small intestine, mature into adult worms, attach to the mucosa, and suck blood (0.2 mL/d per *Ancylostoma* adult) and interstitial fluid.

***Clinical Manifestations*** Most infections are asymptomatic. Chronic infection causes iron deficiency and—in marginally nourished persons—progressive anemia and hypoproteinemia, weakness, and shortness of breath. Larvae may cause pruritic rash ("ground itch") at the site of skin penetration as well as serpiginous tracks of SC migration (similar to those of cutaneous larva migrans).

***Laboratory Findings*** Hookworm eggs (40 by 60 μm) can be found in the feces. Stool concentration may be needed for the diagnosis of light infections.

**TREATMENT HOOKWORM**

- Albendazole (400 mg once) or mebendazole (500 mg once) is effective, although there is some concern that these agents are becoming less effective. Nutritional support, iron replacement, and deworming are undertaken as needed.

### Strongyloidiasis

***Microbiology and Epidemiology*** Unlike other helminths, *Strongyloides stercoralis* can replicate in the human host, permitting ongoing cycles of autoinfection from endogenously produced larvae.

- Infection results when filariform larvae in fecally contaminated soil penetrate the skin or mucous membranes.
  - Larvae travel through the bloodstream to the lungs, break through into alveolar spaces, ascend the bronchial tree, are swallowed, reach the small intestine, mature

into adult worms, and penetrate the mucosa of the proximal small bowel; eggs hatch in the intestinal mucosa.
  - Rhabditiform larvae can pass with the feces into the soil or can develop into filariform larvae that penetrate the colonic wall or perianal skin and enter the circulation to establish ongoing autoinfection.
- Autoinfection is constrained by unknown factors of the host immune system, disruption of which (e.g., by glucocorticoid therapy) can lead to hyperinfection.

***Clinical Features*** Uncomplicated disease is associated with mild cutaneous and/or abdominal manifestations such as recurrent urticaria, larva currens (a pathognomonic serpiginous, pruritic, erythematous eruption along the course of larval migration that may advance up to 10 cm/h), abdominal pain, nausea, diarrhea, bleeding, and weight loss.

- Disseminated disease involves tissues outside the GI tract and lungs, including the CNS, peritoneum, liver, and kidney.
  - Gram-negative sepsis, pneumonia, or meningitis can complicate or dominate the clinical course.
  - Disease can be fatal in pts given glucocorticoids; disseminated infection is uncommon among pts with HIV-1 infection.
- Fluctuating eosinophilia is common in uncomplicated disease but is uncommon in disseminated disease.

***Diagnosis*** A single stool examination detects rhabditiform larvae (~250 μm long) in about one-third of uncomplicated infections. Duodenojejunal contents can be sampled if stool examinations are repeatedly negative.

- Antibodies can be detected by ELISA.
- In disseminated infection, filariform larvae can be found in stool or at sites of larval migration (e.g., sputum, bronchoalveolar lavage fluid, surgical drainage fluid).

**TREATMENT STRONGYLOIDIASIS**

- Ivermectin (200 μg/kg daily for 2 days) is more effective than albendazole (400 mg daily for 3 days). Asymptomatic pts should be treated, given the potential for later fatal hyperinfection.
- Disseminated disease should be treated with ivermectin for at least 5–7 days (or until the parasites are eradicated).
- In immunocompromised hosts, the course of ivermectin should be repeated 2 weeks after initial treatment.

### Enterobiasis

***Microbiology and Epidemiology*** Enterobiasis (pinworm) is caused by *Enterobius vermicularis* and affects ~40 million people in the United States (primarily children).

- Gravid female worms migrate nocturnally from the cecum to the perianal region, each releasing up to 2000 immature eggs that become infective within hours.
- Autoinfection and person-to-person transmission result from perianal scratching and transport of infective eggs to the mouth.

***Clinical Manifestations*** Perianal pruritus is the cardinal symptom and is often worst at night. Eosinophilia is uncommon.

***Diagnosis*** Eggs (55 by 25 μm and flattened on one side) are detected by microscopic examination of cellulose acetate tape applied to the perianal region in the morning.

**TREATMENT ENTEROBIASIS**

- One dose of mebendazole (100 mg) or albendazole (400 mg) is given, with the same treatment repeated after 2 weeks. Household members should also be treated to avoid reservoirs of potential reinfection.

## Filarial and Related Infections

Filarial worms, which infect >170 million people worldwide, are nematodes that dwell in the SC tissue and lymphatics. Usually, infection is established only with repeated and prolonged exposures to infective larvae; however, filarial disease is characteristically more intense and acute in newly exposed individuals than in natives of endemic areas.

- Filarial parasites have a complex life cycle, including infective larval stages carried by insects and adult worms that reside in humans.
  - The offspring of adults are microfilariae (200–250 μm long, 5–7 μm wide) that either circulate in the blood or migrate through the skin.
  - Microfilariae are ingested by the arthropod vector and develop over 1–2 weeks into new infective larvae.
- A bacterial endosymbiont, *Wolbachia*, is found in all stages of *Brugia*, *Wuchereria*, *Mansonella*, and *Onchocerca* spp. and has become a target for antifilarial chemotherapy.

### Lymphatic Filariasis

***Microbiology*** Lymphatic filariasis is caused by *Wuchereria bancrofti* (most commonly), *Brugia malayi*, or *B. timori*, which can reside in and cause inflammatory damage to lymphatic channels or lymph nodes.

***Clinical Manifestations*** Subclinical microfilaremia, hydrocele, acute adenolymphangitis (ADL), and chronic lymphatic disease are the main clinical presentations.

- ADL is associated with high fever, lymphatic inflammation, and transient local edema. Both the upper and lower extremities can be involved in both bancroftian and brugian filariasis, but *W. bancrofti* almost exclusively affects genital lymphatics.
- ADL may progress to more chronic lymphatic obstruction and elephantiasis with brawny edema, thickening of the SC tissues, and hyperkeratosis. Superinfection is a problem.

***Diagnosis*** Detection of the parasite is difficult, but microfilariae can be found in peripheral blood, hydrocele fluid, and occasionally other body fluids.

- Timing of blood collection is critical and should be based on the periodicity of the microfilariae in the endemic region involved (primarily nocturnal in many regions).
- Two assays are available to detect *W. bancrofti* circulating antigens, and a PCR has been developed to detect DNA of both *W. bancrofti* and *B. malayi* in the blood.
- High-frequency ultrasound (with Doppler techniques) of the scrotum or the female breast can identify motile adult worms.
- The presence of antifilarial antibody supports the diagnosis, but cross-reactivity with other helminthic infections makes interpretation of this finding difficult.

**TREATMENT LYMPHATIC FILARIASIS**

- Pts with active lymphatic filariasis (defined by microfilaremia, antigen positivity, or adult worms on ultrasound) should be treated with diethylcarbamazine (DEC, 6 mg/kg daily for 12 days), which has macro- and microfilaricidal properties.

Albendazole (400 mg bid for 21 days), albendazole and DEC both given daily for 7 days, doxycycline (100 mg bid for 4–6 weeks), and the addition of DEC to a 3-week course of doxycycline are alternative regimens with macrofilaricidal efficacy.

- A single dose of albendazole (400 mg) combined with DEC (6 mg/kg) or ivermectin (200 μg/kg) has sustained microfilaricidal activity and is used in lymphatic filariasis eradication campaigns.
- For pts with chronic lymphatic filariasis, treatment regimens should focus on hygiene, prevention of secondary bacterial infections, and physiotherapy. Drug treatment should be reserved for individuals with evidence of active infection, although a 6-week course of doxycycline improves filarial lymphedema irrespective of disease activity.

### Onchocerciasis

***Microbiology and Epidemiology*** Onchocerciasis ("river blindness") is caused by *Onchocerca volvulus*, which infects 37 million people worldwide and is transmitted by the bite of an infected blackfly near free-flowing rivers and streams.

- Larvae deposited by the blackfly develop into adult worms (females and males are ~40–60 cm and ~3–6 cm in length, respectively) that are found in SC nodules (*onchocercomata*). About 7 months to 3 years after infection, the gravid female releases microfilariae that migrate out of the nodules and concentrate in the dermis.
- In contrast to lymphatic filariasis, onchocerciasis is characterized by microfilarial induction of inflammation.

***Clinical Manifestations*** Onchocerciasis most commonly presents as dermatologic manifestations (an intensely pruritic papular rash or firm nontender onchocercomata), but visual impairment is the most serious complication in pts with moderate or heavy infections.

- Conjunctivitis with photophobia is an early ocular finding.
- Sclerosing keratitis (the leading cause of onchocercal blindness in Africa, affecting 1–5% of pts), anterior uveitis, iridocyclitis, and secondary glaucoma due to pupillary deformities are more serious ocular complications.

***Diagnosis*** A definitive diagnosis is based on the finding of an adult worm in an excised nodule or of microfilariae in a skin snip.

- Specific antibody assays and PCR to detect onchocercal DNA are available in reference laboratories.
- Eosinophilia and elevated serum IgE levels are common but nonspecific.

**TREATMENT ONCHOCERCIASIS**

- Ivermectin (a single dose of 150 μg/kg), given yearly or semiannually, is microfilaricidal and is the mainstay of treatment.
  - In African regions where *O. volvulus* is coendemic with *Loa loa*, ivermectin is contraindicated because of the risk of severe posttreatment encephalopathy.
  - Doxycycline therapy for 6 weeks is macrofilaristatic, rendering adult female worms sterile for long periods, and also targets the *Wolbachia* endosymbiont.
- Nodules on the head should be excised to avoid ocular infection.

## TREMATODES

- The trematodes, or flatworms, may be classified according to the tissues invaded by the adult stage of the fluke: blood, biliary tree, intestines, or lungs.

- The life cycle involves a definitive mammalian host (e.g., humans), in whom adult worms produce eggs through sexual reproduction, and an intermediate host (e.g., snails), in which miracidial forms undergo asexual reproduction to form cercariae. Worms do not multiply within the definitive host.
- Human infection results from either direct penetration of intact skin or ingestion.
- Infections with trematodes that migrate through or reside in host tissues are associated with a moderate to high degree of peripheral-blood eosinophilia.

### Schistosomiasis

***Microbiology and Epidemiology*** Five species cause human schistosomiasis: *Schistosoma mansoni*, *S. japonicum*, *S. mekongi*, and *S. intercalatum* cause intestinal and hepatic schistosomiasis, and *S. haematobium* causes urogenital schistosomiasis.

- After infective cercariae penetrate intact skin, they mature into schistosomula and migrate through venous or lymphatic vessels to the lungs and ultimately the liver parenchyma. Sexually mature worms migrate to the veins of the bladder and pelvis (*S. haematobium*) or the mesentery (*S. mansoni*, *S. japonicum*, *S. mekongi*, *S. intercalatum*) and deposit eggs.
  - Some mature ova are extruded into the intestinal or urinary lumina, from which they may be voided and ultimately may reach water and perpetuate the life cycle.
  - The persistence of ova in tissues leads to a granulomatous host response and fibrosis.
- These blood flukes infect 200–300 million persons (mostly children and young adults) in South America, the Caribbean, Africa, the Middle East, and Southeast Asia.

***Clinical Manifestations***

Schistosomiasis occurs in three stages that vary by species, intensity of infection, and host factors (e.g., age, genetics).

- *Cercarial invasion*, most often with *S. mansoni* and *S. japonicum* infections, causes a pruritic maculopapular rash ("swimmers' itch") 2–3 days later.
- *Acute schistosomiasis* (Katayama fever) presents 4–8 weeks after skin invasion as a serum sickness–like illness characterized by fever, generalized lymphadenopathy, hepatosplenomegaly, and significant eosinophilia.
- *Chronic schistosomiasis* causes manifestations that depend primarily on the schistosome species.
  - Intestinal species cause colicky abdominal pain, bloody diarrhea, anemia, hepatosplenomegaly, portal hypertension, and esophageal varices with bleeding.
  - Urinary species cause dysuria, frequency, hematuria (sometimes only at the end of voiding), obstruction with hydroureter and hydronephrosis, fibrosis of bladder granulomas, and late development of squamous cell carcinoma of the bladder.
  - Pulmonary disease (e.g., endarteritis obliterans, pulmonary hypertension, cor pulmonale) and CNS disease (e.g., Jacksonian epilepsy, transverse myelitis) can occur and are due to granulomas and fibrosis.

***Diagnosis*** Diagnosis is based on geographic history, clinical presentation, and presence of schistosome ova in excreta.

- Serologic assays for schistosomal antibodies (available through the CDC in the United States) may yield positive results before eggs are seen in excreta.
- Infection may also be diagnosed by examination of tissue samples, typically from rectal biopsies.

## TREATMENT SCHISTOSOMIASIS

- Because antischistosomal therapy has no significant impact on maturing worms, supportive measures and the consideration of glucocorticoid treatment constitute initial management for acute schistosomiasis.

- After the acute critical phase has resolved, a single day of treatment with praziquantel (20 mg/kg bid for *S. mansoni*, *S. intercalatum*, and *S. haematobium* infections; 20 mg/kg tid for *S. japonicum* and *S. mekongi* infections) results in parasitologic cure in ~85% of cases and reduces egg counts by >90%.
- Late established manifestations, such as fibrosis, do not improve with treatment.

***Prevention*** Travelers to endemic regions should avoid contact with all freshwater bodies.

#### Liver (Biliary) Flukes

- Clonorchiasis (due to *Clonorchis sinensis*) and opisthorchiasis (due to *Opisthorchis viverrini* and *O. felineus*) occur in Southeast Asia and Eastern Europe.
  - Infection is acquired by ingestion of contaminated raw freshwater fish; larvae travel through the ampulla of Vater and mature in biliary canaliculi.
  - Most infected individuals are minimally symptomatic; chronic or repeated infection causes cholangitis, cholangiohepatitis, and biliary obstruction and is associated with cholangiocarcinoma.
  - Therapy for acute infection consists of praziquantel administration (25 mg/kg tid for 2 or 3 days).
- Fascioliasis (due to *Fasciola hepatica* and *F. gigantica*) is endemic in sheep-raising countries and has a worldwide prevalence of 17 million cases.
  - Infection is acquired by ingestion of contaminated aquatic plants (e.g., watercress, water caltrop, water chestnuts).
  - Acute disease develops 1–2 weeks after infection and causes fever, RUQ pain, hepatomegaly, and eosinophilia. Chronic infection is infrequently associated with bile duct obstruction and biliary cirrhosis.
  - For treatment, triclabendazole is given as a single dose of 10 mg/kg.
- Stool ova and parasite (O & P) examination diagnoses infection with liver flukes. Serologic testing is helpful, particularly in lightly infected pts.

#### Lung Flukes

- Infection with *Paragonimus* spp. is acquired by ingestion of contaminated crayfish and freshwater crabs.
- Acute infection causes lung hemorrhage, necrosis with cyst formation, and parenchymal eosinophilic infiltrates. A productive cough with brownish or bloody sputum, in association with peripheral-blood eosinophilia, is the usual presentation in pts with heavy infection.
  - In chronic cases, bronchitis or bronchiectasis may predominate.
  - CNS disease can also occur and can result in seizures.
- The diagnosis is made by O & P examination of sputum or stool; serology can be helpful.
- Praziquantel (25 mg/kg tid for 2 days) is the recommended therapy.

## CESTODES

The cestodes, or tapeworms, are segmented worms that can be classified into two groups according to whether humans are the definitive or the intermediate host. The tapeworm attaches to intestinal mucosa via sucking cups or hooks located on the scolex. Proglottids (segments) form behind the scolex and constitute the bulk of the tapeworm.

#### Taeniasis Saginata and Taeniasis Asiatica

***Microbiology*** Humans are the definitive host for *Taenia saginata*, the beef tapeworm, and *T. asiatica*, the swine tapeworm, which inhabit the upper jejunum. Eggs are excreted in feces and ingested by cattle or other herbivores (*T. saginata*) or pigs

(*T. asiatica*); larvae encyst (cysticerci) in the striated muscles of these animals. When humans ingest raw or undercooked meat, the cysticerci mature into adult worms in ~2 months.

***Clinical Manifestations*** Pts become aware of the infection by noting passage of motile proglottids in their feces. They may experience perianal discomfort, mild abdominal pain, nausea, change in appetite, weakness, and weight loss.

***Diagnosis*** The diagnosis is made by detection of eggs or proglottids in the stool; eggs may be detected in the perianal area by the cellophane-tape test (as in pinworm infection). Eosinophilia and elevated IgE levels may occur.

## TREATMENT TAENIASIS SAGINATA AND TAENIASIS ASIATICA

Praziquantel is given in a single dose of 10 mg/kg.

### Taeniasis Solium and Cysticercosis

***Microbiology and Pathogenesis*** Humans are the definitive host and pigs the usual intermediate host for *T. solium*, the pork tapeworm.

- The disease has two forms, which depend on the form of parasite ingested.
  - By ingesting undercooked pork containing cysticerci, humans develop intestinal tapeworms and a disease similar to taeniasis saginata.
  - If humans ingest *T. solium* eggs (e.g., as a result of close contact with a tapeworm carrier or via autoinfection), they develop cysticercosis due to larvae penetrating the intestinal wall and migrating to many tissues.

***Clinical Manifestations*** Intestinal infections are generally asymptomatic except for fecal passage of proglottids. The presentation of cysticercosis depends on the number and location of cysticerci as well as the extent of associated inflammatory responses or scarring.

- Cysticerci can be found anywhere in the body but most often are detected in the brain, skeletal muscle, SC tissue, or eye.
- Neurologic manifestations are most common and include seizures (due to inflammation surrounding cysticerci in the brain), hydrocephalus (from obstruction of CSF flow by cysticerci and accompanying inflammation or by arachnoiditis), and signs of increased intracranial pressure (e.g., headache, nausea, vomiting, changes in vision).

***Diagnosis*** Intestinal infection is diagnosed by detection of eggs or proglottids in stool. A consensus conference has delineated criteria for the diagnosis of cysticercosis (Table 109-1). Findings on neuroimaging include cystic lesions with or without enhancement, one or more nodular calcifications, or focal enhancing lesions.

## TREATMENT TAENIASIS SOLIUM AND CYSTICERCOSIS

- Intestinal infections respond to a single dose of praziquantel (10 mg/kg), but this treatment may evoke an inflammatory response in the CNS if there is cryptic cysticercosis.
- Neurocysticercosis can be treated with albendazole (15 mg/kg per day for 8–28 days) or praziquantel (50–100 mg/kg daily in three divided doses for 15–30 days). A combination of albendazole and praziquantel (50 mg/kg in three divided doses per day) may be more effective in pts with multiple lesions.
  - Given the potential for an inflammatory response to treatment, pts should be carefully monitored, and high-dose glucocorticoids should be used during treatment.

**TABLE 109-1 DIAGNOSTIC CRITERIA FOR HUMAN CYSTICERCOSIS[a]**

1. Absolute criteria
   a. Demonstration of cysticerci by histologic or microscopic examination of biopsy material
   b. Visualization of the parasite in the eye by funduscopy
   c. Neuroradiologic demonstration of cystic lesions containing a characteristic scolex
2. Major criteria
   a. Neuroradiologic lesions suggestive of neurocysticercosis
   b. Demonstration of antibodies to cysticerci in serum by enzyme-linked immunoelectrotransfer blot
   c. Resolution of intracranial cystic lesions spontaneously or after therapy with albendazole or praziquantel alone
3. Minor criteria
   a. Lesions compatible with neurocysticercosis detected by neuroimaging studies
   b. Clinical manifestations suggestive of neurocysticercosis
   c. Demonstration of antibodies to cysticerci or cysticercal antigen in cerebrospinal fluid by enzyme-linked immunosorbent assay
   d. Evidence of cysticercosis outside the central nervous system (e.g., cigar-shaped soft-tissue calcifications)
4. Epidemiologic criteria
   a. Residence in a cysticercosis-endemic area
   b. Frequent travel to a cysticercosis-endemic area
   c. Household contact with an individual infected with *Taenia solium*

[a]Diagnosis is confirmed by either one absolute criterion or a combination of two major criteria, one minor criterion, and one epidemiologic criterion. A probable diagnosis is supported by the fulfillment of (1) one major criterion plus two minor criteria; (2) one major criterion plus one minor criterion and one epidemiologic criterion; or (3) three minor criteria plus one epidemiologic criterion.
***Source:*** Modified from OH Del Brutto et al: *Neurology* 57:177, 2001.

– Since glucocorticoids induce praziquantel metabolism, cimetidine should be given with praziquantel to inhibit this effect.
– Supportive measures include antiepileptic administration and treatment of hydrocephalus as indicated.

**Echinococcosis**

***Microbiology and Epidemiology*** Humans are an intermediate host for *Echinococcus* larvae and acquire echinococcal disease by ingesting eggs spread by canine feces (for *E. granulosus*).

- After ingestion, embryos escape from the eggs, penetrate the intestinal mucosa, enter the portal circulation, and are carried to many organs but particularly the liver and lungs. Larvae develop into fluid-filled unilocular hydatid cysts within which daughter cysts develop, as do germinating cystic structures (*brood capsules*). Cysts expand over years.

- Echinococcosis is prevalent on all continents, particularly in areas where livestock is raised in association with dogs.
- *E. multilocularis*, found in Arctic or sub-Arctic regions, is similar to *E. granulosus*, but wild canines (e.g., foxes) are the definitive hosts and rodents are the intermediate hosts. The parasite is multilocular, and vesicles progressively invade host tissue.

***Clinical Manifestations*** Expanding cysts exert the effects of space-occupying lesions, causing symptoms in the affected organ (usually liver and lung); the liver is involved in two-thirds of *E. granulosus* infections and ~100% of *E. multilocularis* infections.

- Pts with hepatic disease most commonly present with abdominal pain or a palpable mass in the RUQ. Compression of a bile duct may mimic biliary disease, and rupture or leakage from a hydatid cyst may cause fever, pruritus, urticaria, eosinophilia, or anaphylaxis.
- Pulmonary cysts may rupture into the bronchial tree or pleural cavity and cause cough, salty phlegm, chest pain, or hemoptysis.
- Rupture of cysts may result in multifocal dissemination.
- *E. multilocularis* disease may present as a hepatic tumor, with destruction of the liver and extension into adjoining (e.g., lungs, kidneys) or distant (e.g., brain, spleen) organs.

***Diagnosis*** Radiographic imaging is important in detecting and evaluating echinococcal cysts.

- Daughter cysts within a larger cyst are pathognomonic of *E. granulosus*. Eggshell or mural calcification on CT is also indicative of *E. granulosus* infection.
- Serologic testing yields positive results in ~90% of pts with hepatic disease, but results can be negative in up to half of pts with lung cysts.
- Aspiration of cysts usually is not attempted because leakage of cyst fluid can cause dissemination or anaphylactic reactions.

## TREATMENT ECHINOCOCCOSIS

- Therapy is based on considerations of the size, location, and manifestations of cysts and the overall health of the pt. Ultrasound staging is recommended for *E. granulosus* infection.
- For some uncomplicated lesions, PAIR (*p*ercutaneous *a*spiration, *i*nfusion of scolicidal agents [95% ethanol or hypertonic saline], and *r*easpiration) is recommended.
  - Albendazole (7.5 mg/kg bid for 2 days before the procedure and for at least 4 weeks afterward) is given for prophylaxis of secondary peritoneal echinococcosis due to inadvertent spillage of fluid during this treatment.
  - PAIR is contraindicated for superficial cysts, for cysts with multiple thick internal septal divisions, and for cysts communicating with the biliary tree.
- Surgical resection is the treatment of choice for complicated *E. granulosus* cysts.
  - Albendazole should also be given prophylactically, as just described. Praziquantel (50 mg/kg daily for 2 weeks) may hasten the death of protoscolices.
  - Medical therapy alone with albendazole for 12 weeks to 6 months results in cure in ~30% of cases and in clinical improvement in another 50%.
- *E. multilocularis* infection is treated surgically, and albendazole is given for at least 2 years after presumptively curative surgery. If surgery is not curative, albendazole should be continued indefinitely.

### Diphyllobothriasis

*Diphyllobothrium latum*, the longest tapeworm (up to 25 m), attaches to the ileal and occasionally the jejunal mucosa. Humans are infected by consumption of infected

raw or smoked fish. Symptoms are rare and usually mild, but infection, particularly in Scandinavia, can cause vitamin $B_{12}$ deficiency because the tapeworm absorbs large amounts of vitamin $B_{12}$ and interferes with ileal $B_{12}$ absorption. Up to 2% of infected pts, especially the elderly, have megaloblastic anemia resembling pernicious anemia and can suffer neurologic sequelae due to $B_{12}$ deficiency. The diagnosis is made by detection of eggs in the stool. Praziquantel (5–10 mg/kg once) is highly effective.

## ECTOPARASITES

Ectoparasites are arthropods or helminths that infest the skin or hair of animals, from which they derive sustenance and shelter. These organisms can inflict direct injury, elicit hypersensitivity, or inoculate toxins or pathogens.

### Scabies

***Etiology and Epidemiology*** Scabies is caused by the human itch mite *Sarcoptes scabiei* var. *hominis*, which infests ~300 million people worldwide.

- Gravid female mites burrow within the stratum corneum, deposit eggs that mature in ~8 days, and emerge as adults to reinvade the same or another host.
- Scabies transmission is facilitated by direct skin-to-skin contact with an infested person and by crowding, uncleanliness, or contact with multiple sexual partners.

***Clinical Manifestations*** Itching, which is due to a sensitization reaction against excreta of the mite, is worst at night and after a hot shower. Burrows appear as dark wavy lines (3–15 mm in length), with most lesions located along the digital web spaces or on the volar wrists, elbows, scrotum, and penis. *Crusted* scabies (formerly termed *Norwegian* scabies)—hyperinfestation with thousands of mites—is associated with glucocorticoid use and immunodeficiency diseases.

***Diagnosis*** Scrapings from unroofed burrows reveal the mite, its eggs, or fecal pellets.

**TREATMENT SCABIES**

- Permethrin cream (5%) should be applied thinly behind the ears and from the neck down after bathing and removed 8–14 h later with soap and water. A dose of ivermectin (200 μg/kg) is also effective but has not yet been approved by the FDA for scabies treatment.
- For crusted scabies, first a keratolytic agent (e.g., 6% salicylic acid) and then scabicides are applied to the scalp, face, and ears in addition to the rest of the body. Two doses of ivermectin, separated by an interval of 1–2 weeks, may be required for pts with crusted scabies.
- Itching and hypersensitivity may persist for weeks or months in scabies and should be managed with symptom-based treatment. Bedding and clothing should be washed in hot water and dried in a heated dryer, and close contacts (regardless of symptoms) should be treated to prevent reinfestations.
- Scabies infestations become noncommunicable within 1 day of effective treatment.

### Pediculiasis

***Etiology and Epidemiology*** Nymph and adult forms of human lice—*Pediculus capitis* (the head louse), *P. humanus* (the body louse), and *Pthirus pubis* (the pubic louse)—feed at least once a day and ingest human blood exclusively. The saliva of these lice produces an irritating rash in sensitized persons. Eggs are cemented firmly to hair or clothing, and empty eggs (nits) remain affixed for months after hatching. Lice are generally transmitted from person to person. Head lice are transmitted among

schoolchildren and body lice among disaster victims and indigent people; pubic lice are usually transmitted sexually. The body louse is a vector for the transmission of diseases such as louse-borne typhus, relapsing fever, and trench fever.

***Diagnosis*** The diagnosis can be suspected if nits are detected, but confirmatory measures should include the demonstration of a live louse.

**TREATMENT PEDICULIASIS**

- If live lice are found, treatment with 1% permethrin (two 10-min applications 10 days apart) is usually adequate. If this course fails, treatment for ≤12 h with 0.5% malathion may be indicated. Eyelid infestations should be treated with petrolatum applied for 3–4 days.
- Body lice usually are eliminated by bathing and by changing to laundered clothes.
  - Pediculicides applied from head to foot may be needed in hirsute pts to remove body lice.
  - Clothes and bedding should be deloused by placement in a hot dryer for 30 min or by heat pressing.

### Myiasis

In this infestation, maggots invade living or necrotic tissue or body cavities and produce clinical syndromes that vary with the species of fly. Certain flies are attracted to blood and pus, and newly hatched larvae enter wounds or diseased skin. Treatment consists of maggot removal and tissue debridement.

### Leech Infestations

Medicinal leeches can reduce venous congestion in surgical flaps or replanted body parts. Pts occasionally develop sepsis from *Aeromonas hydrophila*, which colonizes the gullets of commercially available leeches.

For a more detailed discussion, see Reed SL, Davis CE: Laboratory Diagnosis of Parasitic Infections, Chap. 245e; Moore TA: Agents Used to Treat Parasitic Infections, Chap. 246e; Weller PF: Trichinellosis and Other Tissue Nematode Infections, Chap. 256, p. 1410; Weller PF, Nutman TB: Intestinal Nematode Infections, Chap. 257, p. 1413; Nutman TB, Weller PF: Filarial and Related Infections, Chap. 258, p. 1417; King CH, Mahmoud AAF: Schistosomiasis and Other Trematode Infections, Chap. 259, p. 1423; White AC Jr, Weller PF: Cestode Infections, Chap. 260, p. 1430; Pollack RJ, Norton SA: Ectoparasite Infestations and Arthropod Injuries, Chap. 475, p. 2744, in HPIM-19.

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# 110 Physical Examination of the Heart

General examination of a pt with suspected heart disease should include vital signs (respiratory rate, pulse, blood pressure) and observation of skin color (e.g., cyanosis, pallor, jaundice), clubbing, edema, evidence of decreased perfusion (cool and diaphoretic skin), and hypertensive changes in optic fundi. Examine abdomen for evidence of hepatomegaly, ascites, or abdominal aortic aneurysm. An ankle-brachial index (systolic bp at ankle divided by arm systolic bp) <0.9 indicates lower extremity arterial obstructive disease. Important findings on cardiovascular examination include:

## CAROTID ARTERY PULSE (FIG. 110-1)

- *Pulsus parvus:* Weak upstroke due to decreased stroke volume (hypovolemia, LV failure, aortic or mitral stenosis [MS])
- *Pulsus tardus:* Delayed upstroke (aortic stenosis)
- *Bounding (hyperkinetic) pulse:* Hyperkinetic circulation, aortic regurgitation, patent ductus arteriosus, marked vasodilation
- *Pulsus bisferiens:* Double systolic pulsation (aortic regurgitation, hypertrophic cardiomyopathy)
- *Pulsus alternans:* Regular alteration in pulse pressure amplitude (severe LV dysfunction)
- *Pulsus paradoxus:* Exaggerated inspiratory fall (>10 mmHg) in systolic bp (pericardial tamponade, severe obstructive lung disease)

## JUGULAR VENOUS PULSATION (JVP)

Jugular venous distention develops in right-sided heart failure, constrictive pericarditis, pericardial tamponade, obstruction of superior vena cava. JVP normally falls with inspiration but may rise (Kussmaul sign) in constrictive pericarditis. Abnormalities in examination include:

- *Large "a" wave:* Tricuspid stenosis (TS), pulmonic stenosis (PS), atrioventricular (AV) dissociation (right atrium contracts against closed tricuspid valve)
- *Large "v" wave:* Tricuspid regurgitation, atrial septal defect
- *Steep "y" descent:* Constrictive pericarditis
- *Slow "y" descent:* TS

## PRECORDIAL PALPATION

Cardiac apical impulse is normally localized at the fifth intercostal space, midclavicular line. Abnormalities include:

- *Forceful apical thrust:* Left ventricular hypertrophy
- *Lateral and downward displacement of apex impulse:* Left ventricular dilatation
- *Prominent presystolic impulse:* Hypertension, aortic stenosis, hypertrophic cardiomyopathy
- *Double systolic apical impulse:* Hypertrophic cardiomyopathy

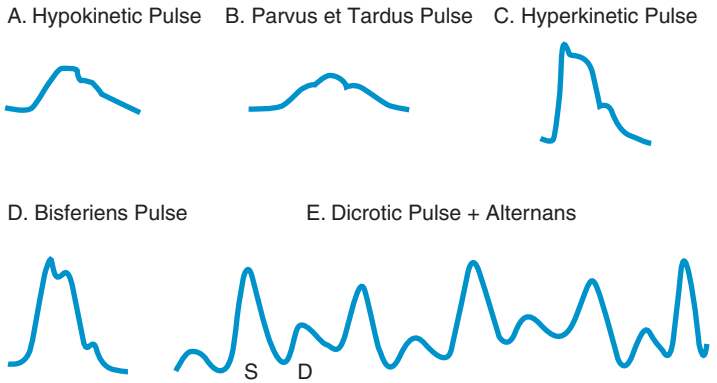



**FIGURE 110-1** Carotid artery pulse patterns.

- *Sustained "lift" at lower left sternal border:* Right ventricular hypertrophy
- *Dyskinetic (outward bulge) impulse:* Ventricular aneurysm, large dyskinetic area post MI, cardiomyopathy

## AUSCULTATION

### HEART SOUNDS (FIG. 110-2)

#### $S_1$

*Loud:* Mitral stenosis (MS), short PR interval, hyperkinetic heart, thin chest wall. *Soft:* Long PR interval, heart failure, mitral regurgitation, thick chest wall, pulmonary emphysema.

#### $S_2$

Normally $A_2$ precedes $P_2$ and splitting increases with inspiration; abnormalities include:

- *Widened* splitting: Right bundle branch block, PS, mitral regurgitation
- *Fixed* splitting (no respiratory change in splitting): Atrial septal defect
- *Narrow* splitting: Pulmonary hypertension
- *Paradoxical* splitting (splitting narrows with inspiration): Aortic stenosis, left bundle branch block, heart failure
- *Loud* $A_2$: Systemic hypertension
- *Soft* $A_2$: Aortic stenosis (AS)
- *Loud* $P_2$: Pulmonary arterial hypertension
- *Soft* $P_2$: Pulmonic stenosis (PS)

#### $S_3$

Low-pitched, heard best with bell of stethoscope at apex, following $S_2$; normal in children; after age 30–35, indicates LV failure or volume overload.

#### $S_4$

Low-pitched, heard best with bell at apex, preceding $S_1$; reflects atrial contraction into a noncompliant ventricle; found in AS, hypertension, hypertrophic cardiomyopathy, and coronary artery disease (CAD).

#### Opening Snap (OS)

High-pitched; follows $S_2$ (by 0.06–0.12 s), heard at lower left sternal border and apex in MS; the more severe the MS, the shorter the $S_2$–OS interval.

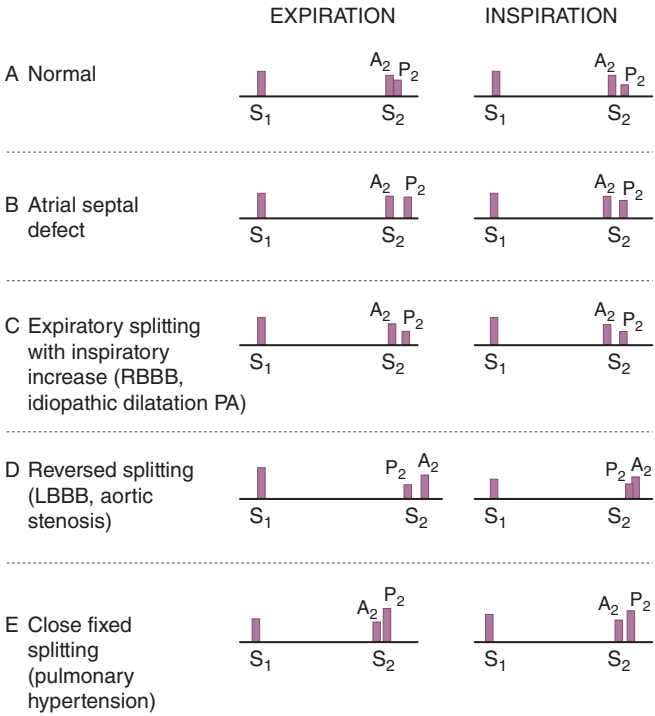



**FIGURE 110-2** Heart sounds. **A.** Normal. $S_1$, first heart sound; $S_2$, second heart sound; $A_2$, aortic component of the second heart sound; $P_2$, pulmonic component of the second heart sound. **B.** Atrial septal defect with fixed splitting of $S_2$. **C.** Physiologic but wide splitting of $S_2$ with right bundle branch block. **D.** Reversed or paradoxical splitting of $S_2$ with left bundle branch block. **E.** Narrow splitting of $S_2$ with pulmonary hypertension. *(From NO Fowler: Diagnosis of Heart Disease. New York, Springer-Verlag, 1991, p 31.)*

## Ejection Clicks

High-pitched sounds following $S_1$ typically loudest at left sternal border; observed in dilation of aortic root or pulmonary artery, congenital AS or PS; when due to the latter, click decreases with inspiration.

## Midsystolic Clicks

At lower left sternal border and apex, often followed by late systolic murmur in mitral valve prolapse.

# HEART MURMURS (FIG. 110-3; TABLES 110-1 AND 110-2)

## Systolic Murmurs

May be "crescendo-decrescendo" ejection type, pansystolic, or late systolic; right-sided murmurs (e.g., tricuspid regurgitation) typically increase with inspiration.

## Diastolic Murmurs

- *Early diastolic murmurs:* Begin immediately after $S_2$, are high-pitched, and are usually caused by aortic or pulmonary regurgitation.

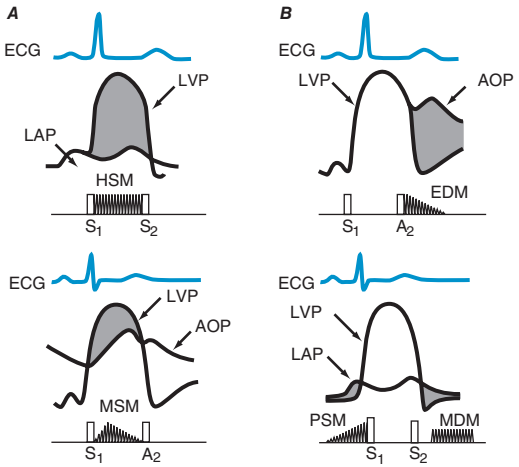



**FIGURE 110-3 A.** Schematic representation of ECG, aortic pressure (AOP), left ventricular pressure (LVP), and left atrial pressure (LAP). The gray areas indicated a transvalvular pressure difference during systole. HSM, holosystolic murmur; MSM, midsystolic murmur. **B.** Graphic representation of ECG, AOP, LVP, and LAP with gray areas indicating transvalvular diastolic pressure difference. EDM, early diastolic murmur; MDM, middiastolic murmur; PSM, presystolic murmur.

**TABLE 110-1 HEART MURMURS**

| | |
|---|---|
| **Systolic Murmurs** | |
| Ejection-type | Aortic outflow tract<br>Aortic valve stenosis<br>Hypertrophic obstructive cardiomyopathy<br>Aortic flow murmur<br>Pulmonary outflow tract<br>Pulmonic valve stenosis<br>Pulmonic flow murmur |
| Holosystolic | Mitral regurgitation<br>Tricuspid regurgitation<br>Ventricular septal defect |
| Late-systolic | Mitral or tricuspid valve prolapse |
| **Diastolic Murmurs** | |
| Early diastolic | Aortic valve regurgitation<br>Pulmonic valve regurgitation |
| Mid-to-late diastolic | Mitral or tricuspid stenosis<br>Flow murmur across mitral or tricuspid valves |
| Continuous | Patent ductus arteriosus<br>Coronary AV fistula<br>Ruptured sinus of Valsalva aneurysm |

***Abbreviation:*** AV, atrioventricular.

**TABLE 110-2 EFFECTS OF PHYSIOLOGIC AND PHARMACOLOGIC INTERVENTIONS ON THE INTENSITY OF HEART MURMURS AND SOUNDS**

| |
|---|
| **Respiration** |
| Systolic murmurs due to TR or pulmonic blood flow through a normal or stenotic valve and diastolic murmurs of TS or PR generally increase with inspiration, as do right-sided $S_3$ and $S_4$. Left-sided murmurs and sounds usually are louder during expiration, as is the pulmonic ejection sound. |
| **Valsalva Maneuver** |
| Most murmurs decrease in length and intensity. Two exceptions are the systolic murmur of HCM, which usually becomes much louder, and that of MVP, which becomes longer and often louder. Following release of the Valsalva maneuver, right-sided murmurs tend to return to control intensity earlier than left-sided murmurs. |
| **After VPB or AF** |
| Murmurs originating at normal or stenotic semilunar valves increase in the cardiac cycle following a VPB or in the cycle after a long cycle length in AF. By contrast, systolic murmurs due to AV valve regurgitation either do not change, diminish (papillary muscle dysfunction), or become shorter (MVP). |
| **Positional Changes** |
| With *standing*, most murmurs diminish, two exceptions being the murmur of HCM, which becomes louder, and that of MVP, which lengthens and often is intensified. With *squatting*, most murmurs become louder, but those of HCM and MVP usually soften and may disappear. Passive leg raising usually produces the same results. |
| **Exercise** |
| Murmurs due to blood flow across normal or obstructed valves (e.g., PS, MS) become louder with both isotonic and submaximal isometric (handgrip) exercise. Murmurs of MR, VSD, and AR also increase with handgrip exercise. However, the murmur of HCM often decreases with near maximum handgrip exercise. Left-sided $S_4$ and $S_3$ are often accentuated by exercise, particularly when due to ischemic heart disease. |

***Abbreviations:*** AR, aortic regurgitation; HCM, hypertrophic cardiomyopathy; MR, mitral regurgitation; MS, mitral stenosis; MVP, mitral valve prolapse; PR, pulmonic regurgitation; PS, pulmonic stenosis; TR, tricuspid regurgitation; TS, tricuspid stenosis; VPB, ventricular premature beat; VSD, ventricular septal defect.

- *Mid-to-late diastolic murmurs:* Low-pitched, heard best with bell of stethoscope; observed in MS or TS; less commonly due to atrial myxoma.
- *Continuous murmurs:* Present in systole and diastole (envelops $S_2$); found in patent ductus arteriosus and sometimes in coarctation of aorta; less common causes are systemic or coronary AV fistula, aortopulmonary septal defect, ruptured aneurysm of sinus of Valsalva.

For a more detailed discussion, see O'Gara PT, Loscalzo J: Physical Examination of the Cardiovascular System, Chap. 267, p. 1442, in HPIM-19.

# 111 Electrocardiography

## STANDARD APPROACH TO THE ECG

Normally, voltage standardization is 1.0 mV per 10 mm, and paper speed is 25 mm/s (each horizontal small box = 0.04 s).

### Heart Rate

Beats/min = 300 divided by the number of *large* boxes (each 5 mm apart) between consecutive QRS complexes. For faster heart rates, divide 1500 by number of *small* boxes (1 mm apart) between each QRS.

### Rhythm

*Sinus rhythm* is present if every P wave is followed by a QRS, PR interval ≥0.12 s, every QRS is preceded by a P wave, and the P wave is upright in leads I, II, and III. Arrhythmias are discussed in Chaps. 122 and 123.

### Mean Axis

If QRS is primarily positive in limb leads I and II, then axis is *normal*. Otherwise, find limb lead in which QRS is most isoelectric (R = S). The mean axis is perpendicular to that lead (Fig. 111-1). If the QRS complex is *positive* in that perpendicular lead, then

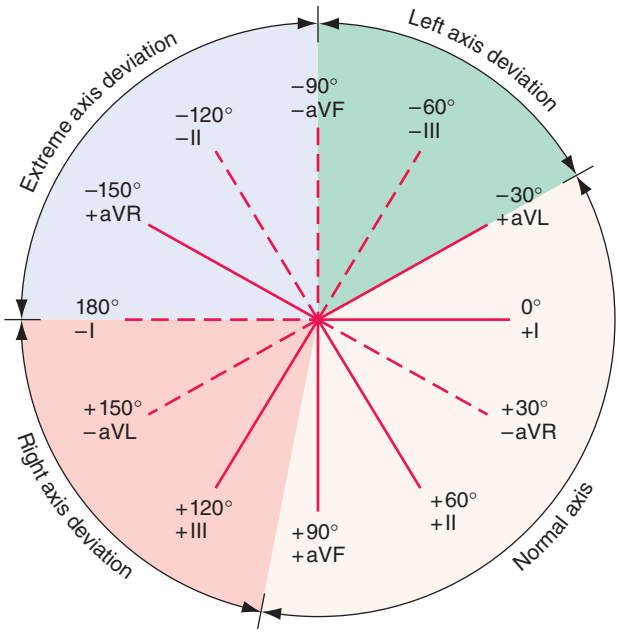



**FIGURE 111-1** Electrocardiographic lead systems: The hexaxial frontal plane reference system to estimate electrical axis. Determine leads in which QRS deflections are maximum and minimum. For example, a maximum positive QRS in I which is isoelectric in aVF is oriented to 0°. Normal axis ranges from −30° to +90°. An axis > +90° is right-axis deviation and <30° is left-axis deviation.

mean axis is in the direction of that lead; if *negative*, then mean axis points directly away from that lead.

*Left-axis deviation* (more negative than –30°) occurs in diffuse left ventricular disease, inferior MI, and in left anterior hemiblock (small R, deep S in leads II, III, and aVF).

*Right-axis deviation* (>90°) occurs in right ventricular hypertrophy (R > S in $V_1$) and left posterior hemiblock (small Q and tall R in leads II, III, and aVF). Mild right-axis deviation is common in thin, healthy individuals (up to 110°).

## INTERVALS (NORMAL VALUES IN PARENTHESES)

### PR (0.12–0.20 s)

- *Short:* (1) preexcitation syndrome (look for slurred QRS upstroke due to "delta" wave), (2) nodal rhythm (inverted P in aVF).
- *Long:* first-degree atrioventricular (AV) block (Chap. 122).

### QRS (0.06–0.10 s)

*Widened:* (1) ventricular premature beats, (2) bundle branch blocks: *right* (RsR′ in $V_1$, deep S in $V_6$) and *left* (RR′ in $V_6$ [Fig. 111-2]), (3) toxic levels of certain drugs (e.g., flecainide, propafenone, quinidine), (4) severe hypokalemia.

### QT (<50% of RR interval; corrected QT ≤0.44 s)

*Prolonged:* congenital, hypokalemia, hypocalcemia, drugs (e.g., class IA and class III antiarrhythmics, tricyclics).

## HYPERTROPHY

- *Right atrium:* P wave ≥2.5 mm in lead II.

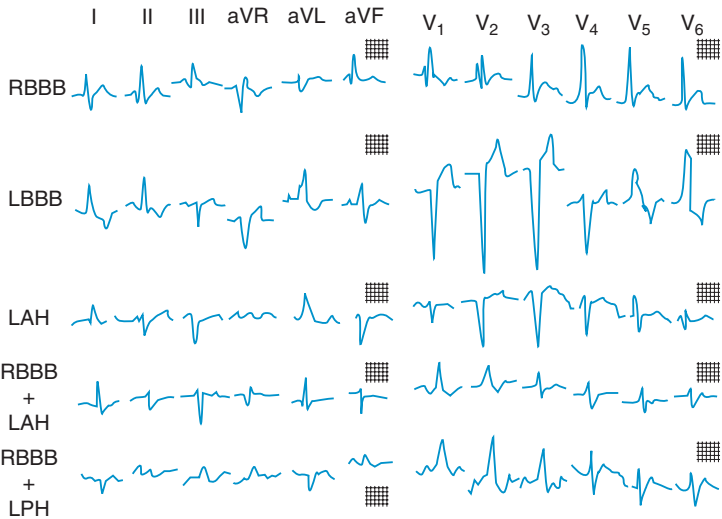



**FIGURE 111-2** Intraventricular conduction abnormalities. Illustrated are right bundle branch block (RBBB); left bundle branch block (LBBB); left anterior hemiblock (LAH); right bundle branch block with left anterior hemiblock (RBBB + LAH); and right bundle branch block with left posterior hemiblock (RBBB + LPH).

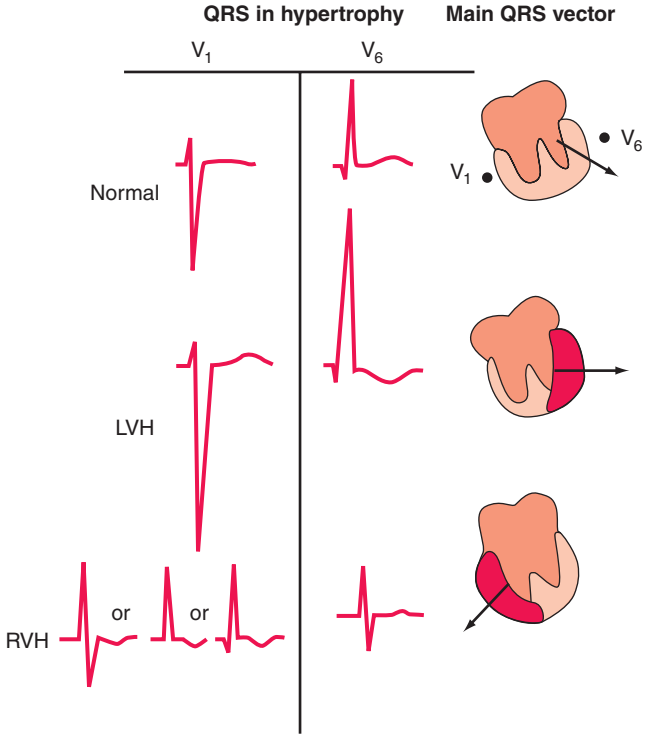



**FIGURE 111-3** Left ventricular hypertrophy (LVH) increases the amplitude of electrical forces directed to the left and posteriorly. In addition, repolarization abnormalities may cause ST-segment depression and T-wave inversion in leads with a prominent R wave. Right ventricular hypertrophy (RVH) may shift the QRS vector to the right; this effect usually is associated with an R, RS, or qR complex in lead $V_1$. T-wave inversions may be present in the right precordial leads.

- *Left atrium:* P biphasic (positive, then negative) in $V_1$, with terminal negative force wider than 0.04 s.
- *Right ventricle:* R > S in $V_1$ and R in $V_1$ > 5 mm; deep S in $V_6$; right-axis deviation (Fig. 111-3).
- *Left ventricle:* S in $V_1$ plus R in $V_5$ or $V_6$ ≥35 mm or R in aVL >11 mm (**Fig. 111-3**).

## Infarction (Fig. 111-4)

Following acute ST-segment elevation MI without successful reperfusion: *Pathologic Q waves* (≥0.04 s and ≥25% of total QRS height) in leads shown in Table 111-1; acute *non-ST-segment elevation MI* shows ST-T changes in these leads without Q-wave development. A number of conditions (other than acute MI) can cause Q waves (Table 111-2).

### ST-T WAVES

- *ST elevation:* Acute MI, coronary spasm, pericarditis (concave upward) (see Fig. 116-1 and Table 116-2), LV aneurysm, Brugada pattern (RBBB with ST elevation in $V_1$–$V_2$).

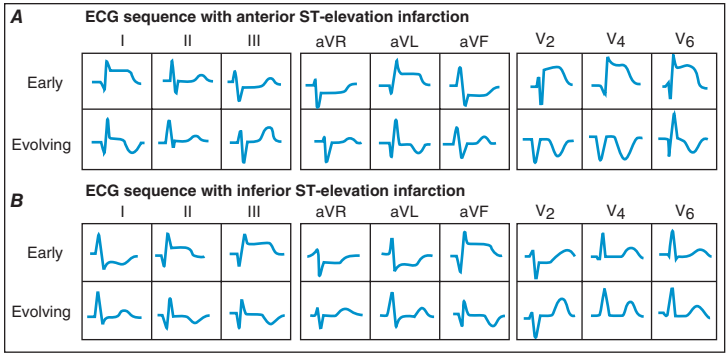



**FIGURE 111-4** Sequence of depolarization and repolarization changes with **A.** acute anterior and **B.** acute inferior ST-elevation infarctions (in the absence of successful early reperfusion). With anterior infarcts, ST elevation in leads I, aVL, and the precordial leads may be accompanied by reciprocal ST depressions in leads II, III, and aVF. Conversely, acute inferior (or posterior) infarcts may be associated with reciprocal ST depressions in leads $V_1$–$V_3$. (*Modified from AL Goldberger et al: Goldberger's Clinical Electrocardiography: A Simplified Approach, 8th ed. Philadelphia Elsevier, 2013.*)

**TABLE 111-1 LEADS WITH ABNORMAL Q WAVES IN MI**

| Leads with Abnormal Q Waves | Site of Infarction |
|---|---|
| $V_1$–$V_2$ | Anteroseptal |
| $V_3$–$V_4$ | Apical |
| I, aVL, $V_5$–$V_6$ | Anterolateral |
| II, III, aVF | Inferior |
| $V_1$–$V_2$ (tall R, *not* deep Q) | True posterior |

**TABLE 111-2 DIFFERENTIAL DIAGNOSIS OF Q WAVES (WITH SELECTED EXAMPLES)**

| |
|---|
| Physiologic or positional factors |
| 1. Normal "septal" Q waves |
| 2. Left pneumothorax or dextrocardia |
| Myocardial injury or infiltration |
| 1. Acute processes: myocardial infarction, myocarditis, hyperkalemia |
| 2. Chronic processes: cardiomyopathy, amyloid, sarcoid, scleroderma, myocardial tumor |
| Ventricular hypertrophy/enlargement |
| 1. Left ventricular (poor R-wave progression)[a] |
| 2. Right ventricular (reversed R-wave progression) |
| 3. Hypertrophic cardiomyopathy |
| Conduction abnormalities |
| 1. Left bundle branch block |
| 2. Wolff-Parkinson-White patterns |

[a]Small or absent R waves in the right to midprecordial leads.
***Source:*** Modified from AL Goldberger: *Myocardial Infarction: Electrocardiographic Differential Diagnosis*, 4th ed. St. Louis, Mosby-Year Book, 1991.

- *ST depression:* Digitalis effect, strain (due to ventricular hypertrophy), ischemia, or nontransmural MI.
- *Tall peaked T:* Hyperkalemia; acute MI ("hyperacute T").
- *Inverted T:* Non-Q-wave MI, ventricular "strain" pattern, drug effect (e.g., digitalis), hypokalemia, hypocalcemia, increased intracranial pressure (e.g., subarachnoid bleed).

For a more detailed discussion, see Goldberger AL: Electrocardiography, Chap. 268, p. 1450 in HPIM-19.

# 112 Noninvasive Examination of the Heart

## ECHOCARDIOGRAPHY (TABLE 112-1 AND FIG. 112-1)

Visualizes heart in real time with ultrasound; Doppler recordings noninvasively assess hemodynamics and abnormal flow patterns. Imaging may be compromised in pts with chronic obstructive lung disease, thick chest wall, or narrow intercostal spaces.

### Chamber Size and Ventricular Performance

Assessment of atrial and ventricular dimensions, global and regional systolic wall motion abnormalities, ventricular hypertrophy/infiltration, evaluation for pulmonary hypertension: RV systolic pressure (RVSP) is calculated from maximum velocity of tricuspid regurgitation (TR):

$$\text{RVSP} = 4 \times (\text{TR velocity})^2 + \text{RA pressure}$$

**TABLE 112-1 CLINICAL USES OF ECHOCARDIOGRAPHY**

| 2-D Echo | Transesophageal Echocardiography |
|---|---|
| Cardiac chambers: size, hypertrophy, wall motion abnormalities | Superior to 2-D echo to identify: Infective endocarditis |
| Valves: morphology and motion | Cardiac source of embolism |
| Pericardium: effusion, tamponade | Prosthetic valve dysfunction |
| Aorta: aneurysm, dissection | Aortic dissection |
| Assess intracardiac masses | |
| **Doppler Echocardiography** | **Stress Echocardiography** |
| Valvular stenosis and regurgitation<br>Intracardiac shunts<br>Diastolic filling/dysfunction<br>Approximate intracardiac pressures | Assess myocardial ischemia and viability |

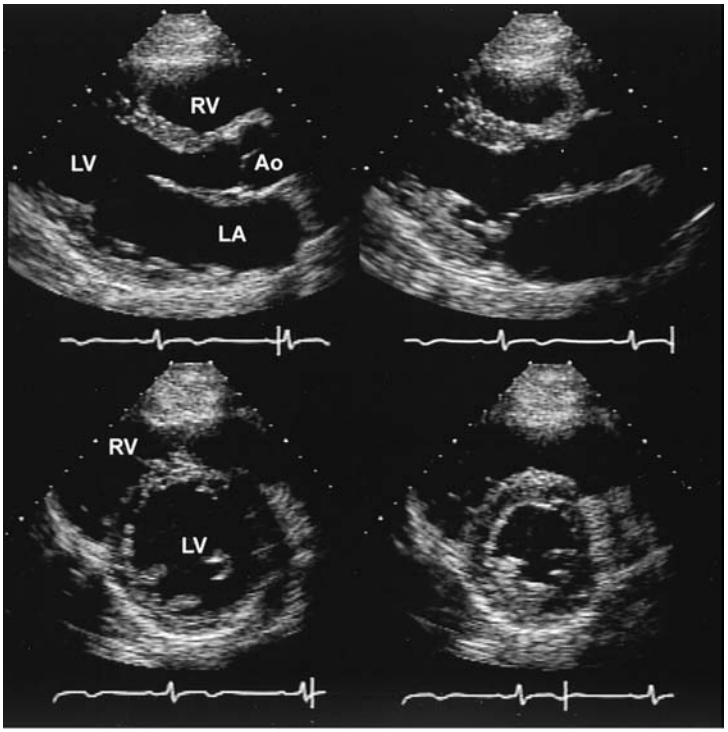



**FIGURE 112-1** Two-dimensional echocardiographic still-frame images of a normal heart. *Upper:* Parasternal long axis view during systole and diastole (*left*) and systole (*right*). During systole, there is thickening of the myocardium and reduction in the size of the left ventricle (LV). The valve leaflets are thin and open widely. *Lower:* Parasternal short axis view during diastole (*left*) and systole (*right*) demonstrating a decrease in the left ventricular cavity size during systole as well as an increase in wall thickness. Ao, aorta. (*Reproduced from RJ Myerburg: HPIM-12.*)

(RA pressure is same as JVP estimated by physical examination.) In absence of RV outflow obstruction, RVSP = pulmonary artery systolic pressure.

LV diastolic function is assessed by transmitral Doppler (see Fig. 270e-8, in HPIM-19) and Doppler tissue imaging, which measures velocity of myocardial relaxation.

## Valvular Abnormalities

Thickness, mobility, calcification, and regurgitation of each cardiac valve can be assessed. Severity of valvular stenosis is calculated by Doppler [peak gradient = 4 × (peak velocity)$^2$]. Structural lesions (e.g., flail leaflet, vegetation) resulting in regurgitation may be identified, and Doppler (Fig. 112-2) estimates severity of regurgitation.

## Pericardial Disease

Echo is noninvasive modality of choice to rapidly identify pericardial effusion and assess its hemodynamic significance; in tamponade there is diastolic RA and RV

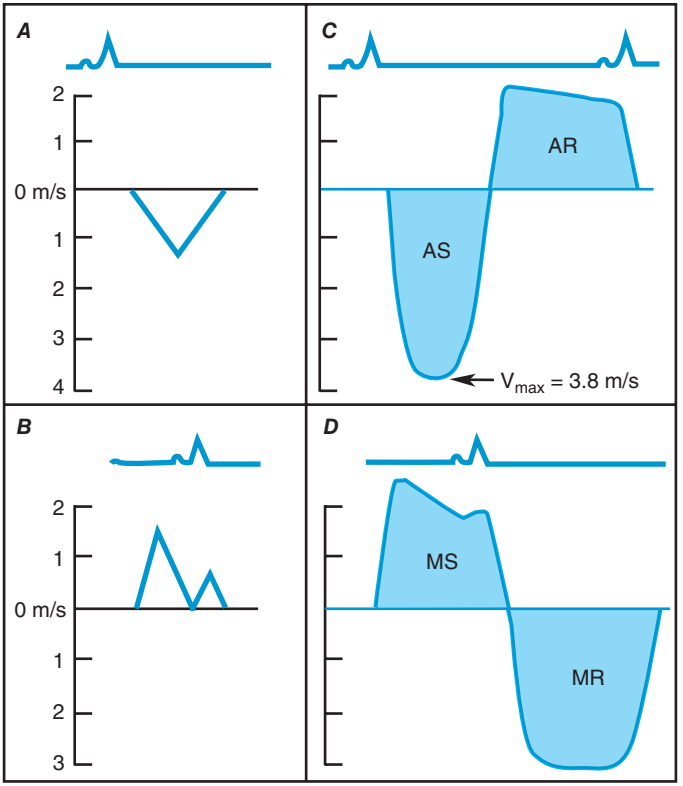



**FIGURE 112-2** Schematic presentation of normal Doppler flow across the aortic **(A)** and mitral **(B)** valves. Abnormal continuous wave Doppler profiles: **C.** Aortic stenosis (AS) [peak transaortic gradient = $4 \times V_{max}^2 = 4 \times (3.8)^2 = 58$ mmHg] and regurgitation (AR). **D.** Mitral stenosis (MS) and regurgitation (MR).

collapse, dilatation of IVC, exaggerated respiratory alterations in transvalvular Doppler velocities. Actual thickness of pericardium (e.g., in suspected constrictive pericarditis) is better measured by CT or MRI.

## Intracardiac Masses

May visualize atrial or ventricular thrombus, intracardiac tumors, and valvular vegetations. Yield of identifying cardiac source of embolism is low in the absence of cardiac history or physical findings. Transesophageal echocardiography (TEE) is more sensitive than standard transthoracic study for masses <1 cm in diameter.

## Aortic Disease

Aneurysm and dissection of the aorta may be evaluated and complications (aortic regurgitation, tamponade) assessed (Chap. 125) by standard transthoracic echo. TEE is more sensitive and specific for aortic dissection.

### Congenital Heart Disease (See Chap. 113)

Echo, Doppler, and IV saline contrast echo are useful to identify congenital lesions and shunts.

### Stress Echocardiography

Echo performed prior to, and after, treadmill or bicycle exercise identifies regions of prior MI and inducible myocardial ischemia (↓ regional contraction with exercise). Dobutamine pharmacologic stress echo can be substituted for pts who cannot exercise.

## NUCLEAR CARDIOLOGY

Uses nuclear isotopes to assess LV perfusion and contractile function.

### Ventricular Function Assessment

Contractile function can be assessed during gated single-photon emission computed tomography (SPECT) myocardial perfusion exercise test imaging (see below). Occasionally, blood pool imaging is obtained by injecting IV $^{99m}$Tc-labeled albumin or RBCs to quantify LV ejection fraction.

### Nuclear Myocardial Perfusion Assessment

SPECT imaging, most commonly using $^{99m}$Tc-labeled compounds (sestamibi or tetrofosmin), or PET imaging ($^{82}$Rb or $^{13}NH_3$), obtained at peak stress and at rest, depicts zones of prior infarction as fixed defects and regions of inducible myocardial ischemia as reversible defects. Nuclear imaging is more sensitive, but less specific, than stress echocardiography for detection of ischemia.

For pts who cannot exercise, pharmacologic perfusion imaging with adenosine, regadenoson, dipyridamole, or dobutamine is used instead (Chap. 121). For pts with LBBB, perfusion imaging with adenosine or dipyridamole is preferred to avoid artifactual septal defects that are common with exercise imaging.

Pharmacologic PET scanning is especially useful in imaging obese pts and to assess myocardial viability. Thallium-201 SPECT imaging can also be utilized to assess viability.

## MAGNETIC RESONANCE IMAGING

Delineates cardiac structures with high resolution without ionizing radiation. Excellent technique to quantitate LV mass, to characterize the pericardium, great vessels, anatomic relationships in congenital heart disease, abnormal cardiac masses, and to evaluate valvular heart disease as a complement to echocardiography. MRI with delayed gadolinium enhancement (avoid in pts with renal insufficiency) differentiates ischemic from nonischemic cardiomyopathy and is useful in assessing myocardial viability. Pharmacologic stress testing with MR identifies significant CAD and detects subendocardial ischemia with higher sensitivity than SPECT imaging.

## COMPUTED TOMOGRAPHY

Provides high-resolution images of cardiac structures (including the pericardium and cardiac masses) and detects coronary calcification in atherosclerosis with high sensitivity. CT angiography (CTA) delineates abnormalities of the great vessels, including aortic aneurysms and dissection, and pulmonary embolism. Multislice spiral CT provides high-resolution images of coronary anatomy. It is most useful in evaluation of suspected coronary anatomic anomalies and to exclude high-grade coronary stenoses in pts with chest pain and intermediate pretest probability of coronary artery disease. Its greatest accuracy is in detection of left main and proximal

**TABLE 112-2 SELECTION OF IMAGING TESTS**

| | Echo | Nuclear | CT | MRI[a] |
|---|---|---|---|---|
| LV size/ function | Initial modality of choice<br>Low cost, portable<br>Provides ancillary structural and hemodynamic information | Available from gated SPECT stress imaging | Best resolution<br>High cost | Best resolution<br>High cost |
| Valve disease | Initial modality of choice<br>Valve motion<br>Doppler hemodynamics | | | Visualize valve motion<br>Delineate abnormal flow |
| Pericardial disease | Pericardial effusion<br>Doppler hemodynamics | | Pericardial thickening | Pericardial thickening |
| Aortic disease | TEE rapid diagnosis of acute dissection[c] | | Image entire aorta<br>Aortic aneurysms<br>Aortic dissection | Image entire aorta<br>Aortic aneurysms<br>Chronic dissection |
| Cardiac masses | TTE—large intra-cardiac masses<br>TEE—smaller intracardiac masses[b] | | Extracar-diac masses<br>Myocardial masses | Extracardiac masses<br>Myocardiac masses |

[a]Relative contraindication: pacemakers, metallic objects, claustrophobic.
[b]When not seen on TTE.
***Abbreviations:*** Echo, echocardiography; SPECT, single-photon emission CT; TEE, transesophageal echocardiography; TTE, transthoracic echocardiogram.

LAD and circumflex disease. CTA is also helpful in assessing the patency of bypass grafts.

Table 112-2 summarizes key diagnostic features of the noninvasive imaging modalities. Figure 112-3 provides an algorithm for diagnostic imaging assessment of suspected CAD.

For a more detailed discussion, see DiCarli MF, Kwong RY, Solomon SD: Noninvasive Cardiac Imaging: Echocardiography, Nuclear Cardiology, and Magnetic Resonance/Computed Tomography Imaging, Chap. 270e, in HPIM-19.

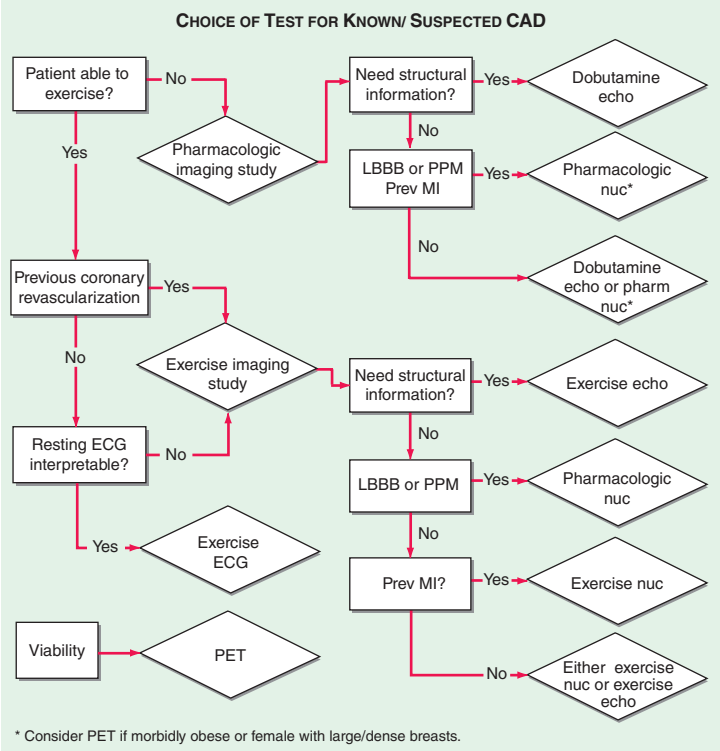



**FIGURE 112-3** Flow diagram showing selection of initial stress test in a pt with chest pain. LBBB, left bundle branch block; Prev MI-Reg ischemia, previous MI with a need to detect regional ischemia; Nuc, SPECT nuclear imaging study; Pharm, pharmacologic.

# 113 Congenital Heart Disease in the Adult

## ACYANOTIC CONGENITAL HEART LESIONS WITH LEFT-TO-RIGHT SHUNT

### ATRIAL SEPTAL DEFECT (ASD)

Most common is *ostium secundum* ASD, located at mid interatrial septum. *Sinus venosus* type ASD involves the high atrial septum and may be associated with anomalous pulmonary venous connection to the right heart. *Ostium primum* ASDs (e.g., typical of Down syndrome) appear at lower atrial septum, adjacent to atrioventricular (AV) valves.

### History

Usually asymptomatic until third or fourth decades, when exertional dyspnea, fatigue, and palpitations may occur. Onset of symptoms may be associated with development of pulmonary hypertension (see below).

### Physical Examination

Prominent right ventricular (RV) impulse, wide fixed splitting of $S_2$, systolic murmur from flow across pulmonic valve, diastolic flow rumble across tricuspid valve, prominent jugular venous *v* wave.

### ECG

Incomplete RBBB (rSR' in right precordial leads) common. Left axis deviation frequently present with ostium primum defect. Ectopic atrial pacemaker or first degree AV block occur in sinus venosus defects.

### CXR

Increased pulmonary vascular markings, prominence of right atrium (RA), RV, and main pulmonary artery (LA enlargement *not* usually present).

### Echocardiogram

RA, RV, and pulmonary artery enlargement; Doppler shows abnormal turbulent transatrial flow. Echo contrast (agitated saline injection into peripheral systemic vein) may visualize transatrial shunt. Transesophageal echo usually diagnostic if transthoracic echo is ambiguous.

**TREATMENT ATRIAL SEPTAL DEFECT**

In the absence of contraindications an ASD with a significant pulmonary-to-systemic flow (PF:SF) ratio (≥1.5:1.0) should be considered for surgical or percutaneous transcatheter closure. Closure is usually contraindicated with significant pulmonary hypertension and is not undertaken for small defects with trivial left-to-right shunt flow.

## VENTRICULAR SEPTAL DEFECT (VSD)

Congenital VSDs may close spontaneously during childhood. Symptoms relate to size of the defect and pulmonary vascular resistance.

### History

CHF may develop in infancy. Adults may be asymptomatic or develop fatigue and reduced exercise tolerance.

### Physical Examination

Holosystolic murmur at lower left sternal border, which may be accompanied by a palpaple thrill, loud $P_2$; diastolic flow murmur across mitral valve.

### ECG

Normal with small defects. Large shunts result in LA and LV enlargement.

### CXR

Enlargement of main pulmonary artery, LA, and LV, with increased pulmonary vascular markings.

### Echocardiogram

LA and LV enlargement; defect may be directly visualized. Color Doppler demonstrates flow across the defect.

**TREATMENT VENTRICULAR SEPTAL DEFECT**

Fatigue and mild dyspnea are treated with diuretics and afterload reduction (Chap. 124). Surgical closure is indicated if PF:SF >1.5:1 in absence of very high pulmonary vascular resistance.

### PATENT DUCTUS ARTERIOSUS (PDA)

Abnormal communication between the descending aorta and pulmonary artery; associated with birth at high altitudes and maternal rubella.

#### History

Asymptomatic or fatigue and dyspnea on exertion.

#### Physical Examination

Hyperactive LV impulse; loud continuous "machinery" murmur at upper left sternal border. If pulmonary hypertension develops, diastolic component of the murmur may disappear.

#### ECG

LV hypertrophy is common; RV hypertrophy if pulmonary hypertension develops.

#### CXR

Increased pulmonary vascular markings: enlarged main pulmonary artery, LV, ascending aorta; occasionally, calcification of ductus.

#### Echocardiography

Hyperdynamic, enlarged LV; the PDA can often be visualized on two-dimensional echo; Doppler demonstrates abnormal flow through it.

**TREATMENT PATENT DUCTUS ARTERIOSUS**

In absence of pulmonary hypertension, PDA should be surgically ligated or divided to prevent infective endocarditis, LV dysfunction, and pulmonary hypertension. Transcatheter device closure is frequently possible.

### PROGRESSION TO PULMONARY HYPERTENSION (PHT)

Pts with large, uncorrected left-to-right shunts (e.g., ASD, VSD, or PDA) may develop progressive, irreversible PHT with reverse shunting of desaturated blood into the arterial circulation (right-to-left direction), resulting in *Eisenmenger syndrome*. Fatigue, lightheadedness, and chest pain due to RV ischemia are common, accompanied by cyanosis, clubbing of digits, loud $P_2$, murmur of pulmonary valve regurgitation, and signs of RV failure. ECG and echocardiogram show RV hypertrophy. Therapeutic options are limited and include pulmonary artery vasodilators (see Chap. 127) and consideration of single lung transplant with repair of the cardiac defect, or heart-lung transplantation.

## ACYANOTIC CONGENITAL HEART LESIONS WITHOUT A SHUNT

### PULMONIC STENOSIS (PS)

A transpulmonary valve gradient < 30 mmHg indicates mild PS, 30–50 mmHg is moderate PS, and >50 mmHg is considered severe PS. Mild to moderate PS rarely causes symptoms, and progression tends not to occur. Pts with higher gradients may manifest dyspnea, fatigue, light-headedness, chest pain (RV ischemia).

### Physical Examination

Jugular venous distention with prominent *a* wave, RV parasternal impulse, wide splitting of $S_2$ with soft $P_2$, ejection click followed by "diamond-shaped" systolic murmur at upper left sternal border, right-sided $S_4$.

### ECG

Normal in mild PS; RA and RV enlargement in advanced PS.

### CXR

Often shows poststenotic dilatation of the pulmonary artery and RV enlargement.

### Echocardiography

RV hypertrophy and systolic "doming" of the pulmonic valve. Doppler accurately measures transvalvular gradient.

**TREATMENT PULMONIC STENOSIS**

Symptomatic or severe stenosis requires balloon valvuloplasty or surgical correction.

## CONGENITALLY BICUSPID AORTIC VALVE

One of the most common congenital heart malformations (up to 1.4% of the population); rarely results in childhood aortic stenosis (AS), but is a cause of AS and/or regurgitation later in life. May go undetected in early life or suspected by the presence of a systolic ejection click; often identified during echocardiography that was obtained for another reason. See Chap. 114 for typical history, physical findings, and treatment of subsequent clinical aortic valve disease.

## COARCTATION OF THE AORTA

Aortic constriction just distal to the origin of the left subclavian artery is a surgically correctable form of hypertension (Chap. 117). Usually asymptomatic, but may cause headache, fatigue, or claudication of lower extremities. Often accompanied by bicuspid aortic valve.

### Physical Examination

Hypertension in upper extremities; delayed femoral pulses with decreased pressure in lower extremities. Pulsatile collateral arteries may be palpated in the intercostal spaces. Systolic (and sometimes also diastolic) murmur is best heard over the upper back at the left interscapular space.

### ECG

LV hypertrophy.

### CXR

Notching of the ribs due to collateral arteries; "figure 3" appearance of distal aortic arch.

### Echocardiography

Can delineate site and length of coarctation, and Doppler determines the pressure gradient across it. MR or CT angiography also visualizes the site of coarctation and can identify associated collateral vessel formation.

**TREATMENT** COARCTATION OF THE AORTA

Surgical correction (or percutaneous transcatheter stent dilation in selected pts), although hypertension may persist. Recoarctation after surgical repair may be amenable to percutaneous balloon dilatation.

## COMPLEX CONGENITAL HEART LESIONS

Such lesions are often accompanied by cyanosis. Examples include:

### TETRALOGY OF FALLOT

The four main components are (1) malaligned VSD, (2) obstruction to RV outflow, (3) aorta that overrides the VSD, and (4) RV hypertrophy (RVH). Degree of RV outflow obstruction largely determines clinical presentation; when severe, the large right-to-left shunt causes cyanosis and systemic hypoxemia. *ECG* shows RVH. *CXR* demonstrates "boot-shaped" heart with prominent RV. *Echocardiography* delineates VSD, overriding aorta, and RVH and quantitates degree of RV outflow obstruction.

### COMPLETE TRANSPOSITION OF THE GREAT ARTERIES

Accounts for 10% of pts with cyanotic congenital heart disease. Aorta and pulmonary artery arise abnormally from the right and left ventricles respectively, creating two separate parallel circulations; a communication must exist between the two sides (ASD, PDA, or VSD) to sustain life. Development of RV dysfunction and heart failure are common by the third decade. *Echocardiography* reveals the aberrant anatomy.

### EBSTEIN ANOMALY

Abnormal downward placement of tricuspid valve within the RV; tricuspid regurgitation, hypoplasia of RV, and a right-to-left shunt are common. *Echocardiography* shows apical displacement of tricuspid septal leaflet, abnormal RV size, and quantitates degree of tricuspid regurgitation.

## ENDOCARDITIS PROPHYLAXIS IN CONGENITAL HEART DISEASE

American Heart Association 2007 Guidelines recommend antibiotic prophylaxis only in specific pts with congenital heart disease, i.e., those who are to undergo a dental procedure associated with bacteremia who have:

1. Unrepaired cyanotic congenital heart disease (e.g., tetralogy of Fallot)
2. Repaired congenital heart disease with residual defects adjacent to site of a prosthetic patch or transcatheter device
3. A history of complete repair of congenital defects with prosthetic material or a transcatheter device within the previous 6 months

For a more detailed discussion, see Aboulhosn JA, Child JS: Congenital Heart Disease in the Adult, Chap. 282, p. 1519, in HPIM-19.

# 114 Valvular Heart Disease

## MITRAL STENOSIS (MS)

### Etiology

Most commonly rheumatic, although history of acute rheumatic fever is now uncommon; rare causes include congenital MS and calcification of the mitral annulus with extension onto the leaflets.

### History

Symptoms most commonly begin in the fourth decade, but MS often causes severe disability at earlier ages in developing nations. Principal symptoms are dyspnea and pulmonary edema precipitated by exertion, excitement, fever, anemia, tachycardia, pregnancy, sexual intercourse, etc.

### Physical Examination

Right ventricular lift; palpable $S_1$; opening snap (OS) follows $A_2$ by 0.06–0.12 s; OS–$A_2$ interval inversely proportional to severity of obstruction. Diastolic rumbling murmur with presystolic accentuation when in sinus rhythm. Duration of murmur correlates with severity of obstruction.

### Complications

Hemoptysis, pulmonary embolism, pulmonary infection, systemic embolization; endocarditis is uncommon in pure MS.

### Laboratory ECG

Typically shows atrial fibrillation (AF) or left atrial (LA) enlargement when sinus rhythm is present. Right-axis deviation and RV hypertrophy in the presence of pulmonary hypertension.

### CXR

Shows LA and RV enlargement and Kerley B lines.

### Echocardiogram

Most useful noninvasive test; shows reduced separation, calcification and thickening of valve leaflets and subvalvular apparatus, and LA enlargement. Doppler flow recordings provide estimation of transvalvular gradient, mitral valve area, and degree of pulmonary hypertension (Chap. 112).

## TREATMENT MITRAL STENOSIS (SEE FIG. 114-1)

At-risk pts should receive prophylaxis for recurrent rheumatic fever (penicillin V 250–500 mg PO bid or benzathine penicillin G 1–2 M units IM monthly). In the presence of dyspnea, sodium restriction and oral diuretic therapy; beta blockers, rate-limiting calcium channel antagonists (i.e., verapamil or diltiazem), or digoxin to slow ventricular rate in AF. Warfarin (with target INR 2.0–3.0) for pts with AF or history of thromoembolism. For AF of recent onset, consider conversion (chemical or electrical) to sinus rhythm, ideally after ≥3 weeks of anticoagulation. Mitral valvotomy in the presence of symptoms and mitral orifice ≤ ~1.5 $cm^2$. In uncomplicated MS, percutaneous balloon valvuloplasty is the procedure of choice; if not feasible, then open surgical valvotomy (Fig. 114-1).

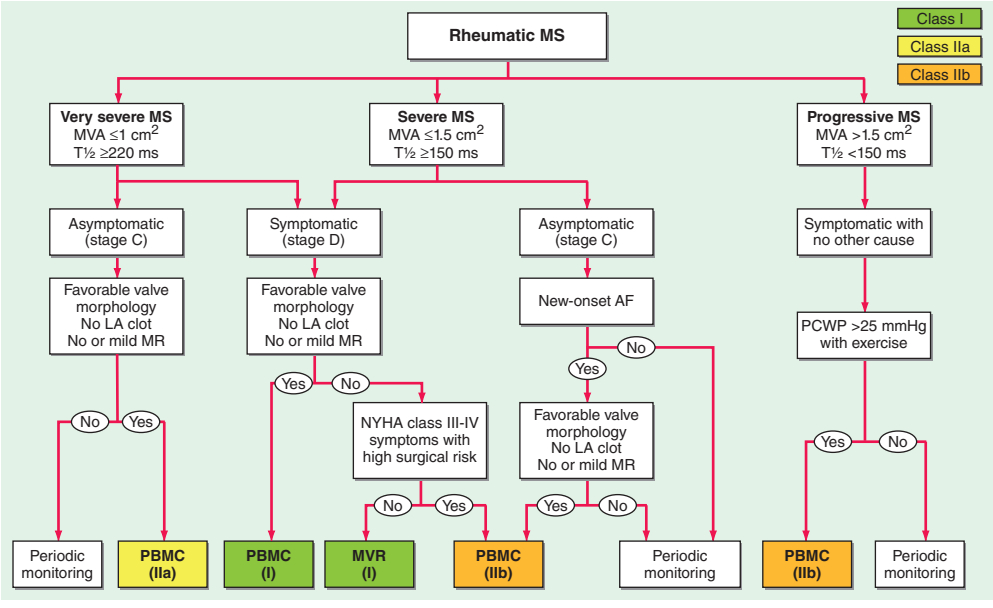



**FIGURE 114-1** Management of rheumatic mitral stenosis. MR, mitral regurgitation; MS, mitral stenosis; MVA, mitral valve area; MVR, mitral valve surgery (repair or replacement); NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure; PMBC, percutaneous mitral balloon commissurotomy; and T ½, pressure half-time. *(Adapted from RA Nishimura et al: 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease. J Am Coll Cardiol 63:e57, 2014.)*

## MITRAL REGURGITATION (MR)

### Etiology

Mitral valve prolapse (see below), rheumatic heart disease, ischemic heart disease with papillary muscle dysfunction, LV dilatation of any cause, mitral annular calcification, hypertrophic cardiomyopathy, infective endocarditis, congenital.

### Clinical Manifestations

Fatigue, weakness, and exertional dyspnea. Physical examination: sharp low-volume upstroke of carotid arterial pulse, LV lift, $S_1$ diminished: wide splitting of $S_2$; $S_3$ common; loud holosystolic murmur at the apex (less than holosystolic in acute severe MR) and often a brief early-mid-diastolic murmur due to increased transvalvular flow.

### Echocardiogram

Enlarged LA, hyperdynamic LV, identifies mechanism of MR; Doppler analysis helpful in diagnosis and assessment of severity of MR and degree of pulmonary hypertension.

**TREATMENT** MITRAL REGURGITATION (SEE FIG. 114-2)

For severe/decompensated MR, treat as for heart failure (Chap. 124). IV vasodilators (e.g., nitroprusside) are beneficial for acute, severe MR. Anticoagulation is indicated in the presence of atrial fibrillation. For chronic primary MR, surgical treatment, either valve repair or replacement, is appropriate if pt has symptoms or evidence of progressive LV dysfunction (e.g., LV ejection fraction [LVEF] ≤60% or end-systolic LV diameter by echo ≥40 mm). Operation should be carried out before development of chronic heart failure symptoms. Pts with functional ischemic MR may require coronary artery revascularization along with valve repair. Functional nonischemic MR due to LV enlargement with impaired contractile function should be treated with aggressive heart failure therapies and consideration of cardiac resynchronization therapy (Chap. 124).

## MITRAL VALVE PROLAPSE (MVP)

### Etiology

Most commonly idiopathic; may accompany Marfan syndrome, Ehlers-Danlos syndrome.

### Pathology

Redundant mitral valve tissue with myxedematous degeneration and elongated chordae tendineae.

### Clinical Manifestations

More common in females. Most pts are asymptomatic and remain so. Potential symptoms include vague chest pain and supraventricular and ventricular arrhythmias. Most important complication is progressive MR. Rarely, systemic emboli from platelet-fibrin deposits on valve. Sudden death is a very rare outcome.

### Physical Examination

Mid or late systolic click(s) followed by late systolic murmur at the apex; exaggeration by Valsalva maneuver, reduced by squatting and isometric exercise (Chap. 110).

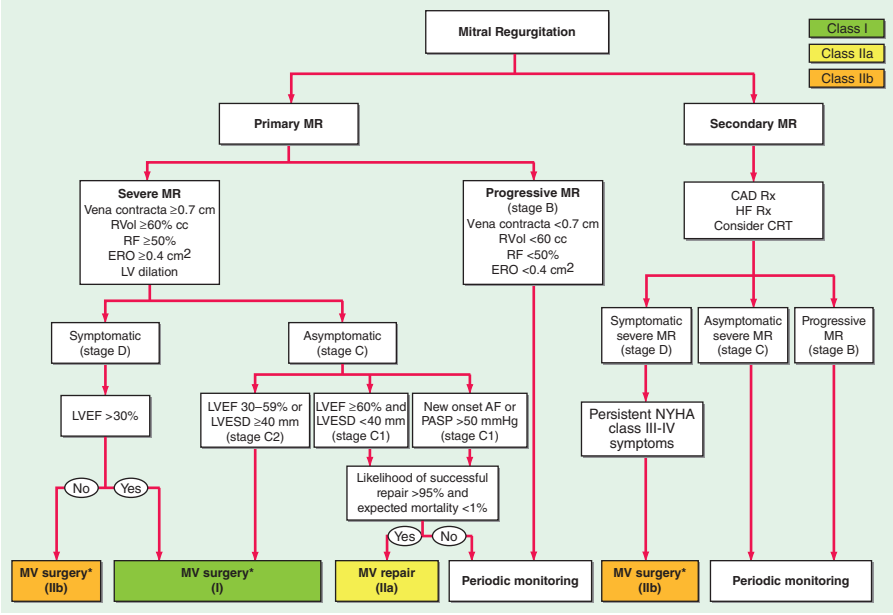



**FIGURE 114-2** Management of mitral regurgitation. CAD, coronary artery disease; CRT, cardiac resynchronization therapy; ERO, effective regurgitant orifice; HF, heart failure; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; MR, mitral regurgitation, MV, mitral valve; MVR, mitral valve replacement; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; RF, regurgitant fraction; RVol, regurgitant volume; and Rx, therapy. Mitral valve repair preferred over MVR when possible. *(Adapted from RA Nishimura et al: 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease. J Am Coll Cardiol 63:e57, 2014.)*

### Echocardiogram

Shows posterior displacement of one or both mitral leaflets late in systole.

**TREATMENT** MITRAL VALVE PROLAPSE

Asymptomatic pts should be reassured. Beta blockers may lessen chest discomfort and palpitations. Prophylaxis for infective endocarditis is indicated only if prior history of endocarditis. Valve repair or replacement for pts with severe mitral regurgitation; aspirin or anticoagulants for pts with history of TIA or embolization.

## AORTIC STENOSIS (AS)

### Etiologies

Most common are (1) degenerative calcification of a congenitally bicuspid valve, (2) chronic deterioration and calcification of a trileaflet valve, and (3) rheumatic disease (almost always associated with rheumatic *mitral* disease).

### Symptoms

Exertional dyspnea, angina, and syncope are cardinal symptoms; they occur late, after years of obstruction and aortic valve area ≤1.0 $cm^2$.

### Physical Examination

Weak and delayed (parvus et tardus) arterial pulses with carotid thrill. $A_2$ soft or absent; $S_4$ common. Crescendo-decrescendo systolic murmur, often with systolic thrill. Murmur is typically loudest at second right intercostal space, with radiation to carotids and sometimes to the apex (*Gallavardin effect*).

### ECG

Often shows LV hypertrophy, but not useful for predicting gradient.

### Echocardiogram

Shows LV hypertrophy, calcification and thickening of aortic valve cusps with reduced systolic opening. Dilatation and reduced contraction of LV indicate poor prognosis. Doppler quantitates systolic gradient and allows calculation of valve area.

**TREATMENT** AORTIC STENOSIS (SEE FIG. 114-3)

Avoid strenuous activity in severe AS, even in asymptomatic phase. Treat heart failure in standard fashion (Chap. 124), but use vasodilators with caution in pts with advanced disease. Valve replacement is indicated in adults with symptoms resulting from AS and hemodynamic evidence of severe obstruction. Transcatheter aortic valve implantation (TAVI) is an alternative approach for pts at excessive or prohibitive surgical risk.

## AORTIC REGURGITATION (AR)

### Etiology

*Valvular:* Rheumatic (especially if rheumatic mitral disease is present), bicuspid valve, endocarditis. *Dilated aortic root:* dilatation due to cystic medial necrosis, aortic dissection, ankylosing spondylitis, syphilis. Three-fourths of pts are male.

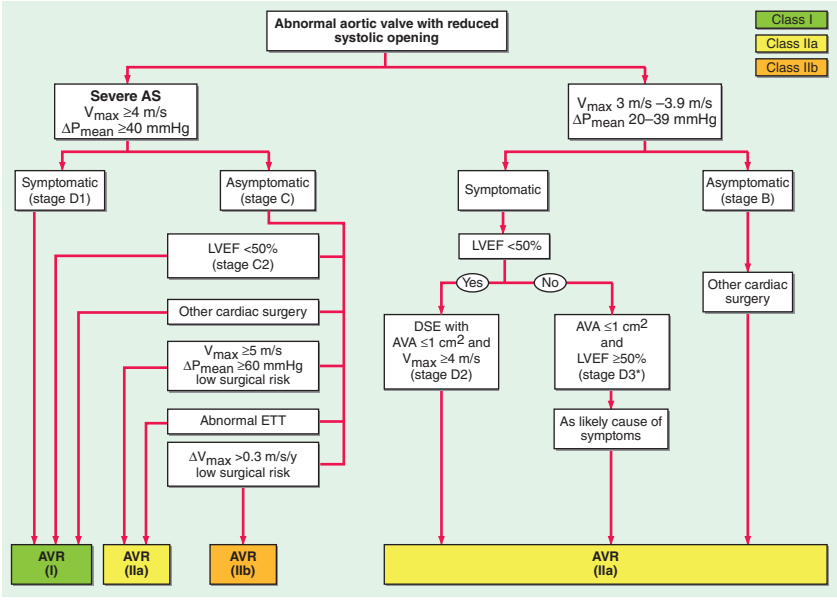



**FIGURE 114-3** Algorithm for the management of aortic stenosis (AS). See Figure 283-2, p. 1533, in HPIM 19 for explanation of specific stages A-D of disease progression. AS, aortic stenosis; AVA; aortic valve area; AVR, aortic valve replacement by either surgical or transcatheter approach; DSE, dobutamine stress echocardiography; ETT, exercise treadmill test; LVEF, left ventricular ejection fraction; $\Delta P_{mean}$, mean pressure gradient; and $V_{max}$, maximum velocity. *(Adapted from RA Nishimura et al: 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease. J Am Coll Cardiol 63:e57, 2014.)*

## Clinical Manifestations

Exertional dyspnea and awareness of forceful heartbeat, angina pectoris, and signs of LV failure. Wide pulse pressure, "water hammer" pulse, capillary pulsations (Quincke's sign), $A_2$ soft or absent, $S_3$ may be present. Blowing, decrescendo diastolic murmur along left sternal border (along right sternal border when due to aortic dilatation). In acute severe AR, the pulse pressure is typically not widened and the diastolic murmur is often short (i.e., occurring only in early diastole) and soft.

## Laboratory ECG and CXR

LV enlargement.

## Echocardiogram

LA enlargement, LV enlargement, high-frequency diastolic fluttering of mitral valve. Failure of coaptation of aortic valve leaflets may be present. Doppler studies useful in detection and quantification of AR. Cardiac magnetic resonance imaging helpful if echo is inadequate.

### TREATMENT AORTIC REGURGITATION

Standard therapy for LV failure (Chap. 124). Vasodilators (ACE inhibitor or long-acting nifedipine) are recommended if hypertension present. Avoid beta blockers, which prolong diastolic filling. Surgical valve replacement should be carried out in pts with severe AR when symptoms develop or in asymptomatic pts with LV dysfunction (e.g., LVEF <50%, end-systolic diameter >50 mm, or LV diastolic dimension >65 mm) by imaging studies.

# TRICUSPID STENOSIS (TS)

## Etiology

Usually rheumatic; most common in females; almost invariably associated with MS.

## Clinical Manifestations

Hepatomegaly, ascites, edema, jaundice, jugular venous distention with slow *y* descent (Chap. 110). Diastolic rumbling murmur along left sternal border increased by inspiration with loud presystolic component. Right atrial and superior vena caval enlargement on chest x-ray. Doppler echocardiography demonstrates thickened valve and impaired separation of leaflets and provides estimate of transvalvular gradient.

### TREATMENT TRICUSPID STENOSIS

In severe TS, surgical relief is indicated, with valvular repair or replacement.

# TRICUSPID REGURGITATION (TR)

## Etiology

Usually functional and secondary to marked RV dilatation of any cause and often associated with pulmonary hypertension.

## Clinical Manifestations

Severe RV failure, with edema, hepatomegaly, and prominent *v* waves in jugular venous pulse with rapid *y* descent (Chap. 110). Systolic murmur along lower left sternal edge is increased by inspiration. Doppler echocardiography confirms diagnosis and estimates severity.

**TREATMENT TRICUSPID REGURGITATION**

Intensive diuretic therapy when right-sided heart failure signs are present. In severe cases (in absence of severe pulmonary hypertension), surgical treatment consists of tricuspid annuloplasty or valve replacement.

For a more detailed discussion, see O'Gara PT, Loscalzo J: Aortic Valve Disease, Chap. 283, p. 1528; Mitral Valve Disease, Chap. 284, p. 1539; Tricuspid and Pulmonary Valve Disease, Chap. 285, p. 1547; Multiple and Mixed Valvular Disease, Chap. 286, p. 1550 in HPIM-19.

# 115 Cardiomyopathies and Myocarditis

Cardiomyopathies are primary diseases of heart muscle. Table 115-1 summarizes distinguishing presenting features of the three major types of cardiomyopathy. Table 115-2 details the comprehensive initial evaluation of suspected cardiomyopathies.

## DILATED CARDIOMYOPATHY (CMP)

Symmetrically dilated left ventricle (LV), with poor systolic contractile function; right ventricle (RV) commonly involved.

### Etiology

Approximately one-third of pts have a familial form, including those cases due to mutations in genes encoding sarcomeric proteins. Other causes include previous myocarditis, toxins (ethanol, certain antineoplastic agents [doxorubicin, trastuzumab, imatinib]), connective tissue disorders, hemochromatosis, sarcoidosis, muscular dystrophies, "peripartum." Impaired LV function owing to severe coronary disease/infarction or chronic aortic/mitral regurgitation may behave similarly.

### Symptoms

Congestive heart failure (Chap. 124); tachyarrhythmias and peripheral emboli from LV mural thrombus occur.

### Physical Examination

Jugular venous distention (JVD), rales, diffuse and dyskinetic LV apex, $S_3$, hepatomegaly, peripheral edema; murmurs of mitral and tricuspid regurgitation are common.

### Laboratory ECG

Left bundle branch block and ST-T-wave abnormalities common.

### CXR

Cardiomegaly, pulmonary vascular redistribution, pulmonary effusions common.

**TABLE 115-1 PRESENTATION WITH SYMPTOMATIC CARDIOMYOPATHY**

| | Dilated | Restrictive | Hypertrophic |
|---|---|---|---|
| Ejection fraction (normal >55%) | Usually <30% when symptoms severe | 25–50% | >60% |
| Left ventricular diastolic dimension (normal <55 mm) | ≥60 mm | <60 mm (may be decreased) | Often decreased |
| Left ventricular wall thickness | Normal or decreased | Normal or increased | Markedly increased |
| Atrial size | Increased | Increased; may be massive | Increased |
| Valvular regurgitation | Related to annular dilation | Related to endocardial involvement; frequent mitral and tricuspid regurgitation, rarely severe | Related to valve-septum interaction; mitral regurgitation |
| Common first symptoms | Exertional intolerance | Exertional intolerance, fluid retention early | Exertional intolerance; may have chest pain |
| Congestive symptoms[a] | Left before right, except right prominent in young adults | Right often dominates | Left-sided congestion may develop late |
| Arrhythmia | Ventricular tachyarrhythmia; conduction block in Chagas' disease, and some families. Atrial fibrillation. | Ventricular uncommon except in sarcoidosis conduction block in sarcoidosis and amyloidosis. Atrial fibrillation. | Ventricular tachyarrhythmias; atrial fibrillation |

[a]Left-sided symptoms of pulmonary congestion: dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea. Right-sided symptoms of systemic versus congestion: discomfort on bending, hepatic and abdominal distention, peripheral edema.

## Echocardiogram, CT, and Cardiac MRI

LV and RV enlargement with globally impaired contraction. *Regional* wall motion abnormalities suggest coronary artery disease rather than primary cardiomyopathy.

## B-Type Natriuretic Peptide (BNP)

Level elevated in heart failure/cardiomyopathy but not in pts with dyspnea due to lung disease.

## TREATMENT DILATED CARDIOMYOPATHY

Standard therapy of heart failure (Chap. 124): Diuretic for volume overload, vasodilator therapy with ACE inhibitor (preferred), angiotensin receptor blocker or hydralazine-nitrate combination shown to limit disease progression and improve longevity. Add beta blocker in most pts. Consider aldosterone antagonist

**TABLE 115-2 INITIAL EVALUATION OF CARDIOMYOPATHY**

| |
|---|
| **Clinical Evaluation** |
| Thorough history and physical examination to identify cardiac and noncardiac disorders[a] |
| Detailed family history of heart failure, cardiomyopathy, skeletal myopathy, conduction disorders and tachyarrhythmias, sudden death |
| History of alcohol, illicit drugs, chemotherapy, or radiation therapy[a] |
| Assessment of ability to perform routine and desired activities[a] |
| Assessment of volume status, orthostatic blood pressure, body mass index[a] |
| **Laboratory Evaluation** |
| Electrocardiogram[a] |
| Chest radiograph[a] |
| Two-dimensional and Doppler echocardiogram[a] |
| Magnetic resonance imaging to assess myocardial inflammation and fibrosis |
| Chemistry: |
| Serum sodium,[a] potassium,[a] calcium,[a] magnesium[a] |
| Fasting glucose (glycohemoglobin in DM) |
| Creatinine, [a] blood urea nitrogen[a] |
| Albumin,[a] total protein,[a] liver function tests[a] |
| Lipid profile |
| Thyroid-stimulating hormone[a] |
| Serum iron, transferrin saturation |
| Urinalysis |
| Hematology: |
| Hemoglobin/hematocrit[a] |
| White blood cell count with differential,[a] including eosinophils |
| Erythrocyte sedimentation rate |
| **Initial Evaluation Only in Pts Selected for Possible Specific Diagnosis** |
| Titers for infection in presence of clinical suspicion: |
| Acute viral (e.g., coxsackievirus, echovirus, influenza virus) |
| Human immunodeficiency virus, |
| Chagas' disease, Lyme disease, toxoplasmosis |
| Catheterization with coronary angiography in pts with angina who are candidates for intervention[a] |
| Serologies for active rheumatologic disease |
| Endomyocardial biopsy including sample for electron microscopy when suspecting specific diagnosis with therapeutic implications |
| Screening for sleep-disordered breathing |

[a]Level I Recommendations from ACC/AHA Practice Guidelines for Chronic Heart Failure in the adult.
***Source:*** From SA Hunt et al: *Circulation* 112: 2005.

therapy for pts with class II–IV heart failure, and chronic anticoagulation if there is accompanying atrial fibrillation (AF), prior embolism, or recent large anterior MI. Antiarrhythmic drugs (e.g., amiodarone or dofetilide) may be useful to maintain sinus rhythm in pts with AF. Consider implanted cardioverter defibrillator for pts with ≥ class III heart failure and LVEF <35%. For those with persistent class III–IV heart failure, LVEF <35%, and QRS duration >120 ms, consider biventricular

pacing. Possible trial of immunosuppressive drugs, if active myocarditis present on RV biopsy (controversial as long-term efficacy has not been demonstrated). In selected pts, consider cardiac transplantation.

## RESTRICTIVE CARDIOMYOPATHY

Increased myocardial stiffness impairs ventricular relaxation; diastolic ventricular pressures are elevated. Etiologies include infiltrative disease (amyloid, sarcoid, hemochromatosis, eosinophilic disorders), endomyocardial fibrosis, Fabry's disease, and prior mediastinal irradiation.

### Symptoms

Typically presents with heart failure, often predominantly right-sided.

### Physical Examination

Especially signs of right-sided heart failure: JVD, hepatomegaly, peripheral edema, murmur of tricuspid regurgitation. $S_4$ is common.

### Laboratory ECG

Low limb lead voltage, sinus tachycardia, ST-T-wave abnormalities.

### CXR

Mild LV enlargement.

### Echocardiogram, CT, Cardiac MRI

Bilateral atrial enlargement; increased ventricular thickness ("speckled pattern") in infiltrative disease, especially amyloidosis. Systolic function is usually normal but may be mildly reduced.

### Cardiac Catheterization

Increased LV and RV diastolic pressures with "dip and plateau" pattern; RV biopsy useful in detecting infiltrative disease (rectal or fat pad biopsy useful in diagnosis of amyloidosis).

***Note:*** Must distinguish restrictive cardiomyopathy from constrictive pericarditis, which is surgically correctable. Thickening of pericardium on CT or MR imaging is apparent in >80% of pts with constrictive pericarditis.

### TREATMENT RESTRICTIVE CARDIOMYOPATHY

Salt restriction and diuretics ameliorate pulmonary and systemic congestion. ***Note:*** Increased sensitivity to digitalis in amyloidosis. Anticoagulation often indicated, particularly in pts with eosinophilic endomyocarditis. For specific therapy of hemochromatosis and sarcoidosis, see Chaps. 428 and 390, respectively, in HPIM-19.

## HYPERTROPHIC CARDIOMYOPATHY

Marked LV hypertrophy; often asymmetric, without underlying hypertension or valvular disease. Systolic function is usually normal; increased LV stiffness results in elevated diastolic filling pressures. Typically results from mutations in sarcomeric proteins (autosomal dominant transmission).

### Symptoms

Secondary to elevated diastolic pressure, dynamic LV outflow obstruction (if present), and arrhythmias; dyspnea on exertion, angina, and presyncope; sudden death may occur.

## Physical Examination

Brisk carotid upstroke with pulsus bisferiens; $S_4$, harsh systolic murmur along left sternal border, blowing murmur of mitral regurgitation at apex; murmur enhances with Valsalva and other maneuvers that decrease LV filling (Chap. 110).

## Laboratory ECG

LV hypertrophy with prominent "septal" Q waves in leads I, aVL, $V_{5-6}$. Periods of AF or ventricular tachycardia (VT) are often detected by Holter monitor.

## Echocardiogram

LV hypertrophy, often with asymmetric involvement, especially of the septum or apex; LV contractile function typically excellent with small end-systolic volume. If LV outflow tract obstruction is present, systolic anterior motion (SAM) of mitral valve and midsystolic partial closure of aortic valve are present. Doppler shows early systolic accelerated blood flow through LV outflow tract.

## TREATMENT HYPERTROPHIC CARDIOMYOPATHY

Strenuous exercise should be avoided. Beta blockers, verapamil, or disopyramide used individually to reduce symptoms. Digoxin, other inotropes, diuretics, and vasodilators are generally *contraindicated*. Endocarditis antibiotic prophylaxis (Chap. 80) is necessary only in pts with a prior history of endocarditis. Antiarrhythmic agents, especially amiodarone, may suppress atrial and ventricular arrhythmias. However, consider implantable cardioverter defibrillator for pts with high-risk profile, e.g., history of syncope or aborted cardiac arrest, nonsustained VT, marked LVH (>3 cm), exertional hypotension, or family history of sudden death. In selected pts, LV outflow gradient can be reduced by controlled septal infarction by ethanol injection into the septal artery. Surgical myectomy may be useful in pts refractory to medical therapy.

# MYOCARDITIS

Inflammation of the myocardium that may progress to chronic dilated cardiomyopathy, most commonly due to acute viral infection (e.g., parvovirus B19, human herpesvirus 6, Epstein-Barr virus, coxsackievirus, adenovirus). Myocarditis may also develop in pts with HIV infection, hepatitis C or Lyme disease. Chagas' disease is a common cause of myocarditis in endemic areas, typically Central and South America. Noninfective causes of myocarditis include granulomatous disease (e.g., sarcoid, giant cell myocarditis), which should be considered if VT or conduction blocks dominate the presentation of heart failure in the absence of CAD.

## History

Fever, fatigue, palpitations; if LV dysfunction develops, symptoms of heart failure are present. Viral myocarditis may be preceded by URI.

## Physical Examination

Fever, tachycardia, soft $S_1$; $S_3$ common.

## Laboratory

CK-MB isoenzyme and cardiac troponins may be elevated in absence of MI. Convalescent antiviral antibody titers may rise.

## ECG

Transient ST-T-wave abnormalities.

### CXR

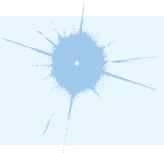
Cardiomegaly

### Echocardiogram, Cardiac MRI

Depressed LV function; pericardial effusion present if accompanying pericarditis present. MRI demonstrates mid-wall gadolinium enhancement.

**TREATMENT MYOCARDITIS**

Rest; treat as heart failure (Chap. 124); efficacy of immunosuppressive therapy (e.g., steroids) has not been demonstrated except in isolated conditions such as sarcoidosis and giant cell myocarditis. In fulminant cases, cardiac transplantation may be indicated.



For a more detailed discussion, see Lakdawala NK, Stevenson LW, Loscalzo J: Cardiomyopathy and Myocarditis, Chap. 287, p. 1553, in HPIM-19.

# 116 Pericardial Disease

## ACUTE PERICARDITIS

### Etiologies (See Table 116-1)

### History

Chest pain, which may be intense, mimicking acute MI, but characteristically sharp, pleuritic, and positional (relieved by leaning forward); fever and palpitations are common. Typical pain may not be present in slowly developing pericarditis (e.g., tuberculous, post-irradiation, neoplastic, uremic).

### Physical Examination

Rapid or irregular pulse, coarse pericardial friction rub, which may vary in intensity and is loudest with pt sitting forward.

### Laboratory ECG (See Table 116-2 and Fig. 116-1)

Diffuse ST elevation (concave upward) usually present in all leads except aVR and $V_1$; PR-segment depression (and/or PR elevation in lead aVR) may be present; *days* later (unlike acute MI), ST returns to baseline and T-wave inversion develops. Atrial premature beats and atrial fibrillation may appear. Differentiate from ECG of early repolarization (ER) (ratio of ST elevation/T wave height <0.25 in ER, but >0.25 in pericarditis).

**TABLE 116-1 ETIOLOGIES OF PERICARDITIS**

| |
|---|
| "Idiopathic" |
| Infections (particularly viral) |
| Connective tissue disease (e.g., rheumatoid arthritis, SLE) |
| Post-cardiac injury (i.e., following heart surgery or myocardial infarction) |
| Uremia |
| Neoplasms |
| Mediastinal radiation therapy |
| Drug reaction (e.g., procainamide, hydralazine) |

### CXR

Symmetrically increased size of cardiac silhouette if large (>250 mL) pericardial effusion is present.

### Echocardiogram

Most readily available test for detection of pericardial effusion, which commonly accompanies acute pericarditis.

**TREATMENT ACUTE PERICARDITIS**

Aspirin 650–975 mg qid or other NSAIDs (e.g., ibuprofen 400–600 mg tid or indomethacin 25–50 mg tid); addition of colchicine 0.6 mg bid may be beneficial and reduces frequency of recurrences. For *severe*, *refractory* pain, glucocorticoids (e.g., prednisone) can be prescribed. Intractable, prolonged pain or frequently recurrent episodes may require pericardiectomy. Anticoagulants are relatively contraindicated in acute pericarditis because of risk of pericardial hemorrhage.

## CARDIAC TAMPONADE

Life-threatening condition resulting from accumulation of pericardial fluid under pressure; impaired filling of cardiac chambers and decreased cardiac output.

**TABLE 116-2 ECG IN ACUTE PERICARDITIS VS ACUTE ST-ELEVATION MI**

| ST-Segment Elevation | ECG Lead Involvement | Evolution of ST and T Waves | PR-Segment Deviation |
|---|---|---|---|
| **Pericarditis** | | | |
| Concave upward | All leads involved except aVR and $V_1$ | ST remains elevated for several days; after ST returns to baseline, T waves invert | Yes, in majority |
| **Acute ST elevation MI** | | | |
| Convex upward | ST elevation over infarcted region only; reciprocal ST depression in opposite leads | In absence of successful reperfusion therapies: T waves invert within hours, while ST still elevated; followed by Q-wave development | No |

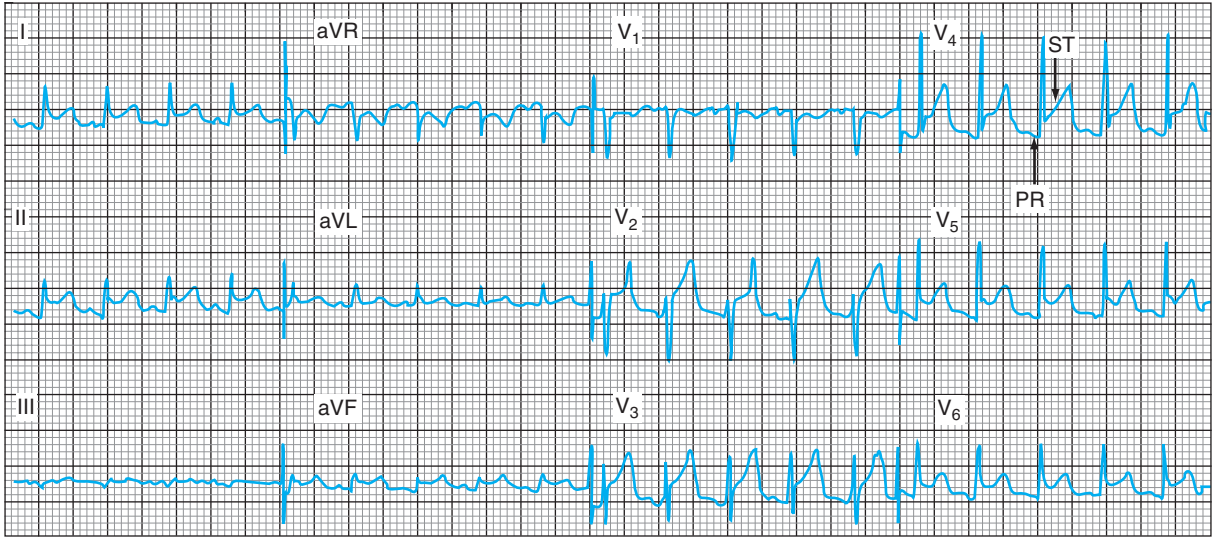



**FIGURE 116-1** Electrocardiogram in acute pericarditis. Note diffuse ST-segment elevation and PR-segment depression.

### Etiology

Previous pericarditis (most commonly metastatic tumor, uremia, viral or idiopathic pericarditis), cardiac trauma, or myocardial perforation during intravascular procedures.

### History

Hypotension may develop suddenly; subacute symptoms include dyspnea, weakness, confusion.

### Physical Examination

Tachycardia, hypotension, pulsus paradoxus (inspiratory fall in systolic blood pressure >10 mmHg), jugular venous distention with preserved *x* descent but loss of *y* descent; heart sounds distant. If tamponade develops subacutely, peripheral edema, hepatomegaly, and ascites may be present.

### Laboratory ECG

Low limb lead voltage; large effusions may cause electrical alternans (alternating size of QRS complex due to swinging of heart).

### CXR

Enlarged cardiac silhouette if large (>250 mL) effusion present.

### Echocardiogram

Swinging motion of heart within large effusion; prominent respiratory alteration of RV dimension with RA and RV collapse during diastole. Doppler shows marked respiratory variation of transvalvular flow velocities.

### Cardiac Catheterization

Confirms diagnosis; shows elevated pericardial pressure with equalization of diastolic pressures in all cardiac chambers.

**TREATMENT** CARDIAC TAMPONADE

Immediate pericardiocentesis and IV volume expansion.

## CONSTRICTIVE PERICARDITIS

Condition in which a rigid pericardium impairs cardiac filling, causing elevation of systemic and pulmonary venous pressures, and decreased cardiac output. Results from healing and scar formation in some pts with previous pericarditis. Viral, tuberculosis (mostly in developing nations), previous cardiac surgery, collagen vascular disorders, uremia, neoplastic, and radiation-associated pericarditis are potential causes.

### History

Gradual onset of dyspnea, fatigue, pedal edema, abdominal swelling; symptoms of LV failure uncommon.

### Physical Examination

Tachycardia, jugular venous distention (with prominent *y* descent) that increases further on inspiration (Kussmaul sign); hepatomegaly, ascites, peripheral edema are common; sharp diastolic sound, pericardial knock following $S_2$ sometimes present.

### Laboratory ECG

Low limb lead voltage; atrial arrhythmias are common.

**TABLE 116-3 NONINVASIVE FEATURES THAT HELP DIFFERENTIATE CONSTRICTIVE PERICARDITIS FROM RESTRICTIVE CARDIOMYOPATHY**

| | Constrictive Pericarditis | Restrictive Cardiomyopathy |
|---|---|---|
| **Physical examination** | | |
| Kussmaul sign | Present | May be present |
| Pericardial knock | May be present | Absent |
| **Chest X-ray** | | |
| Pericardial calcification | May be present | Absent |
| **Echocardiography** | | |
| Thickened pericardium | Present | Absent |
| Thickened myocardium | Absent | Often present |
| Exaggerated variation in transvalvular velocities | Present | Absent |
| **CT or MRI** | | |
| Thickened pericardium | Present | Absent |

## CXR

Rim of pericardial calcification is most common in tuberculous pericarditis.

## Echocardiogram

Thickened pericardium, normal ventricular contraction; abrupt halt in ventricular filling in early diastole. Dilatation of IVC is common. Dramatic effects of respiration are typical: During inspiration the ventricular septum shifts to the left with prominent reduction of blood flow velocity across mitral valve; pattern reverses during expiration.

## CT or MRI

More precise than echocardiogram for demonstrating thickened pericardium (present in >80% of pts with constrictive pericarditis).

## Cardiac Catheterization

Equalization of diastolic pressures in all chambers; ventricular pressure tracings show "dip and plateau" appearance. Differentiate from restrictive cardiomyopathy (Table 116-3).

## TREATMENT CONSTRICTIVE PERICARDITIS

Surgical stripping of the pericardium. Progressive improvement ensues over several months.

## APPROACH TO THE PATIENT: Asymptomatic Pericardial Effusion of Unknown Cause

If careful history and physical examination do not suggest etiology, the following may lead to diagnosis:

- Testing for tuberculosis (Chap. 94)
- Serum albumin and urine protein measurement (nephrotic syndrome)
- Serum creatinine and BUN (uremia)

- Thyroid function tests (myxedema)
- Antineutrophil antibodies (SLE and other collagen-vascular disease)
- Search for a primary tumor (especially lung and breast)

For a more detailed discussion, see Braunwald E: Pericardial Disease, Chap. 288, p. 1571, in HPIM-19.

# 117 Hypertension

## DEFINITION

Chronic elevation in bp (systolic ≥140 mmHg or diastolic ≥90 mmHg); etiology unknown in 80–95% of pts ("essential hypertension"). Always consider a secondary correctable form of hypertension, especially in pts under age 30 or those who become hypertensive after 55. Isolated systolic hypertension (systolic ≥140, diastolic <90) most common in elderly pts, due to reduced vascular compliance.

## SECONDARY HYPERTENSION

### Renal Artery Stenosis (Renovascular Hypertension)

Due to either atherosclerosis (older men) or fibromuscular dysplasia (young women). Presents with recent onset of hypertension, refractory to usual antihypertensive therapy. Abdominal bruit is present in 50% of cases; hypokalemia due to activation of the renin-angiotensin-aldosterone system may be present.

### Renal Parenchymal Disease

Elevated serum creatinine and/or abnormal urinalysis, containing protein, cells, or casts.

### Coarctation of Aorta

Presents in children or young adults (including 35% of pts with Turner syndrome); constriction is usually present in aorta at origin of left subclavian artery. Examination shows diminished, delayed femoral pulsations; late systolic murmur loudest over the midback. CXR shows indentation of the aorta at the level of the coarctation and rib notching (due to development of collateral arterial flow).

### Pheochromocytoma

A catecholamine-secreting tumor, typically of the adrenal medulla or extraadrenal paraganglion tissue, that presents as paroxysmal or sustained hypertension in young to middle-aged pts. Sudden episodes of headache, palpitations, and profuse diaphoresis are common. Associated findings include chronic weight loss, orthostatic *hypotension*, and impaired glucose tolerance. Pheochromocytomas may be localized

to the bladder wall and may present with micturition-associated symptoms of catecholamine excess. Diagnosis is suggested by elevated plasma metanephrine level or urinary catecholamine metabolites in a 24-h urine collection (see below); the tumor is then localized by CT scan or MRI.

## Hyperaldosteronism

Usually due to aldosterone-secreting adenoma or bilateral adrenal hyperplasia. Should be suspected when hypokalemia is present in a hypertensive pt off diuretics (Chap. 171).

## Other Causes

Oral contraceptive usage, obstructive sleep apnea (Chap. 137), Cushing's and adrenogenital syndromes (Chap. 171), thyroid disease (Chap. 170), hyperparathyroidism, and acromegaly (Chap. 168). In pts with systolic hypertension and wide pulse pressure, consider thyrotoxicosis, aortic regurgitation (Chap. 114), and systemic AV fistula.

## APPROACH TO THE PATIENT: **Hypertension**

*History*: Most pts are asymptomatic. Severe hypertension may lead to headache, dizziness, or blurred vision.

*Clues to specific forms of secondary hypertension*: Use of medications (e.g., birth control pills, glucocorticoids, decongestants, erythropoietin, NSAIDs, cyclosporine); paroxysms of headache, sweating, or tachycardia (pheochromocytoma); history of renal disease or abdominal trauma (renal hypertension); daytime somnolence and snoring (sleep apnea).

*Physical examination*: Measure bp with appropriate-sized cuff (large cuff for large arm). Measure bp in both arms as well as a leg (to evaluate for aortic coarctation). Signs of hypertension include retinal arteriolar changes (narrowing/nicking); left ventricular lift, loud $A_2$, $S_4$. Clues to secondary forms of hypertension include cushingoid appearance, thyromegaly, abdominal bruit (renal artery stenosis), delayed femoral pulses (coarctation of aorta).

### LABORATORY WORKUP

*Screening tests for secondary hypertension*: Should be carried out on all pts with documented hypertension: (1) serum creatinine, BUN, and urinalysis (renal parenchymal disease); (2) serum $K^+$ measured off diuretics (hypokalemia prompts workup for hyperaldosteronism or renal artery stenosis); (3) CXR (rib notching or indentation of distal aortic arch in coarctation of the aorta); (4) ECG (LV hypertrophy suggests chronicity of hypertension); (5) other useful screening blood tests including CBC, glucose, lipid levels, calcium, uric acid; (6) thyroid-stimulating hormone if thyroid disease suspected.

*Further workup*: Indicated for specific diagnoses if screening tests are abnormal or bp is refractory to antihypertensive therapy: (1) *renal artery stenosis:* magnetic resonance angiography, captopril radionuclide scan, renal duplex ultrasound, renal arteriography; (2) *Cushing's syndrome:* dexamethasone suppression test (Chap. 171); (3) *pheochromocytoma:* 24-h urine collection for catecholamines, metanephrines, and vanillylmandelic acid and/or measurement of plasma metanephrine; (4) *primary hyperaldosteronism:* depressed plasma renin activity and hypersecretion of aldosterone, both of which fail to change with volume expansion; (5) *renal parenchymal disease* (Chap. 139).

## TREATMENT HYPERTENSION

Helpful lifestyle modifications include weight reduction (to attain BMI <25 kg/m$^2$); sodium restriction; diet rich in fruits, vegetables, and low-fat dairy products; regular exercise; and moderation of alcohol consumption.

### DRUG THERAPY OF ESSENTIAL HYPERTENSION (SEE TABLE 117-1 AND FIG. 117-1)

Goal is to control hypertension with minimal side effects. A combination of medications with complementary actions is often required. First-line agents include diuretics, ACE inhibitors, angiotensin receptor antagonists, calcium channel antagonists, and sometimes beta blockers. On-treatment blood pressure goal is <135–140 systolic, <80–85 diastolic.

**Diuretics** Often the cornerstone of antihypertensive regimes. Thiazides preferred over loop diuretics because of longer duration of action; however, the latter are more potent when serum creatinine >2.5 mg/dL. Major side effects include hypokalemia, hyperglycemia, and hyperuricemia, which can be minimized by using low dosage (e.g., hydrochlorothiazide 6.25–50 mg qd). Diuretics are particularly effective in elderly and African-American pts. Prevention of hypokalemia is especially important in pts on digitalis glycosides.

**ACE Inhibitors and Angiotensin II Receptor Blockers (ARBs)** ACE inhibitors and ARBs are well tolerated with low frequency of side effects. May be used as monotherapy or in combination with a diuretic, calcium antagonist, or beta blocker. Side effects are uncommon and include angioedema (<1% of pts; more common with ACE inhibitors than ARBs), hyperkalemia, and azotemia (particularly in pts with elevated baseline serum creatinine). A nonproductive cough may develop in the course of therapy in up to 15% of pts on an ACE inhibitor, prompting substitution with an ARB (cough is not common side effect) or alternate antihypertensives. Note that renal function may deteriorate rapidly as a result of inhibition of the renin-angiotensin system in pts with bilateral renal artery stenosis.

Potassium supplements and potassium-sparing diuretics should be used cautiously with ACE inhibitors or ARBs to prevent hyperkalemia.

**Calcium Antagonists** Direct arteriolar vasodilators; all have negative inotropic effects (particularly verapamil) and should be used cautiously if LV dysfunction is present. Verapamil and, to a lesser extent, diltiazem can result in bradycardia and AV block, so combination with beta blockers is generally avoided. Use sustained-release formulations, as short-acting dihydropyridine calcium channel blockers may increase incidence of coronary events. Common side effects include peripheral edema and constipation.

If bp proves refractory to drug therapy, work up for secondary forms of hypertension, especially renal artery stenosis and pheochromocytoma.

**Beta Blockers** May be useful in young pts with "hyperkinetic" circulation. Begin with low dosage (e.g., metoprolol succinate 25–50 mg daily). Relative contraindications: bronchospasm, CHF, AV block, bradycardia, and "brittle" insulin-dependent diabetes.

Table 117-2 lists compelling indications for specific initial drug treatment.

### SPECIAL CIRCUMSTANCES

**Pregnancy** Most commonly used antihypertensives include methyldopa (250–1000 mg PO bid-tid), labetalol (100–200 mg bid), and hydralazine (10–150 mg PO bid-tid). Calcium channel blockers (e.g., nifedipine, long-acting, 30–90 mg daily) also appear to be safe in pregnancy. Beta blockers should be used cautiously; fetal hypoglycemia and low birth weights have been reported. ACE inhibitors and ARBs are *contraindicated* in pregnancy.

**TABLE 117-1 ORAL DRUGS COMMONLY USED IN TREATMENT OF HYPERTENSION**

| Drug Class | Examples | Usual Total Daily Dose (Dosing Frequency/Day) | Potential Adverse Effects |
|---|---|---|---|
| Diuretics | | | |
| Thiazides | Hydrochlorothiazide | 6.25–50 mg (1–2) | Hypokalemia, hyperuricemia, hyperglycemia, ↑ cholesterol, ↑ triglycerides |
| Thiazide-like | Chlorthalidone | 25–50 mg (1) | same as above |
| Loop diuretics | Furosemide | 40–80 mg (2–3) | Hypokalemia, hyperuricemia |
| | Ethacrynic acid | 50–100 mg (2-3) | |
| Aldosterone antagonists | Spironolactone | 25–100 mg (1–2) | Hyperkalemia, gynecomastia |
| | Eplerenone | 50–100 mg (1–2) | Hyperkalemia |
| $K^+$-retaining | Amiloride | 5–10 mg (1–2) | |
| | Triamterene | 50–100 mg (1–2) | |
| Beta blockers | | | |
| $\beta_1$-selective | Atenolol | 25–100 mg (1–2) | Bronchospasm, bradycardia, heart block, fatigue, sexual dysfunction, ↑ triglycerides, ↓ HDL |
| | Metoprolol | 25–100 mg (1–2) | same as above |
| Nonselective | Propranolol | 40–160 mg (2) | same as above |
| | Propranolol LA | 60–180 mg (1) | same as above |
| Combined alpha/beta | Labetolol | 200–800 mg (2) | Bronchospasm, bradycardia, heart block |
| | Carvedilol | 12.5–50 mg (2) | |

| | | | |
|---|---|---|---|
| ACE inhibitors | Captopril | 25–200 mg (2) | Cough, hyperkalemia, azotemia, angioedema |
| | Lisinopril | 10–40 mg (1) | |
| | Ramipril | 2.5–20 mg (1–2) | |
| Angiotensin II receptor blockers | Losartan | 25–100 mg (1–2) | Hyperkalemia, azotemia |
| | Valsartan | 80–320 mg (1) | |
| | Candesartan | 2–32 mg (1–2) | |
| Calcium channel antagonists | | | |
| Dihydropyridines | Nifedipine long-acting | 30–60 mg (1) | Edema, constipation |
| Nondihydropyridines | Verapamil long-acting | 120–360 mg (1–2) | Edema, constipation, bradycardia, heart block |
| | Diltiazem long-acting | 180–420 mg (1) | |

**TABLE 117-2 GUIDELINES FOR SELECTING INITIAL DRUG TREATMENT OF HYPERTENSION**

| Class of Drug | Compelling Indications | Possible Indications | Compelling Contraindications | Possible Contraindications |
|---|---|---|---|---|
| Diuretics | Heart failure<br>Elderly pts<br>Systolic hypertension | | Gout | |
| Beta blockers | Angina<br>After MI<br>Tachyarrhythmias | Heart failure<br>Pregnancy | Uncontrolled asthma and COPD<br>Heart block[a] | Athletes and physically active pts<br>Peripheral vascular disease |
| ACE inhibitors | Heart failure<br>LV dysfunction<br>After MI<br>Diabetic nephropathy | Chronic renal parenchymal disease | Pregnancy<br>Hyperkalemia<br>Bilateral renal artery stenosis | |
| Angiotensin receptor blockers | ACE inhibitor cough<br>Heart failure<br>Diabetic nephropathy | Chronic renal parenchymal disease | Pregnancy<br>Bilateral renal artery stenosis<br>Hyperkalemia | |
| Calcium channel blockers | Angina<br>Elderly pts<br>Systolic hypertension | Peripheral vascular disease | Heart block[b] | Congestive heart failure[c] |

[a]Second- or third-degree atrioventricular block.
[b]Second- or third-degree atrioventricular block with verapamil or diltiazem.
[c]Verapamil or diltiazem.
***Abbreviations:*** ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease.

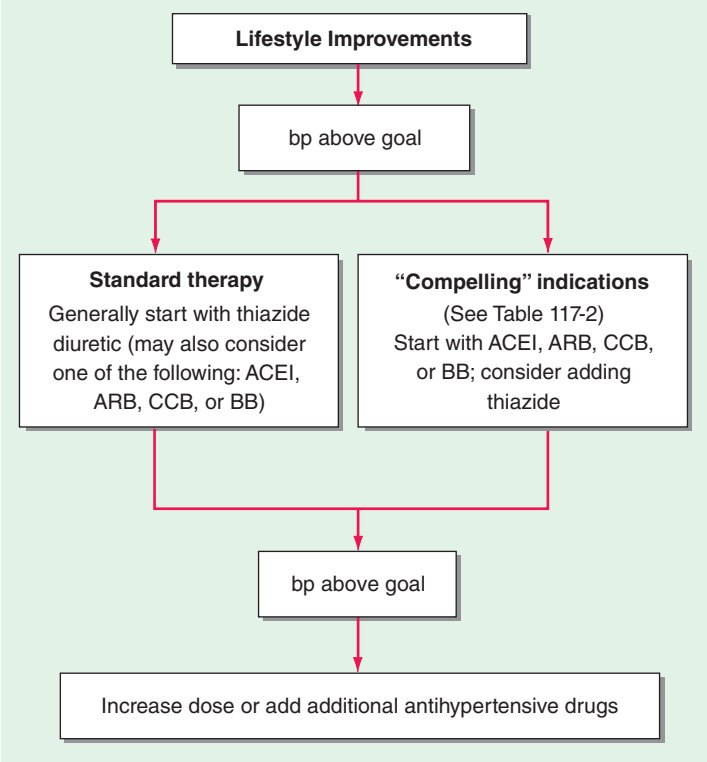



**FIGURE 117-1** Initiation of therapy in pts with hypertension. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; BB, beta blocker.

**Renal Disease** Standard thiazide diuretics may not be effective. Consider metolazone, furosemide, or bumetanide, alone or in combination.

**Diabetes** Goal bp <130/80. Consider ACE inhibitors and angiotensin receptor blockers as first-line therapy to control bp and slow renal function deterioration.

**Malignant Hypertension** Defined as an abrupt increase in bp in pt with chronic hypertension or sudden onset of severe hypertension; a medical emergency. Immediate therapy is mandatory if there is evidence of cardiac decompensation (CHF, angina), encephalopathy (headache, seizures, visual disturbances), or deteriorating renal function. Inquire about use of cocaine, amphetamines, or monoamine oxidase inhibitors. Drugs to treat hypertensive crisis are listed in Table 117-3. Replace with PO antihypertensive as pt becomes asymptomatic and bp improves.

**TABLE 117-3 USUAL INTRAVENOUS DOSES OF ANTIHYPERTENSIVE AGENTS USED IN HYPERTENSIVE EMERGENCIES[a]**

| Antihypertensive Agent | IV Dose |
|---|---|
| Nitroprusside | Initial 0.3 (mg/kg)/min; usual 2–4 (mg/kg)/min; maximum 10 (mg/kg)/min for 10 min |
| Nicardipine | Initial 5 mg/h; titrate by 2.5 mg/h at 5–15 min intervals; max 15 mg/h |
| Labetalol | 2 mg/min up to 300 mg *or* 20 mg over 2 min, then 40–80 mg at 10-min intervals up to 300 mg total |
| Enalaprilat | Usual 0.625–1.25 mg over 5 min every 6–8 h |
| Esmolol | Initial 80–500 mg/kg over 1 min, then 50–300 (mg/kg)/min |
| Phentolamine | 5–15 mg bolus |
| Nitroglycerin | Initial 5 mcg/min, then titrate by 5 mcg/min at 3–5 min intervals; if no response is seen at 20 mcg/min, incremental increases of 10–20 mcg/min may be used |
| Hydralazine | 10–50 mg at 30-min intervals |

[a]Constant blood pressure monitoring is required. Start with the lowest dose. Subsequent doses and intervals of administration should be adjusted according to the blood pressure response and duration of action of the specific agent.

For a more detailed discussion, see Kotchen TA: Hypertensive Vascular Disease, Chap. 298, p. 1611, in HPIM-19.

# 118 Metabolic Syndrome

The *metabolic syndrome* (*insulin resistance syndrome*, *syndrome X*) is an important risk factor for cardiovascular disease and type 2 diabetes; it consists of a constellation of metabolic abnormalities that includes central obesity, insulin resistance, hypertension, and dyslipidemia, high triglycerides, and low HDL. The prevalence of metabolic syndrome varies among ethnic groups; it increases with age, degree of obesity, and propensity to type 2 diabetes.

## ETIOLOGY

Overweight/obesity (especially central adiposity), sedentary lifestyle, increasing age, and lipodystrophy are all risk factors for the metabolic syndrome. The exact cause is not known and may be multifactorial. Insulin resistance is central to the

development of the metabolic syndrome. Increased intracellular fatty acid metabolites contribute to insulin resistance by impairing insulin-signaling pathways and accumulating as triglycerides in skeletal and cardiac muscle, while stimulating hepatic glucose and triglyceride production. Excess adipose tissue leads to increased production of proinflammatory cytokines.

## CLINICAL FEATURES

There are no specific symptoms of the metabolic syndrome. The major features include central obesity, hypertriglyceridemia, low HDL cholesterol, hyperglycemia, and hypertension (Table 118-1). Associated conditions include cardiovascular disease, type 2 diabetes, nonalcoholic fatty liver disease, hyperuricemia/gout, polycystic ovary syndrome, and obstructive sleep apnea.

## DIAGNOSIS

The diagnosis of the metabolic syndrome relies on satisfying the criteria listed in Table 118-1. Screening for associated conditions should be undertaken.

**TABLE 118-1 NCEP:ATPIII[a] 2001 AND HARMONIZING DEFINITION CRITERIA FOR THE METABOLIC SYNDROME**

| NCEP:ATPIII 2001 | Harmonizing Definition[b] | | |
|---|---|---|---|
| **Three or more of the following:** | **Three of the following:** | | |
| • Central obesity: waist circumference >102 cm (M), >88 cm (F) | Waist circumference (cm) | | |
| | **Men** | **Women** | **Ethnicity** |
| | ≥94 | ≥80 | Europid, sub-Saharan African, Eastern and Middle Eastern |
| • Hypertriglyceridemia: triglyceride level ≥150 mg/dL or specific medication | ≥90 | ≥80 | South Asian, Chinese, and ethnic South and Central American |
| Low HDL[c] cholesterol: <40 mg/dL and <50 mg/dL for men and women, respectively, or specific medication | ≥85 | ≥90 | Japanese |
| | • Fasting triglyceride level >150 mg/dL or specific medication | | |
| | • HDL cholesterol level <40 mg/dL and <50 mg/dL for men and women, respectively, or specific medication | | |
| • Hypertension: blood pressure ≥130 mmHg systolic or ≥85 mmHg diastolic or specific medication | • Blood pressure >130 mm systolic or >85 mm diastolic or previous diagnosis or specific medication | | |
| • Fasting plasma glucose level ≥100 mg/dL or specific medication or previously diagnosed type 2 diabetes | • Fasting plasma glucose level ≥100 mg/dL (alternative indication: drug treatment of elevated glucose levels) | | |

[a]National Cholesterol Education Program and Adult Treatment Panel III.
[b]In this analysis, the following thresholds for waist circumference were used: white men, ≥94 cm; African-American men, ≥94 cm; Mexican-American men, ≥90 cm; white women, ≥80 cm; African-American women, ≥80 cm; Mexican-American women, ≥80 cm. For participants whose designation was "other race—including multiracial," thresholds that were once based on Europid cutoffs (≥94 cm for men and ≥80 cm for women) and on South Asian cutoffs (≥90 cm for men and ≥80 cm for women) were used. For participants who were considered "other Hispanic," the International Diabetes Federation thresholds for ethnic South and Central Americans were used.
[c]High-density lipoprotein.

## TREATMENT METABOLIC SYNDROME

Obesity is the driving force behind the metabolic syndrome. Thus, weight reduction is the primary approach to this disorder. In general, recommendations for weight loss include a combination of caloric restriction, increased physical activity, and behavior modification. Weight loss drugs or bariatric surgery are adjuncts that may be considered for obesity management (Chap. 172). Hypertension (Chap. 117), impaired fasting glucose or diabetes (Chap. 173), and lipid abnormalities (Chap. 178) should be managed according to current guidelines. The antihypertensive regimen should include an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker when possible.

For a more detailed discussion, see Eckel RH: The Metabolic Syndrome, Chap. 422, p. 2449, in HPIM-19.

# 119 ST-Segment Elevation Myocardial Infarction

Early recognition and immediate treatment of acute ST-segment elevation myocardial infarction (STEMI) are essential; diagnosis is based on characteristic history, ECG, and serum cardiac markers.

## Symptoms

Chest pain similar to angina (Chap. 31) but more intense and persistent; not fully relieved by rest or nitroglycerin, often accompanied by nausea, sweating, apprehension. However, ~25% of MIs are clinically silent.

## Physical Examination

Pallor, diaphoresis, tachycardia, $S_4$, dyskinetic cardiac impulse may be present. If CHF exists, rales and $S_3$ are present. Jugular venous distention is common in right ventricular infarction.

## ECG

ST elevation, followed (if acute reperfusion is not achieved) by T-wave inversion, then Q-wave development over several hours.

## Cardiac Biomarkers

Cardiac-specific troponins T and I are highly specific for myocardial injury and are the preferred biochemical markers for diagnosis of acute MI. They remain elevated for 7–10 days. Creatine phosphokinase (CK) level rises within 4–8 h, peaks at 24 h, and returns to normal by 48–72 h. CK-MB isoenzyme is more specific for MI but may also be elevated with myocarditis or after electrical cardioversion. Serum cardiac markers should be measured at presentation, 6–9 h later, and then at 12–24 h.

## Noninvasive Imaging Techniques

Useful when diagnosis of MI is not clear. *Echocardiography* detects infarct-associated regional wall motion abnormalities (but cannot distinguish acute MI from a previous myocardial scar). Echo is also useful in detecting RV infarction, LV aneurysm, and LV thrombus. *MRI with delayed gadolinium enhancement* accurately indicates regions of infarction, but is technically difficult to obtain in acutely ill pts.

# TREATMENT STEMI

## INITIAL THERAPY

Initial goals are to (1) quickly identify if pt is candidate for reperfusion therapy, (2) relieve pain, and (3) prevent/treat arrhythmias and mechanical complications.

- Aspirin should be administered immediately (162–325 mg chewed at presentation, then 75–162 mg PO qd), unless pt is aspirin-intolerant.
- Perform targeted history, examination, and ECG to identify STEMI (>1 mm ST elevation in two contiguous limb leads, ≥2 mm ST elevation in two contiguous precordial leads, or new LBBB) and appropriateness of reperfusion therapy (percutaneous coronary intervention [PCI] or IV fibrinolytic agent), which reduces infarct size, LV dysfunction, and mortality.
- Primary PCI is generally more effective than fibrinolysis and is preferred at experienced centers capable of performing the procedure rapidly (Fig. 119-1), especially when diagnosis is in doubt, cardiogenic shock is present, bleeding risk is increased, or symptoms have been present for >3 h.
- Proceed with IV fibrinolysis if PCI is not available or if logistics would delay PCI >1 h longer than fibrinolysis could be initiated (Fig. 119-1). Door-to-needle time should be <30 min for maximum benefit. Ensure absence of contraindications (Fig. 119-2) before administering fibrinolytic agent. Those treated within 1–3 h benefit most; can still be useful up to 12 h if chest pain is persistent or ST remains elevated in leads that have not developed new Q waves. Complications include bleeding, reperfusion arrhythmias, and, in case of streptokinase (SK), allergic reactions. Enoxaparin or heparin (60 U/kg [maximum 4000 U], then 12 [U/kg]/h [maximum 1000 U/h]) should be initiated with fibrinolytic agents (Fig. 119-2); maintain activated partial thromboplastin time (aPTT) at 1.5–2.0 × control (~50–70 s).
- If chest pain or ST elevation persists >90 min after fibrinolysis, consider referral for rescue PCI. Coronary angiography after fibrinolysis should also be considered for pts with recurrent angina or high-risk features (**Fig. 119-2**) including extensive ST elevation, signs of heart failure (rales, $S_3$, jugular venous distension, left ventricular ejection fraction [LVEF] ≤35%), or systolic bp <100 mmHg.

The initial management of NSTEMI (non-Q MI) is different (Chap. 120). In particular, fibrinolytic therapy should not be administered.

## ADDITIONAL STANDARD TREATMENT

(Whether or not reperfusion therapy is undertaken):

- *Hospitalize in CCU* with continuous ECG monitoring.
- *IV line* for emergency arrhythmia treatment.
- *Pain control:* (1) Morphine sulfate 2–4 mg IV q5–10 min until pain is relieved or side effects develop (nausea, vomiting, respiratory depression [treat with naloxone 0.4–1.2 mg IV], hypotension [if bradycardic, treat with atropine 0.5 mg IV; otherwise use careful volume infusion]); (2) nitroglycerin 0.3 mg SL if systolic bp >100 mmHg; for refractory pain: IV nitroglycerin (begin at 10 μg/min, titrate upward to maximum of 200 μg/min, monitoring bp closely); do not administer

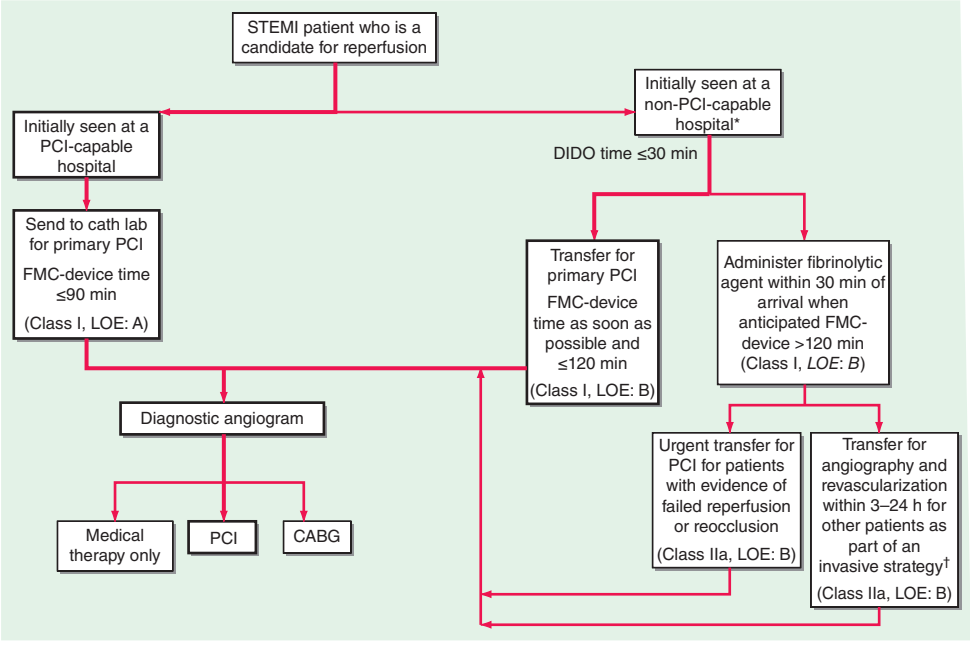



**FIGURE 119-1** Reperfusion strategies in STEMI. DIDO, door-in-door-out; FMC, first medical contact; LOC, level of evidence. *(Adapted from P O'Gara, et al: Circulation 127:e362, 2013.)*

**SELECTION CRITERIA**

1. Acute chest discomfort characteristic of myocardial infarction
2. ECG criteria for ST-elevation MI (a, b, or c):
   a. ST elevation ≥0.1 mV (1 mm) in at least 2 leads of either:
      Inferior group: II, III, aVF
      Lateral group: I, aVL, $V_5$, $V_6$
   b. ST elevation ≥0.2 mV (1 mm) in at least 2 contiguous anterior leads ($V_1$–$V_4$)
   c. New LBBB
3. Primary PCI not available, or delay to PCI from first medical contact would be >120 min.

↓

**ASSESS FOR CONTRAINDICATIONS**

- Prior intracranial bleeding
- Intracranial malignancy or vascular malformation
- Ischemic stroke or head trauma in previous 3 months
- Aortic dissection
- Active bleeding (with exception of menses)
- Internal bleeding in previous 4 weeks
- Severe hypertension (systolic >180 or diastolic >110)
- Prolonged (>10 min) CPR chest compressions
- INR ≥ 2.0 on warfarin, or known bleeding diathesis
- Pregnancy

↓

| FIBRINOLYTIC DRUG | INTRAVENOUS DOSAGE |
|---|---|
| Streptokinase | 1.5 million U over 60 min |
| Alteplase | 15-mg bolus, then 0.75 mg/kg (up to 50 mg) over 30 min, then 0.5 mg/kg (up to 35 mg) over 60 min |
| Reteplase | 10 U over 2 min; repeat same dose 30 min later |
| Tenecteplase | Single bolus of 0.53 mg/kg over 10 s |

Also administer IV heparin 60-U/kg bolus (maximum 4000 U) followed by 12 (U/kg)/h (maximum 1000 U/h), then adjusted to maintain aPTT at 1.5–2 x control (~50–70 s) for 48 h (evidence for heparin benefit with streptokinase is weak)

↓

**SUBSEQUENT CORONARY ANGIOGRAPHY FOR**

- Failure of reperfusion (persistent chest pain or ST elevation after 90 min)
- Spontaneous recurrent ischemia during hospitalization
- High-risk features: e.g., extensive ST elevation, heart failure, hypotension

**FIGURE 119-2** Algorithm for fibrinolytic therapy of acute STEMI.

nitrates within 24 h of sildenafil or within 48 h of tadalafil (used for erectile dysfunction); (3) β-adrenergic antagonists (see below).

- *Oxygen:* 2–4 L/min by nasal cannula (if needed to maintain $O_2$ saturation >90%).
- Mild *sedation* (e.g., diazepam 5 mg, oxazepam 15–30 mg, or lorazepam 0.5–2 mg PO three to four times daily).
- *Soft diet* and stool softeners (e.g., docusate sodium 100–200 mg/d).

- β-*Adrenergic blockers* (Chap. 117) reduce myocardial $O_2$ consumption, limit infarct size, and reduce mortality. Especially useful in pts with hypertension, tachycardia, or persistent ischemic pain; contraindications include active CHF, systolic bp <95 mmHg, heart rate <50 beats/min, AV block, or history of bronchospasm. Consider IV (e.g., metoprolol 5 mg q2–5min to total dose of 15 mg) if pt is hypertensive. Otherwise, begin PO regimen (e.g., metoprolol tartrate 25–50 mg four times daily).
- *Anticoagulants:* Most pts with STEMI should receive an anticoagulant (typically unfractionated heparin [UFH] or bivalirudin for those undergoing PCI [discontinued at end of procedure or shortly thereafter]; enoxaparin [for up to 8 days, or until discharge, whichever is earlier] or UFH [for ≥2 days] for those receiving fibrinolysis or no reperfusion therapy). Continued full-dose IV heparin (PTT 1.5–2 × control) or LMWH (e.g., enoxaparin 1 mg/kg SC q12h) followed by warfarin is recommended for pts with high risk of thromboembolism (severe LV dysfunction, presence of ventricular thrombus, large dyskinetic region in acute anterior MI, or pulmonary embolism). If used, warfarin is continued for 3–6 months.
- *Antiplatelet agents:* Continue aspirin 162–325 md daily and an oral $P2Y_{12}$ platelet receptor antagonist after STEMI (e.g., ticagrelor, clopidogrel, or prasugrel [the latter only if PCI is undertaken]).
- *ACE inhibitors* reduce mortality in pts following acute MI and should be prescribed within 24 h of hospitalization for pts with STEMI—e.g., captopril (6.25 mg PO test dose advanced to 50 mg PO tid). ACE inhibitors should be continued indefinitely after discharge in pts with heart failure or those with asymptomatic LV dysfunction (ejection fraction ≤40%); if pt is ACE inhibitor intolerant, use ARB (e.g., valsartan or candesartan).
- *Aldosterone antagonists (spironolactone or eplerenone 25–50 mg daily)* further reduce mortality in pts with LVEF ≤40% and either symptomatic heart failure or diabetes; do not use in pts with advanced renal insufficiency (e.g., creatinine ≥2.5 mg/dL) or hyperkalemia.
- *Serum magnesium* level should be measured and repleted if necessary to reduce risk of arrhythmias.

## COMPLICATIONS

(For arrhythmias, see also Chaps. 122 and 123)

### Ventricular Arrhythmias

Isolated ventricular premature beats (VPBs) occur frequently. Precipitating factors should be corrected (hypoxemia, acidosis, hypokalemia, hypomagnesemia, CHF, arrhythmogenic drugs). Routine beta blocker administration (see above) diminishes ventricular ectopy. Other in-hospital antiarrhythmic therapy should be reserved for pts with sustained ventricular arrhythmias.

### Ventricular Tachycardia

If hemodynamically unstable, perform immediate electrical countershock (unsynchronized discharge of 200–300 J or 50% less if using biphasic device). If hemodynamically tolerated, use IV amiodarone (bolus of 150 mg over 10 min, then infusion of 1.0 mg/min for 6 h, then 0.5 mg/min).

### Ventricular Fibrillation

VF requires immediate defibrillation (200–400 J). If unsuccessful, initiate cardiopulmonary resuscitation (CPR) and standard resuscitative measures (Chap. 10). Ventricular arrhythmias that appear several days or weeks following MI often reflect

pump failure and may warrant invasive electrophysiologic study and implantation of a cardioverter defibrillator (ICD).

## Accelerated Idioventricular Rhythm

Wide QRS complex, regular rhythm, rate 60–100 beats/min, is common and usually benign; if it causes hypotension, treat with atropine 0.6 mg IV.

## Supraventricular Arrhythmias

*Sinus tachycardia* may result from heart failure, hypoxemia, pain, fever, pericarditis, hypovolemia, administered drugs. If no cause is identified, suppressive beta blocker therapy may be beneficial to reduce myocardial oxygen demand. Other *supraventricular arrhythmias* (paroxysmal supraventricular tachycardia, atrial flutter, and fibrillation) are often secondary to heart failure. If hemodynamically unstable, proceed with electrical cardioversion. In absence of acute heart failure, suppressive alternatives include beta blockers, verapamil, or diltiazem (Chap. 123).

## Bradyarrhythmias and AV Block

(See Chap. 122) In *inferior MI*, usually represent heightened vagal tone or discrete AV nodal ischemia. If hemodynamically compromised (CHF, hypotension, emergence of ventricular arrhythmias), treat with atropine 0.5 mg IV q5min (up to 2 mg). If no response, use temporary external or transvenous pacemaker. Isoproterenol should be avoided. In *anterior MI*, AV conduction defects usually reflect extensive tissue necrosis. Consider temporary external or transvenous pacemaker for (1) complete heart block, (2) Mobitz type II block (Chap. 122), (3) new bifascicular block (LBBB, RBBB + left anterior hemiblock, RBBB + left posterior hemiblock), (4) any bradyarrhythmia associated with hypotension or CHF.

## Heart Failure

CHF may result from systolic "pump" dysfunction, increased LV diastolic "stiffness," and/or acute mechanical complications.

**Symptoms** Dyspnea, orthopnea, tachycardia.

**Examination** Jugular venous distention, $S_3$ and $S_4$ gallop, pulmonary rales; systolic murmur if acute mitral regurgitation or ventricular septal defect (VSD) has developed.

### TREATMENT HEART FAILURE (SEE CHAPS. 13 AND 124)

Initial therapy includes diuretics (begin with furosemide 10–20 mg IV), inhaled $O_2$, and vasodilators, particularly nitrates (PO, topical, or IV [Chap. 124] unless pt is hypotensive [systolic bp <100 mmHg]); digitalis is usually of little benefit in acute MI. Diuretic, vasodilator, and inotropic therapy (Table 119-1) may be guided by invasive hemodynamic monitoring (Swan-Ganz pulmonary artery catheter, arterial line), particularly in pts with accompanying hypotension (Table 119-2; Fig. 119-3). In acute MI, an acceptable pulmonary capillary wedge (PCW) pressure is 15–20 mmHg; in the absence of hypotension, PCW >20 mmHg is treated with diuretic plus vasodilator therapy (IV nitroglycerin [begin at 10 μg/min] or nitroprusside [begin at 0.5 μg/kg per min]) and titrated to optimize bp, PCW, and systemic vascular resistance (SVR).

$$\text{SVR} = \frac{(\text{mean arterial pressure} - \text{mean RA pressure}) \times 80}{\text{cardiac output}}$$

Normal SVR = 900 – 1350 dyne • s/cm$^5$. If PCW >20 mmHg and pt is hypotensive (Table 119-2 and Fig. 119-3), evaluate for VSD or acute mitral regurgitation,

**TABLE 119-1 IV VASODILATORS AND INOTROPIC DRUGS USED IN ACUTE MI**

| Drug | Usual Dosage Range | Comment |
|---|---|---|
| Nitroglycerin | 5–100 μg/min | May improve coronary blood flow to ischemic myocardium |
| Nitroprusside | 0.5–10 (μg/kg)/min | More potent vasodilator, but improves coronary blood flow less than nitroglycerin<br>With therapy >24 h or in renal failure, watch for thiocyanate toxicity (blurred vision, tinnitus, delirium) |
| Dobutamine | 2–20 (μg/kg)/min | Results in ↑ cardiac output, ↓ PCW, but does not raise bp |
| Dopamine | 2–20 (μg/kg)/min | More appropriate than dobutamine if hypotensive<br>Hemodynamic effect depends on dose: (μg/kg)/min<br><5: ↑ renal blood flow<br>2.5–10: positive inotrope<br>>10: vasoconstriction |
| Norepinephrine | 0.5–30 μg/min | Less likely than dopamine to cause arrhythmias in cardiogenic shock |

consider dobutamine (begin at 1–2 [μg/kg]/min), titrate upward to maximum of 10 (μg/kg)/min; beware of drug-induced tachycardia or ventricular ectopy.

After stabilization on parenteral vasodilator therapy, oral therapy follows with an ACE inhibitor or an ARB (Chap. 124). Consider addition of long-term aldosterone antagonist (spironolactone 25–50 mg daily or eplerenone 25–50 mg daily) to ACE inhibitor if LVEF ≤40% or symptomatic heart failure or diabetes are present—do not use if renal insufficiency or hyperkalemia are present.

## Cardiogenic Shock

(See Chap. 11) Severe LV failure with hypotension (bp <90 mmHg), elevated PCW (>20 mmHg), cardiac index <2.2 L/min/m$^2$, accompanied by oliguria, peripheral vasoconstriction, dulled sensorium, and metabolic acidosis.

### TREATMENT CARDIOGENIC SHOCK (FIG. 119-3)

Swan-Ganz catheter and intraarterial bp monitoring are not always essential but may be helpful; aim for mean PCW of 18–20 mmHg with adjustment of volume (diuretics or infusion) as needed. Vasopressors (e.g., norepinephrine or dopamine [Table 119-1]) and/or intraaortic balloon counterpulsation may be necessary to maintain systolic bp >90 mmHg and reduce PCW. Administer high concentration of $O_2$ by mask; if pulmonary edema coexists, consider bilateral positive airway pressure (BiPAP) or intubation and mechanical ventilation. Acute mechanical complications (see below) should be sought and promptly treated.

If cardiogenic shock develops within 36 h of acute STEMI, reperfusion by PCI or coronary artery bypass grafting (CABG) may markedly improve LV function.

## Hypotension

May also result from *right ventricular MI*, which should be suspected in inferior or posterior MI, if jugular venous distention and elevation of right-heart pressures

**TABLE 119-2 HEMODYNAMIC COMPLICATIONS IN ACUTE MI**

| Condition | Cardiac Index, (L/min)/m² | PCW, mmHg | Systolic bp, mmHg | Treatment |
|---|---|---|---|---|
| Uncomplicated | >2.5 | ≤18 | >100 | — |
| Hypovolemia | <2.5 | <15 | <100 | Successive boluses of normal saline<br>In setting of inferior wall MI, consider RV infarction (esp. if RA pressure >10) |
| Volume overload | >2.5 | >20 | >100 | Diuretic (e.g., furosemide 10–20 mg IV)<br>Nitroglycerin, topical paste or IV (Table 119-1) |
| LV failure | <2.5 | >20 | >100 | Diuretic (e.g., furosemide 10–20 mg IV)<br>IV nitroglycerin (or if hypertensive, use IV nitroprusside) |
| Severe LV failure | <2.5 | >20 | <100 | If bp ≥90: IV dobutamine ± IV nitroglycerin or sodium nitroprusside<br>If bp <90: IV dopamine<br>If accompanied by pulmonary edema: attempt diuresis with IV furosemide; may be limited by hypotension<br>If new systolic murmur present, consider acute VSD or mitral regurgitation |
| Cardiogenic shock | <2.2 | >20 | <90 with oliguria and confusion | IV norepinephrine or dopamine<br>Intraaortic balloon pump<br>Reperfusion by PCI or CABG may be life-saving |

***Abbreviations:*** CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; PCW, pulmonary capillary wedge pressure; RA, right atrium; VSD, ventricular septal defect.

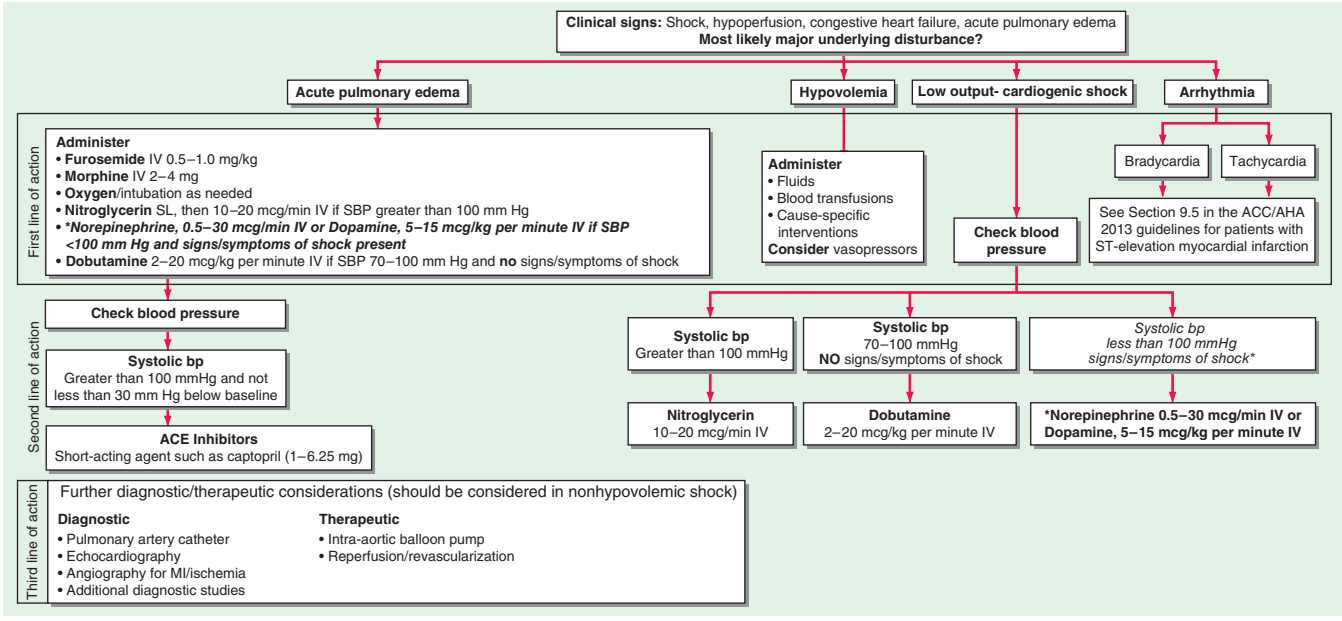



**FIGURE 119-3** Emergency management of cardiogenic shock and pulmonary edema. *(Modified from Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Part 7: The era of reperfusion: Section 1: Acute coronary syndromes [acute myocardial infarction]. The American Heart Association in collaboration with the International Liaison Committee on Resuscitation. Circulation 102:1172, 2000.)*

predominate (rales are typically absent and PCW may be normal); right-sided ECG leads typically show ST elevation, and echocardiography may confirm diagnosis. *Treatment* consists of volume infusion. Noncardiac causes of hypotension should be considered: hypovolemia, acute arrhythmia, or sepsis.

## Acute Mechanical Complications

Ventricular septal rupture and acute mitral regurgitation due to papillary muscle ischemia/infarct develop during the first week following MI and are characterized by sudden onset of CHF and new systolic murmur. Echocardiography and Doppler interrogation can confirm presence of these complications. PCW tracings may show large *v* waves in either condition, but an oxygen "step-up" as the catheter is advanced from right atrium to right ventricle suggests septal rupture.

Acute medical therapy of these conditions includes vasodilator therapy (IV nitroprusside: begin at 10 μg/min and titrate to maintain systolic bp ~100 mmHg); intraaortic balloon pump may be required to maintain cardiac output. Mechanical correction is the definitive therapy. Acute ventricular free-wall rupture presents with sudden loss of bp, pulse, and consciousness, while ECG shows an intact rhythm (pulseless electrical activity); emergent surgical repair is crucial, and mortality is high.

## Pericarditis

Characterized by *pleuritic*, *positional* pain, and pericardial rub (Chap. 116); atrial arrhythmias are common; must be distinguished from recurrent angina. Often responds to aspirin, 650 mg PO qid. Anticoagulants should be avoided when pericarditis is suspected to avoid development of pericardial bleeding/tamponade.

## Ventricular Aneurysm

Localized "bulge" of LV chamber due to infarcted myocardium. *True aneurysms* consist of scar tissue and do not rupture. However, complications include CHF, ventricular arrhythmias, and thrombus formation. Typically an aneurysm is confirmed by echocardiography or by left ventriculography. The presence of thrombus within the aneurysm, or a large aneurysmal segment due to anterior MI, warrants consideration of oral anticoagulation with warfarin for 3–6 months.

*Pseudoaneurysm* is a form of cardiac rupture contained by a local area of pericardium and organized thrombus; direct communication with the LV cavity is present; surgical repair usually necessary to prevent rupture.

## Recurrent Angina

Usually associated with transient ST-T wave changes; signals high incidence of reinfarction; when it occurs in early post-MI period, proceed directly to coronary arteriography, to identify those who would benefit from revascularization.

### SECONDARY PREVENTION

For pts who have not already undergone coronary angiography and PCI, submaximal exercise testing should be performed prior to or soon after discharge. A positive test in certain subgroups (angina at a low workload, a large region of provocable ischemia, or provocable ischemia with a reduced LVEF) suggests need for cardiac catheterization to evaluate myocardium at risk of recurrent infarction. *Beta blockers* (e.g., metoprolol, 25–200 mg daily) should be prescribed routinely for at least 2 years following acute MI, unless contraindications present (asthma, active heart failure, bradycardia). Continue oral antiplatelet agents (e.g., aspirin 81–325 mg daily and a P2Y12 platelet receptor antagonist) to reduce incidence of reinfarction. If LVEF ≤40%, an ACE inhibitor or ARB (if ACE inhibitor is not tolerated) should be used indefinitely. Consider addition of aldosterone antagonist (see "Heart Failure," above).

Modification of cardiac risk factors must be encouraged: discontinue smoking; control hypertension, diabetes, and serum lipids (typically atorvastatin 80 mg daily in immediate post-MI period—see Chap. 178); and pursue graduated exercise.

For a more detailed discussion, see Antman EM, Loscalzo J: ST-Segment Elevation Myocardial Infarction, Chap. 295, p. 1599; and Hochman JS, Ingbar DH: Cardiogenic Shock and Pulmonary Edema, Chap. 326, p. 1759, in HPIM-19.

# 120 Unstable Angina and Non-ST-Elevation Myocardial Infarction

Unstable angina (UA) and non-ST-elevation MI (NSTEMI) are acute coronary syndromes with similar mechanisms, clinical presentations, and treatment strategies.

## Clinical Presentation

UA includes (1) new onset of severe angina, (2) angina at rest or with minimal activity, and (3) recent increase in frequency and intensity of chronic angina. NSTEMI is diagnosed when symptoms of UA are accompanied by evidence of myocardial necrosis (e.g., elevated cardiac biomarkers). Some pts with NSTEMI present with symptoms identical to STEMI—the two are differentiated by ECG findings.

## Physical Examination

May be normal or include diaphoresis, pale cool skin, tachycardia, $S_4$, basilar rales; if large region of ischemia, may demonstrate $S_3$, hypotension.

## Electrocardiogram

May include ST depression and/or T-wave inversion; unlike STEMI, there is no Q-wave development.

## Cardiac Biomarkers

Cardiac-specific troponins (specific and sensitive markers of myocardial necrosis) and CK-MB (less sensitive marker) are elevated in NSTEMI. Small troponin elevations may also occur in pts with CHF, myocarditis, or pulmonary embolism.

## TREATMENT UNSTABLE ANGINA AND NON-ST-ELEVATION MYOCARDIAL INFARCTION

First step is appropriate triage based on likelihood of coronary artery disease (CAD) and acute coronary syndrome (Fig. 120-1) as well as identification of higher-risk pts (Fig. 120-2). Pts with low likelihood of active ischemia are initially monitored by serial ECGs and serum cardiac biomarkers, and for recurrent chest discomfort; if these are negative, stress testing (or CT angiography if probability of CAD is low) can be used for further therapeutic planning.

Therapy of UA/NSTEMI is directed (1) against the inciting intracoronary thrombus, and (2) toward restoration of balance between myocardial oxygen supply and demand. Pts with the highest-risk scores (Fig. 120-2) benefit the most from aggressive interventions.

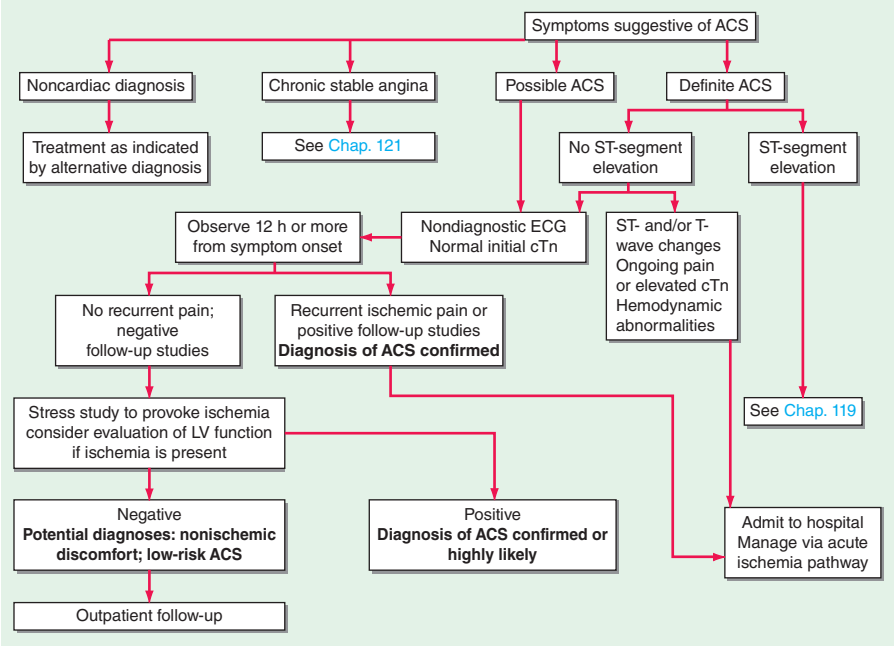



**FIGURE 120-1** Algorithm for evaluation and treatment of pts with a suspected acute coronary syndrome. ACS, acute coronary syndrome; cTn, cardiac troponin. *(Adapted from JL Anderson et al: J Am Coll Cardiol 61:e179, 2013.)*

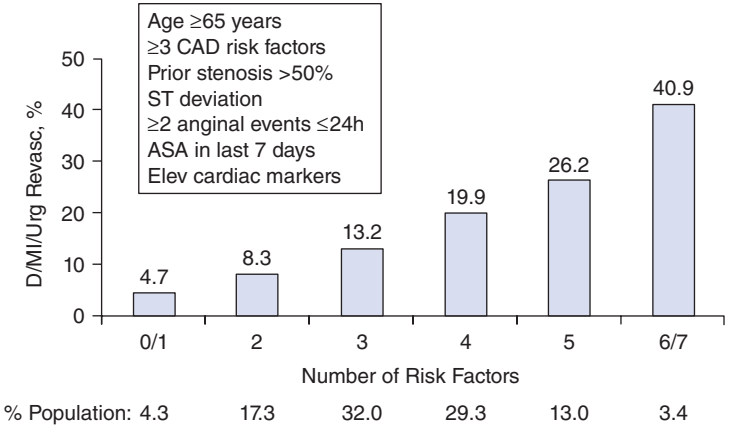



**FIGURE 120-2** The TIMI Risk Score for UA/NSTEMI. The quantity of listed attributes correlates with risk of death, MI, or need for urgent revascularization over 14 days. *(Modified from E Antman et al: JAMA 284:835, 2000.)*

## ANTITHROMBOTIC THERAPIES

- Aspirin (325 mg initially, then 75–100 mg/d).
- Platelet P2Y12 receptor antagonist (unless excessive risk of bleeding or immediate coronary artery bypass grafting [CABG] likely): Clopidogrel (300–600 mg PO load, then 75 mg/d), ticagrelor (180 mg PO, then 90 mg PO bid [chronic aspirin dose should not exceed 100 mg daily]) or prasugrel (60 mg PO, then 10 mg daily—use prasugrel only if PCI is planned).
- Anticoagulant: Unfractionated heparin (UFH) [70–100 U/kg (maximum 5000 U) then 12 (U/kg)/h (maximum 1000 U/h)] to achieve aPTT 1.5–2.5 × control, *or* low-molecular-weight heparin (e.g., enoxaparin 1 mg/kg SC q12h), which is superior to UFH in reduction of future cardiac events. Alternatives include (1) the factor Xa inhibitor fondaparinux (2.5 mg SC daily), which is associated with lower bleeding risk, or (2) the direct thrombin inhibitor bivalirudin [0.75-mg/kg bolus, then 1.75 (mg/kg)/h], which causes less bleeding in pts undergoing catheterization compared with UFH plus a GP IIb/IIIa inhibitor.
- For high-risk unstable pts who undergo PCI, consider an IV GP IIb/IIIa antagonist [e.g., tirofiban, 25 (μg/kg)/min load, then 0.15 (μg/kg)/min for up to 18 h; or eptifibatide, 180-μg/kg bolus, then 2.0 (μg/kg)/min for 72–96 h].

## ANTI-ISCHEMIC THERAPIES

- Nitroglycerin 0.3–0.6 mg sublingually or by buccal spray. If chest discomfort persists after three doses given 5 min apart, consider IV nitroglycerin (5–10 μg/min, then increase by 10 μg/min every 3–5 min until symptoms relieved or systolic bp <100 mmHg). Do not use nitrates in pts with recent use of phosphodiesterase-5 inhibitors for erectile dysfunction (e.g., not within 24 h of sildenafil or within 48 h of tadalafil).
- Beta blockers (e.g., metoprolol 25–50 mg PO q6h) targeted to a heart rate of 50–60 beats/min. In pts with contraindications to beta blockers (e.g., bronchospasm), consider long-acting verapamil or diltiazem (Table 166-1) if LV contractile function is not impaired.

**TABLE 120-1 CLASS I RECOMMENDATIONS FOR USE OF AN EARLY INVASIVE STRATEGY**

| |
|---|
| Recurrent angina/ischemia at rest or minimal exertion despite anti-ischemic therapy |
| Elevated cardiac TnT or TnI |
| New ST-segment depression |
| CHF symptoms, rales or worsening mitral regurgitation |
| Positive stress test |
| LVEF <0.40 |
| Hemodynamic instability or hypotension |
| Sustained ventricular tachycardia |
| PCI within previous 6 months, or prior CABG |
| Diabetes |
| Renal dysfunction |
| High-risk score |

***Abbreviations:*** CABG, coronary artery bypass grafting; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; TnI, troponin I; TnT, troponin T.
***Source:*** Modified from JL Anderson et al: *J Am Coll Cardiol* 61:e179, 2013.

## ADDITIONAL RECOMMENDATIONS

- Admit to unit with continuous ECG monitoring, initially with bed rest.
- Consider morphine sulfate 2–5 mg IV q5–30min for refractory chest discomfort.
- Add HMG-CoA reductase inhibitor (initially at high dose, e.g., atorvastatin 80 mg daily) and consider ACE inhibitor (Chap. 119).

## INVASIVE VS CONSERVATIVE STRATEGY

In highest-risk pts (Table 120-1), an early invasive strategy (coronary arteriography within ~48 h followed by percutaneous intervention or CABG) improves outcomes. In lower-risk pts, angiography can be deferred but should be pursued if myocardial ischemia recurs spontaneously (angina or ST deviations at rest or with minimal activity) or is provoked by stress testing.

## LONG-TERM MANAGEMENT

- Stress importance of smoking cessation, achieving optimal weight, diet low in saturated and trans fats, regular exercise; these principles can be reinforced by encouraging pt to enter cardiac rehabilitation program.
- Continue aspirin (75–100 mg/d), a P2Y12 receptor antagonist (clopidogrel, prasugrel or ticagrelor), beta blocker, high-dose statin, and ACE inhibitor or angiotensin receptor blocker (especially if hypertensive, or diabetic, or LV ejection fraction is reduced).

For a more detailed discussion, see Cannon CP, Braunwald E: Non-ST-Segment Elevation Acute Coronary Syndrome (Non-ST-Segment Elevation Myocardial Infarction and Unstable Angina), Chap. 294, p. 1593, in HPIM-19.

# 121 Chronic Stable Angina

## ANGINA

Angina pectoris, the most common clinical manifestation of coronary artery disease (CAD), results from an imbalance between myocardial $O_2$ supply and demand, most often due to atherosclerotic coronary artery obstruction. Other major conditions that upset this balance and result in angina include aortic valve disease (Chap. 114), hypertrophic cardiomyopathy (Chap. 115), and coronary artery spasm (see below).

### Symptoms

Angina is typically associated with exertion or emotional upset; relieved quickly by rest or nitroglycerin (Chap. 31). Major risk factors are cigarette smoking, hypertension, hypercholesterolemia (↑LDL; ↓HDL), diabetes, obesity, and family history of CAD before age 55.

### Physical Examination

Often normal; arterial bruits or retinal vascular abnormalities suggest generalized atherosclerosis; $S_4$ is common. During acute anginal episode, other signs may appear: e.g., an $S_4$, diaphoresis, rales, and a transient murmur of mitral regurgitation due to papillary muscle ischemia.

### Laboratory ECG

May be normal between anginal episodes or show old infarction (Chap. 111). During angina, ST- and T-wave abnormalities typically appear (ST-segment depression reflects subendocardial ischemia; ST-segment elevation may reflect acute infarction or transient coronary artery spasm). Ventricular arrhythmias frequently accompany acute ischemia.

### Stress Testing

Enhances diagnosis of CAD (Fig. 121-1). Exercise is performed on treadmill or bicycle until target heart rate is achieved or pt becomes symptomatic (chest pain, lightheadedness, hypotension, marked dyspnea, ventricular tachycardia) or develops diagnostic ST-segment changes. Useful information includes duration of exercise achieved; peak heart rate and bp; depth, morphology, and persistence of ST-segment depression; and whether and at which level of exercise pain, hypotension, or ventricular arrhythmias develop. Exercise testing with radionuclide, echocardiographic, or magnetic resonance imaging increases sensitivity and specificity and is particularly useful if baseline ECG abnormalities prevent interpretation of test. ***Note:*** Exercise testing should not be performed in pts with acute MI, unstable angina, or severe aortic stenosis. If the pt is unable to exercise, pharmacologic stress with IV dipyridamole, adenosine, regadenoson, or dobutamine can be performed in conjunction with radionuclide or echocardiographic imaging. (Table 121-1). Pts with LBBB on baseline ECG should be referred for adenosine or dipyridamole radionuclide imaging, which is most specific for diagnosis of CAD in this setting.

The prognostic utility of coronary calcium detection (by electron-beam or multidetector CT) in the diagnosis and management of CAD has not yet been fully defined.

Some pts do not experience chest pain during ischemic episodes with exertion ("silent ischemia") but are identified by transient ST-T-wave abnormalities during stress (see below).

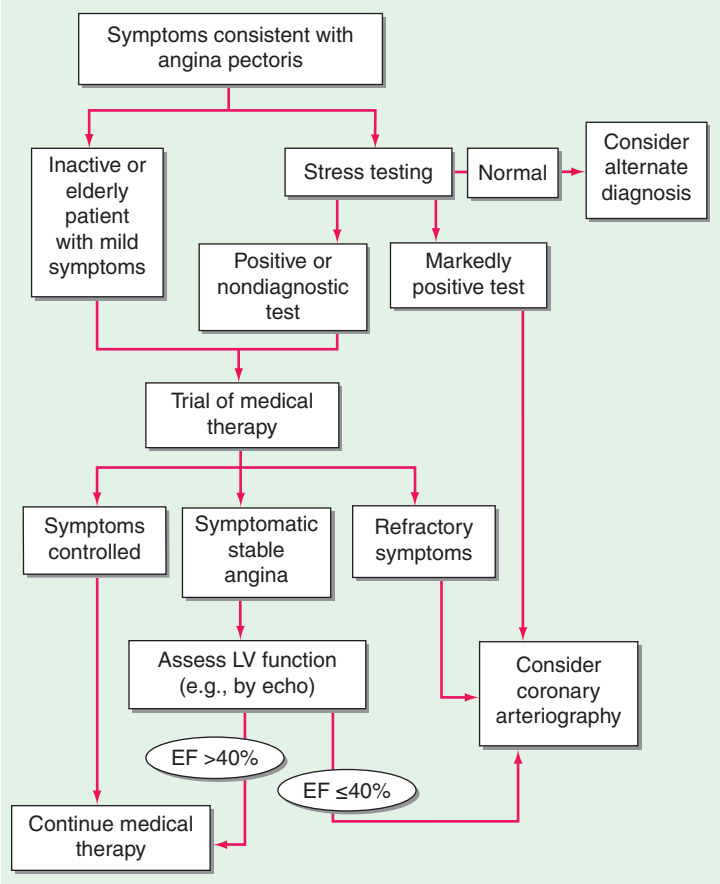



**FIGURE 121-1** Role of exercise testing in management of CAD; EF, left ventricular ejection fraction. (*Modified from LS Lilly, in Textbook of Primary Care Medicine, 3rd ed., J Noble [ed.]. St. Louis, Mosby, 2001, p. 552.*)

## Coronary Arteriography

The definitive test for assessing severity of CAD; major indications are (1) angina refractory to medical therapy, (2) markedly positive exercise test (≥2-mm ST-segment depression, onset of ischemia at low workload, or ventricular tachycardia or hypotension with exercise) suggestive of left main or three-vessel disease, (3) recurrent angina or positive exercise test after MI, (4) to assess for coronary artery spasm, and (5) to evaluate pts with perplexing chest pain in whom noninvasive tests are not diagnostic.

The role of newer *noninvasive* coronary imaging techniques (CT and MR angiography) continues to be defined.

**TABLE 121-1 STRESS TESTING RECOMMENDATIONS**

| Subgroup | Recommended Study |
|---|---|
| Pt able to exercise | |
| If baseline ST-T on ECG is normal | Standard exercise test (treadmill, bicycle, or arm ergometry) |
| If baseline ST-T impairs test interpretation (e.g., LVH with strain, digoxin) | Standard exercise test (above) combined with *either* |
| | Perfusion scintigraphy (thallium-201, $^{99m}$Tc-sestamibi) *or* |
| | Echocardiography |
| Pt *not* able to exercise (regardless of baseline ST-T abnormality) | Pharmacologic stress test (IV dobutamine, dipyridamole, or adenosine) combined with imaging: |
| | Perfusion scintigraphy [thallium 201, $^{99m}$Tc-sestamibi, or PET (rubidium-82 or N-13 ammonia)] *or* |
| | Echocardiography *or* |
| | Cardiac MRI |
| LBBB on baseline ECG | Adenosine (or dipyridamole) $^{99m}$Tc-sestamibi or PET scintigraphy |

## TREATMENT CHRONIC STABLE ANGINA

### GENERAL

- Identify and treat risk factors: mandatory cessation of smoking; treatment of diabetes, hypertension, and lipid disorders (Chap. 178); advocate a diet low in saturated fat and trans fats.
- Correct exacerbating factors contributing to angina: morbid obesity, CHF, anemia, hyperthyroidism.
- Reassurance and pt education.

### DRUG THERAPY

Sublingual nitroglycerin (TNG 0.3–0.6 mg); may be repeated at 5-min intervals; warn pts of possible headache or light-headedness; teach prophylactic use of TNG prior to activity that regularly evokes angina. If chest pain persists for >10 min despite 2–3 TNG, pt should report promptly to nearest medical facility for evaluation of possible acute coronary syndrome.

**Long-Term Angina Suppression** The following classes of drugs are used, frequently in combination.

**Long-Acting Nitrates** May be administered by many routes (Table 121-2); start at the lowest dose and frequency to limit tolerance and side effects of headache, light-headedness, tachycardia.

**Beta Blockers (See Table 117-1)** All have antianginal properties; $\beta_1$-selective agents are less likely to exacerbate airway or peripheral vascular disease. Dosage should be titrated to resting heart rate of 50–60 beats/min. *Contraindications* to beta blockers include CHF, AV block, bronchospasm, "brittle" diabetes. Side effects include fatigue, bronchospasm, depressed LV function, impotence, depression, and masking of hypoglycemia in diabetics.

**Calcium Antagonists (See Table 117-1)** Useful for stable and unstable angina, as well coronary vasospasm. Combination with other antianginal agents is beneficial,

**TABLE 121-2 EXAMPLES OF COMMONLY USED NITRATES**

| | Usual Dose | Recommended Dosing Frequency |
|---|---|---|
| **Short-acting agents** | | |
| Sublingual TNG | 0.3–0.6 mg | As needed |
| Aerosol TNG | 0.4 mg (1 inhalation) | As needed |
| Sublingual ISDN | 2.5–10 mg | As needed |
| **Long-acting agents** | | |
| ISDN | | |
| Oral | 5–30 mg | tid |
| Sustained-action | 40 mg | bid (once in the A.M., then 7 h later) |
| TNG ointment (2%) | 0.5–2 | qid (with one 7- to 10-h nitrate-free interval) |
| TNG skin patches | 0.1–0.6 mg/h | Apply in morning, remove at bedtime |
| ISMO | | |
| Oral | 20–40 mg | bid (once in the A.M., then 7 h later) |
| Sustained-action | 30–240 mg | Daily |

***Abbreviations:*** TNG, nitroglycerin; ISDN, isosorbide dinitrate; ISMO, isosorbide mononitrate.

but verapamil should be administered cautiously to pts on beta blockers (additive effects on slowing heart rate). Use sustained-release, not short-acting, calcium antagonists; the latter are associated with increased coronary mortality.

**Ranolazine** For pts who continue to experience stable angina despite the above standard medications, consider addition of ranolazine (500–1000 mg PO bid), which reduces anginal frequency and improves exercise capacity without affecting blood pressure or heart rate. Ranolazine is contraindicated in hepatic impairment, in pts with prolongation of the $QT_c$ interval, or in combination with drugs that inhibit its metabolism (e.g., ketoconazole, macrolide antibiotics, HIV protease inhibitors, diltiazem, and verapamil).

**Aspirin** 81–162 mg/d reduces the incidence of MI in chronic stable angina, following MI, and in asymptomatic men. It is recommended in pts with CAD in the absence of contraindications (GI bleeding or allergy). Consider clopidogrel (75 mg/d) for aspirin-intolerant individuals.

The addition of an ACE inhibitor is recommended in pts with CAD and LV ejection fraction <40%, hypertension, diabetes, or chronic kidney disease.

## MECHANICAL REVASCULARIZATION

Used in conjunction with, not as replacement for, risk factor modification and medical therapies.

**Percutaneous Coronary Intervention (PCI)** Technique of balloon dilatation, usually with intracoronary stent implantation. Performed on anatomically suitable stenoses of native vessels and bypass grafts; more effective than medical therapy for relief of angina. Has not been shown to reduce risk of MI or death in chronic stable angina; should not be performed on asymptomatic or only mildly symptomatic individuals. With PCI initial relief of angina occurs in 95% of pts; however, restenosis develops in 30–45% following balloon dilatation alone, in ~20% after bare metal stenting, but in only <10% after drug-eluting stent (DES) implantation. Late

**TABLE 121-3 COMPARISON OF REVASCULARIZATION PROCEDURES IN MULTIVESSEL DISEASE**

| Procedure | Advantages | Disadvantages |
|---|---|---|
| Percutaneous coronary revascularization | Less invasive<br>Shorter hospital stay<br>Lower initial cost<br>Effective in relieving symptoms | Restenosis requiring repeat procedure<br>Possible incomplete revascularization<br>Limited to specific anatomic subsets |
| Coronary artery bypass grafting | Lower rate of recurrent angina<br>Ability to achieve complete revascularization | Cost<br>Risk of a repeat procedure due to late graft closure<br>Morbidity and mortality of major surgery |

***Source:*** Modified from DP Faxon, in GA Beller (ed), Chronic Ischemic Heart Disease, in E Braunwald (series ed), *Atlas of Heart Disease*, Philadelphia, Current Medicine, 1994.

stent thrombosis may occur rarely in pts with DES; it is diminished by prolonged antiplatelet therapy (aspirin indefinitely and a platelet P2Y12 receptor antagonist for a minimum of 12 months).

**Coronary Artery Bypass Graft (CABG)** Appropriately used for angina refractory to medical therapy or when the latter is not tolerated (and when lesions are not amenable to PCI) or if severe CAD is present (e.g., left main, three-vessel disease with impaired LV function). In type 2 diabetics with multivessel CAD, CABG plus optimal medical therapy is superior to medical therapy alone in prevention of major coronary events.

The relative advantages of PCI and CABG are summarized in Table 121-3.

## PRINZMETAL'S VARIANT ANGINA (CORONARY VASOSPASM)

Intermittent focal spasm of coronary artery; often associated with atherosclerotic lesion near site of spasm. Chest discomfort is similar to angina but more severe and occurs typically at rest, with transient ST-segment elevation. Acute infarction or malignant arrhythmias may develop during spasm-induced ischemia. Evaluation includes observation of ECG for transient ST elevation during discomfort; diagnosis confirmed at coronary angiography using provocative (e.g., IV acetylcholine) testing. Primary treatment consists of long-acting nitrates and calcium antagonists. Prognosis is better in pts with anatomically normal coronary arteries than in those with fixed coronary stenoses.

For a more detailed discussion, see Antman EM, and Loscalzo J: Ischemic Heart Disease, Chap. 293, p. 1578, in HPIM-19.

# 122 Bradyarrhythmias

Bradyarrhythmias arise from (1) failure of impulse initiation (sinoatrial node dysfunction) or (2) impaired electrical conduction (e.g., AV conduction blocks).

## SINOATRIAL (SA) NODE DYSFUNCTION

Etiologies are either *intrinsic* (degenerative, ischemic, inflammatory, infiltrative [e.g., senile amyloid], or rare mutations in sodium channel or pacemaker current genes) or *extrinsic* (e.g., drugs [beta blockers, $Ca^{++}$ channel blockers, digoxin], autonomic dysfunction, hypothyroidism).

Symptoms are due to *bradycardia* (fatigue, weakness, lightheadedness, syncope) and/or episodes of associated *tachycardia* (e.g., rapid palpitations, angina) in pts with sick sinus syndrome (SSS).

### Diagnosis

Examine ECG for evidence of sinus bradycardia (sinus rhythm at <60 beats/min) or failure of rate to increase with exercise, sinus pauses, or exit block. In pts with SSS, periods of tachycardia (i.e., atrial fibrillation/flutter) occur. Prolonged ECG monitoring (24–48 h Holter, 30-day loop recorder, or long-term implanted monitor) aids in identifying these abnormalities. Invasive electrophysiologic testing is rarely necessary to establish diagnosis.

**TREATMENT SINOATRIAL NODE DYSFUNCTION**

Remove or treat extrinsic causes such as contributing drugs or hypothyroidism. Otherwise, symptoms of bradycardia respond to permanent pacemaker placement. In SSS, treat associated atrial fibrillation or flutter as indicated in Chap. 123.

## AV BLOCK

Impaired conduction from atria to ventricles may be structural and permanent, or reversible (e.g., autonomic, metabolic, drug-related)—see Table 122-1.

### First Degree (See Fig. 122-1A)

Prolonged, constant PR interval (>0.20 s). May be normal or secondary to increased vagal tone or drugs (e.g., beta blocker, diltiazem, verapamil, digoxin); treatment not usually required.

### Second Degree (See Fig. 122-1B)

### Mobitz I (Wenckebach)

Narrow QRS, progressive increase in PR interval until a ventricular beat is dropped, then sequence is repeated (Fig. 122-1D). Seen with drug intoxication (digitalis, beta blockers), increased vagal tone, inferior MI. Usually transient, no therapy required; if symptomatic, use atropine (0.6 mg IV, repeated × 3–4) or temporary pacemaker.

### Mobitz II

Fixed PR interval with occasional dropped beats, in 2:1, 3:1, or 4:1 pattern; the QRS complex is usually wide. Seen with MI or degenerative conduction system disease; more serious than Mobitz I—may progress suddenly to complete AV block; permanent pacemaker is indicated.

**TABLE 122-1 ETIOLOGIES OF ATRIOVENTRICULAR BLOCK**

| | |
|---|---|
| **Autonomic** | |
| Carotid sinus hypersensitivity | Vasovagal |
| **Metabolic/Endocrine** | |
| Hyperkalemia | Hypothyroidism |
| Hypermagnesemia | Adrenal insufficiency |
| **Drug-Related** | |
| Beta blockers | Adenosine |
| Calcium channel blockers | Antiarrhythmics (class I and III) |
| Digitalis | Lithium |
| **Infectious** | |
| Endocarditis | Tuberculosis |
| Lyme disease | Diphtheria |
| Chagas' disease | Toxoplasmosis |
| Syphilis | |
| **Heritable/Congenital** | |
| Congenital heart disease | Kearns-Sayre syndrome (OMIM #530000) |
| Maternal SLE | Myotonic dystrophy |
| **Inflammatory** | |
| SLE | MCTD |
| Rheumatoid arthritis | Scleroderma |
| **Infiltrative** | |
| Amyloidosis | Hemochromatosis |
| Sarcoidosis | |
| **Neoplastic/Traumatic** | |
| Lymphoma | Radiation |
| Mesothelioma | Catheter ablation |
| Melanoma | |
| **Degenerative** | |
| Lev disease | Lenégre disease |
| **Coronary Artery Disease** | |
| Acute MI | |

***Abbreviations:*** MCTD, mixed connective tissue disease; MI, myocardial infarction; OMIM, Online Mendelian Inheritance in Man (database).

## Third Degree (Complete AV Block) (See Fig. 122-1C)

Complete failure of conduction from atria to ventricles; atria and ventricles depolarize independently. May occur with MI, digitalis toxicity, or degenerative conduction system disease. Permanent pacemaker is usually indicated, except when reversible (e.g., drug-related or appears only transiently in MI without associated bundle branch block).

For a more detailed discussion, see Spragg DD, Tomaselli GF: The Bradyarrhythmias: Disorders of the Sinoatrial Node, Chap. 274, p. 1466; and Chap. 275, and Spragg DD, Tomaselli GF: The Bradyarrhythmias: Disorders of the Atrioventricular Node, p. 1470, in HPIM-19.

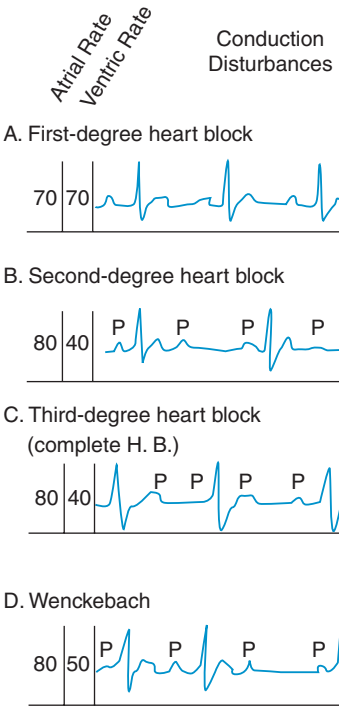



**FIGURE 122-1** Bradyarrhythmias. (*Modified from BE Sobel, E Braunwald: HPIM-9, p. 1052.*)

# 123 Tachyarrhythmias

Tachyarrhythmias may appear in the presence or absence of structural heart disease; they are more serious in the former. Conditions that provoke arrhythmias include (1) myocardial ischemia, (2) heart failure, (3) hypoxemia, (4) hypercapnia, (5) hypotension, (6) electrolyte disturbances (e.g., hypokalemia and/or hypomagnesemia), (7) drug toxicity (digoxin, pharmacologic agents that prolong the QT interval), (8) caffeine consumption, (9) ethanol consumption.

## Diagnosis

Examine ECG for evidence of ischemic changes (Chap. 111), prolonged or shortened QT interval, characteristics of Wolff-Parkinson-White (WPW) syndrome (see below), or ST elevation in leads $V_1$–$V_3$ typical of Brugada syndrome. See Table 123-1 for diagnosis of tachyarrhythmias; always identify atrial activity and relationship between P waves and QRS complexes. To aid the diagnosis:

**TABLE 123-1 CLINICAL AND ELECTROCARDIOGRAPHIC FEATURES OF COMMON ARRHYTHMIAS**

| Rhythm | Atrial Rate | Features | Carotid Sinus Massage | Precipitating Conditions | Initial Treatment |
|---|---|---|---|---|---|
| **Narrow QRS complex** | | | | | |
| Atrial premature beats | — | P wave abnormal; QRS width normal | — | Can be normal or due to anxiety, CHF, hypoxia, caffeine, abnormal electrolytes ($\downarrow K^+$ $\downarrow Mg^{2+}$) | Remove precipitating cause; if symptomatic: beta blocker |
| Sinus tachycardia | 100–160 | Normal P wave contour | Rate gradually slows | Fever, anxiety, dehydration, pain, CHF, hyperthyroidism, COPD | Remove precipitating cause; if symptomatic: beta blocker |
| AV nodal tachycardia (reentrant) | 120–250 | Absent or retrograde P wave | Abruptly converts to sinus rhythm (or no effect) | Can occur in healthy individuals | Vagal maneuvers; if unsuccessful: adenosine, verapamil, beta blocker, cardioversion (100–200 J). To prevent recurrence: beta blocker, verapamil, diltiazem, digoxin, class IC agent, or catheter ablation |
| Atrial tachycardia | 130–200 | P contour different from sinus P wave; AV block may occur; automatic form shows "warm-up" in rate in first several beats | AV block may $\uparrow$ | Digitalis toxicity; pulmonary disease; scars from prior cardiac surgery | If digitalis toxic: hold digoxin, correct [$K^+$]<br>In absence of digoxin toxicity: slow rate with beta blocker, verapamil, or diltiazem; can attempt conversion with IV procainamide or amiodarone; if unsuccessful, proceed to cardioversion or catheter ablation |

| | | | | | |
|---|---|---|---|---|---|
| Atrial flutter<br>Atrial fibrillation | 260–300<br>>350 | "Sawtooth" flutter waves; 2:1, 4:1 block<br>No discrete P; irregularly spaced QRS | ↑ AV block with ↓ventricular rate<br>↓ Ventricular rate | Mitral valve disease, hypertension, pulmonary embolism, pericarditis, post–cardiac surgery, hyperthyroidism; obstructive lung disease, EtOH, idiopathic | 1. Slow the ventricular rate: beta blocker, verapamil, diltiazem, or digoxin<br>2. Convert to NSR (after anticoagulation if chronic) electrically (50–100 J for atrial flutter, 100–200 J for atrial fibrillation) or chemically with IV ibutilide or oral class IC, III, or IA[a] agent<br>Atrial flutter may respond to rapid atrial pacing, and radio frequency ablation highly effective to prevent recurrences; consider ablation for recurrences of atrial fibrillation |
| Multifocal atrial tachycardia | 100–150 | More than three different P wave shapes with varying PR intervals | No effect | Severe respiratory insufficiency | Treat underlying lung disease; verapamil or diltiazem may be used to slow ventricular rate; class IC agents or amiodarone may ↓ episodes |
| **Wide QRS Complex** | | | | | |
| Ventricular premature beats | | Fully compensatory pause between normal beats | No effect | CAD, MI, CHF, hypoxia, hypokalemia, digitalis toxicity, prolonged QT interval (congenital or drug-related) | May not require therapy; if needed for symptomatic suppression, use beta blocker |
| Ventricular tachycardia | | QRS rate 100–250; slightly irregular rate | No effect | | If unstable: electrical conversion/defibrillation (≥200 J monophasic, or 100 J biphasic)<br>Otherwise: acute (IV): amiodarone, lidocaine, procainamide; chronic management: usually ICD<br>Pts without structural heart disease (e.g., focal outflow tract ventricular tachycardia) may respond to beta blockers or verapamil |

(*Continued*)

**TABLE 123-1 CLINICAL AND ELECTROCARDIOGRAPHIC FEATURES OF COMMON ARRHYTHMIAS (*CONTINUED*)**

| Rhythm | Atrial Rate | Features | Carotid Sinus Massage | Precipitating Conditions | Initial Treatment |
|---|---|---|---|---|---|
| Accelerated idioventricular rhythm (AIVR) | | Gradual onset and offset; QRS rate 40–120 | | Acute MI, myocarditis | Usually none; for symptoms, use atropine or atrial pacing |
| Ventricular fibrillation | | Erratic electrical activity | No effect | | Immediate defibrillation |
| Torsade de pointes | | Ventricular tachycardia with sinusoidal oscillations of QRS height | No effect | Prolonged QT interval (congenital or drug-related) | IV magnesium (1- to 2-g bolus); overdrive pacing; isoproterenol for bradycardia-dependent torsades (unless CAD present); lidocaine<br>Drugs that prolong QT interval are contraindicated |
| Supraventricular tachycardias with aberrant ventricular conduction | | P wave typical of the supraventricular rhythm; wide QRS complex due to conduction through partially refractory pathways | | Etiologies of the respective supraventricular rhythms listed above; atrial fibrillation with rapid, wide QRS may be due to preexcitation (WPW) | Same as treatment of respective supraventricular rhythm; if ventricular rate rapid (>200), treat as WPW (see text) |

[a]Antiarrhythmic drug groups listed in Table 123-2.

***Abbreviations:*** CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; EtOH, ethyl alcohol; ICD, implantable cardioverter defibrillator; NSR, normal sinus rhythm; WPW, Wolff-Parkinson-White.

**TABLE 123-2 EXAMPLES OF ANTIARRHYTHMIC DRUGS**

| Drug | Loading Dose | Maintenance Dose | Side Effects | Excretion |
|---|---|---|---|---|
| **Class IA** | | | | |
| Quinidine | | PO: 300–600 mg q6h | Diarrhea, tinnitus, QT prolongation, hypotension, anemia, thrombocytopenia | Hepatic |
| Procainamide | IV: 15 mg/kg over 60 min | IV: 1–4 mg/min<br>PO: 500–1000 mg q4h | Nausea, lupus-like syndrome, agranulocytosis, QT prolongation | Renal and hepatic |
| Sustained-release | | PO: 1000–2500 mg q12h | | |
| Disopyramide | | PO: 100–300 mg q6–8h | Myocardial depression, AV block, QT prolongation anticholinergic effects | Renal and hepatic |
| Sustained-release | | PO: 200–400 mg q12h | | |
| **Class IB** | | | | |
| Lidocaine | IV: 1-mg/kg bolus followed by 0.5-mg/kg bolus q8–10 min to total 3 mg/kg | IV: 1–4 mg/min | Confusion, seizures, respiratory arrest | Hepatic |
| Mexiletine | | PO: 150–300 mg q8–12h | Nausea, tremor, gait disturbance | Hepatic |
| **Class IC** | | | | |
| Flecainide | | PO: 50–200 mg q12h | Nausea, exacerbation of ventricular arrhythmia, prolongation of PR and QRS intervals | Hepatic and renal |
| Propafenone | | PO: 150–300 mg q8h | | Hepatic |
| **Class II** | | | | |
| Metoprolol | IV: 5–10 mg q5min × 3 | PO: 25–100 mg q6h | Bradycardia, AV block, CHF, bronchospasm | Hepatic |
| Esmolol | IV: 500 μg/kg over 1 min | IV: 50 (μg/kg)/min | | |

(*Continued*)

**TABLE 123-2 EXAMPLES OF ANTIARRHYTHMIC DRUGS (*CONTINUED*)**

| Drug | Loading Dose | Maintenance Dose | Side Effects | Excretion |
|---|---|---|---|---|
| **Class III** | | | | |
| Amiodarone | PO: 800–1600 mg qd × 1–2 weeks, then 400–600 mg/d × 3 weeks<br>IV: 150 mg over 10 min | PO: 100–400 mg qd<br>IV: 1 mg/min × 6 h, then 0.5 mg/min | Thyroid abnormalities, pulmonary fibrosis, transaminitis, bluish skin | Hepatic |
| Ibutilide | IV (≥60 kg): 1 mg over 10 min, can repeat after 10 min | — | Torsade de pointes, hypotension, nausea | Hepatic |
| Dofetilide | | PO: 125–500 μg bid | Torsade de pointes, headache, dizziness | Renal |
| Sotalol | | PO: 80–160 mg q12h | Fatigue, bradycardia, exacerbation of ventricular arrhythmia | Renal |
| Dronedarone | | PO: 400 mg q12h | Bradycardia, AV block, prolonged QT, exacerbation of heart failure, GI discomfort | Hepatic |
| **Class IV** | | | | |
| Verapamil | IV: 2.5–10 mg over 3–5 min | IV: 2.5–10 mg/h<br>PO: 80–120 mg q6–8 h | AV block, CHF, hypotension, constipation | Hepatic |
| Diltiazem | IV: 0.25 mg/kg over 3–5 min (maximum 20 mg) | IV: 5–15 mg/h<br>PO: 30–60 mg q6h | | Hepatic |
| **Other** | | | | |
| Digoxin | IV, PO: 0.75–1.5 mg over 24 h | IV, PO: 0.125–0.25 mg qd | Nausea, AV block, ventricular and supraventricular arrhythmias | Renal |
| Adenosine | IV: 6-mg rapid bolus; if no effect then 12-mg bolus | — | Transient hypotension or atrial standstill | — |

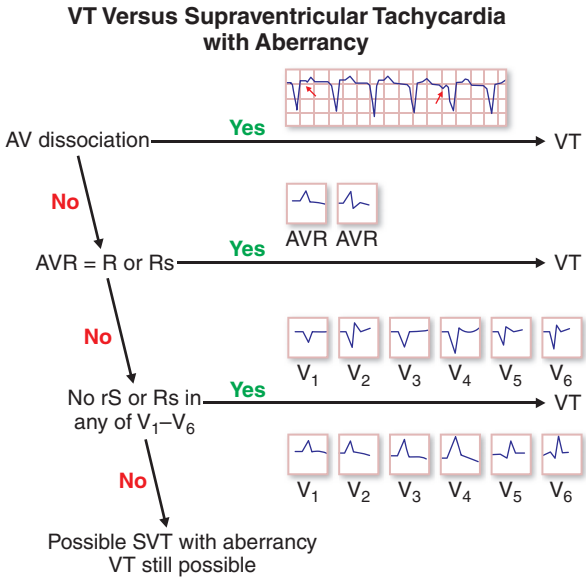



**FIGURE 123-1** Algorithm for differentiation of ventricular tachycardia (VT) from supraventricular tachycardia (SVT).

- Obtain long rhythm strip of lead II, aVF, or $V_1$. P waves can be made more evident by intentionally doubling the ECG voltage.
- Place accessory ECG leads (e.g., right-sided chest leads) to help identify P waves. Record ECG during carotid sinus massage (Table 123-1). ***Note:*** Do not massage both carotids simultaneously.
- For intermittent symptoms, consider 24-h Holter monitor (if symptoms occur daily), a pt-activated or continuously recording event monitor over 2–4 weeks, or, if symptoms are very infrequent but severely symptomatic, an implanted loop monitor. A standard exercise test may be used to provoke arrhythmias for diagnostic purposes.

Tachyarrhythmias with wide QRS complex beats may represent ventricular tachycardia or supraventricular tachycardia with aberrant conduction. Factors favoring ventricular tachycardia include (1) AV dissociation, (2) monomorphic R or Rs in atrioventricular reentry (AVR), (3) concordance of QRS with monophasic R or S waves in V1–V6 (Figure 123-1).

## TREATMENT TACHYARRHYTHMIAS (TABLES 123-1 AND 123-2)

Precipitating causes (listed above) should be corrected. If pt is hemodynamically compromised (angina, hypotension, CHF), proceed to immediate cardioversion.

Do not cardiovert sinus tachycardia; exercise caution if digitalis toxicity is suspected. Initiate drugs as indicated in the tables; follow ECG intervals (esp. QRS and QT). Reduce dosage for pts with hepatic or renal dysfunction as indicated in Table 123-2. Drug efficacy is confirmed by ECG (or Holter) monitoring, stress testing, and, in special circumstances, invasive electrophysiologic study.

Antiarrhythmic agents all have potential toxic side effects, including provocation of ventricular arrhythmias, esp. in pts with LV dysfunction or history of sustained ventricular arrhythmias. Drug-induced QT prolongation and associated torsades de pointes ventricular tachycardia (Table 123-1) is most common with class IA and III agents; the drug should be discontinued if the QTc interval (QT divided by square root of RR interval) increases by >25%. Antiarrhythmic drugs should be avoided in pts with asymptomatic ventricular arrhythmias after MI, since mortality risk increases.

## CHRONIC ATRIAL FIBRILLATION (AF)

Evaluate potential underlying cause (e.g., thyrotoxicosis, mitral stenosis, excessive ethanol consumption, pulmonary embolism). Pts with rheumatic mitral valve disease or $CHA_2DS_2$-VASc score ≥2 (1 point each for CHF, hypertension, diabetes, vascular disease, age 65–75, female gender; 2 points each for age 75, history of stroke or TIA) should receive anticoagulation with either warfarin (INR 2.0–3.0) or, for AF not associated with valvular disease, newer oral anticoagulants that do not require prothrombin time monitoring—e.g., dabigatran 150 mg bid for creatinine clearance (CrCl) >30 mL/min (75 mg bid for CrCl 15–30 mL/min), rivaroxaban 20 mg daily with the evening meal (15 mg daily for CrCl 15–50 mL/min; avoid if CrCl <15), or apixaban 5 mg bid (2.5 mg bid for 2 of the following: age ≥80, weight ≤60 kg, serum creatinine ≥1.5 md/dL). Can also consider anticoagulation for $CHA_2DS_2$-VASc score of 1. Prescribe aspirin, up to 325 mg/d, for $CHA_2DS_2$-VASc of 0–1 or if contraindication to systemic anticoagulation exists.

Control ventricular rate (60–80 beats/min at rest, <100 beats/min with mild exercise) with beta blocker, calcium channel blocker (verapamil, diltiazem), or digoxin.

Consider cardioversion (100–200 J) after ≥3 weeks therapeutic anticoagulation, or acutely if no evidence of left atrial thrombus by transesophageal echo, especially if symptomatic despite rate control. Initiation of class IC, III, or IA agents prior to electrical cardioversion facilitates maintenance of sinus rhythm after successful procedure. Class IC (Table 123-2) drugs are preferred in pts without structural heart disease, and class III drugs are recommended in presence of left ventricular dysfunction or coronary artery disease. Anticoagulation should be continued for a minimum of 3 weeks after successful cardioversion.

Catheter-based ablation (pulmonary vein isolation) can be considered for recurrent symptomatic AF refractory to pharmacologic measures.

## PREEXCITATION SYNDROME (WPW)

Conduction occurs through an accessory pathway between atria and ventricles. Baseline ECG typically shows a short PR interval and slurred upstroke of the QRS ("delta" wave). Associated tachyarrhythmias are of two types:

- Narrow QRS "orthodromic" tachycardia (antegrade conduction through AV node). Treat cautiously with IV adenosine or beta blocker, verapamil, or diltiazem (Table 123-2).
- Wide QRS complex "antidromic" tachycardia (antegrade conduction through accessory pathway); wide complex tachycardia may also be associated with AF with a very rapid (>250/min) ventricular rate, which can degenerate into VF. If hemodynamically compromised, immediate cardioversion is indicated; otherwise, treat with IV procainamide or ibutilide (Table 123-2), *not* digoxin, beta blocker, or verapamil.

Consider catheter ablation of accessory pathway for long-term prevention.

For a more detailed discussion, see Michaud GF, Stevenson WG: Supraventricular Tachyarrhythmias, Chap. 276, p. 1476 and John RM, Stevenson WG: Ventricular Arrhythmias, Chapter 277, p. 1489 in HPIM-19.

# 124 Heart Failure and Cor Pulmonale

## HEART FAILURE

### Definition

Abnormality of cardiac structure and/or function resulting in clinical symptoms (e.g., dyspnea, fatigue) and signs (e.g., edema, rales), hospitalizations, poor quality of life, and shortened survival. It is important to identify the underlying nature of the cardiac disease and the factors that precipitate acute CHF.

### Underlying Cardiac Disease

Includes (1) states that depress systolic ventricular function with reduced ejection fraction (HFrEF; e.g., coronary artery disease [CAD], dilated cardiomyopathies, valvular disease, congenital heart disease); and (2) states of heart failure with preserved ejection fraction (HFpEF; e.g., restrictive cardiomyopathies, hypertrophic cardiomyopathy, fibrosis, endomyocardial disorders), also termed *diastolic failure*.

### Acute Precipitating Factors

Include (1) excessive $Na^+$ intake, (2) noncompliance with heart failure medications, (3) acute MI (may be silent), (4) exacerbation of hypertension, (5) acute arrhythmias, (6) infections and/or fever, (7) pulmonary embolism, (8) anemia, (9) thyrotoxicosis, (10) pregnancy, (11) acute myocarditis or infective endocarditis, and (12) certain drugs (e.g., nonsteroidal anti-inflammatory agents, verapamil).

### Symptoms

Due to inadequate perfusion of peripheral tissues (fatigue) and elevated intracardiac filling pressures (dyspnea, orthopnea, paroxysmal nocturnal dyspnea, peripheral edema).

### Physical Examination

Jugular venous distention, $S_3$ (in HFrEF/volume overload), pulmonary congestion (rales, dullness over pleural effusion), peripheral edema, hepatomegaly, and ascites. Sinus tachycardia is common.

In pts with HFpEF, $S_4$ is often present.

### Laboratory

*CXR* may reveal cardiomegaly, pulmonary vascular redistribution, interstitial edema, pleural effusions. Left ventricular systolic and diastolic dysfunction can be assessed

by *echocardiography* with Doppler, and EF calculated or estimated. In addition, echo can identify underlying valvular, pericardial, or congenital heart disease, and regional wall motion abnormalities typical of CAD. Cardiac MR may be valuable in assessing ventricular structure, mass, volumes, and can help determine cause of heart failure (e.g., CAD, amyloid, hemochromatosis). Measurement of B-type natriuretic peptide (BNP) or N-terminal pro-BNP differentiates cardiac from pulmonary causes of dyspnea (elevated in the former).

## Conditions that Mimic CHF

*Pulmonary Disease*: Chronic bronchitis, emphysema, and asthma (Chaps. 129 and 131); assess for sputum production and abnormalities on CXR and pulmonary function tests. *Other Causes of Peripheral Edema*: Obesity, varicose veins, and venous insufficiency do not cause jugular venous distention. Edema due to renal dysfunction is often accompanied by elevated serum creatinine and abnormal urinalysis (Chap. 36).

## TREATMENT HEART FAILURE

Aimed at symptomatic relief, prevention of adverse cardiac remodeling, and prolonging survival. Overview of treatment shown in Table 124-1; notably, ACE inhibitors and beta blockers are cornerstones of therapy in pts with HFrEF. Once symptoms develop:

- *Control excess fluid retention*: (1) *Dietary sodium restriction* (eliminate salty foods, e.g., potato chips, canned soups, bacon, salt added at table); more stringent requirements (<2 g NaCl/d) in advanced CHF. If dilutional hyponatremia present, restrict fluid intake (<1000 mL/d). (2) *Diuretics: Loop diuretics* (e.g., furosemide or torsemide [Table 124-2]) are most potent and, unlike thiazides, remain effective when GFR <25 mL/min. Combine loop diuretic with thiazide or metolazone for augmented effect.

During acute diuresis, obtain daily weights, aiming for loss of 1–1.5 kg/d.

- *ACE inhibitors* (Table 124-2): Recommended as standard initial CHF therapy. They prolong life in pts with symptomatic CHF, delay the onset of CHF in pts with asymptomatic LV dysfunction, and lower mortality when begun soon after acute MI. ACE inhibitors may result in hypotension in pts who are volume depleted, so start at lowest dosage (e.g., captopril 6.25 mg PO tid). Angiotensin receptor blockers (ARBs) (Table 124-2) may be substituted if pt is intolerant of ACE inhibitor (e.g., because of cough or angioedema). Consider hydralazine plus an oral nitrate instead in pts who develop hyperkalemia or renal insufficiency on ACE inhibitor.
- *Beta blockers* (Table 124-2) administered in gradually augmented dosage improve symptoms and prolong survival in pts with heart failure and reduced EF <40%. Begin at low dosage and increase gradually (e.g., carvedilol 3.125 mg bid, double q2weeks as tolerated to maximum of 25 mg bid [for weight <85 kg] or 50 mg bid [weight >85 kg]).
- Aldosterone antagonist therapy (*spironolactone* or *eplerenone* [Table 124-2]), added to standard therapy in pts with advanced heart failure reduces mortality. Such therapy should be considered in pts with class II-IV heart failure symptoms and LVEF ≤35%. Should be used cautiously when combined with ACE inhibitor or ARB to avoid hyperkalemia.
- *Digoxin* may be useful in heart failure due to (1) marked systolic dysfunction (LV dilatation, low EF, $S_3$) and (2) heart failure with atrial fibrillation (AF) and rapid ventricular rates. Unlike ACE inhibitors and beta blockers, digoxin does not prolong survival in heart failure pts but reduces hospitalizations. Not indicated in CHF due to pericardial disease, restrictive cardiomyopathy, or mitral stenosis

**TABLE 124-1 THERAPY FOR CHRONIC HEART FAILURE**

1. General measures
   a. Restrict salt intake
   b. Avoid NSAIDs
   c. Immunize against influenza and pneumococcal pneumonia
2. Diuretics
   a. Use in volume-overloaded pts to achieve normal JVP and relief of edema
   b. Weigh daily to adjust dose
   c. For diuretic resistance, administer IV or use 2 diuretics in combination (e.g., furosemide plus metolazone)
3. ACE inhibitor or angiotensin receptor blocker
   a. For all pts with LV systolic heart failure or asymptomatic LV dysfunction
   b. Contraindications: Serum $K^+$ >5.5, advanced renal disease (e.g., creatinine >3 mg/dL), bilateral renal artery stenosis, pregnancy
4. Beta blocker
   a. For pts with symptomatic or asymptomatic heart failure and LVEF <40%, combined with ACE inhibitor and diuretics
   b. Contraindications: Bronchospasm, symptomatic bradycardia or advanced heart block, unstable heart failure
5. Aldosterone antagonist
   a. Consider for class II–IV heart failure and LVEF <35%
   b. Avoid if $K^+$ >5.0 or creatinine >2.5 mg/dL
6. Digitalis
   a. For persistently symptomatic pts with systolic heart failure (especially if atrial fibrillation present) added to ACE inhibitor, diuretics, beta blocker
7. Other measures
   a. Consider combination of hydralazine and oral nitrate if not tolerant of ACE inhibitor/ARB
   b. Consider ivabradine for LVEF ≤35%, if in sinus rhythm, rate > 70, already on maximum tolerated beta blocker, or if contraindication to beta-blocker
   c. Consider ventricular resynchronization (biventricular pacemaker) for pts with class III or IV heart failure, LVEF <35%, and QRS >120 ms
   d. Consider implantable cardioverter-defibrillator in pts with class II–III heart failure and ejection fraction <35%

(unless AF is present). Digoxin is contraindicated in hypertrophic cardiomyopathy and in pts with AV conduction blocks.

– Digoxin dosing (0.125–0.25 mg qd) depends on age, weight, and renal function and can be guided by measurement of serum digoxin level (maintain level <1.0 ng/mL).

– *Digitalis toxicity* may be precipitated by hypokalemia, hypoxemia, hypercalcemia, hypomagnesemia, hypothyroidism, or myocardial ischemia. Early signs of toxicity include anorexia, nausea, and lethargy. *Cardiac toxicity* includes ventricular and supraventricular dysrhythmias and all degrees of AV block. At first sign of digitalis toxicity, discontinue the drug; maintain serum $K^+$

**TABLE 124-2 DRUGS FOR THE TREATMENT OF CHRONIC HEART FAILURE WITH REDUCED EF**

| | Initiating Dose | Maximal Dose |
|---|---|---|
| **Diuretics** | | |
| Furosemide | 20–40 mg qd or bid | 400 mg/d |
| Torsemide | 10–20 mg qd bid | 200 mg/d |
| Bumetanide | 0.5–1.0 mg qd or bid | 10 mg/d |
| Hydrochlorothiazide | 25 mg qd | 100 mg/d |
| Metolazone | 2.5–5.0 mg qd or bid | 20 mg/d |
| **Angiotensin-converting enzyme inhibitors** | | |
| Captopril | 6.25 mg tid | 50 mg tid |
| Enalapril | 2.5 mg bid | 10–20 mg bid |
| Lisinopril | 2.5–5.0 mg qd | 20–40 mg qd |
| Ramipril | 1.25–2.5 mg bid | 2.5–5 mg bid |
| Trandolapril | 0.5 mg qd | 4 mg qd |
| **Angiotensin receptor blockers** | | |
| Valsartan | 40 mg bid | 160 mg bid |
| Candesartan | 4 mg qd | 32 mg qd |
| Losartan | 25–50 mg qd | 150 mg qd |
| **β receptor blockers** | | |
| Carvedilol | 3.125 mg bid | 25–50 mg bid |
| Bisoprolol | 1.25 mg qd | 10 mg qd |
| Metoprolol succinate CR | 12.5–25 mg qd | 200 mg qd |
| **Aldosterone antagonists** | | |
| Spironolactone | 12.5–25 mg qd | 25–50 mg qd |
| Eplerenone | 25 mg qd | 50 mg qd |
| **Additional therapies** | | |
| Combination of hydralazine/isosorbide dinitrate | 10–25 mg/10 mg tid | 75 mg/40 mg tid |
| Fixed dose of hydralazine/isosorbide dinitrate | 37.5 mg/20 mg (one tablet) tid | 75 mg/40 mg (two tablets) tid |
| Digoxin | 0.125 mg qd | Guided by renal function and serum level |

concentration between 4.0 and 5.0 mmol/L. Bradyarrhythmias and AV block may respond to atropine (0.6 mg IV); otherwise, a temporary pacemaker may be required. Antidigoxin antibodies are available for massive overdose.

- The combination of the oral vasodilators *hydralazine* (10–75 mg tid) and *isosorbide dinitrate* (10–40 mg tid) may be of benefit for chronic administration in pts intolerant of ACE inhibitors and ARBs and is also beneficial as part of standard therapy, along with ACE inhibitor and beta blocker, in African Americans with class II–IV heart failure.
- Ivabradine, an inhibitor of the sinoatrial nodal $I_f$ current, has been shown to reduce hospitalizations and cardiovascular endpoints in heart failure and was recently approved for that purpose. It is a second line agent that can be prescribed (starting at 2.5–5.0 mg orally twice daily) to pts with left ventricular ejection fraction (LVEF) ≤35%, in sinus rhythm with heart rate >70 bpm, already on maximally tolerated beta-blocker dose or have a contraindication to beta-blocker use.
- In sicker, hospitalized pts, IV vasodilator therapy (Table 124-3) is often necessary. *Nitroprusside* is a potent mixed vasodilator for pts with markedly elevated

**TABLE 124-3 DRUGS FOR TREATMENT OF ACUTE HEART FAILURE**

| | Initiating Dose | Maximal Dose |
|---|---|---|
| **Vasodilators** | | |
| Nitroglycerin | 20 μg/min | 40–400 μg/min |
| Nitroprusside | 10 μg/min | up to 5 μg/kg/min |
| Nesiritide | Bolus 2 μg/kg | 0.01 μg/kg per min[a] |
| **Inotropes** | | |
| Dobutamine | 1–2 μg/kg per min | 2–20 μg/kg per min |
| Milrinone | Bolus 50 μg/kg slowly over 10 min | 0.1–0.75 μg/kg per min |
| Dopamine | 1–2 μg/kg per min | 2–4 μg/kg per min |
| Levosimendan | Bolus 6–12 μg/kg over 10 min | 0.1–0.2 μg/kg per min[a] |

[a]Approved outside of the United States for the management of acute heart failure.

systemic vascular resistance. It is metabolized to thiocyanate, which is excreted via the kidneys. To avoid thiocyanate toxicity (seizures, altered mental status, nausea), follow thiocyanate levels in pts with renal dysfunction or if administered for >2 days. IV *nesiritide* (Table 124-3), a purified preparation of BNP, is a vasodilator that reduces pulmonary capillary wedge pressure in pts with acutely decompensated CHF, but has neutral effects on mortality or sense of dyspnea. It should be considered only in pts with refractory heart failure.

- IV inotropic agents (see Table 124-3) are administered to hospitalized pts for refractory symptoms or acute exacerbation of CHF to augment cardiac output. They are contraindicated in hypertrophic cardiomyopathy. *Dobutamine* augments cardiac output without significant peripheral vasoconstriction or tachycardia. *Dopamine* at low dosage (1–5 [μg/kg]/min) facilitates diuresis; at higher dosage (5–10 [μg/kg]/min) positive inotropic effects predominate; peripheral vasoconstriction is greatest at dosage >10 (μg/kg)/min. *Milrinone* (0.1–0.75 [μg/kg]/min after 50-μg/kg loading dose) is a nonsympathetic positive inotrope and vasodilator. The above vasodilators and inotropic agents may be used together for additive effect.
- The initial approach to treatment of acute decompensated heart failure can rely on the pt's hemodynamic profile (Fig. 124-1) based on clinical examination and, if necessary, invasive hemodynamic monitoring:

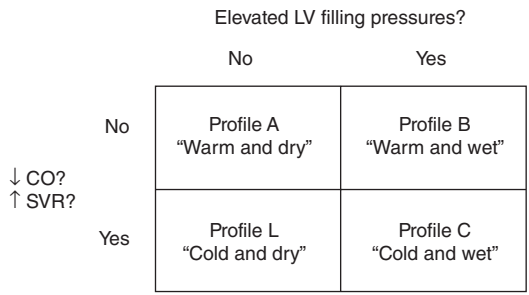



**FIGURE 124-1** Hemodynamic profiles in pts with acute heart failure. CO, cardiac output; SVR, systemic vascular resistance. *(Modified from Grady KL et al: Circulation 102:2443, 2000.)*

– *Profile A "Warm and dry":* Symptoms due to conditions other than heart failure (e.g., acute ischemia). Treat underlying condition.

– *Profile B "Warm and wet":* Treat with diuretic and vasodilators.

– *Profile C "Cold and wet":* Treat with IV vasodilators and inotropic agents.

– *Profile L "Cold and dry":* If low filling pressure (PCW <12 mmHg) confirmed, consider trial of volume repletion.

- Consider implantable cardioverter defibrillator (ICD) prophylactically for chronic class II–III heart failure and LVEF <35%. Pts with an LVEF <35%, refractory CHF (NYHA class III–IV), and QRS >120 ms may be candidates for biventricular pacing (cardiac resynchronization therapy), typically in combination with an ICD. Pts with severe disease and very limited, short-term expected survival, and who meet stringent criteria, may be candidates for cardiac transplantation or prolonged-assisted mechanical circulation (see HPIM-19, **Chap. 281**, p. 1516).
- Pts with predominantly diastolic heart failure are treated with salt restriction and diuretics. Beta blockers and ACE inhibitors may be of benefit in blunting neurohormonal activation.

## COR PULMONALE

RV enlargement and/or altered function resulting from primary lung disease; leads to RV hypertrophy and eventually to RV failure. Etiologies include:

- *Pulmonary parenchymal or airway disease* leading to hypoxemic vasoconstriction: e.g., chronic obstructive pulmonary disease (COPD), interstitial lung diseases, bronchiectasis, cystic fibrosis (**Chaps. 131** and **134**).
- *Diseases of the pulmonary vasculature*: e.g., recurrent pulmonary emboli, pulmonary arterial hypertension (PAH) (**Chap. 127**), vasculitis, sickle cell anemia.
- *Inadequate mechanical ventilation (chronic hypoventilation).* Kyphoscoliosis, neuromuscular disorders, marked obesity, sleep apnea (**Chap. 137**).

### Symptoms

Depend on underlying disorder but include dyspnea, cough, fatigue, and sputum production (in parenchymal diseases).

### Physical Examination

Tachypnea, RV impulse along left sternal border, loud $P_2$, right-sided $S_4$; cyanosis, clubbing are late findings. If RV failure develops, elevated jugular venous pressure, hepatomegaly with ascites, pedal edema; murmur of tricuspid regurgitation is common.

### Laboratory ECG

RV hypertrophy and RA enlargement (**Chap. 111**); tachyarrhythmias are common.

### Radiologic Studies

CXR shows RV and pulmonary artery enlargement; if PAH present, tapering of the pulmonary artery branches. Chest CT identifies emphysema, interstitial lung disease, and acute pulmonary embolism; V/Q scan is more reliable for diagnosis of chronic thromboemboli. Pulmonary function tests and ABGs characterize intrinsic pulmonary disease.

### Echocardiogram

RV hypertrophy; LV function typically normal. RV systolic pressure can be estimated from Doppler measurement of tricuspid regurgitant flow. If imaging is

difficult because of air in distended lungs, RV volume and wall thickness can be evaluated by MRI.

### Right-Heart Catheterization

Can confirm presence of pulmonary hypertension and exclude left-heart failure as cause.

**TREATMENT COR PULMONALE**

Aimed at underlying pulmonary disease and may include bronchodilators, antibiotics, oxygen administration, and noninvasive mechanical ventilation. For pts with PAH, pulmonary vasodilator therapy may be beneficial to reduce RV afterload (Chap. 127). See Chap. 133 for specific treatment of pulmonary embolism.

If RV failure is present, treat as heart failure, instituting low-sodium diet and diuretics; digoxin is of uncertain benefit and must be administered cautiously (toxicity increased due to hypoxemia, hypercapnia, acidosis). Loop diuretics must also be used with care to prevent significant metabolic alkalosis that blunts respiratory drive.

For a more detailed discussion, see Mann DL, Chakinala M: Heart Failure: Pathophysiology and Diagnosis, Chap. 279, p. 1500, and Mehra MR: Heart Failure: Management, Chap. 280, p. 1507, in HPIM-19.

# 125 Diseases of the Aorta

## AORTIC ANEURYSM

Abnormal dilatation of the abdominal or thoracic aorta; in ascending aorta most commonly secondary to cystic medial necrosis (e.g., familial, Marfan's syndrome, Ehlers-Danlos syndrome type IV); aneurysms of descending thoracic and abdominal aorta are primarily atherosclerotic. Rare causes of aneurysms are infections (syphilitic, tuberculous, mycotic) and vasculitides (e.g., Takayasu's arteritis, giant cell arteritis).

### History

May be clinically silent, but thoracic aortic aneurysms can result in deep, diffuse chest pain, dysphagia, hoarseness, hemoptysis, dry cough; abdominal aneurysms may result in abdominal pain or thromboemboli to the lower extremities.

### Physical Examination

Abdominal aneurysms are often palpable, most commonly in periumbilical area. Pts with ascending thoracic aneurysms may show features of Marfan's syndrome (Chap. 427, HPIM-19).

### Laboratory

Suspect thoracic aneurysm by abnormal *CXR* (enlarged aortic silhouette) and confirm by *echocardiography*, *contrast CT*, or *MRI*. Confirm abdominal aneurysm by *abdominal plain film* (rim of calcification), *ultrasound*, *CT*, *MRI*, or *contrast aortography*. If clinically suspected, obtain serologic test for syphilis, especially if ascending thoracic aneurysm shows thin shell of calcification. Screening abdominal ultrasound to assess for abdominal aortic aneurysm (AAA) is recommended for men aged 65–75 who have ever smoked, for individuals with a history of a thoracic aortic aneurysm, and for first degree relatives of pts with AAA.

**TREATMENT AORTIC ANEURYSM**

Pharmacologic control of hypertension (Chap. 117) is essential, usually including a beta blocker. Surgical resection for symptoms, for large aneurysms (ascending thoracic aortic aneurysms >5.5 cm, descending thoracic aortic aneurysms >6.0 cm, or abdominal aortic aneurysm >5.5 cm), for persistent pain despite bp control, or for evidence of rapid expansion. In pts with Marfan's syndrome thoracic aortic aneurysms >5 cm usually warrant repair. Less invasive endovascular repair is an option for some pts with descending thoracic or abdominal aortic aneurysms.

## AORTIC DISSECTION (FIG. 125-1)

Potentially life-threatening condition in which disruption or aortic intima allows dissection of blood into vessel wall; may involve ascending aorta (type II), descending aorta (type III), or both (type I). Alternative classification: Type A—dissection involves ascending aorta; type B—limited to transverse and/or descending aorta. Involvement of the ascending aorta is most lethal form. Variant acute aortic syndromes include intramural hematoma without an intimal flap, and penetrating atherosclerotic ulcer.

### Etiology

Ascending aortic dissection is associated with hypertension, cystic medial necrosis, Marfan's and Ehlers-Danlos syndromes; descending dissections are commonly associated with atherosclerosis or hypertension. Incidence is increased in pts with coarctation of aorta, bicuspid aortic valve, and rarely in third trimester of pregnancy in otherwise normal women.

### Symptoms

Sudden onset of severe anterior or posterior chest pain, with "ripping" quality; maximal pain may travel if dissection propagates. Additional symptoms relate to obstruction of aortic branches (stroke, MI), dyspnea (acute aortic regurgitation), or symptoms of low cardiac output due to cardiac tamponade (dissection into pericardial sac).

### Physical Examination

Sinus tachycardia common; if cardiac tamponade develops, hypotension, pulsus paradoxus, and pericardial rub appear. Asymmetry of carotid or brachial pulses, aortic regurgitation, and neurologic abnormalities associated with interruption of carotid artery flow are possible findings.

### Laboratory

*CXR:* Widening of mediastinum; dissection can be confirmed by *CT*, *transesophageal echocardiography, or MRI*. Aortography is rarely required, as sensitivity of these noninvasive techniques is >90%.

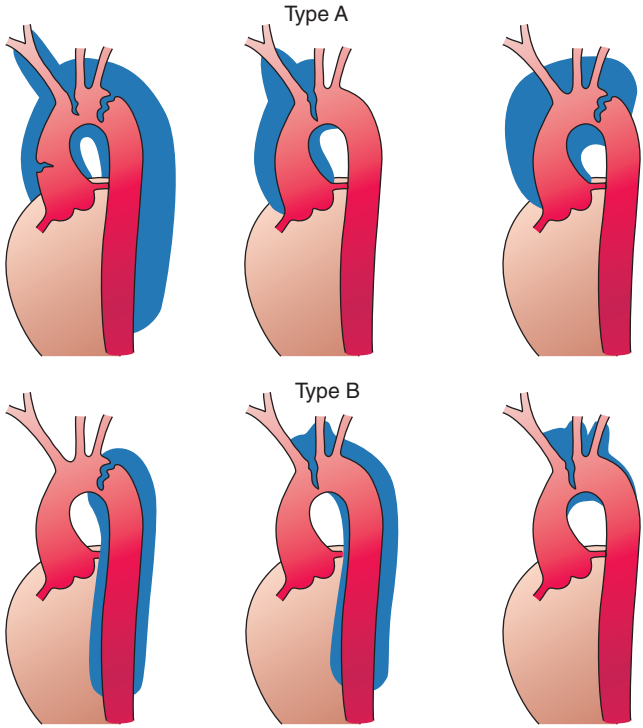



**FIGURE 125-1** Classification of aortic dissections. Stanford classification: Top panels illustrate type A dissections that involve the ascending aorta independent of site of tear and distal extension; type B dissections (bottom panels) involve transverse and/or descending aorta without involvement of the ascending aorta. DeBakey classification: Type I dissection involves ascending to descending aorta (top left); type II dissection is limited to ascending or transverse aorta, without descending aorta (top center + top right); type III dissection involves descending aorta only (bottom left). *(From DC Miller, in RM Doroghazi, EE Slater [eds].* Aortic Dissection. *New York, McGraw-Hill, 1983, with permission.)*

## TREATMENT AORTIC DISSECTION

Reduce cardiac contractility and treat hypertension to maintain systolic bp between 100 and 120 mmHg using IV agents (Table 125-1), e.g., sodium nitroprusside accompanied by a beta blocker (e.g., IV metoprolol, labetolol, or esmolol, aiming for heart rate of 60 beats per min), followed by oral therapy. If beta blocker contraindicated, consider IV verapamil or diltiazem (see Table 123-2). Avoid direct vasodilators (e.g., hydralazine) because they may increase shear stress. Ascending aortic dissection (type A) requires surgical repair emergently or, if pt can be stabilized with medications, semielectively. Descending aortic dissections are stabilized medically (maintain systolic bp between 110 and 120 mmHg) with oral antihypertensive agents (esp. beta blockers); surgical repair is not usually indicated unless continued pain or extension of dissection is observed (by serial MRI or CT performed every 6–12 months).

**TABLE 125-1 TREATMENT OF AORTIC DISSECTION**

| Preferred Regimen | Dose |
|---|---|
| Sodium nitroprusside | 20–400 μg/min IV |
| *plus* a beta blocker: | |
| Propranolol *or* | 0.5 mg IV; then 1 mg q5min, to total of 0.15 mg/kg |
| Esmolol *or* | 500 μg/kg IV over 1 min; then 50–200 (μg/kg)/min |
| Labetalol | 20 mg IV over 2 min, then 40–80 mg q10–15min to max of 300 mg |

## OTHER ABNORMALITIES OF THE AORTA

### Atherosclerotic Occlusive Disease of Abdominal Aorta

Particularly common in presence of diabetes mellitus or cigarette smoking. Symptoms include intermittent claudication of the buttocks and thighs and impotence (Leriche syndrome); femoral and other distal pulses are absent. Diagnosis is established by noninvasive leg pressure measurements and Doppler velocity analysis, and confirmed by MRI, CT, or aortography. Catheter-based endovascular treatment or aortic-femoral bypass surgery is required for symptomatic treatment.

### Takayasu's ("Pulseless") Disease

Arteritis of aorta and major branches predominantly in young women. Anorexia, weight loss, fever, and night sweats occur. Localized symptoms relate to occlusion of aortic branches (cerebral ischemia, claudication, and loss of pulses in arms). ESR and C-reactive protein are increased; diagnosis confirmed by CT, MRI, or aortography. Glucocorticoid and immunosuppressive therapy may be beneficial.

For a more detailed discussion, see Creager MA, Loscalzo J: Diseases of the Aorta, Chap. 301, p. 1637, in HPIM-19.

# 126 Peripheral Vascular Disease

Occlusive or inflammatory disease that develops within the peripheral arteries, veins, or lymphatics. Pathologic contributors include atherosclerosis, thromboembolism, vasculitis, and fibromuscular dysplasia.

## ARTERIOSCLEROSIS OF PERIPHERAL ARTERIES

### History

*Intermittent claudication* is muscular cramping with exercise, quickly relieved by rest. Pain in buttocks and thighs suggests aortoiliac disease; calf muscle pain implies femoral or popliteal artery disease. More advanced arteriosclerotic obstruction

results in pain at rest; painful ulcers of the feet (sometimes painless in diabetics) may result.

### Physical Examination

Decreased peripheral pulses (ankle:brachial index <1.0, <0.5 with severe ischemia), blanching of affected limb with elevation, dependent rubor (redness). Ischemic ulcers or gangrene of toes may be present.

### Laboratory

Segmental pressure measurements and Doppler ultrasound of peripheral pulses before and immediately after exercise localizes stenoses; magnetic resonance angiography, computed tomographic angiography (CTA), or conventional arteriography is performed if mechanical revascularization (surgical or percutaneous) is planned.

**TREATMENT ARTERIOSCLEROSIS**

Most pts can be managed medically with daily exercise program, careful foot care (especially in diabetics), treatment of hypercholesterolemia, and local debridement of ulcerations. Abstinence from cigarettes is mandatory. Antiplatelet and statin therapies are indicated to reduce future cardiovascular events. Some, but not all, pts note symptomatic improvement with drug therapy (cilostazol or pentoxifylline). Pts with severe claudication, rest pain, or gangrene are candidates for revascularization (arterial reconstructive surgery or percutaneous transluminal angioplasty/stent placement).

## OTHER CONDITIONS THAT IMPAIR PERIPHERAL ARTERIAL FLOW

### Arterial Embolism

Results from thrombus or vegetation within the heart or aorta, or paradoxically from a venous thrombus through a right-to-left intracardiac shunt.

### History

Sudden pain or numbness in an extremity in the absence of previous history of claudication.

### Physical Examination

Absent pulse, pallor, and decreased temperature of limb distal to the occlusion. Lesion is identified by angiography.

**TREATMENT ARTERIAL EMBOLISM**

IV heparin is administered to prevent propagation of clot. For acute severe ischemia, immediate endovascular or surgical embolectomy is indicated. Thrombolytic therapy (e.g., tissue plasminogen activator, reteplase, or tenecteplase) may be effective for recent thrombus within atherosclerotic vessel or arterial bypass graft.

### Atheroembolism

A subset of acute arterial occlusion due to embolization of fibrin, platelets, and cholesterol debris from more proximal atheromas or aneurysm; typically occurs after intraarterial instrumentation. Depending on location, may lead to stroke, renal insufficiency, or pain and tenderness in embolized tissue. Atheroembolism to lower extremities results in blue toe syndrome, which can progress to necrosis and

**TABLE 126-1 CLASSIFICATION OF RAYNAUD'S PHENOMENON**

| Primary or idiopathic Raynaud's phenomenon: Raynaud's disease |
|---|
| Secondary Raynaud's phenomenon |
| Collagen vascular diseases: scleroderma, systemic lupus erythematosus, rheumatoid arthritis, dermatomyositis, polymyositis |
| Arterial occlusive diseases: atherosclerosis of the extremities, thromboangiitis obliterans, acute arterial occlusion, thoracic outlet syndrome |
| Pulmonary hypertension |
| Neurologic disorders: intervertebral disk disease, syringomyelia, spinal cord tumors, stroke, poliomyelitis, carpal tunnel syndrome |
| Blood dyscrasias: cold agglutinins, cryoglobulinemia, cryofibrinogenemia, myeloproliferative disorders, Waldenström's macroglobulinemia |
| Trauma: vibration injury, hammer hand syndrome, electric shock, cold injury, typing, piano playing |
| Drugs: ergot derivatives, methysergide, β-adrenergic receptor blockers, bleomycin, vinblastine, cisplatin |

gangrene. Treatment is supportive; for recurrent episodes, surgical intervention in the proximal atherosclerotic vessel or aneurysm may be required.

### Vasospastic Disorders

Manifest by Raynaud's phenomenon in which cold exposure results in triphasic color response: blanching of the fingers, followed by cyanosis, then rubor. Usually a benign disorder. However, suspect an underlying disease (Table 126-1) if tissue necrosis occurs, if disease is unilateral, or if it develops after age 50.

**TREATMENT VASOSPASTIC DISORDERS**

Keep extremities warm. Tobacco use is contraindicated. Dihydropyridine calcium channel blockers (e.g., nifedipine XL 30–90 mg PO qd) or $\alpha_1$-adrenergic antagonists (e.g., prazosin 1–5 mg tid) may be effective. Phosphodiesterase-5 inhibitors (e.g., sildenafil) may improve symptoms in secondary Raynaud's phenomenon.

### Thromboangiitis Obliterans (Buerger's Disease)

Occurs in young men who are heavy smokers and involves both upper and lower extremities; nonatheromatous inflammatory reaction develops in veins and small arteries, leading to superficial thrombophlebitis and arterial obstruction with ulceration or gangrene of digits. Imaging with CT, MR, or conventional angiography shows smooth tapering lesions in distal vessels, often without proximal atherosclerotic disease. Abstinence from tobacco is essential.

## VENOUS DISEASE

### Superficial Thrombophlebitis

A benign disorder characterized by erythema, tenderness, and edema along involved vein. Conservative therapy includes local heat, elevation, and anti-inflammatory drugs such as aspirin. More serious conditions such as cellulitis or lymphangitis may present similarly, but these are associated with fever, chills, lymphadenopathy, and red superficial streaks along inflamed lymphatic channels.

### Deep-Vein Thrombosis (DVT)

More serious condition that may lead to pulmonary embolism as described in Chap. 133.

### Chronic Venous Insufficiency

Results from prior DVT or venous valvular incompetence and manifests as chronic dull ache in leg that worsens with prolonged standing, edema, and superficial varicosities. May lead to erythema, hyperpigmentation, and recurrent cellulitis; ulcers may appear at medial and lateral malleoli. Treatment includes graduated compression stockings and leg elevation.

## LYMPHEDEMA

Chronic, painless edema, usually of the lower extremities; may be primary (inherited) or secondary to lymphatic damage or obstruction (e.g., recurrent lymphangitis, tumor, filariasis).

### Physical Examination

Marked pitting edema in early stages; limb becomes indurated with *non*pitting edema chronically. Differentiate from chronic *venous* insufficiency, which displays hyperpigmentation, stasis dermatitis, and superficial venous varicosities.

### Laboratory

Abdominal and pelvic ultrasound or CT or MRI to identify obstructing lesions. Lymphangiography or lymphoscintigraphy (rarely done) to confirm diagnosis. If *unilateral* edema, differentiate from DVT by noninvasive venous studies (above).

**TREATMENT LYMPHEDEMA**

(1) Meticulous foot hygiene to prevent infection, (2) leg elevation, (3) compression stockings and/or pneumatic compression boots. Diuretics should be *avoided* to prevent intravascular volume depletion.

For a more detailed discussion, see Creager MA, Loscalzo J: Arterial Diseases of the Extremities, Chap. 302, p. 1643; Creager MA, Loscalzo J: Chronic Venous Disease and Lymphedema, Chap. 303, p. 1650, in HPIM-19.

# 127 Pulmonary Hypertension

### Definition

Elevation of pulmonary artery (PA) pressure due to pulmonary vascular or parenchymal disease, increased left heart filling pressures, or a combination. Table 127-1 lists etiologies by categories.

**TABLE 127-1 CLASSIFICATION OF PULMONARY HYPERTENSION**

1. **Pulmonary Arterial Hypertension**
   - Idiopathic
   - Heritable (mutations/familial cases)
   - Collagen vascular diseases (e.g., scleroderma, SLE, RA)
   - Congenital systemic to pulmonary shunts (e.g., ventricular septal defect, patent ductus arteriosus, atrial septal defect)
   - Portal hypertension
   - HIV infection
   - Drugs or toxins (e.g., fenfluramine)
2. **Pulmonary Hypertension Due to Left Heart Disease**
   - LV systolic or diastolic dysfunction
   - Left-sided valvular disease
3. **Pulmonary Hypertension Due to Lung Disease or Hypoxia**
   - Chronic obstructive lung disease
   - Interstitial lung disease
   - Sleep-disordered breathing
   - Chronic hypoventilation
4. **Chronic Pulmonary Thromboembolic Disease**
   - Chronic pulmonary embolism
5. **Miscellaneous**
   - Systemic conditions (e.g., sarcoidosis, pulmonary histiocytosis)
   - Hematologic conditions (e.g., myeloproliferative diseases)

***Abbreviations:*** RA, rheumatoid arthritis.

## Symptoms

Exertional dyspnea, fatigue, angina (due to RV ischemia), syncope, peripheral edema.

## Physical Examination

Jugular venous distention, RV lift, increased $P_2$, right-sided $S_4$, tricuspid regurgitation. Peripheral cyanosis and edema are late manifestations.

## Laboratory Findings

*CXR* shows enlarged central PA. *ECG* may demonstrate RV hypertrophy and RA enlargement. *Echocardiogram* shows RV and RA enlargement, RV hypertrophy; RV systolic pressure can be estimated from Doppler recording of tricuspid regurgitation. *Pulmonary function tests* (*PFTs*) identify underlying obstructive or restrictive lung disease; impaired CO diffusion capacity is common. *Chest CT* identifies contributing interstitial lung disease or pulmonary thromboembolic disease. *ANA titer*, rheumatoid factor, anti-Scl-70 antibodies are elevated in specific collagen vascular conditions that can result in pulmonary hypertension. *HIV testing* should be performed in individuals at risk. *Cardiac catheterization* accurately assesses PA pressures, cardiac output, and pulmonary vascular resistance, and quantifies underlying congenital vascular shunts; during procedure, response to short-acting vasodilators can be assessed.

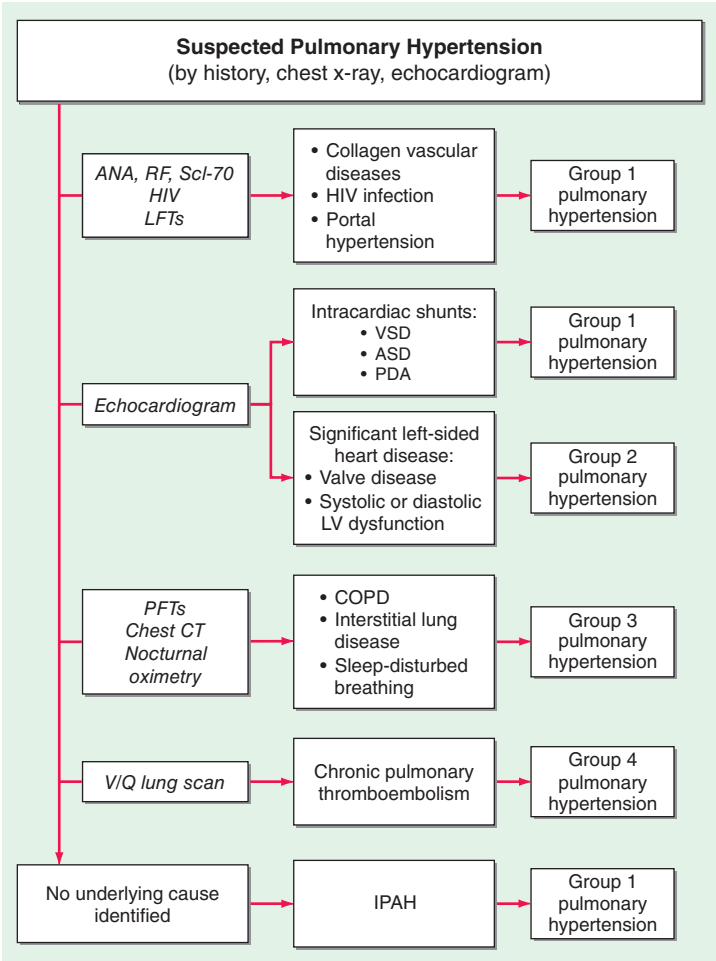



**FIGURE 127-1** An algorithm to assess for causes of pulmonary hypertension. In the absence of an identifiable etiology, idiopathic pulmonary arterial hypertension would be suspected. ASD, atrial septal defect; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; IPAH, idiopathic pulmonary arterial hypertension; PDA, patent ductus arteriosus; PFTs, pulmonary function tests; RF, rheumatoid factor; Scl-70, anti-topoisomerase 1 antibodies; V/Q, ventilation/perfusion; VSD, ventricular septal defect.

Figure 127-1 summarizes a testing approach for pts with unexplained pulmonary hypertension.

## PULMONARY ARTERIAL HYPERTENSION (PAH)

Uncommon (two cases per million), very serious form of pulmonary hypertension. Most pts present in fourth and fifth decades, female >> male predominance; up to 20% of cases are familial. Major symptom is dyspnea, often with insidious onset. Mean survival <3 years in absence of therapy.

## Physical Examination

Prominent *a* wave in jugular venous pulse, right ventricular heave, narrowly split $S_2$ with accentuated $P_2$. Terminal course is characterized by signs of right-sided heart failure.

## Laboratory

*CXR:* RV and central pulmonary arterial prominence. Pulmonary arteries taper sharply. *PFTs:* usually normal or mild restrictive defect. *ECG:* RV enlargement, right axis deviation, and RV hypertrophy. *Echocardiogram:* RA and RV enlargement and tricuspid regurgitation. Cardiac catheterization demonstrates a mean pulmonary artery pressure ≥25 mmHg, pulmonary vascular resistance >240 dyne-s/cm$^5$, with a mean pulmonary capillary wedge pressure ≤15 mmHg.

## Differential Diagnosis (Fig. 127-1)

Other disorders of heart, lungs, and pulmonary vasculature must be considered. Lung function studies will identify chronic pulmonary disease causing pulmonary hypertension and cor pulmonale. Interstitial diseases (PFTs, CT scan) and hypoxic pulmonary hypertension (ABGs, $SaO_2$) should be excluded. Perfusion lung scan should be considered to exclude chronic pulmonary embolism (PE). Cardiovascular disorders that may present similarly and need to be excluded include PA and pulmonic valve stenosis, ventricular and atrial shunts with secondary pulmonary vascular disease (Eisenmenger syndrome), and clinically silent mitral stenosis.

## TREATMENT PULMONARY ARTERIAL HYPERTENSION

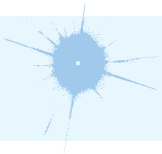
Limit physical activities, use diuretics for peripheral edema, $O_2$ supplementation if $PO_2$ reduced, and chronic warfarin anticoagulation (target INR = 2.0–3.0).

If short-acting vasodilators are beneficial during acute testing in catheterization laboratory, pt may benefit from high-dose *calcium channel blocker* (e.g., nifedipine, up to 240 mg/d, or amlodipine up to 20 mg/d); must monitor for hypotension or worsening of right heart failure during such therapy.

Additional approved therapies for PAH include:

1. Endothelin receptor antagonists: *bosentan* (62.5 mg PO bid × 1 month, then 125 mg PO bid) and *ambrisentan* (5–10 mg daily) significantly improve exercise tolerance. Hepatic transaminases should be monitored. Bosentan is contraindicated in pts taking cyclosporine (which greatly increases bosentan plasma levels) or glyburide (combination is associated with increased hepatic transaminases).
2. Phosphodiesterase-5 inhibitors: *sildenafil* (20–80 mg PO tid) and *tadalafil* (40 mg daily) also improve exercise tolerance in PAH. Do not prescribe concurrently with nitrates; the combination could result in marked hypotension.
3. Prostaglandins (*iloprost* by inhalation, *epoprostenol* by continuous IV infusion, and *treprostinil* by IV, SC, or inhalation routes) improve symptoms, exercise tolerance, and, in the case of epoprostenol, survival. The most common side effect is flushing.
4. The oral soluble guanylyl cyclase stimulator riociguat has been shown to improve exertional capacity in pts with PAH.

For selected pts with persistent right heart failure, lung transplantation may be considered.



For a more detailed discussion, see Waxman AB, Loscalzo J: Pulmonary Hypertension, Chap. 304, p. 1655, in HPIM-19.

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# 128 Respiratory Function and Pulmonary Diagnostic Procedures

## RESPIRATORY FUNCTION

The major classes of lung diseases include obstructive lung diseases (e.g., asthma, chronic obstructive pulmonary disease, and bronchiectasis), restrictive lung diseases (e.g., interstitial lung diseases, chest wall abnormalities, and neuromuscular diseases), and vascular abnormalities (e.g., pulmonary thromboembolism, pulmonary arterial hypertension, and pulmonary veno-occlusive disease). The respiratory system includes not only the lungs but also the chest wall, pulmonary circulation, and central nervous system. There are three key types of respiratory system physiologic disturbances that occur in varying combinations in different lung diseases: ventilatory function, pulmonary circulation, and gas exchange.

### Disturbances in Ventilatory Function

Ventilation involves the delivery of gas to the alveoli. Pulmonary function tests are used to assess ventilatory function. The classification of lung volumes, which are measured with pulmonary function testing, is shown in Fig. 128-1. Spirometry involves forced exhalation from total lung capacity (TLC) to residual volume (RV); key measurements from a spirogram are the forced expiratory volume in 1 s ($FEV_1$) and the forced vital capacity (FVC). Expiratory flow rates may be plotted against lung volumes to yield a flow-volume curve. Plateau of the inspiratory curve on the flow-volume loop suggests extrathoracic large airway obstruction, while plateau of the expiratory curve suggests intrathoracic large airway obstruction. Other lung volumes, including TLC and RV, are measured under static conditions using either inert gas dilution or body plethysmography. Lung volumes and flow rates are typically compared with population-based normal values that adjust for the age, height, sex, and race of the pt.

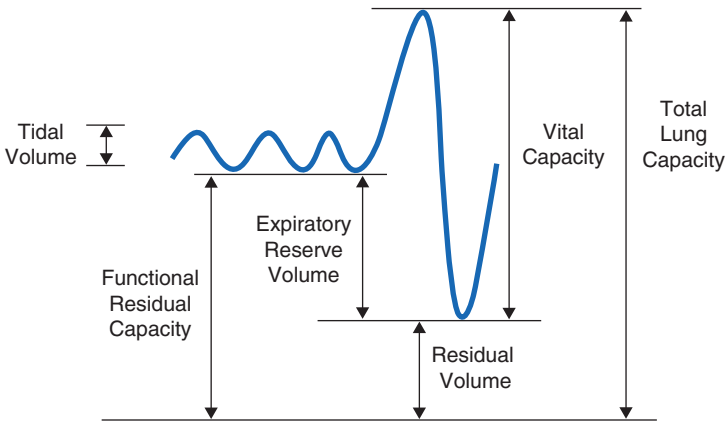


**FIGURE 128-1** Spirogram of a slow vital capacity maneuver demonstrating various lung volumes.

**TABLE 128-1 COMMON RESPIRATORY DISEASES BY DIAGNOSTIC CATEGORIES**

| | |
|---|---|
| **Obstructive** | |
| Asthma | Bronchiectasis |
| Chronic obstructive pulmonary disease | Cystic fibrosis |
| | Bronchiolitis |
| **Restrictive—Parenchymal** | |
| Sarcoidosis | Pneumoconiosis |
| Idiopathic pulmonary fibrosis | Drug- or radiation-induced interstitial lung disease |
| Desquamative interstitial pneumonitis | Asbestosis |
| **Restrictive—Extraparenchymal** | |
| Neuromuscular | Chest wall/Pleural disease |
| Diaphragmatic weakness/paralysis | Kyphoscoliosis |
| Myasthenia gravis | Obesity |
| Guillain-Barré syndrome | Ankylosing spondylitis |
| Muscular dystrophies | Chronic pleural effusions |
| Cervical spine injury | |
| Amyotrophic lateral sclerosis | |
| **Pulmonary Vascular Disease** | |
| Pulmonary embolism | Pulmonary arterial hypertension |
| **Malignancy** | |
| Bronchogenic carcinoma (small cell or non-small-cell) | Cancer metastatic to lung |
| **Infectious Diseases** | |
| Pneumonia | Tracheitis |
| | Bronchitis |

There are two major patterns of abnormal ventilatory function detected by pulmonary function testing: restrictive and obstructive (Tables 128-1 and 128-2). The presence of obstruction is determined by a reduced ratio of $FEV_1$/FVC (with abnormal often defined as <0.7), and the severity of airflow obstruction is determined by the level of reduction of $FEV_1$. With airflow obstruction, TLC may be normal or increased, and RV is typically elevated. With severe airflow obstruction, the FVC is often also reduced.

The presence of a restrictive pattern is determined by a reduction in TLC to <80% of the pt's predicted value. When pulmonary parenchymal processes cause restriction, RV is also decreased, but the $FEV_1$/FVC is normal. With extraparenchymal etiologies of restrictive ventilatory defects, such as neuromuscular weakness or chest

**TABLE 128-2 ALTERATIONS IN PULMONARY FUNCTION IN DIFFERENT RESPIRATORY DISEASE CATEGORIES**

| | TLC | RV | VC | $FEV_1$/FVC |
|---|---|---|---|---|
| Obstructive | N to ↑ | ↑ | ↓ | ↓ |
| Restrictive | | | | |
| Pulmonary parenchymal | ↓ | ↓ | ↓ | N to ↑ |
| Extraparenchymal—neuromuscular weakness | ↓ | Variable | ↓ | Variable |
| Extraparenchymal—chest wall deformity | ↓ | Variable | ↓ | N |

***Abbreviations:*** $FEV_1$, forced expiratory volume in 1 s; FVC, forced vital capacity; N, normal; RV, residual volume.

wall abnormalities, the impact on RV and $FEV_1$/FVC is more variable. Weakness of the respiratory muscles can be assessed by measuring maximal inspiratory and expiratory pressures.

## Disturbances in Pulmonary Circulation

The pulmonary vasculature normally handles the right ventricular output (~5 L/min) at a low pressure. Normal mean pulmonary artery pressure (PAP) is 15 mmHg. When cardiac output increases, pulmonary vascular resistance (PVR) normally falls, leading to only small increases in mean PAP.

Assessment of the pulmonary vasculature requires measuring pulmonary vascular pressures and cardiac output to derive PVR. PVR rises with hypoxemia (due to vasoconstriction), intraluminal thrombi (due to diminished cross-sectional area from obstruction), or destruction of small pulmonary vessels (due to scarring or loss of the alveolar walls).

All diseases of the respiratory system causing hypoxemia are capable of causing pulmonary hypertension. However, pts with prolonged hypoxemia related to chronic obstructive pulmonary disease, interstitial lung disease, chest wall disease, and obesity-hypoventilation/obstructive sleep apnea are particularly likely to develop pulmonary hypertension. When pulmonary vessels are directly affected, as with recurrent pulmonary emboli, the decrease in cross-sectional area of the pulmonary vasculature is the primary mechanism for increased PVR, rather than hypoxemia.

## Disturbances in Gas Exchange

The primary functions of the respiratory system are to remove $CO_2$ from blood entering the pulmonary circulation and to provide $O_2$ to blood leaving the pulmonary circulation. Normal tidal volume is approximately 500 mL and normal respiratory rate is approximately 15 breaths/min, leading to a total minute ventilation of approximately 7.5 L/min. Because of anatomic dead space, alveolar ventilation is approximately 5 L/min. Gas exchange depends on alveolar ventilation rather than total minute ventilation.

Partial pressure of $CO_2$ in arterial blood ($Pa_{CO_2}$) is directly proportional to the amount of $CO_2$ produced each minute ($\dot{V}_{CO_2}$) and inversely proportional to alveolar ventilation ($\dot{V}A$).

$$Pa_{CO_2} = 0.863 \times \dot{V}_{CO_2}/\dot{V}A$$

Adequate movement of gas between alveoli and pulmonary capillaries by diffusion is required for normal gas exchange. Diffusion can be tested by measuring the diffusing capacity of the lung for a low (and safe) concentration of carbon monoxide (DLCO) during a 10-s breath hold. DLCO measurement is typically corrected for the pt's hemoglobin level. Diffusion abnormalities rarely result in arterial hypoxemia at rest but can cause hypoxemia with exercise. A restrictive ventilatory defect with reduced DLCO suggests parenchymal lung disease. The pattern of normal spirometry, normal lung volumes, and reduced DLCO is consistent with pulmonary vascular disease. Gas exchange is critically dependent on proper matching of ventilation and perfusion.

Assessment of gas exchange is commonly performed with arterial blood gases, which provide measurements of the partial pressures of $O_2$ and $CO_2$. The actual content of $O_2$ in blood is determined by both $P_{O_2}$ and hemoglobin concentration. The alveolar-arterial $O_2$ difference ([A-a] gradient) is reduced in diseases causing ventilation-perfusion mismatch or shunt physiology. The normal (A-a) gradient is <15 mmHg under age 30 but increases with aging. In order to calculate the (A-a) gradient, the alveolar $P_{O_2}$ ($Pa_{CO_2}$) must be calculated:

$$Pa_{O_2} = [FIO_2 \times (PB - PH_2O)] - (Pa_{CO_2}/R)$$

where $FIO_2$ = fractional concentration of inspired $O_2$ (0.21 while breathing room air), PB = barometric pressure (760 mmHg at sea level), $PH_2O$ = water vapor pressure (47 mmHg when air is saturated at 37°C [98.6°F]), and R = respiratory quotient (the ratio

of $CO_2$ production to $O_2$ consumption, usually assumed to be 0.8). Severe arterial hypoxemia rarely occurs purely due to alveolar hypoventilation while breathing air at sea level. The (A-a) gradient is calculated by subtracting the measured $Pa_{O_2}$ from the calculated $P_{AO_2}$.

Adequacy of $CO_2$ removal is reflected in the partial pressure of $CO_2$ measured in an arterial blood gas. Pulse oximetry is a valuable, widely used, and noninvasive tool to assess $O_2$ saturation, but it provides no information about $Pa_{CO_2}$. Other limitations of pulse oximetry include relative insensitivity to oxygenation changes when $Pa_{O_2}$ is >60 mmHg, problems with obtaining an adequate signal when cutaneous perfusion is decreased, and inability to distinguish oxyhemoglobin from other forms of hemoglobin, such as carboxyhemoglobin and methemoglobin.

## Mechanisms of Abnormal Respiratory Function

The four basic mechanisms of hypoxemia are: (1) decrease in inspired $P_{O_2}$, (2) alveolar hypoventilation, (3) shunt, and (4) ventilation/perfusion mismatch. Decrease in inspired $P_{O_2}$ (e.g., at high altitude) and hypoventilation (characterized by an increased $Pa_{CO_2}$) both lower arterial oxygenation by reducing alveolar oxygenation; thus, the (A-a) gradient is normal. Shunting (e.g., intracardiac shunt) causes hypoxemia by bypassing the alveolar capillaries. Shunting is characterized by an elevated (A-a) gradient and is relatively refractory to oxygenation improvement with supplemental $O_2$. Ventilation/perfusion mismatch is the most common cause of hypoxemia; it is associated with an elevated (A-a) gradient, but supplemental $O_2$ corrects the hypoxemia by raising the $O_2$ content of blood from regions with low ventilation/perfusion ratios. An algorithm for approaching the hypoxemic pt is shown in Fig. 128-2.

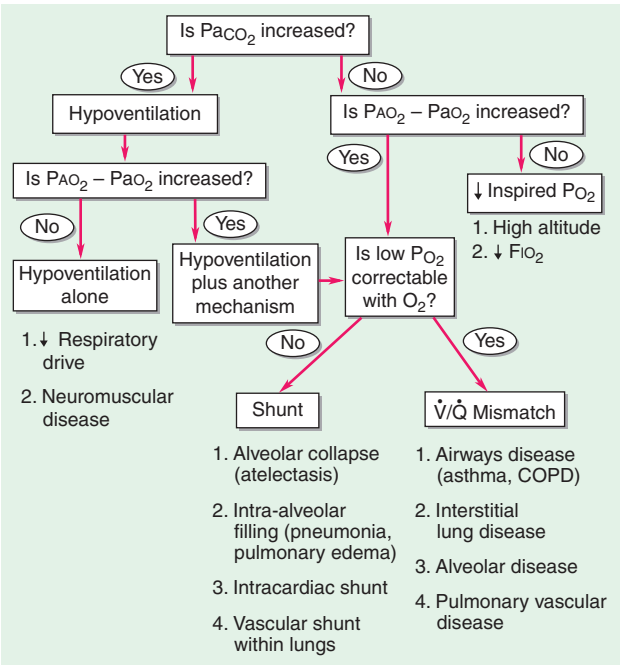


**FIGURE 128-2** Flow diagram outlining the diagnostic approach to the pt with hypoxemia. COPD, chronic obstructive pulmonary disease. *(From SE Weinberger: Principles of Pulmonary Medicine, 4th ed. Philadelphia, Saunders, 2004; with permission.)*

Hypercapnia is caused by inadequate alveolar ventilation. Potential contributing factors include (1) increased $CO_2$ production, (2) decreased ventilatory drive, (3) malfunction of the respiratory pump or increased airway resistance, and (4) inefficiency of gas exchange (increased dead space or ventilation/perfusion mismatch).

Although diffusion abnormalities rarely cause hypoxemia at rest, assessment of DLCO can be used to determine the functional integrity of the alveolar-capillary membrane. Diseases that solely affect the airways typically do not reduce the DLCO. DLCO is reduced in interstitial lung disease, emphysema, and pulmonary vascular disease. DLCO can be elevated in alveolar hemorrhage, asthma, and congestive heart failure.

## DIAGNOSTIC PROCEDURES

### NONINVASIVE PROCEDURES

#### Radiographic Studies

The chest x-ray (CXR), generally including both posteroanterior and lateral views, is often the first diagnostic study in pts presenting with respiratory symptoms. With some exceptions (e.g., pneumothorax), the CXR pattern is usually not sufficiently specific to *establish* a diagnosis; instead, the CXR serves to *detect* disease, assess magnitude, and guide further diagnostic investigation. With diffuse lung disease, CXR can detect an alveolar, interstitial, or nodular pattern. CXR can also detect pleural effusion and pneumothorax, as well as abnormalities in the hila and mediastinum. Lateral decubitus views can be used to estimate the size of freely flowing pleural effusions.

Chest CT, typically performed with helical scanning and multiple detectors, is widely used to clarify radiographic abnormalities detected by CXR. Advantages of chest CT compared with CXR include (1) ability to distinguish superimposed structures due to cross-sectional imaging; (2) superior assessment of tissue density, permitting accurate assessment of the size and density of pulmonary nodules and improved identification of abnormalities adjacent to the chest wall, such as pleural disease; (3) with the use of IV contrast, ability to distinguish vascular from nonvascular structures, which is especially useful in assessing hilar and mediastinal abnormalities; (4) with CT angiography, ability to detect pulmonary emboli; and (5) due to superior visible detail, improved recognition of parenchymal and airway diseases, including emphysema, bronchiectasis, lymphangitic carcinoma, and interstitial lung disease.

A variety of other imaging techniques are used less commonly to assess respiratory disease. Magnetic resonance imaging (MRI) is generally less useful than CT for evaluation of the respiratory system but can be helpful to assist in the evaluation of intrathoracic cardiovascular pathology without radiation exposure and to distinguish vascular and nonvascular structures without IV contrast. Ultrasound is not useful for assessing the pulmonary parenchyma, but it can detect pleural abnormalities and guide thoracentesis of a pleural effusion. Pulmonary angiography can assess the pulmonary arterial system for venous thromboembolism but has largely been replaced by CT angiography.

#### Nuclear Medicine Imaging

Ventilation-perfusion lung scans can be used to assess for pulmonary thromboembolism but have also largely been replaced by CT angiography. Positron emission tomographic (PET) scanning assesses the uptake and metabolism of a radiolabeled glucose analogue. Because malignant lesions usually have increased metabolic activity, PET scanning, especially when combined with CT images in PET/CT, is useful to assess pulmonary nodules for potential malignancy and to stage lung cancer. PET studies are limited in assessing lesions <1 cm in diameter; false-negative screening for malignancy can result from lesions with low metabolic activity, such as carcinoid

tumors or bronchioloalveolar cell carcinoma. False-positive PET signals can be observed in inflammatory conditions such as pneumonia.

### Sputum Examination

Sputum can be obtained by spontaneous expectoration or induced by inhalation of an irritating aerosol like hypertonic saline. Sputum is distinguished from saliva by the presence of bronchial epithelial cells and alveolar macrophages as opposed to squamous epithelial cells. Sputum examination should include gross inspection for blood, color, and odor, as well as Gram's stain and routine bacterial culture. Bacterial culture of expectorated sputum may be misleading due to contamination with oropharyngeal flora. Sputum samples can also be assessed for a variety of other pathogens, including mycobacteria, fungi, and viruses. Sputum samples induced by hypertonic saline can be stained for the presence of *Pneumocystis jirovecii*. Cytologic examination of sputum samples can be used as an initial screen for malignancy.

## INVASIVE PROCEDURES

### Bronchoscopy

Bronchoscopy is a procedure that provides direct visualization of the tracheobronchial tree, typically to the subsegmental level. The fiberoptic bronchoscope is used in most cases, but rigid bronchoscopy is valuable in specific circumstances, including massive hemorrhage and foreign body removal. Flexible fiberoptic bronchoscopy allows visualization of the airways; identification of endobronchial abnormalities, including tumors and sites of bleeding; and collection of diagnostic specimens by washing, brushing, biopsy, or lavage. Washing involves instilling sterile saline through the bronchoscope channel onto the surface of a lesion; part of the saline is suctioned back through the bronchoscope and processed for cytology and microorganisms. Bronchial brushings can be obtained from the surface of an endobronchial lesion or from a more distal mass or infiltrate (potentially with fluoroscopic guidance) for cytologic and microbiologic studies. Biopsy forceps can be used to obtain biopsies of endobronchial lesions or passed into peribronchial alveolar tissue (often with fluoroscopic guidance) to obtain transbronchial biopsies of more distal lung tissue. Transbronchial biopsy is particularly useful in diagnosing diffuse infectious processes, lymphangitic spread of cancer, and granulomatous diseases. Complications of transbronchial biopsy include hemorrhage and pneumothorax.

Bronchoalveolar lavage (BAL) is an adjunct to fiberoptic bronchoscopy, permitting collection of cells and fluid from distal air spaces. After wedging the bronchoscope in a subsegmental airway, saline is instilled and then suctioned back through the bronchoscope for analyses, which can include cytology, microbiology, and cell counts. BAL is especially useful in the diagnosis of *P. jirovecii* pneumonia and some other infections.

Additional bronchoscopic approaches to obtain tissue samples from locations adjacent to the trachea or large bronchi for cytologic assessment of malignancy include transbronchial needle aspiration (TBNA). TBNA can be supplemented with endobronchial ultrasound (EBUS), which can allow guided aspiration of hilar and mediastinal lymph nodes based on real-time ultrasound images.

### Percutaneous Needle Aspiration of the Lung

A needle can be inserted through the chest wall and into a pulmonary lesion to aspirate material for cytologic and microbiologic studies. Percutaneous needle aspiration is usually performed under CT guidance. Owing to the small size of the sample obtained, sampling error is a limitation of the procedure.

### Thoracentesis

Thoracentesis should be performed as an early step in the evaluation of a pleural effusion of uncertain etiology. Analysis of pleural fluid can determine the etiology

of the effusion (Chap. 135). Large-volume thoracentesis can be therapeutic by palliating dyspnea.

### Mediastinoscopy

Tissue biopsy of mediastinal masses or lymph nodes is often required for cancer diagnosis and staging. Mediastinoscopy is performed from a suprasternal approach, and a rigid mediastinoscope is inserted—from which biopsies can be obtained. Lymph nodes in the aortopulmonary location typically require a parasternal mediastinotomy to provide access for biopsy.

### Video-Assisted Thoracic Surgery

Video-assisted thoracic surgery (VATS), also known as thoracoscopy, is widely used for the diagnosis of pleural lesions as well as peripheral parenchymal infiltrates and nodules. VATS, which requires that the pt tolerate single-lung ventilation during the procedure, involves passing a rigid scope with a camera through a trocar and into the pleural space; instruments can be inserted and manipulated through separate intercostal incisions. VATS has largely replaced "open biopsy," which requires a thoracotomy.

For a more detailed discussion, see Kritek P, Choi AMK: Approach to the Patient with Disease of the Respiratory System, Chap. 305, p. 1661; Naureckas ET, Solway J: Disturbances of Respiratory Function, Chap. 306e; Fuhlbrigge AL, Choi AMK: Diagnostic Procedures in Respiratory Disease, Chap. 307, p. 1663, in HPIM-19.

# 129 Asthma

## Definition and Epidemiology

Asthma is a syndrome characterized by airflow obstruction that varies both spontaneously and with specific treatment. Chronic airway inflammation causes airway hyperresponsiveness to a variety of triggers, leading to airflow obstruction and respiratory symptoms including dyspnea and wheezing. Although asthmatics typically have periods of normal lung function with intermittent airflow obstruction, a subset of pts develop chronic airflow obstruction.

The prevalence of asthma has increased markedly over the past 30 years. In developed countries, approximately 10% of adults and 15% of children have asthma. The majority of asthmatics have childhood-onset disease. Most asthmatics have atopy, and they often have atopic dermatitis (eczema) and/or allergic rhinitis. A minority of asthmatic pts do not have atopy (negative skin prick tests to common allergens and normal serum total IgE levels). These individuals, occasionally referred to as *intrinsic asthmatics*, often have adult-onset disease. Occupational asthma can result from a variety of chemicals, including toluene diisocyanate and trimellitic anhydride, and often has onset in adulthood.

Asthmatics can develop increased airflow obstruction and respiratory symptoms in response to a variety of different triggers. Inhaled allergens can be potent asthma triggers for individuals with specific sensitivity to those agents. Viral upper respiratory infections (URIs) commonly trigger asthma exacerbations. β-Adrenergic blocking medications can markedly worsen asthma symptoms and should typically be avoided in asthmatics. Exercise often triggers increased asthma symptoms, which usually begin after exercise has ended. Other triggers of increased asthma symptoms include air pollution, cold air, occupational exposures, and stress.

## Clinical Evaluation of the Patient History

Common respiratory symptoms in asthma include wheezing, dyspnea, and cough. These symptoms often vary widely within a particular individual, and they can change spontaneously or with age, season of the year, and treatment. Symptoms may be worse at night, and nocturnal awakenings are an indicator of inadequate asthma control. The severity of a pt's asthmatic symptoms, as well as the pt's need for systemic steroid treatment, hospitalization, and intensive care treatment, are important to ascertain. Types of asthmatic triggers for the particular pt, and their recent exposure to them, should be determined. Approximately 1–5% of asthmatics have sensitivity to aspirin and other cyclooxygenase inhibitors; they typically are nonatopic and have nasal polyps. Cigarette smoking leads to more hospital admissions and more rapid decline in lung function in asthmatics; smoking cessation is essential.

## Physical Examination

It is important to assess for signs of respiratory distress, including tachypnea, use of accessory respiratory muscles, and cyanosis. On lung examination, there may be wheezing and rhonchi throughout the chest, typically more prominent in expiration than inspiration. Localized wheezing may indicate an endobronchial lesion. Evidence of allergic nasal, sinus, or skin disease should be assessed. When asthma is adequately controlled, the physical examination may be normal.

## Pulmonary Function Tests

Spirometry often shows airflow obstruction, with a reduction in forced expiratory volume in 1 s ($FEV_1$) and $FEV_1$/forced vital capacity (FVC) ratio. However, spirometry may be normal, especially if asthma symptoms are adequately treated. Bronchodilator reversibility is demonstrated by an increase in $FEV_1$ by ≥200 mL and ≥12% from baseline $FEV_1$ 15 min after a short-acting β agonist (often albuterol metered-dose inhaler two puffs or 180 μg). Many but not all asthmatics will demonstrate significant bronchodilator reversibility; optimal pharmacologic treatment may reduce bronchodilator reversibility. Airway hyperresponsiveness is characteristic of asthma; it can be assessed by exposure to direct bronchoconstrictors such as methacholine or histamine. Greater airway responsiveness is associated with increased asthmatic symptoms. The peak expiratory flow rate (PEFR) can be used by the pt to track asthma control objectively at home. Measurement of lung volumes is not typically performed, but increases in total lung capacity and residual volume may be observed. The diffusing capacity for carbon monoxide is usually normal.

## Other Laboratory Tests

Blood tests are usually not helpful. CBC may demonstrate eosinophilia. Specific IgE measurements for inhaled allergens (radioallergosorbent test [RAST]) or allergy skin testing may assist in determining allergic triggers. Total serum IgE is markedly elevated in bronchopulmonary aspergillosis (BPA). Exhaled nitric oxide levels can provide an assessment of eosinophilic airway inflammation.

## Radiographic Findings

Chest x-ray is usually normal. In acute exacerbations, pneumothorax may be identified. In BPA, eosinophilic pulmonary infiltrates may be observed. Chest CT scan is not typically performed in routine asthma but may show central bronchiectasis in BPA.

## Differential Diagnosis

The differential diagnosis of asthma includes other disorders that can cause wheezing and dyspnea. Upper airway obstruction by tumor or laryngeal edema can mimic asthma, but stridor in the large airways is typically noted on physical examination. Localized wheezing in the chest may indicate an endobronchial tumor or foreign body. Congestive heart failure can cause wheezing but is typically accompanied by bibasilar crackles. Eosinophilic pneumonias and Churg-Strauss syndrome may present with wheezing. Vocal cord dysfunction can mimic severe asthma and may require direct laryngoscopy to assess. When asthma involves chronic airflow obstruction, distinguishing it from chronic obstructive pulmonary disease (COPD) can be very difficult.

## TREATMENT CHRONIC ASTHMA

If a specific inciting agent for asthmatic symptoms can be identified and eliminated, that is an optimal part of treatment. In most cases, pharmacologic therapy is required. The two major classes of drugs are bronchodilators, which provide rapid symptomatic relief by relaxing airway smooth muscle, and controllers, which limit airway inflammation.

**Bronchodilators** The most widely used class of bronchodilators is $\beta_2$-adrenergic agonists, which relax airway smooth muscle by activating $\beta_2$-adrenergic receptors. Two types of inhaled $\beta_2$ agonists are widely used in asthma treatment: short-acting $\beta_2$ agonists (SABAs) and long-acting $\beta_2$ agonists (LABAs). SABAs, which include albuterol, have rapid onset of action and last for up to 6 h. SABAs are effective rescue medications, but excessive use indicates inadequate asthma control. SABAs can prevent exercise-induced asthma if administered before exercise. LABAs, which include salmeterol and formoterol, have a slower onset of action but last for >12 h. LABAs have replaced regularly scheduled use of SABAs, but they do not control airway inflammation and should not be used without inhaled corticosteroid (ICS) therapy. Combinations of LABAs with ICS reduce asthma exacerbations and provide an excellent long-term treatment option for asthma severity of moderate persistent degree or greater.

Common side effects of $\beta_2$-adrenergic agonists include muscle tremors and palpitations. These side effects are more prominent with oral formulations, which should not generally be used. There have been ongoing concerns about mortality risks associated with $\beta_2$-adrenergic agonists, which have not been completely resolved. LABAs taken without concomitant inhaled steroid treatment may increase this risk.

Other available bronchodilator medications include anticholinergics and theophylline. Anticholinergics, which are available in short-acting and long-acting inhaled formulations, are commonly used in COPD. They appear to be less effective than $\beta_2$-adrenergic agonists in asthma, and they are typically considered as an additional treatment option only if other asthma medications do not provide adequate asthma control. Theophylline may have both bronchodilator and anti-inflammatory effects; it is not widely used due to the potential toxicities associated with high plasma levels. Low doses of theophylline may have additive effects with ICS at levels below the standard therapeutic range, and this can be a useful treatment option for severe asthma.

**Controller Therapies** ICSs are the most effective controller treatments for asthma. ICSs are usually given twice daily; a variety of ICS medications are available. Although

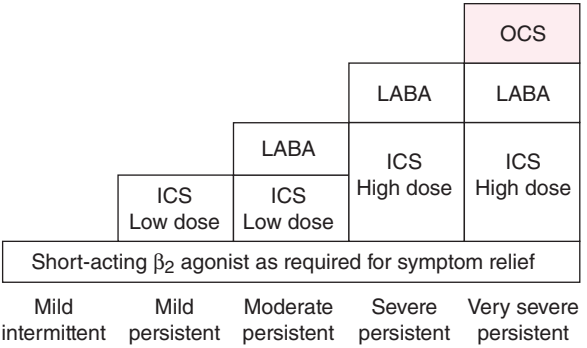


**FIGURE 129-1** Stepwise approach to asthma therapy according to the severity of asthma and ability to control symptoms. ICS, inhaled corticosteroid; LABA, long-acting $\beta_2$ agonists; OCS, oral corticosteroid.

they do not provide immediate symptom relief, respiratory symptoms and lung function often begin to improve within several days of initiating treatment. ICS reduces exercise-induced symptoms, nocturnal symptoms, and acute exacerbations. ICS treatment typically leads to reductions in airway hyperresponsiveness.

ICS side effects include hoarseness and oral candidiasis; these effects may be minimized by use of a spacer device and by rinsing out the mouth after taking ICS.

Other available controller therapies for asthma include systemic corticosteroids. Although quite helpful in the management of acute asthma exacerbations, oral or IV steroid use should be avoided if at all possible in the chronic management of asthma due to multiple potential side effects. Antileukotrienes, such as montelukast, may be quite beneficial in some pts. Cromolyn sodium and nedocromil sodium are not widely used due to their brief durations of action and typically modest effects. Omalizumab is a blocking antibody that neutralizes IgE; with SC injection every 2–4 wk, it appears to reduce acute asthma exacerbation frequency in severe asthmatics. However, it is expensive and considered only for highly selected pts with elevated total serum IgE levels and refractory asthma symptoms despite maximal inhaled bronchodilator and ICS therapy.

**Overall Treatment Approach** In addition to limiting exposure to their environmental triggers for asthma, pts should receive stepwise therapy appropriate for their disease severity (Fig. 129-1). Asthmatics with mild intermittent symptoms are typically managed adequately with SABAs taken on an as-needed basis. Use of SABAs more than three times a week suggests that controller therapy, typically with an ICS twice per day, is required. If symptoms are not adequately controlled with ICS, LABAs can be added. If symptoms are still not adequately controlled, higher doses of ICS and/or alternative controller therapies should be considered.

## ASTHMA EXACERBATIONS

### Clinical Features

Asthma exacerbations are periods of acute worsening of asthma symptoms that may be life threatening. Exacerbations are commonly triggered by viral URIs, but other triggers also can be involved. Symptoms often include increased dyspnea, wheezing, and chest tightness. Physical examination can reveal tachypnea, tachycardia, and

lung hyperinflation. Pulmonary function testing reveals a reduction in $FEV_1$ and PEF. Hypoxemia can result; $Pco_2$ is usually reduced due to hyperventilation. Normal or rising $Pco_2$ can signal impending respiratory failure.

## TREATMENT ASTHMA EXACERBATIONS

The mainstays of asthma exacerbation treatment are high doses of SABAs and systemic corticosteroids. SABAs may be administered by nebulizer or metered-dose inhaler with a spacer; very frequent dosing (q1h or more often) may be required initially. Inhaled anticholinergic bronchodilator medication can be added to the SABAs. IV corticosteroids, such as methylprednisolone (e.g., 80 mg IV q8h), may be used, although oral corticosteroids (e.g., prednisone 30–45 mg once daily for 5–10 days) also may be used. Supplemental oxygen should be provided to maintain adequate oxygen saturation (>90%). If respiratory failure occurs, mechanical ventilation should be instituted, with care to minimize airway pressures and auto-PEEP. Because bacterial infections rarely trigger asthma exacerbations, antibiotics are not routinely administered unless there are signs of pneumonia.

In an effort to treat asthma exacerbations before they become severe, asthma pts should receive written action plans with instructions for self-initiation of treatment based on respiratory symptoms and reductions in PEF.

For a more detailed discussion, see Barnes PJ: Asthma, Chap. 309, p. 1669, in HPIM-19.

# 130 Environmental Lung Diseases

The susceptibility to develop many pulmonary diseases is influenced by environmental factors. This chapter will focus on occupational and toxic chemical exposures. However, a variety of nonoccupational indoor exposures such as environmental tobacco smoke exposure (lung cancer), radon gas (lung cancer), and biomass fuel cooking (chronic obstructive pulmonary disease [COPD]) also should be considered. Particle size is an important determinant of the impact of inhaled environmental exposures on the respiratory system. Particles >10 μm in diameter typically are captured by the upper airway. Particles 2.5–10 μm in diameter will likely deposit in the upper tracheobronchial tree, while smaller particles (including nanoparticles) will reach the alveoli. Water-soluble gases like ammonia are absorbed in the upper airways and produce irritative and bronchoconstrictive responses, while less water-soluble gases (e.g., phosgene) may reach the alveoli and cause a life-threatening acute chemical pneumonitis.

## APPROACH TO THE PATIENT: Environmental Lung Diseases

Because there are many types of occupational lung disease (pneumoconiosis) that can mimic diseases not known to relate to environmental factors, obtaining a careful occupational history is essential. In addition to the types of occupation

performed by the pt, the specific environmental exposures, use of protective respiratory devices, and ventilation of the work environment can provide key information. Assessing the temporal development of symptoms relative to the pt's work schedule also can be very useful.

The physical examination may indicate the type and severity of lung disease, but usually does not assist in identifying a specific environmental etiology. Pulmonary function tests should be used to assess the severity of impairment, but they typically do not suggest a specific diagnosis. Changes in spirometry before and after a work shift can provide strong evidence for bronchoconstriction in suspected occupational asthma. Chest x-ray is helpful in the assessment of environmental lung disease, but it may over- or underestimate the functional impact of pneumoconioses. Some chest x-ray patterns are distinctive for certain occupational lung diseases; chest CT scans can provide a more detailed evaluation. Specific laboratory tests can be invaluable for diagnosing certain environmental lung diseases, such as evaluation of urinary heavy metal concentrations to assess cadmium in battery plant workers.

## OCCUPATIONAL EXPOSURES AND PULMONARY DISEASE

### INORGANIC DUSTS

#### Asbestos-Related Diseases

In addition to exposures to asbestos that may occur during the production of asbestos products (from mining to manufacturing), common occupational asbestos exposures occur in shipbuilding and other construction trades (e.g., pipefitting, boilermaking) and in the manufacture of safety garments and friction materials (e.g., brake and clutch linings). Along with worker exposure in these areas, bystander exposure (e.g., spouses) can be responsible for some asbestos-related lung diseases.

A range of respiratory diseases has been associated with asbestos exposure. Pleural plaques indicate that asbestos exposure has occurred, but they are typically not symptomatic. Interstitial lung disease, often referred to as asbestosis, is pathologically and radiologically similar to idiopathic pulmonary fibrosis; it is typically accompanied by a restrictive ventilatory defect with reduced diffusing capacity of the lung for carbon monoxide (DLCO) on pulmonary function testing. Asbestosis usually develops at least 10 years after exposure, and no specific therapy is available.

Benign pleural effusions can also occur from asbestos exposure. Lung cancer is clearly associated with asbestos exposure, but does not typically present for at least 15 years after initial exposure. The lung cancer risk increases multiplicatively with cigarette smoking. In addition, mesotheliomas (both pleural and peritoneal) are strongly associated with asbestos exposure, but they are not related to smoking. Relatively brief asbestos exposures may lead to mesotheliomas, which typically do not develop for decades after the initial exposure. Biopsy of pleural tissue, typically by thoracoscopic surgery, is required for diagnosing mesothelioma.

#### Silicosis

Silicosis results from exposure to free silica (crystalline quartz), which occurs in mining, stone cutting, abrasive industries (e.g., stone, clay, glass, and cement manufacturing), foundry work, and quarrying. Heavy exposures over relatively brief time periods (as little as 10 months) can cause acute silicosis—which is pathologically similar to pulmonary alveolar proteinosis and associated with a characteristic chest CT pattern known as "crazy paving." Acute silicosis can be severe and progressive; whole lung lavage may be of some therapeutic benefit.

Longer-term exposures can result in simple silicosis, with small rounded opacities in the upper lobes of the lungs. Calcification of hilar lymph nodes can give a

characteristic "eggshell" appearance on radiographic studies. Progressive nodular fibrosis can result in masses >1 cm in diameter in complicated silicosis. When such masses become very large, the term *progressive massive fibrosis* is used to describe the condition. Due to impaired cell-mediated immunity, silicosis pts are at increased risk of tuberculosis, atypical mycobacterial infections, and fungal infections. Silica may also be a lung carcinogen.

### Coal Worker's Pneumoconiosis

Occupational exposure to coal dust predisposes to coal worker's pneumoconiosis (CWP), which is less common among coal workers in the western United States due to a lower risk from the bituminous coal found in that region. Simple CWP is defined radiologically by small nodular opacities and is not typically symptomatic; however, an increased risk of COPD may occur. The development of larger nodules (>1 cm in diameter), usually in the upper lobes, characterizes complicated CWP. Complicated CWP is often symptomatic and is associated with reduced pulmonary function and increased mortality.

### Berylliosis

Beryllium exposure may occur in the manufacturing of alloys, ceramics, and electronic devices. Although acute beryllium exposure can rarely produce acute pneumonitis, a chronic granulomatous disease very similar to sarcoidosis is much more common. Radiologically, chronic beryllium disease, like sarcoidosis, is characterized by pulmonary nodules along septal lines. As in sarcoidosis, either a restrictive or obstructive ventilatory pattern with reduced DLCO on pulmonary function testing can be seen. Bronchoscopy with transbronchial biopsy is typically required to diagnose chronic beryllium disease. The most effective way to distinguish chronic beryllium disease from sarcoidosis is to assess for delayed hypersensitivity to beryllium by performing a lymphocyte proliferation test using blood or bronchoalveolar lavage lymphocytes. Removal from further beryllium exposure is required, and corticosteroids may be beneficial.

## ORGANIC DUSTS

### Cotton Dust (Byssinosis)

Cotton dust exposures occur in the production of yarns for textiles and rope making. At the early stages of byssinosis, chest tightness occurs near the end of the first day of the workweek. In progressive cases, symptoms are present throughout the workweek. After at least 10 years of exposure, chronic airflow obstruction can develop. In symptomatic individuals, limiting further exposure is essential.

### Grain Dust

Farmers and grain elevator operators are at risk for grain dust–related lung disease, which is similar to COPD. Symptoms include productive cough, wheezing, and dyspnea. Pulmonary function tests typically show airflow obstruction.

### Farmer's Lung

Exposure to moldy hay containing spores of thermophilic actinomycetes can lead to the development of hypersensitivity pneumonitis. Within 8 h after exposure, the acute presentation of farmer's lung includes fever, cough, and dyspnea. With repeated exposures, chronic and patchy interstitial lung disease can develop.

### Toxic Chemicals

Many toxic chemicals can affect the lung in the form of vapors and gases. For example, smoke inhalation can be lethal to firefighters and fire victims through a variety of mechanisms; carbon monoxide poisoning can cause life-threatening hypoxemia, while combustion of plastics and polyurethanes can release toxic agents including

cyanide. Occupational asthma can result from exposure to diisocyanates in polyurethanes and acid anhydrides in epoxies. Radon gas, released from earth materials and concentrated within buildings, is a risk factor for lung cancer.

## PRINCIPLES OF MANAGEMENT

Treatment of environmental lung diseases typically involves limiting or avoiding exposures to the toxic substance. Chronic interstitial lung diseases (e.g., asbestosis, CWP) are not responsive to glucocorticoids, but acute organic dust exposures may respond to corticosteroids. Therapy of occupational asthma (e.g., diisocyanates) follows usual asthma guidelines (Chap. 129), and therapy of occupational COPD (e.g., byssinosis) follows usual COPD guidelines (Chap. 131).

For a more detailed discussion, see Balmes JR, Speizer FE: Occupational and Environmental Lung Disease, Chap. 311, p. 1687, in HPIM-19.

# 131 Chronic Obstructive Pulmonary Disease

## DEFINITION AND EPIDEMIOLOGY

Chronic obstructive pulmonary disease (COPD) is a disease state characterized by chronic airflow obstruction; thus, pulmonary function testing is central to its diagnosis. The presence of airflow obstruction is determined by a reduced ratio of the forced expiratory volume in 1 s ($FEV_1$) to the forced vital capacity (FVC). Among individuals with a reduced $FEV_1$/FVC ratio, the severity of airflow obstruction is determined by the level of reduction in $FEV_1$ (Table 131-1): ≥80% is stage I, 50–80% is stage II, 30–50% is stage III, and <30% is stage IV. Cigarette smoking is the major environmental risk factor for COPD. The risk of COPD increases with cigarette smoking intensity, which is typically quantified as pack-years. (One pack of cigarettes smoked per day for 1 year equals 1 pack-year.) Individuals with airway hyperresponsiveness and

**TABLE 131-1 GOLD SPIROMETRIC GRADING CRITERIA FOR COPD SEVERITY**

| GOLD Stage | Severity | Spirometry |
|---|---|---|
| I | Mild | $FEV_1$/FVC <0.7 and $FEV_1$ ≥80% predicted |
| II | Moderate | $FEV_1$/FVC <0.7 and $FEV_1$ ≥50% but <80% predicted |
| III | Severe | $FEV_1$/FVC <0.7 and $FEV_1$ ≥30% but <50% predicted |
| IV | Very severe | $FEV_1$/FVC <0.7 and $FEV_1$ <30% predicted |

***Abbreviation:*** GOLD, Global Initiative for Lung Disease.
***Source:*** From the Global Strategy for Diagnosis, Management and Prevention of COPD 2014. Available from http://www.goldcopd.org; with permission.

certain occupational exposures (e.g., coal mining, gold mining, and cotton textiles) are likely also at increased risk for COPD. In countries in which biomass combustion with poor ventilation is used for cooking, an increased risk of COPD among women has been reported. COPD is a progressive disorder; however, the rate of loss of lung function often slows markedly if smoking cessation occurs. In normal individuals, $FEV_1$ reaches a lifetime peak at around age 25 years, enters a plateau phase, and subsequently declines gradually and progressively. Subjects can develop COPD by having reduced maximally attained lung function, shortened plateau phase, or accelerated decline in lung function.

Symptoms often occur only when COPD is advanced; thus, early detection requires spirometric testing. The $PaO_2$ typically remains near normal until the $FEV_1$ falls to <50% of the predicted value. Hypercarbia and pulmonary hypertension are most common after $FEV_1$ has fallen to <25% of predicted. COPD pts with similar $FEV_1$ values can vary markedly in their respiratory symptoms and functional impairment. COPD often includes periods of increased respiratory symptoms, such as dyspnea, cough, and phlegm production, which are known as exacerbations. Exacerbations are often triggered by bacterial and/or viral respiratory infections. These exacerbations become more common as COPD severity increases, but some individuals are much more susceptible to developing exacerbations than others with similar degrees of airflow obstruction.

## CLINICAL MANIFESTATIONS

### History

Subjects with COPD usually have smoked ≥20 pack-years of cigarettes. Common symptoms include cough and phlegm production; individuals with chronic productive cough for 3 months per year for two consecutive years have chronic bronchitis. However, chronic bronchitis without airflow obstruction is not included within COPD. Exertional dyspnea is a common and potentially disabling symptom in COPD pts. Exercise involving upper-body activity is especially difficult for severe COPD pts. Weight loss and cachexia are common in advanced disease.

Exacerbations are more frequent as disease progresses and are most often triggered by respiratory infections, often with a bacterial component. The history of prior exacerbations is a strong predictor of future exacerbations.

### Physical Findings

The physical examination may be normal until COPD is fairly advanced. As disease progresses, signs of hyperinflation may become more prominent, including barrel chest and poor diaphragmatic excursion. Expiratory wheezing may be observed, but it does not predict the severity of obstruction or response to therapy. Persistently localized wheezing and digital clubbing raise the possibility of lung cancer.

During COPD exacerbations, signs of respiratory distress may be prominent, including tachycardia, tachypnea, use of accessory muscles of respiration, and cyanosis.

### Radiographic Findings

Plain chest x-ray may show hyperinflation, emphysema, and pulmonary hypertension. It is typically performed to exclude other disease processes during routine evaluation and to exclude pneumonia during exacerbations. Chest CT scanning has much greater sensitivity for detecting emphysema, but is typically reserved for the evaluation of advanced disease when surgical options such as lung volume reduction and lung transplantation are being considered, or as part of lung cancer screening in smokers.

### Pulmonary Function Tests

Objective documentation of airflow obstruction is essential for diagnosing COPD. Standardized staging of COPD is based on post-bronchodilator spirometry. In

COPD, the $FEV_1$/FVC ratio is reduced below 0.7. Despite prolonged expiratory efforts, subjects may not be able to achieve a plateau in their FVC. Increases in total lung capacity and residual volume, as well as reduced diffusing capacity for carbon monoxide, are typically seen in emphysema.

## Laboratory Tests

$\alpha_1$ Antitrypsin ($\alpha_1$AT) testing, typically by measurement of the protein level in the bloodstream, is recommended to exclude severe $\alpha_1$AT deficiency. Augmentation therapy (a weekly IV infusion) is available for individuals with severe $\alpha_1$AT deficiency (e.g., PI Z). Pulse oximetry can determine the $O_2$ saturation. However, arterial blood gases remain useful to assess the severity of $CO_2$ retention as well as acid-base disorders. During acute exacerbations, arterial blood gases should be considered in pts with mental status changes, significant respiratory distress, very severe COPD, or a history of hypercarbia. Complete blood counts are useful in advanced disease to assess for erythrocytosis, which can occur secondary to hypoxemia, and anemia, which can worsen dyspnea.

# TREATMENT COPD

## OUTPATIENT MANAGEMENT

**Smoking Cessation** Elimination of tobacco smoking has been convincingly shown to reduce decline in pulmonary function and to prolong survival in pts with COPD. Although lung function does not typically improve substantially after smoking cessation, the rate of decline in $FEV_1$ often reverts to that of nonsmokers. Pharmacologic treatment to assist with smoking cessation is often beneficial. Use of nicotine replacement therapy (available as a transdermal patch, gum, lozenge, nasal spray, and oral inhaler) can increase rates of smoking cessation; oral bupropion (150 mg twice per day after starting at 150 mg per day for 3 days) also produces significant benefit and can be combined successfully with nicotine replacement. Varenicline, a partial agonist for nicotinic acetylcholine receptors, also can promote smoking cessation. All adult, nonpregnant smokers without specific contraindications should be offered pharmacologic treatment to assist with smoking cessation.

**Nonpharmacologic Treatment** Pulmonary rehabilitation improves dyspnea and functional status and reduces hospitalizations. Annual influenza vaccinations are strongly recommended; in addition, pneumococcal vaccination is recommended.

**Bronchodilators** Although inhaled bronchodilator medications have not been proven to increase longevity in COPD, they may significantly reduce respiratory symptoms. Short- and long-acting β-adrenergic agonists, short- and long-acting anticholinergics, and theophylline derivatives all may be used. Although oral medications are associated with greater rates of adherence, inhaled medications generally have fewer side effects.

Pts with mild disease can usually be managed with an inhaled short-acting anticholinergic such as ipratropium or a short-acting β agonist such as albuterol. Combination therapy and long-acting β agonists and/or long-acting anticholinergics should be added in pts with severe disease. The narrow toxic-therapeutic ratio of theophylline compounds limits their use, and either low doses or regular monitoring of serum levels are required.

**Corticosteroids** Chronic systemic corticosteroid treatment is not recommended in COPD pts due to the risk of multiple complications, including osteoporosis, weight gain, cataracts, and diabetes mellitus. Although inhaled steroids have not been proven to reduce the rate of decline of $FEV_1$ in COPD, inhaled steroid medications reduce the frequency of exacerbations in individuals with severe COPD. Combinations of inhaled steroids and long-acting β agonists reduce COPD

exacerbations and may reduce mortality—although that has not been conclusively shown.

**Oxygen** Long-term supplemental oxygen therapy has been shown to reduce symptoms and improve survival in COPD pts who are chronically hypoxemic. Documentation of the need for $O_2$ requires a measurement of $PaO_2$ or oxygen saturation ($SaO_2$) after a period of stability. Pts with a $PaO_2$ ≤55 mmHg or $SaO_2$ ≤88% should receive $O_2$ to raise the $SaO_2$ to ≥90%. $O_2$ is also indicated for pts with $PaO_2$ of 56–59 mmHg or $SaO_2$ <90% if associated with signs and symptoms of pulmonary hypertension or cor pulmonale. For individuals who meet these guidelines, continuous $O_2$ therapy is recommended because the number of hours per day of oxygen use is directly related to the mortality benefit. Supplemental oxygen may also be prescribed for selected COPD pts who desaturate only with exercise or during sleep, although the evidence for benefit is less compelling.

**Surgical Options for Severe COPD** Two main types of surgical options are available for end-stage COPD. Lung volume reduction surgery can reduce mortality and improve lung function in selected pts with upper lobe–predominant emphysema and low exercise capacity (after pulmonary rehabilitation). Individuals who meet the criteria for the high-risk group ($FEV_1$ <20% predicted and either a diffuse distribution of emphysema or lung carbon monoxide diffusing capacity <20% predicted) should not be considered for lung volume reduction surgery. Lung transplantation should be considered for COPD pts who have very severe chronic airflow obstruction and disability at a relatively young age despite maximal medical therapy.

## MANAGEMENT OF COPD EXACERBATIONS

COPD exacerbations are a major cause of morbidity and mortality. Critical decisions in management include whether hospitalization is required. Although there are no definitive guidelines to determine which COPD pts require hospitalization for an exacerbation, the development of respiratory acidosis, worsening hypoxemia, severe underlying COPD, pneumonia, or social situations without adequate home support for the treatment required should prompt consideration of hospitalization. Chronic treatment with azithromycin or roflumilast has been shown to reduce the frequency of COPD exacerbations.

Key components of exacerbation treatment include bronchodilators, antibiotics, and short courses of systemic glucocorticoids.

**Antibiotics** Because bacterial infections often trigger COPD exacerbations, antibiotic therapy should be strongly considered, especially with increased sputum volume or change in sputum color. Common pathogens include *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. Antibiotic choice should depend on the local antibiotic sensitivity patterns and the severity of disease. Trimethoprim-sulfamethoxazole, doxycycline, and amoxicillin are reasonable choices for subjects with mild to moderate COPD; broader-spectrum antibiotics should be considered for subjects with more severe underlying COPD and/or more severe exacerbations.

**Bronchodilators** Bronchodilator therapy is essential during COPD exacerbations. Short-acting β-adrenergic agonists by inhalation (e.g., albuterol q1–2h) are used; addition of anticholinergics is likely of benefit (e.g., ipratropium q4–6h). Administration of bronchodilators by nebulizer is often used initially because it is easier to administer to pts in respiratory distress. Conversion to metered-dose inhaler administration can be successfully achieved with appropriate training of the pt and staff.

**Glucocorticoids** Systemic steroids hasten resolution of symptoms and reduce relapses and subsequent exacerbations for up to 6 months. Dosing is not well

worked out, but 30–40 mg of prednisone daily (or IV equivalent) is standard, with a total course of 10–14 days. Hyperglycemia is the most commonly reported complication and should be monitored.

**Oxygen** Hypoxemia often worsens during COPD exacerbations. Supplemental $O_2$ should be administered to maintain $SaO_2$ ≥90%. Very high $O_2$ delivery can worsen hypercarbia, primarily due to increasing ventilation-perfusion mismatch. However, providing adequate $O_2$ to obtain saturation of ~90% is the key goal. Therefore, supplemental $O_2$ delivery should be focused on providing adequate oxygenation without providing unnecessarily high $O_2$ saturations. Pts may require use of supplemental $O_2$ after hospital discharge until the exacerbation completely resolves.

**Ventilatory Support** Numerous studies suggest that noninvasive mask ventilation (noninvasive ventilation [NIV]) can improve outcomes in acute COPD exacerbations with respiratory failure ($PaCO_2$ >45 mmHg). Contraindications to NIV include cardiovascular instability, impaired mental status, inability to cooperate, copious secretions, craniofacial abnormalities or facial trauma, extreme obesity, or significant burns. Progressive hypercarbia, refractory hypoxemia, or alterations in mental status that compromise ability to comply with NIV therapy, hemodynamic instability, and respiratory arrest may necessitate endotracheal intubation for mechanical ventilation. Sufficient expiratory time is required to avoid the development of auto-PEEP.

For a more detailed discussion, see Reilly JJ Jr., Silverman EK, Shapiro SD: Chronic Obstructive Pulmonary Disease, Chap. 314, p. 1700, in HPIM-19.

# 132 Pneumonia, Bronchiectasis, and Lung Abscess

## PNEUMONIA

Pneumonia, an infection of the lung parenchyma, is classified as community-acquired (CAP) or health care–associated (HCAP). The HCAP category is subdivided into hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP). HCAP is associated with current hospitalization for ≥48 h, hospitalization for ≥2 days in the prior 3 months, residence in a nursing home or extended-care facility, antibiotic therapy in the preceding 3 months, chronic dialysis, home infusion therapy, home wound care, and contact with a family member who has a multidrug-resistant (MDR) infection.

### PATHOPHYSIOLOGY

- Microorganisms gain access to the lower respiratory tract via microaspiration from the oropharynx (the most common route), inhalation of contaminated droplets, hematogenous spread, or contiguous extension from an infected pleural or mediastinal space.

- Before disease manifests, the size of the organism burden must overcome the ability of macrophages and other components of innate immunity (e.g., surfactant proteins A and D) to clear bacteria.
- Classic pneumonia (typified by that due to *Streptococcus pneumoniae*) presents as a lobar pattern and evolves through four phases characterized by changes in the alveoli:
  - *Edema:* Proteinaceous exudates are present in the alveoli.
  - *Red hepatization:* Erythrocytes and neutrophils are present in the intraalveolar exudate.
  - *Gray hepatization:* Neutrophils and fibrin deposition are abundant.
  - *Resolution:* Macrophages are the dominant cell type.
- In VAP, respiratory bronchiolitis can precede a radiologically apparent infiltrate.

## COMMUNITY-ACQUIRED PNEUMONIA

### Microbiology

Although many bacteria, viruses, fungi, and protozoa can cause CAP, most cases are caused by relatively few pathogens. In >50% of cases, a specific etiology is never determined.

- Typical bacterial pathogens include *S. pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, and gram-negative bacteria such as *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*.
- Atypical organisms include *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella* spp., and respiratory viruses (e.g., influenza viruses, adenoviruses, human metapneumovirus, respiratory syncytial viruses).
  - A virus may be responsible for a large proportion of CAP cases that require hospital admission, even in adults.
  - 10–15% of CAP cases are polymicrobial and involve a combination of typical and atypical organisms.
- Involvement of anaerobes, which play a significant role in CAP only when aspiration precedes presentation by days or weeks, often results in significant empyemas.

### Epidemiology

CAP affects >5 million adults each year in the United States, 80% of whom are treated on an outpatient basis. CAP causes >55,000 deaths annually and is associated with an overall yearly cost of ~$12 billion.

- Incidence rates of CAP are highest at the extremes of age (i.e., <4 and >60 years).
- Risk factors for CAP include alcoholism, asthma, immunosuppression, institutionalization, and an age of ≥70 years (vs. 60–69 years).
- Many factors—e.g., tobacco smoking, chronic obstructive pulmonary disease, colonization with methicillin-resistant *S. aureus* (MRSA), recent hospitalization or antibiotic therapy—influence the types of pathogens that should be considered in the etiologic diagnosis.

### Clinical Manifestations

Pts frequently have fever, chills, sweats, cough (either nonproductive or productive of mucoid, purulent, or blood-tinged sputum), pleuritic chest pain, and dyspnea.

- Other common symptoms include nausea, vomiting, diarrhea, fatigue, headache, myalgias, and arthralgias.
- Elderly pts may present atypically, with confusion but few other manifestations.
- Physical examination often reveals tachypnea; increased or decreased tactile fremitus; dull or flat percussion reflecting consolidation and pleural fluid, respectively; crackles; bronchial breath sounds; or a pleural friction rub.

## Diagnosis

Both confirmation of the diagnosis and assessment of the likely etiology are required. Although no data have demonstrated that treatment directed at a specific pathogen is superior to empirical treatment, an etiologic diagnosis allows narrowing of the empirical regimen, identification of organisms with public safety implications (e.g., *Mycobacterium tuberculosis*, influenza virus), and monitoring of antibiotic susceptibility trends.

- *Chest radiography* is often required to differentiate CAP from other conditions, particularly since the sensitivity and specificity of physical exam findings for CAP are only 58% and 67%, respectively.
  - CT of the chest may be helpful for pts with suspected postobstructive pneumonia or suspected cavitary disease.
  - Some radiographic patterns suggest an etiology; e.g., pneumatoceles suggest *S. aureus*.
- *Sputum samples* must have >25 WBCs and <10 squamous epithelial cells per high-power field to be appropriate for culture. The sensitivity of sputum cultures is highly variable; in cases of proven bacteremic pneumococcal pneumonia, the yield of positive cultures from sputum samples is ≤50%.
- *Blood cultures* are positive in 5–14% of cases, most commonly yielding *S. pneumoniae*. Blood cultures are optional for most CAP pts but should be performed for high-risk pts (e.g., pts with chronic liver disease or asplenia).
- *Urine antigen tests* for *S. pneumoniae* and *Legionella pneumophila* type 1 can be helpful.
- *PCR* of nasopharyngeal swabs has become the standard for diagnosis of respiratory viral infection and is also useful for detection of many atypical bacteria.
- *Serology:* A fourfold rise in titer of specific IgM antibody can assist in the diagnosis of pneumonia due to some pathogens; however, the time required to obtain a final result makes serology of limited clinical utility.

## TREATMENT COMMUNITY-ACQUIRED PNEUMONIA

### DECIDING WHETHER TO HOSPITALIZE PTS

- Two sets of criteria identify pts who will benefit from hospital care. It is not clear which set is superior, and application of each tool should be tempered by a consideration of factors relevant to the individual pt.
  - Pneumonia Severity Index (PSI): Points are given for 20 variables, including age, coexisting illness, and abnormal physical and laboratory findings. On this basis, pts are assigned to one of five classes of mortality risk.
  - CURB-65: Five variables are included: confusion (C); urea >7 mmol/L (U); respiratory rate ≥30/min (R); blood pressure, systolic ≤90 mmHg or diastolic ≤60 mmHg (B); and age ≥65 years (65). Pts with a score of 0 can be treated at home, pts with a score of 2 should be hospitalized, and pts with a score of ≥3 may require management in the ICU.

### ANTIBIOTIC THERAPY

- For recommendations on empirical antibiotic treatment of CAP, see Table 132-1. U.S. guidelines always target *S. pneumoniae* and atypical pathogens. Retrospective data suggest that this approach lowers the mortality rate.
- Pts initially treated with IV antibiotics can be switched to oral agents when they can ingest and absorb drugs, are hemodynamically stable, and are improving clinically.
- CAP has historically been treated for 10–14 days, but a 5-day course of a fluoroquinolone is sufficient for cases of uncomplicated CAP. A longer course may be required for pts with bacteremia, metastatic infection, or infection with a particularly virulent pathogen.

**TABLE 132-1 EMPIRICAL ANTIBIOTIC TREATMENT OF COMMUNITY-ACQUIRED PNEUMONIA**

**Outpatients**

1. Previously healthy and no antibiotics in past 3 months
   - A macrolide (clarithromycin [500 mg PO bid] or azithromycin [500 mg PO once, then 250 mg qd]) ***or***
   - Doxycycline (100 mg PO bid)
2. Comorbidities or antibiotics in past 3 months: select an alternative from a different class
   - A respiratory fluoroquinolone (moxifloxacin [400 mg PO qd], gemifloxacin [320 mg PO qd], levofloxacin [750 mg PO qd]) ***or***
   - A β-lactam (preferred: high-dose amoxicillin [1 g tid] or amoxicillin/clavulanate [2 g bid]; alternatives: ceftriaxone [1–2 g IV qd], cefpodoxime [200 mg PO bid], cefuroxime [500 mg PO bid]) *plus* a macrolide[a]
3. In regions with a high rate of "high-level" pneumococcal macrolide resistance,[b] consider alternatives listed above for pts with comorbidities.

**Inpatients, Non-ICU**

- A respiratory fluoroquinolone (e.g., moxifloxacin [400 mg PO or IV qd] or levofloxacin [750 mg PO or IV qd])
- A β-lactam[c] (e.g., ceftriaxone [1–2 g IV qd], ampicillin [1–2 g IV q4–6h], cefotaxime [1–2 g IV q8h], ertapenem [1 g IV qd]) *plus* a macrolide[d] (e.g., oral clarithromycin or azithromycin [as listed above] or IV azithromycin [1 g once, then 500 mg qd])

**Inpatients, ICU**

- A β-lactam[e] (e.g., ceftriaxone [2 g IV qd], ampicillin-sulbactam [2 g IV q8h], or cefotaxime [1–2 g IV q8h]) *plus* either azithromycin or a fluoroquinolone (as listed above for inpatients, non-ICU)

**Special Concerns**

*If Pseudomonas is a consideration:*

- An antipseudomonal β-lactam (e.g., piperacillin/tazobactam [4. 5 g IV q6h], cefepime [1–2 g IV q12h], imipenem [500 mg IV q6h], meropenem [1 g IV q8h]) *plus* either ciprofloxacin (400 mg IV q12h) or levofloxacin (750 mg IV qd)
- The above β-lactams *plus* an aminoglycoside (amikacin [15 mg/kg qd] or tobramycin [1. 7 mg/kg qd]) *plus* azithromycin
- The above β-lactams[f] *plus* an aminoglycoside *plus* an antipneumococcal fluoroquinolone

*If CA-MRSA is a consideration:*

- Add linezolid (600 mg IV q12h) or vancomycin (15 mg/kg q12h initially, with adjusted doses)

[a]Doxycycline (100 mg PO bid) is an alternative to the macrolide.
[b]MICs of >16 μg/mL in 25% of isolates.
[c]A respiratory fluoroquinolone should be used for penicillin-allergic pts.
[d]Doxycycline (100 mg IV q12h) is an alternative to the macrolide.
[e]For penicillin-allergic pts, use a respiratory fluoroquinolone and aztreonam (2 g IV q8h).
[f]For penicillin-allergic pts, substitute aztreonam.
***Abbreviations:*** CA-MRSA, community-acquired methicillin-resistant *Staphylococcus aureus.*

- Fever and leukocytosis usually resolve within 2–4 days. Pts who have not responded to therapy by day 3 should be reevaluated, with consideration of alternative diagnoses, antibiotic resistance in the pathogen, and the possibility that the wrong drug is being given.

### Complications

Common complications of severe CAP include respiratory failure, shock and multiorgan failure, coagulopathy, and exacerbation of comorbid disease. Metastatic infection (e.g., brain abscess, endocarditis) occurs rarely and requires immediate attention.

- Lung abscess may occur in association with aspiration or infection caused by single CAP pathogens (e.g., community-acquired MRSA [CA-MRSA] or *P. aeruginosa*). Drainage should be established and proper antibiotics administered.
- Any significant pleural effusion should be tapped for diagnostic and therapeutic purposes. If the fluid has a pH <7, a glucose level <2.2 mmol/L, and an LDH content >1000 U or if bacteria are seen or cultured, fluid should be drained; a chest tube is usually required.

### Follow-Up

CXR abnormalities may require 4–12 weeks to clear. Pts should receive influenza and pneumococcal vaccines, as appropriate.

## HEALTH CARE–ASSOCIATED PNEUMONIA (SEE ALSO CHAP. 78)

### VENTILATOR-ASSOCIATED PNEUMONIA

### Microbiology

Potential etiologic agents include MDR and non-MDR pathogens; the prominence of the various pathogens depends on the length of hospital stay at the time of infection.

### Epidemiology, Pathogenesis, and Clinical Manifestations

Prevalence estimates of VAP are 6–52 cases per 100 pts, with the highest hazard ratio in the first 5 days of mechanical ventilation.

- Three factors important in the pathogenesis of VAP are colonization of the oropharynx with pathogenic microorganisms, aspiration of these organisms to the lower respiratory tract, and compromise of normal host defense mechanisms.
- Clinical manifestations are similar to those in other forms of pneumonia.

### Diagnosis

Application of clinical criteria consistently results in overdiagnosis of VAP. Use of quantitative cultures to discriminate between colonization and true infection by determining bacterial burden may be helpful; the more distal in the respiratory tree the diagnostic sampling, the more specific the results.

## TREATMENT VENTILATOR-ASSOCIATED PNEUMONIA

- See Table 132-2 for recommended options for empirical therapy for HCAP.
  - Higher mortality rates are associated with inappropriate initial empirical treatment.
  - Broad-spectrum treatment should be modified when a pathogen is identified.
  - Clinical improvement, if it occurs, is usually evident within 48–72 h of the initiation of antimicrobial treatment.
- Treatment failure in VAP is not uncommon, especially when MDR pathogens are involved; MRSA and *P. aeruginosa* are associated with high failure rates.

**TABLE 132-2 EMPIRICAL ANTIBIOTIC TREATMENT OF HEALTH CARE–ASSOCIATED PNEUMONIA**

| |
|---|
| **Patients without Risk Factors for MDR Pathogens** |
| Ceftriaxone (2 g IV q24h) or cefotaxime (2 g IV q6–8 h) ***or*** |
| Moxifloxacin (400 mg IV q24h), ciprofloxacin (400 mg IV q8h), or levofloxacin (750 mg IV q24h) ***or*** |
| Ampicillin/sulbactam (3 g IV q6h) ***or*** |
| Ertapenem (1 g IV q24h) |
| **Patients with Risk Factors for MDR Pathogens** |
| 1. A β-lactam: |
| Ceftazidime (2 g IV q8h) or cefepime (2 g IV q8–12h) ***or*** |
| Piperacillin/tazobactam (4. 5 g IV q6h) ***or*** |
| Imipenem (500 mg IV q6h or 1 g IV q8h) or meropenem (1 g IV q8h) |
| ***plus*** |
| 2. A second agent active against gram-negative bacterial pathogens: |
| Gentamicin or tobramycin (7 mg/kg IV q24h) or amikacin (20 mg/kg IV q24h) ***or*** |
| Ciprofloxacin (400 mg IV q8h) or levofloxacin (750 mg IV q24h) |
| ***plus*** |
| 3. An agent active against gram-positive bacterial pathogens: |
| Linezolid (600 mg IV q12h) ***or*** |
| Vancomycin (15 mg/kg q12h initially with adjusted doses) |

***Abbreviation:*** MDR, multidrug-resistant.

- VAP complications include prolongation of mechanical ventilation, increased length of ICU stay, and necrotizing pneumonia with pulmonary hemorrhage or bronchiectasis. VAP is associated with significant mortality risk.
- Strategies effective for the prevention of VAP are listed in Table 132-3.

## HOSPITAL-ACQUIRED PNEUMONIA

Less well studied than VAP, HAP more commonly involves non-MDR pathogens. Anaerobes may also be more commonly involved in non-VAP pts because of the increased risk of macroaspiration in pts who are not intubated.

## BRONCHIECTASIS

### Etiology and Epidemiology

Bronchiectasis is an irreversible airway dilation that involves the lung in either a focal (due to obstruction) or a diffuse (due to a systemic or infectious process) manner. Bronchiectasis can arise from infectious or noninfectious causes.

- The epidemiology varies greatly with the underlying etiology; in general, the incidence of bronchiectasis increases with age and is higher among women than among men.
- 25–50% of pts with bronchiectasis have idiopathic disease.

### Pathogenesis

The most widely cited mechanism of infectious bronchiectasis is the "vicious cycle hypothesis," in which susceptibility to infection and poor mucociliary clearance

**TABLE 132-3 PATHOGENIC MECHANISMS AND CORRESPONDING PREVENTION STRATEGIES FOR VENTILATOR-ASSOCIATED PNEUMONIA**

| Pathogenic Mechanism | Prevention Strategy |
|---|---|
| Oropharyngeal colonization with pathogenic bacteria | |
| Elimination of normal flora | Avoidance of prolonged antibiotic courses |
| Large-volume oropharyngeal aspiration around time of intubation | Short course of prophylactic antibiotics for comatose pts[a] |
| Gastroesophageal reflux | Postpyloric enteral feeding[b]; avoidance of high gastric residuals, prokinetic agents |
| Bacterial overgrowth of stomach | Avoidance of prophylactic agents that raise gastric pH[b]; selective decontamination of digestive tract with nonabsorbable antibiotics[b] |
| Cross-infection from other colonized pts | Hand washing, especially with alcohol-based hand rub; intensive infection control education[a]; isolation; proper cleaning of reusable equipment |
| Large-volume aspiration | Endotracheal intubation; rapid-sequence intubation technique; avoidance of sedation; decompression of small-bowel obstruction |
| Microaspiration around endotracheal tube | |
| Endotracheal intubation | Noninvasive ventilation[a] |
| Prolonged duration of ventilation | Daily awakening from sedation,[a] weaning protocols[a] |
| Abnormal swallowing function | Early percutaneous tracheostomy[a] |
| Secretions pooled above endotracheal tube | Head of bed elevated[a]; continuous aspiration of subglottic secretions with specialized endotracheal tube[a]; avoidance of reintubation; minimization of sedation and pt transport |
| Altered lower respiratory host defenses | Tight glycemic control[b]; lowering of hemoglobin transfusion threshold |

[a]Strategies demonstrated to be effective in at least one randomized controlled trial.
[b]Strategies with negative randomized trials or conflicting results.

result in microbial colonization of the bronchial tree. Proposed mechanisms for noninfectious bronchiectasis include immune-mediated reactions that damage the bronchial wall and parenchymal distortion as a result of lung fibrosis (e.g., postradiation fibrosis or idiopathic pulmonary fibrosis).

## Clinical Manifestations

Presenting pts typically have a persistent productive cough with ongoing production of thick, tenacious sputum.

- Physical examination usually reveals crackles and wheezing on lung auscultation and occasionally reveals digital clubbing.
- Acute exacerbations are associated with increased purulent-sputum production.

## Diagnosis

The diagnosis of bronchiectasis is based on clinical presentation with consistent radiographic findings, such as parallel "tram tracks," a "signet-ring sign" (a cross-sectional area of the airway with a diameter at least 1.5 times that of the adjacent vessel), lack of bronchial tapering, bronchial wall thickening, or cysts emanating from the bronchial wall.

### TREATMENT BRONCHIECTASIS

Treatment of infectious bronchiectasis is directed at the control of active infection and at improvements in secretion clearance and bronchial hygiene.

- Acute exacerbations should be treated with a 7- to 10-day course of antibiotics targeting the causative or presumptive pathogen; *H. influenzae* and *P. aeruginosa* are isolated commonly.
- Hydration and mucolytic administration, aerosolization of bronchodilators and hyperosmolar agents (e.g., hypertonic saline), and chest physiotherapy can be used to enhance secretion clearance.
- For pts with ≥3 recurrences per year, suppressive antibiotic treatment to minimize the microbial load and reduce the frequency of exacerbations has been proposed.
- In select cases, surgery (including lung transplantation) should be considered.

# LUNG ABSCESS

## Microbiology

Lung abscess—necrosis and cavitation of the lung following microbial infection—can be categorized as primary (~80% of cases) or secondary; alternatively, it can be categorized as acute (<4–6 weeks in duration) or chronic (~40% of cases).

- Primary lung abscesses usually arise from aspiration in the absence of an underlying pulmonary or systemic condition, are often polymicrobial (primarily including anaerobic organisms and microaerophilic streptococci), and occur preferentially in dependent segments (posterior upper and superior lower lobes) of the right lung.
- Secondary lung abscesses arise in the setting of an underlying condition (e.g., a postobstructive process, an immunocompromising condition) and can be due to a number of different organisms, among which *P. aeruginosa* and other gram-negative rods are most common.

## Clinical Manifestations

Initial presentation of lung abscess may be similar to that of pneumonia. Anaerobic lung abscesses may have a more chronic and indolent presentation, with night sweats, fatigue, and anemia; in addition, pts may have discolored phlegm and foul-tasting or foul-smelling sputum. Pts with lung abscesses due to non-anaerobic organisms (e.g., *S. aureus*) may present with a more fulminant course characterized by high fevers and rapid progression.

## Diagnosis

Chest CT is the preferred radiographic study for precise delineation of the lesion.

- It is not clear whether invasive diagnostics (e.g., transtracheal aspiration) to identify an etiologic agent in primary lung abscesses is helpful.
- Sputum and blood cultures, serologic studies for opportunistic pathogens, and—if needed—more invasive methods of sample collection (e.g., bronchoalveolar lavage, CT-guided percutaneous aspiration) are recommended for secondary lung abscesses or when empirical therapy fails.

## TREATMENT LUNG ABSCESS

Treatment depends on the presumed or established etiology.

- For primary lung abscesses, the recommended regimens are clindamycin (600 mg IV tid) or an IV-administered β-lactam/β-lactamase combination. After clinical improvement, the pt can be transitioned to an oral regimen (clindamycin, 300 mg qid; or amoxicillin/clavulanate).
- In secondary lung abscesses, antibiotic coverage should be directed at the identified pathogen.
- Continuation of oral treatment is recommended until imaging shows that the lung abscess has cleared or regressed to a small scar.
- Pts who continue to have fever ≥7 days after antibiotic initiation and whose additional diagnostic studies fail to identify an another treatable pathogen may require surgical resection or percutaneous drainage of the abscess.

For a more detailed discussion, see Mandell LA, Wunderink RG: Pneumonia, Chap. 153, p. 803; Baron RM, Baron Barshak M: Lung Abscess, Chap. 154, p. 813; and Baron RM, Baron Barshak M: Bronchiectasis, Chap. 312, p. 1694, in HPIM-19.

# 133 Pulmonary Thromboembolism and Deep-Vein Thrombosis

## DEFINITION AND NATURAL HISTORY

Venous thromboembolism includes both deep-vein thrombosis (DVT) and pulmonary thromboembolism (PE). DVT results from blood clot formation within large veins, usually in the legs. PE results from DVTs that have broken off and traveled to the pulmonary arterial circulation. Isolated calf vein thrombi have much lower risk of PE. Although DVTs are typically related to thrombus formation in the legs and/or pelvis, indwelling venous catheters, pacemakers, and internal cardiac defibrillators have increased the occurrence of upper extremity DVT. In the absence of PE, the major complication of DVT is postthrombotic syndrome, which causes chronic leg swelling and discomfort due to damage to the venous valves of the affected leg. In its most severe form, postthrombotic syndrome causes skin ulceration. PE is often fatal, usually due to progressive right ventricular failure. Chronic thromboembolic pulmonary hypertension is another long-term complication of PE.

Some genetic risk factors, including factor V Leiden and the prothrombin G20210A mutation, have been identified, but they account for only a minority of venous thromboembolic disease. Medical conditions that increase the risk of venous thromboembolism include cancer and antiphospholipid antibody syndrome. A variety of other risk factors have been identified, including immobilization during prolonged travel, obesity, smoking, surgery, trauma, pregnancy, oral contraceptives, and postmenopausal hormone replacement.

Massive PE, with thrombosis affecting at least half of the pulmonary vasculature, often includes dyspnea, syncope, hypotension, and cyanosis. Submassive PE includes RV dysfunction in the setting of normal systemic arterial pressure. Low-risk PE, which includes normal RV function and systemic arterial pressure, has an excellent prognosis.

## CLINICAL EVALUATION

### History

DVTs often present with progressive lower calf discomfort. For PE, dyspnea is the most common presenting symptom. Chest pain, cough, or hemoptysis can indicate pulmonary infarction with pleural irritation. Syncope can occur with massive PE.

### Physical Examination

Tachypnea and tachycardia are common in PE. Low-grade fever, neck vein distention, and a loud $P_2$ on cardiac examination can be seen. Hypotension and cyanosis suggest massive PE. Physical examination with DVT may be notable only for mild calf tenderness. However, with massive DVT, marked thigh swelling and inguinal tenderness can be observed.

### Laboratory Tests

Normal D-dimer level (<500 μg/mL by enzyme-linked immunosorbent assay) essentially rules out PE in pts with low-to-moderate likelihood of PE, although hospitalized pts often have elevated D-dimer levels due to other disease processes. Although hypoxemia and an increased alveolar-arterial $O_2$ gradient may be observed in PE, arterial blood gases are rarely useful in diagnosing PE. Elevated serum troponin, plasma heart-type fatty acid-binding protein, and brain natriuretic peptide levels can be seen in PE. The electrocardiogram can show an S1Q3T3 sign in PE, but that finding is not frequently observed.

### Imaging Studies

Venous ultrasonography can detect DVT by demonstrating loss of normal venous compressibility. For pts with nondiagnostic venous ultrasound studies, CT or MRI can be used to assess for DVT. About one-half of pts with PE have no imaging evidence for DVT.

In PE, a normal chest x-ray (CXR) is common. Although not commonly observed, focal oligemia and peripheral wedge-shaped densities on CXR are well-established findings in PE. Chest CT with IV contrast has become the primary diagnostic imaging test for PE. Ventilation-perfusion lung scanning is primarily used for subjects unable to tolerate IV contrast. Transthoracic echocardiography can identify right ventricular hypokinesis with moderate to large PE, but it is not typically useful for diagnosing the presence of a PE. Transesophageal echocardiography can be used to identify large central PE when IV contrast chest CT scans are not appropriate (e.g., renal failure or severe contrast allergy). With the advent of contrast chest CT scans for PE diagnosis, pulmonary angiography studies are rarely performed.

### Integrated Diagnostic Approach

An integrated diagnostic approach that considers the clinical suspicion for DVT and PE is required. For individuals with a low clinical likelihood of DVT or with a low-to-moderate clinical likelihood of PE, the D-dimer level can be used to determine if further imaging studies are required. An algorithm for imaging studies in both DVT and PE is shown in Fig. 133-1. The differential diagnosis of DVT includes a ruptured Baker's cyst and cellulitis. The differential diagnosis of PE is broad and includes pneumonia, acute myocardial infarction, and aortic dissection.

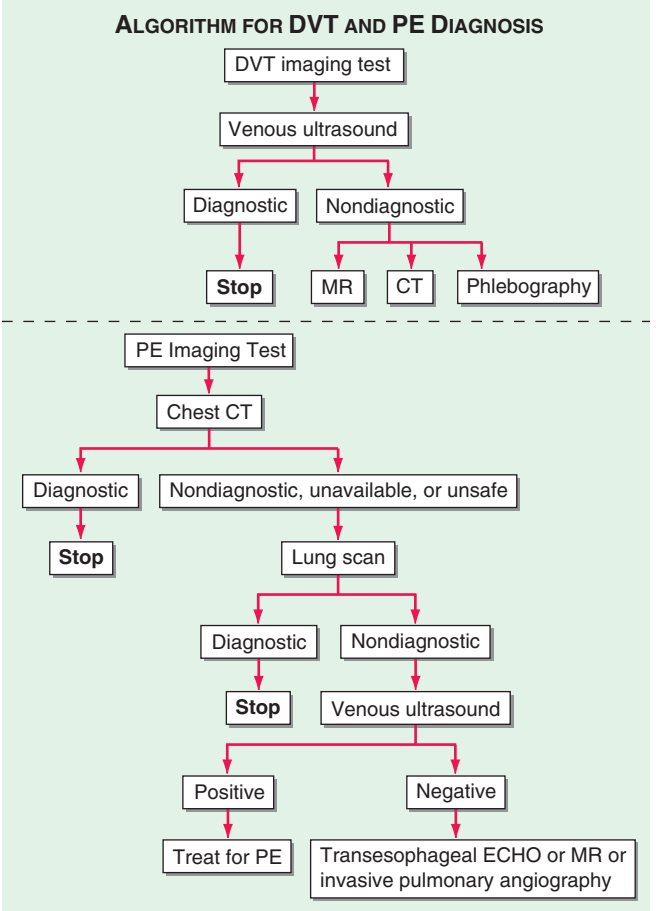


**FIGURE 133-1** Imaging tests useful to diagnose DVT and PE. ECHO, echocardiogram.

## TREATMENT DEEP-VEIN THROMBOSIS AND PULMONARY THROMBOEMBOLISM

**ANTICOAGULATION** Although anticoagulants do not dissolve existing clots in DVT or PE directly, they limit further thrombus formation and allow fibrinolysis to occur. Three general approaches can be used for anticoagulation in DVT and PE: (1) Parenteral therapy with transition to warfarin; (2) parenteral therapy with transition to an oral anticoagulant such as dabigatran or edoxaban; or (3) oral anticoagulation with rivaroxaban or apixaban without parenteral anticoagulation.

Traditionally, intravenous unfractionated heparin (UFH) has been used, with a target activated partial thromboplastin time (aPTT) of 60–80 s. UFH is typically administered with a bolus of 80 U/kg followed by a continuous infusion of approximately 18 U/kg per hour. Frequent dosage adjustments are often required to achieve and maintain a therapeutic aPTT with UFH. Heparin-induced

thrombocytopenia can occur with UFH. However, the short half-life of UFH remains a significant advantage.

Alternatives to UFH for acute anticoagulation include low-molecular-weight heparins (LMWHs) such as enoxaparin and dalteparin. Laboratory monitoring is not required, but doses are adjusted for renal impairment or obesity. Fondaparinux, a synthetic parenteral alternative to UFH, does not require laboratory monitoring but does require dose adjustment for body weight and renal insufficiency. In pts with heparin-induced thrombocytopenia, direct thrombin inhibitors (e.g., argatroban or bivalirudin) should be used.

After initiating treatment with a parenteral agent, warfarin is typically used for long-term oral anticoagulation. Warfarin can be initiated soon after a parenteral agent is given; however, at least 5 days are required for warfarin to achieve therapeutic anticoagulation. Warfarin is given to achieve a therapeutic international normalized ratio (INR) of the prothrombin time, which is typically an INR of 2.0–3.0. Pts vary widely in their required warfarin doses due to effects of genetics, diet, and other drugs; dosing often begins at 5 mg/d, with adjustment based on the INR.

Novel oral anticoagulants, including rivaroxaban, apixaban, and dabigatran, have the advantages of fixed dose regimens, rapid onset of effective anticoagulation, no laboratory monitoring, and fewer drug and dietary interactions. However, anticoagulation with these Factor Xa or thrombin inhibitors is not readily reversed (with the exception of dabigatran, which has been shown in one study to be reversed by idarucizumab [Pollack C et al., N Engl J Med 2015;373:511-520]).

The most troublesome adverse event from anticoagulation treatment is hemorrhage. For severe hemorrhage while undergoing treatment with UFH or LMWH, protamine can be given to reverse anticoagulation. Severe bleeding while anticoagulated with warfarin can be treated with prothrombin complex concentrate; milder hemorrhage or markedly elevated INR values can be treated with vitamin K. Warfarin should be avoided in pregnant pts.

The duration of anticoagulation for an initial DVT or PE is at least 3–6 months. Pts with DVT or PE in the setting of trauma, surgery, indwelling central venous catheters, or high estrogen states have a low recurrence rate after 3–6 months of anticoagulation. However, recurrence rate is high in pts with cancer or with idiopathic, unprovoked DVT or PE, and prolonged anticoagulation should be considered. Recurrent DVT or PE typically requires lifelong anticoagulation.

## OTHER TREATMENT MODALITIES

Although anticoagulation is the mainstay of therapy for venous thromboembolism, additional therapeutic modalities also can be employed, based on risk stratification (Fig. 133-2). Inferior vena cava filters can be used if thrombosis recurs despite adequate anticoagulation or if active bleeding precludes anticoagulation. Fibrinolytic therapy (often with tissue plasminogen activator) should be considered for PE causing right heart failure, although the risk of hemorrhage is significant. Surgical or catheter embolectomy also can be considered for massive PE. Low-dose, catheter-directed thrombolysis can be used for pts with extensive femoral, iliofemoral, or upper extremity DVT.

If PE pts develop chronic thromboembolic pulmonary hypertension, surgical intervention (pulmonary thromboendarterectomy) can be performed.

To reduce the severity of postthrombotic syndrome, below-knee graduated compression stockings can be used for 2 years after a DVT.

Prevention of DVT and PE in hospitalized pts is often performed with low-dose UFH or LMWH. After cancer surgery or hip or knee replacement operations, pharmacological prophylaxis is usually performed for at least 4 weeks.

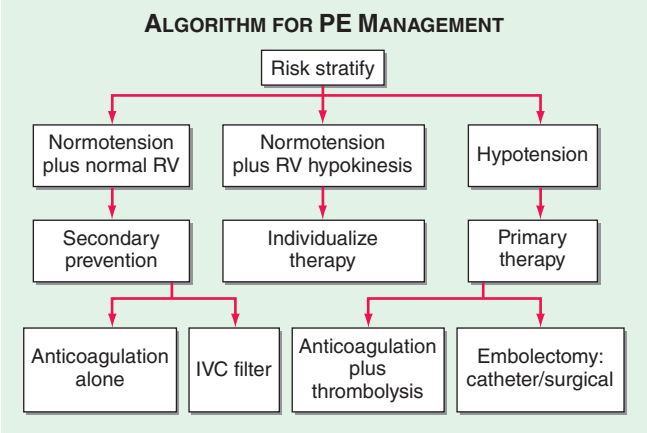


**FIGURE 133-2** Acute management of pulmonary thromboembolism.

For a more detailed discussion, see Goldhaber SZ: Deep Venous Thrombosis and Pulmonary Thromboembolism, Chap. 300, p. 1631, in HPIM-19.

# 134 Interstitial Lung Disease

Interstitial lung diseases (ILDs) are a group of >200 disease entities characterized by diffuse lung parenchymal abnormalities. ILDs can be classified into two major groups: (1) diseases associated with predominant inflammation and fibrosis, and (2) diseases with predominantly granulomatous reaction in interstitial or vascular areas (Table 134-1). ILDs are nonmalignant and noninfectious, and they are typically chronic. The differential diagnosis of ILDs often includes infections (e.g., atypical mycobacteria, fungi) and malignancy (e.g., lymphangitic carcinomatosis). One of the most common ILDs associated with a granulomatous reaction, sarcoidosis, is discussed in Chap. 166. Many ILDs are of unknown etiology; however, some ILDs are known to be associated with specific environmental exposures including asbestos, radiation therapy, and organic dusts.

## APPROACH TO THE PATIENT: Interstitial Lung Disease

*History*: Common presenting symptoms for pts with ILDs include dyspnea and nonproductive cough. Symptom onset and duration can assist in the differential

**TABLE 134-1 MAJOR CATEGORIES OF ALVEOLAR AND INTERSTITIAL INFLAMMATORY LUNG DISEASE**

| | |
|---|---|
| **Lung Response: Alveolitis, Interstitial Inflammation, and Fibrosis** | |
| **Known cause** | |
| Asbestos | Radiation |
| Fumes, gases | Aspiration pneumonia |
| Drugs (antibiotics, amiodarone, gold) and chemotherapy drugs | Residual of adult respiratory distress syndrome |
| Smoking-related | |
| Desquamative interstitial pneumonia | |
| Respiratory bronchiolitis-associated interstitial lung disease | |
| Langerhans cell granulomatosis (eosinophilic granulomatosis of the lung) | |
| **Unknown cause** | |
| Idiopathic interstitial pneumonias | Pulmonary alveolar proteinosis |
| Idiopathic pulmonary fibrosis (usual interstitial pneumonia) | Lymphocytic infiltrative disorders (lymphocytic interstitial pneumonitis associated with connective tissue disease) |
| | Eosinophilic pneumonias |
| Acute interstitial pneumonia (diffuse alveolar damage) | Lymphangioleiomyomatosis |
| | Amyloidosis |
| Cryptogenic organizing pneumonia (bronchiolitis obliterans with organizing pneumonia) | Inherited diseases |
| Nonspecific interstitial pneumonia | Tuberous sclerosis, neurofibromatosis, Niemann-Pick disease, Gaucher's disease, Hermansky-Pudlak syndrome |
| Connective tissue diseases | Gastrointestinal or liver diseases (Crohn's disease, primary biliary cirrhosis, chronic active hepatitis, ulcerative colitis) |
| Systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, systemic sclerosis, Sjögren's syndrome, polymyositis-dermatomyositis | Graft-versus-host disease (bone marrow transplantation; solid organ transplantation) |
| Pulmonary hemorrhage syndromes | |
| Goodpasture's syndrome, idiopathic pulmonary hemosiderosis, isolated pulmonary capillaritis | |

(*Continued*)

**TABLE 134-1 MAJOR CATEGORIES OF ALVEOLAR AND INTERSTITIAL INFLAMMATORY LUNG DISEASE (*CONTINUED*)**

| | |
|---|---|
| **Lung Response: Granulomatous** | |
| **Known cause** | |
| Hypersensitivity pneumonitis (organic dusts) | Inorganic dusts: beryllium, silica |
| **Unknown cause** | |
| Sarcoidosis | Bronchocentric granulomatosis |
| Granulomatous vasculitides | Lymphomatoid granulomatosis |
| Granulomatosis with polyangiitis (Wegener's), allergic granulomatosis of Churg-Strauss | |

diagnosis. Chronic symptoms (over months to years) are typically seen in most ILDs, including idiopathic pulmonary fibrosis (IPF), pneumoconioses, connective tissue diseases, and pulmonary Langerhans cell histiocytosis (PLCH or eosinophilic granuloma). Subacute symptoms (over weeks to months) can also be observed in many ILDs, especially in sarcoidosis, drug-induced ILDs, cryptogenic organizing pneumonitis (COP, also known as bronchiolitis obliterans with organizing pneumonia [BOOP]), and alveolar hemorrhage syndromes. Acute presentations are uncommon for ILDs but are typically observed with acute interstitial pneumonia (AIP), and they can also occur with eosinophilic pneumonia and hypersensitivity (HS) pneumonitis. Sudden onset of dyspnea can indicate a pneumothorax, which occurs in PLCH and tuberous sclerosis/lymphangioleiomyomatosis. Fatigue and weight loss are common in all ILDs. Episodic presentations also are unusual, but they are more typical for eosinophilic pneumonia, hypersensitivity pneumonitis, pulmonary hemorrhage, Churg-Strauss syndrome, and COP.

Age at presentation also can guide the differential diagnosis. IPF pts typically present at age >60, while sarcoidosis, PLCH, lymphangioleiomyomatosis (LAM), and connective tissue disease–related ILD often present between the ages of 20 and 40. LAM occurs exclusively in women, while IPF and ILD in rheumatoid arthritis (RA) occur more often in men. Cigarette smoking is a risk factor for several ILDs including IPF, PLCH, Goodpasture syndrome, pulmonary alveolar proteinosis (PAP), and respiratory bronchiolitis/desquamative interstitial pneumonia. Occupational exposures and hobbies can be important risk factors for many types of hypersensitivity pneumonitis as well as pneumoconioses. Previous medical treatment with radiation and drugs also should be assessed.

*Physical examination*: Tachypnea and bibasilar end-inspiratory crackles are commonly observed in inflammatory ILDs, but they are less frequent in granulomatous ILDs. Clubbing of the digits is observed in some pts with advanced ILD.

*Laboratory studies*: Antinuclear antibodies and rheumatoid factor at low titers are observed in some IPF pts without a connective tissue disorder. Specific serum antibodies can confirm exposure to relevant antigens in hypersensitivity pneumonitis, but they do not prove causation. Anti-GM-CSF antibodies are diagnostic of acquired PAP.

*Chest imaging*: Chest x-ray (CXR) does not typically provide a specific diagnosis but often raises the possibility of ILD by demonstrating a bibasilar reticular pattern. Upper-lung-zone predominance of nodular opacities is noted in several

ILDs, including PLCH, sarcoidosis, chronic hypersensitivity pneumonitis, and silicosis. High-resolution chest CT scans provide improved sensitivity for the early detection of ILDs and may be sufficiently specific to allow a diagnosis to be made in ILDs such as IPF, PLCH, and asbestosis. Honeycombing is indicative of advanced fibrosis.

*Pulmonary function testing*: Lung function measurements can assess the extent of pulmonary involvement in pts with ILD. Most ILDs produce a restrictive ventilatory defect with reduced total lung capacity. The forced expiratory volume in 1 s ($FEV_1$) and forced vital capacity (FVC) are typically reduced, but the ratio of $FEV_1$/FVC is usually normal to increased. Reduction in the diffusing capacity of the lung for carbon monoxide ($DL_{CO}$) is commonly observed. Cardiopulmonary exercise testing and 6-minute walk testing can be useful to detect exercise-induced hypoxemia and to monitor disease activity and response to treatment.

*Tissue and cellular examination*: In order to provide a specific diagnosis and assess disease activity, lung biopsy is often required. Bronchoscopy with transbronchial biopsies can be diagnostic in some ILDs, including sarcoidosis and eosinophilic pneumonia. In addition, bronchoscopy can assist by excluding chronic infections or lymphangitic carcinomatosis. However, the more extensive tissue samples provided by open lung biopsies, typically obtained by video-assisted thoracic surgery, are often required to establish a specific diagnosis. Evidence for diffuse end-stage disease, such as widespread honeycombing, or other major operative risks are relative contraindications to lung biopsy procedures.

## PRINCIPLES OF MANAGEMENT

If a causative agent can be identified (e.g., thermophilic actinomyces in hypersensitivity pneumonitis), cessation of exposure to that agent is imperative. Because the response to treatment among different ILDs is so variable, identification of treatable causes is essential. Glucocorticoids can be highly effective for eosinophilic pneumonias, COP, hypersensitivity pneumonitis (HP), acute radiation pneumonitis, and drug-induced ILD. Prednisone at 0.5–1.0 mg/kg per day is commonly given for 4–12 weeks, followed by a gradual tapering dose. On the other hand, glucocorticoids are usually not beneficial in IPF. Smoking cessation is essential, especially for smoking-related ILDs such as PLCH and respiratory bronchiolitis.

Supportive therapeutic measures include providing supplemental $O_2$ for pts with significant hypoxemia ($Pa_{O2}$ <55 mmHg at rest and/or with exercise). Pulmonary rehabilitation is often beneficial. For younger pts with end-stage ILD, lung transplantation should be considered.

## SELECTED INDIVIDUAL ILDS

### Idiopathic Pulmonary Fibrosis

IPF, which is also known as usual interstitial pneumonia (UIP), is the most common idiopathic interstitial pneumonia. Cigarette smoking is a risk factor for IPF. Common respiratory symptoms include exertional dyspnea and a nonproductive cough. Physical examination is notable for inspiratory crackles at the lung bases. Clubbing may occur. High-resolution chest CT scans show subpleural reticular opacities predominantly in the lower lung fields, which are associated with honeycombing in advanced disease. Surgical lung biopsy is usually required to confirm the diagnosis, although pts with classic UIP patterns on CT scan may not require a biopsy. IPF can include acute exacerbations characterized by accelerated clinical deterioration over days to weeks. IPF is poorly responsive to available

pharmacologic treatment, although recent studies have suggested benefit from pirfenidone and nintedanib.

## Nonspecific Interstitial Pneumonia

Nonspecific interstitial pneumonia (NSIP) is a histologic pattern that can be observed in connective tissue disease, drug-induced ILD, and chronic HP. NSIP is a subacute restrictive process with similar presentation to IPF. High-resolution CT (HRCT) shows bilateral ground-glass opacities, and honeycombing is rare. Unlike IPF, NSIP pts have a good prognosis and typically respond well to systemic glucocorticoid treatment.

## ILD Associated with Connective Tissue Disorders

Pulmonary manifestations may precede systemic manifestations of a connective tissue disorder. In addition to direct pulmonary involvement, it is necessary to consider complications of therapy (e.g., opportunistic infections), respiratory muscle weakness, esophageal dysfunction, and associated malignancies as contributors to pulmonary parenchymal abnormalities in pts with connective tissue disorders.

Progressive systemic sclerosis (scleroderma) commonly includes ILD as well as pulmonary vascular disease. Lung involvement tends to be highly resistant to available treatment.

In addition to pulmonary fibrosis (ILD), RA can involve a range of pulmonary complications, including pleural effusions, pulmonary nodules, and pulmonary vasculitis. ILD in RA pts is more common in men.

Systemic lupus erythematosus (SLE) also can involve a range of pulmonary complications, including pleural effusions, pulmonary vascular disease, pulmonary hemorrhage, and BOOP. Chronic, progressive ILD is not commonly observed.

Except for progressive systemic sclerosis, connective tissue-related ILD is typically treated with systemic glucocorticoids, often along with an immunosuppressive agent.

## Cryptogenic Organizing Pneumonia

When the BOOP pathologic pattern occurs without another primary pulmonary disorder, the term *cryptogenic organizing pneumonia* (*COP*) is used. COP may present with a flu-like illness. Recurrent and migratory pulmonary opacities are common. Glucocorticoid therapy is often effective.

## Desquamative Interstitial Pneumonia and Respiratory Bronchiolitis-Associated ILD

Desquamative interstitial pneumonia (DIP) includes extensive macrophage accumulation in intraalveolar spaces with minimal fibrosis. It is seen almost exclusively in cigarette smokers and improves with smoking cessation. Respiratory bronchiolitis-associated ILD is a subset of DIP that includes bronchial wall thickening, ground-glass opacities, and air trapping on HRCT; it also resolves in most pts after smoking cessation.

## Pulmonary Alveolar Proteinosis

PAP is a rare diffuse lung disease, with a male predominance, that involves the accumulation of lipoproteinaceous material in the distal airspaces, rather than a classic ILD. More common in males, PAP usually presents insidiously, with dyspnea, fatigue, weight loss, cough, and low-grade fever. Whole-lung lavage is often of therapeutic benefit.

## Pulmonary Infiltrates with Eosinophilia

Several disorders are characterized by pulmonary infiltrates and peripheral blood eosinophilia. Acute eosinophilic pneumonia involves fevers and diffuse

pulmonary eosinophilic infiltrates with severe hypoxemia. Chronic eosinophilic pneumonia is often in the differential diagnosis with other ILDs; it includes low-grade fever, cough, dyspnea, and weight loss, with a CXR notable for peripheral lung infiltrates. Eosinophilic pneumonias tend to be rapidly responsive to glucocorticoid therapy. Churg-Strauss syndrome, also known as eosinophilic granulomatosis with polyangiitis, occurs in asthmatics and includes eosinophilic vasculitis with multiorgan system involvement. Parasitic infections can cause Löffler syndrome, which includes migratory pulmonary infiltrates and self-limited clinical symptoms, and tropical eosinophilia. Multiple medications can also cause pulmonary eosinophilia.

## Alveolar Hemorrhage Syndromes

A variety of diseases can cause diffuse alveolar hemorrhage, including systemic vasculitic syndromes (e.g., granulomatosis with polyangiitis [Wegener's]), connective tissue diseases (e.g., SLE), and Goodpasture syndrome. Although typically an acute process, recurrent episodes can lead to pulmonary fibrosis. Hemoptysis may not occur initially in one-third of cases. CXR typically shows patchy or diffuse alveolar opacities. The DLCO may be increased. High doses of IV methylprednisolone are typically required, followed by gradual tapering of systemic steroid doses. Plasmapheresis may be effective for Goodpasture syndrome.

## Pulmonary Langerhans Cell Histiocytosis

PLCH is a smoking-related diffuse lung disease that typically affects men 20–40 years of age. Presenting symptoms often include cough, dyspnea, chest pain, weight loss, and fever. Pneumothorax occurs in 25% of pts. High-resolution chest CT scan reveals upper-zone-predominant nodular opacities and thin-walled cysts, which are virtually diagnostic of this disorder. Smoking cessation is the key therapeutic intervention.

## Hypersensitivity Pneumonitis

HP is an inflammatory lung disorder caused by repeated inhalation of an organic antigen in a susceptible individual. Many different antigens have been implicated. Clinical presentations can be acute, with cough, fever, malaise, and dyspnea developing within 4–8 h after exposure; subacute, with cough and dyspnea that can become progressively worse over weeks; and chronic, which can appear similar to IPF. Serum precipitins can be measured as an indicator of an environmental exposure. Although helpful in implicating specific agents, the presence of a specific serum precipitin is not diagnostic since many exposed individuals without HP will have such precipitins; false-negative results can also occur. Diagnosis is made based on symptoms, physical findings, pulmonary function tests (restrictive or obstructive pattern), and radiographic studies (chest CT scans typically show ground-glass opacification in acute and subacute forms) that are consistent with HP; history of exposure to a recognized antigen; and presence of an antibody to that antigen. In some cases, lung biopsy (transbronchial or open lung) may be required to confirm the diagnosis. Treatment involves avoiding exposure to the causative antigen; systemic corticosteroids may be required in subacute or chronic HP.

For a more detailed discussion, see King TE Jr: Interstitial Lung Diseases, Chap. 315, p. 1708; Akuthota P, Wechsler ME: Hypersensitivity Pneumonitis and Pulmonary Infiltrates with Eosinophilia, Chap. 310, p. 1681, in HPIM-19.

# 135 Diseases of the Pleura and Mediastinum

## PLEURAL EFFUSION

Pleural effusion is defined as excess fluid accumulation in the pleural space. The two major classes of pleural effusions are transudates, which are caused by systemic influences on pleural fluid formation or resorption, and exudates, which are caused by local influences on pleural fluid formation and resorption. Common causes of transudative effusions are left ventricular heart failure, cirrhosis, and nephrotic syndrome. Common causes of exudative effusions are bacterial pneumonia, malignancy, viral infection, and pulmonary embolism. A more comprehensive list of the etiologies of transudative and exudative pleural effusions is provided in Table 135-1. Additional diagnostic procedures are indicated with exudative effusions to define the cause of the local disease.

Exudates fulfill at least one of the following three criteria: high pleural fluid/serum protein ratio (>0.5), pleural fluid lactate dehydrogenase (LDH) greater than two-thirds of the laboratory normal upper limit for serum LDH, or pleural/serum LDH ratio >0.6. Transudative effusions typically do not meet any of these criteria. However, these criteria misidentify about 25% of transudates as exudates. For exudative effusions, pleural fluid should also be tested for pH, glucose, white blood cell count with differential, microbiologic studies, cytology, and amylase. An algorithm for determining the etiology of a pleural effusion is presented in Fig. 135-1.

**TABLE 135-1 DIFFERENTIAL DIAGNOSES OF PLEURAL EFFUSIONS**

**Transudative Pleural Effusions**

1. Congestive heart failure
2. Cirrhosis
3. Pulmonary embolism (Note: Effusion usually is exudative)
4. Nephrotic syndrome
5. Peritoneal dialysis
6. Superior vena cava obstruction
7. Myxedema
8. Urinothorax

**Exudative Pleural Effusions**

1. Neoplastic diseases
   a. Metastatic disease
   b. Mesothelioma
2. Infectious diseases
   a. Bacterial infections
   b. Tuberculosis
   c. Fungal infections
   d. Viral infections
   e. Parasitic infections

(*Continued*)

**TABLE 135-1 DIFFERENTIAL DIAGNOSES OF PLEURAL EFFUSIONS (*CONTINUED*)**

3. Pulmonary embolism
4. Gastrointestinal disease
   a. Esophageal perforation
   b. Pancreatic disease
   c. Intraabdominal abscess
   d. Diaphragmatic hernia
   e. After abdominal surgery
   f. Endoscopic variceal sclerotherapy
   g. After liver transplant
5. Collagen-vascular diseases
   a. Rheumatoid pleuritis
   b. Systemic lupus erythematosus
   c. Drug-induced lupus
   d. Immunoblastic lymphadenopathy
   e. Sjögren's syndrome
   f. Granulomatosis with polyangiitis (Wegener's)
   g. Churg-Strauss syndrome
6. Post-coronary artery bypass surgery
7. Asbestos exposure
8. Sarcoidosis
9. Uremia
10. Meigs' syndrome
11. Yellow nail syndrome
12. Drug-induced pleural disease
    a. Nitrofurantoin
    b. Dantrolene
    c. Methysergide
    d. Bromocriptine
    e. Procarbazine
    f. Amiodarone
    g. Dasatinib
13. Trapped lung
14. Radiation therapy
15. Post-cardiac injury syndrome
16. Hemothorax
17. Iatrogenic injury
18. Ovarian hyperstimulation syndrome
19. Pericardial disease
20. Chylothorax

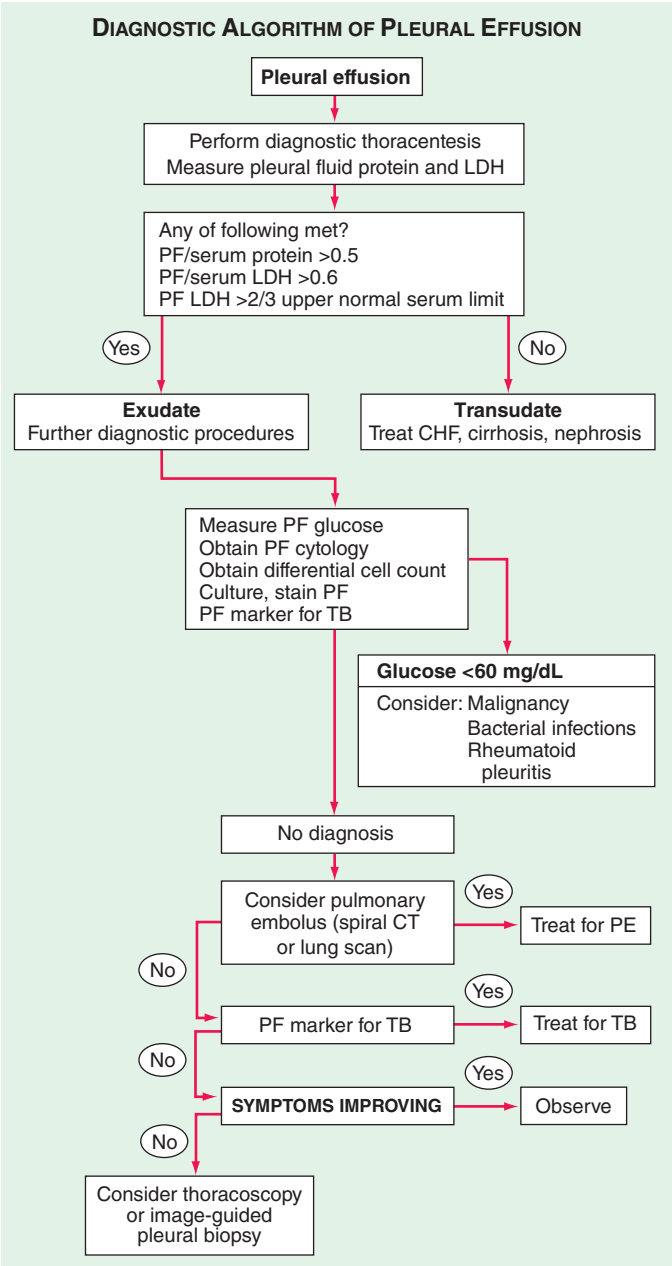


**FIGURE 135-1** Approach to the diagnosis of pleural effusions. PE, pulmonary embolism; PF, pleural fluid; TB, tuberculosis.

## PNEUMOTHORAX

Pneumothorax (Ptx) is defined as gas in the pleural space. Spontaneous Ptx occurs without trauma to the thorax. Primary spontaneous Ptx occurs in the absence of underlying lung disease and typically results from apical pleural blebs. Simple aspiration may be adequate treatment for an initial primary spontaneous Ptx, but recurrence typically requires thoracoscopic intervention. Secondary spontaneous Ptx occurs in the setting of underlying lung disease, most commonly chronic obstructive pulmonary disease. Chest tube placement is typically required for secondary spontaneous Ptx; thoracoscopy and/or pleurodesis (with pleural abrasion or a sclerosing agent) should also be considered.

Traumatic Ptx, resulting from either penetrating or nonpenetrating chest trauma, usually requires chest tube placement. Iatrogenic Ptx can occur from transthoracic needle biopsy, thoracentesis, placement of a central venous catheter, or transbronchial biopsy. Treatment with $O_2$ or aspiration is often adequate for iatrogenic Ptx, but chest tube placement may be required. Tension Ptx can result from trauma or mechanical ventilation. Positive pleural pressure in mechanical ventilation can rapidly lead to a tension Ptx with reduced cardiac output. Urgent treatment is required, either with a chest tube or, if not immediately available, with a large-bore needle inserted into the pleural space through the second anterior intercostal space.

## MEDIASTINAL DISEASE

### Mediastinitis

Mediastinitis can be an acute or chronic process. Acute mediastinitis can result from esophageal perforation or after cardiac surgery with median sternotomy. Esophageal perforation can occur spontaneously or iatrogenically; surgical exploration of the mediastinum, repair of the esophageal perforation, and drainage of the pleural space and mediastinum are required. Mediastinitis after median sternotomy typically presents with wound drainage and is diagnosed by mediastinal needle aspiration. Treatment requires immediate drainage, debridement, and IV antibiotics.

### Mediastinal Masses

Different types of mediastinal masses are found in the anterior, middle, and posterior mediastinal compartments. The most common mass lesions in the anterior mediastinum are thymomas, lymphomas, teratomas, and thyroid lesions. In the middle mediastinum, vascular masses, enlarged lymph nodes (e.g., metastatic cancer or granulomatous disease), and bronchogenic or pleuropericardial cysts are found. Posterior mediastinal masses include neurogenic tumors, gastroenteric cysts, and esophageal diverticula.

Chest CT scans are invaluable for evaluating mediastinal masses. Biopsy procedures are typically required to diagnose mediastinal masses; needle biopsy procedures (e.g., percutaneous or bronchoscopy), mediastinoscopy, and thoracoscopy are potential options.

For a more detailed discussion, see Light RW: Disorders of the Pleura, Chap. 316, p. 1716; Light RW: Disorders of the Mediastinum, Chap. 317, p. 1719, in HPIM-19.

# 136 Disorders of Ventilation

## DEFINITION

Ventilatory disorders, reflected by abnormalities in $PaCO_2$, include alterations in $CO_2$ production, minute ventilation, or respiratory system dead space. Many diseases can cause acute elevations in $CO_2$ production; chronic ventilatory disorders typically relate to inappropriate minute ventilation or dead space fraction.

## HYPOVENTILATION

### ETIOLOGY

Chronic hypoventilation can result from parenchymal lung diseases, chest wall abnormalities (e.g., severe kyphoscoliosis), sleep-disordered breathing, neuromuscular diseases, and abnormal respiratory drive. Obesity-hypoventilation syndrome (OHS) is diagnosed by body mass index ≥30 kg/m$^2$ and $PaCO_2$ >45 mmHg in the absence of other causes of hypercapnia. Sleep-disordered breathing, typically obstructive sleep apnea, is seen in most OHS pts. Central hypoventilation syndrome is a rare disorder that includes a failure of the normal respiratory response to hypoxemia and/or hypercapnia.

### CLINICAL ASSESSMENT

Key symptoms of hypoventilation can include exertional dyspnea, orthopnea, daytime somnolence, morning headache, and anxiety. Parenchymal lung diseases, such as chronic obstructive pulmonary disease and interstitial lung disease, often include dyspnea and cough. Sleep-disordered breathing includes daytime somnolence, snoring, and fragmented sleep. Orthopnea is common in neuromuscular disorders, although weakness of the extremities or other muscle groups often precedes respiratory system muscular weakness. Hypoventilation related to neuromuscular and chest wall disorders typically begins with nocturnal hypoventilation and progresses to daytime hypercapnia. Chronic narcotic use and hypothyroidism can lead to reduced respiratory drive.

Physical examination, chest radiographic studies (CXR and possibly chest CT), and pulmonary function tests reveal most lung parenchymal and chest wall causes of hypoventilation. Measurements of maximal inspiratory and expiratory pressures or forced vital capacity can assess and monitor respiratory muscle strength. Polysomnography to assess for sleep-disordered breathing should also be considered. When pts have hypercapnia with normal pulmonary function, normal respiratory muscle strength, and normal alveolar-arterial $PO_2$ difference, respiratory drive abnormalities may be present, which can be revealed by polysomnography. Laboratory findings include increased $PaCO_2$ and often reduced $PaO_2$ as well. Compensatory increases in plasma bicarbonate levels and normal pH are seen in chronic hypoventilation. Eventually, pulmonary hypertension and cor pulmonale can develop. In central hypoventilation syndrome, hypercapnia worsens substantially during sleep.

## TREATMENT HYPOVENTILATION

In all forms of hypoventilation, supplemental oxygen should be given to correct hypoxemia. OHS is treated with weight reduction and nocturnal noninvasive positive pressure ventilation (NIPPV). Continuous positive airway pressure (CPAP)

during sleep is adequate treatment for many OHS pts, but others require bilevel positive airway pressure (BiPAP).

Noninvasive positive pressure ventilation during sleep can provide ventilatory support and treat sleep apnea associated with neuromuscular disorders, chest wall disorders, and central hypoventilation. With progressive neuromuscular disorders, full-time mechanical ventilatory support is often required. Pts with respiratory drive disorders may benefit from phrenic nerve or diaphragm pacing.

## HYPERVENTILATION

### ETIOLOGY

Hyperventilation is caused by ventilation in excess of requirements based on $CO_2$ production, leading to a reduced $PaCO_2$. Although anxiety can contribute to the initiation and progression of hyperventilation, hyperventilation is not always related to anxiety. Hyperventilation can precede systemic illnesses such as diabetic ketoacidosis.

### CLINICAL ASSESSMENT

Symptoms of chronic hyperventilation can include dyspnea, paresthesias, headache, tetany, visual disturbances, and atypical chest pain. Laboratory findings of chronic hyperventilation include a reduced $PaCO_2$, but low serum bicarbonate level and near normal pH on arterial blood gas analysis.

**TREATMENT HYPERVENTILATION**

Treatment of chronic hyperventilation is problematic. Identification of initiating factors and excluding alternative diagnoses can be helpful.

For a more detailed discussion, see McConville JF, Mokhlesi B, Solway J: Disorders of Ventilation, Chap. 318, p. 1720, in HPIM-19.

# 137 Sleep Apnea

### DEFINITION AND ETIOLOGY

Sleep apnea is defined by the presence of at least five episodes per hour of apnea (no airflow for ≥10 seconds) and/or hypopnea (reduction in airflow by at least 30% from baseline for ≥10 seconds accompanied by oxygen desaturation or arousal from sleep). Obstructive sleep apnea/hypopnea syndrome (OSAHS) is caused by upper airway closure during inspiration, punctuated by brief arousals that terminate apneic episodes. Risk factors for OSAHS include obesity, craniofacial factors such as micrognathia, family history of OSAHS, and male sex. Hypothyroidism and acromegaly are systemic diseases associated with OSAHS. OSAHS increases the risk of multiple

cardiovascular conditions, including coronary artery disease, heart failure, stroke, and arrhythmias.

Central sleep apnea (CSA) is characterized by respiratory pauses during sleep related to absence of respiratory effort. CSA is less common than OSAHS but may occur in conjunction with it. CSA is commonly found in heart failure and stroke pts, but may also occur from opioid medications and hypoxia (e.g., breathing at high altitudes).

## CLINICAL ASSESSMENT

Key symptoms of OSAHS include daytime somnolence and nocturnal breathing disturbances (loud snoring, snorting, gasping, or breathing pauses). Other symptoms may include dry mouth, nocturia, morning headaches, and difficulty concentrating. Sleeping partners can provide essential historical information. Depression and hypertension are associated with OSAHS. Differential diagnosis of OSAHS includes insufficient amount of sleep, somnolence related to shift work, depression, drug effects (both stimulants and sedatives), narcolepsy, and idiopathic hypersomnolence.

Severity of OSAHS is based on the frequency of breathing disturbances (apnea-hypopnea index), duration of apneas and hypopneas, amount of oxygen desaturation during respiratory disturbances, degree of sleep fragmentation, and intensity of daytime somnolence.

Physical examination should include assessment of body mass index, jaw and upper airway structure, and blood pressure. Potentially related systemic illnesses, including acromegaly and hypothyroidism, should be considered.

Diagnostic testing often includes a polysomnogram in a sleep laboratory. However, home sleep studies without neurophysiologic monitoring may be used for screening. Significant daytime somnolence with a negative home screening study should be followed by a full polysomnogram.

## TREATMENT SLEEP APNEA

In pts with OSAHS, efforts to reduce weight in obese pts, limit alcohol use, optimize sleep duration, regulate sleep schedules, treat nasal allergies, and carefully withdraw sedative medications should be pursued.

The primary therapy for OSAHS is continuous positive airway pressure (CPAP), delivered through a nasal or nasal-oral mask. Selecting a comfortable mask delivery system and titrating the appropriate amount of CPAP are essential. Airway drying related to CPAP can be reduced by including a heated humidification component in the CPAP system. Alternative OSAHS therapies include mandibular repositioning splints (oral devices), which hold the jaw and tongue forward to widen the pharyngeal airway. These devices are typically used for mild OSAHS pts or pts who do not tolerate CPAP. Several types of surgical procedures have been used in OSAHS, including bariatric surgery in obese pts, tonsillectomy, jaw advancement surgery, and pharyngeal surgery. Tracheostomy is curative since it bypasses the upper airway obstruction site, but it is rarely used. No drugs have been proven to reduce apneic events.

Treatment of CSA involves managing any predisposing conditions, such as congestive heart failure. Adaptive servoventilation, which provides variable inspiratory ventilatory support in response to apneas and hypopneas, may be helpful in CSA.

For a more detailed discussion, see Wellman A, Redline S: Sleep Apnea, Chap. 319, p. 1723, in HPIM-19.

# 138 Acute Renal Failure

## DEFINITION

Acute renal failure (ARF) or acute kidney injury (AKI), defined as a measurable increase in the serum creatinine (Cr) concentration (usually relative increase of 50% or absolute increase by 44–88 μmol/L [0.5–1.0 mg/dL]), occurs in ~5–7% of hospitalized pts. It is associated with a substantial increase in in-hospital mortality and morbidity. AKI can be anticipated in some clinical circumstances (e.g., after radiocontrast exposure or major surgery), and there are no specific pharmacologic therapies proven helpful at preventing or reversing the condition. Maintaining optimal renal perfusion and intravascular volume appears to be important in most clinical circumstances; important cofactors in AKI include hypovolemia and drugs that interfere with renal perfusion and/or glomerular filtration (nonsteroidal anti-inflammatory drugs [NSAIDs], angiotensin-converting enzyme [ACE] inhibitors, and angiotensin receptor blockers).

## DIFFERENTIAL DIAGNOSIS

The separation into three broad categories (prerenal, intrinsic renal, and postrenal failure) is of considerable clinical utility (Table 138-1). *Prerenal failure* is most common among hospitalized pts. It may result from true volume depletion (e.g., diarrhea, vomiting, GI or other hemorrhage) or "arterial underfilling," i.e., reduced renal perfusion in the setting of adequate or excess blood volume. Reduced renal perfusion may be seen in congestive heart failure (CHF) (due to reduced cardiac output and/

**TABLE 138-1 COMMON CAUSES OF ACUTE KIDNEY INJURY**

| **Prerenal** |
|---|
| Volume depletion |
| Blood loss |
| GI fluid loss (e.g., vomiting, diarrhea) |
| Overzealous diuretic use |
| Volume overload with reduced renal perfusion |
| Congestive heart failure |
| Low-output with systolic dysfunction |
| "High-output" (e.g., anemia, thyrotoxicosis) |
| Hepatic cirrhosis |
| Severe hypoproteinemia |
| Renovascular disease |
| Drugs |
| NSAIDs, cyclosporine, tacrolimus, ACE inhibitors, ARBs, cisplatin, aminoglycosides |
| Other |
| Hypercalcemia, "third spacing" (e.g., pancreatitis, systemic inflammatory response), hepatorenal syndrome |

(*Continued*)

**TABLE 138-1 COMMON CAUSES OF ACUTE KIDNEY INJURY (*CONTINUED*)**

| **Intrinsic** |
|---|
| ATN |
| Hypotension or shock, prolonged prerenal azotemia, postoperative sepsis syndrome, rhabdomyolysis, hemolysis, drugs |
| Radiocontrast, aminoglycosides, cisplatin |
| Other tubulointerstitial disease |
| Allergic interstitial nephritis |
| Pyelonephritis (bilateral, or unilateral in single functional kidney) |
| Heavy metal poisoning |
| Atheroembolic disease—after vascular procedures, thrombolysis, or anticoagulation |
| Glomerulonephritis |
| 1. ANCA-associated: granulomatosis with polyangiitis (GPA), idiopathic pauci-immune GN, PAN |
| 2. Anti-GBM disease; isolated or with pulmonary involvement (Goodpasture's syndrome) |
| 3. Immune complex–mediated |
| Subacute bacterial endocarditis, SLE, cryoglobulinemia (with or without hepatitis C infection), postinfectious GN (classically poststreptococcal) |
| IgA nephropathy and Henoch-Schönlein purpura |
| Glomerular endotheliopathies |
| Thrombotic microangiopathy, malignant hypertension, scleroderma, antiphospholipid syndrome, preeclampsia |
| **Postrenal (urinary tract obstruction)** |
| Bladder neck obstruction, bladder calculi |
| Prostatic hypertrophy |
| Ureteral obstruction due to compression |
| Pelvic or abdominal malignancy, retroperitoneal fibrosis |
| Nephrolithiasis |
| Papillary necrosis with obstruction |

***Abbreviations:*** ANCA, antineutrophil cytoplasmic antibody; ARBs, angiotensin receptor blockers; ATN, acute tubular necrosis; GBM, glomerular basement membrane; GN, glomerulonephritis; GPA, granulomatosis with polyangiitis; PAN, polyarteritis nodosa.

or potent vasodilator therapy), hepatic cirrhosis (due mostly to peripheral vasodilation and arteriovenous shunting), nephrotic syndrome and other states of severe hypoproteinemia (total serum protein <54 g/L [<5.4 g/dL]), and renovascular disease (because of fixed stenosis at the level of the main renal artery or large branch vessels). Several drugs can reduce renal perfusion, most notably NSAIDs. ACE inhibitors and angiotensin II receptor antagonists may reduce glomerular filtration rate but do not tend to reduce renal perfusion.

Causes of *intrinsic renal failure* depend on the clinical setting. Among hospitalized pts, especially on surgical services or in intensive care units, acute tubular necrosis (ATN) is the most common diagnosis. A well-defined ischemic event or toxic exposure (e.g., aminoglycoside therapy) may lead to in-hospital ATN. Alternatively, pts may be admitted to the hospital with ATN associated with rhabdomyolysis; common predisposing factors in rhabdomyolysis include alcoholism, hypokalemia, and various drugs (e.g., statins). Allergic interstitial nephritis, usually due to antibiotics

(e.g., penicillins, cephalosporins, sulfa drugs, quinolones, and rifampin), or NSAIDs, may also be responsible. Radiographic contrast dyes may cause AKI in pts with preexisting kidney disease; the risk is substantially higher in diabetics with chronic kidney disease. Coronary angiography, other vascular procedures, thrombolysis, or anticoagulation may lead to atheroemboli, which cause AKI due to both hemodynamic and inflammatory effects; livedo reticularis, embolic phenomena with preserved peripheral pulses, and eosinophilia are important clues to this diagnosis. Acute glomerulonephritis (Chap. 142) and thrombotic microangiopathies may also cause AKI. Thrombotic microangiopathies can be clinically subdivided into renal-limited forms (e.g., *Escherichia coli*–associated hemolytic uremic syndrome [HUS]) and systemic forms (e.g., thrombotic thrombocytopenic purpura [TTP]). "Atypical HUS," occurring in the absence of HUS-associated bacterial toxins, is associated with hereditary mutations in complement proteins or complement regulatory proteins, leading to exaggerated endothelial sensitivity to complement-mediated cytolysis. A variety of drugs can cause thrombotic microangiopathies, including calcineurin inhibitors (cyclosporine and tacrolimus), quinine, antiplatelet agents (e.g., ticlopidine), inhibitors of the action of vascular endothelial growth factor (VEGF), and chemotherapeutics (e.g., mitomycin C and gemcitabine). Important associated disorders in TTP include HIV infection, bone marrow transplantation, systemic lupus erythematosus (SLE), and antiphospholipid syndrome.

*Postrenal failure* is due to urinary tract obstruction, which is also more common among ambulatory rather than hospitalized pts. More common in men than women, it is most often caused by ureteral or urethral blockade. Occasionally, stones, sloughed renal papillae, or malignancy (primary or metastatic) may cause more proximal obstruction.

## CHARACTERISTIC FINDINGS AND DIAGNOSTIC WORKUP

All pts with AKI manifest some degree of azotemia (increased blood urea nitrogen [BUN] and Cr). Other clinical features depend on the etiology of renal disease. Pts with *prerenal azotemia* due to volume depletion usually demonstrate orthostatic hypotension, tachycardia, low jugular venous pressure, and dry mucous membranes. Pts with prerenal azotemia and CHF ("cardiorenal syndrome") may show jugular venous distention, an $S_3$ gallop, and peripheral and pulmonary edema. Therefore, the physical examination is critical in the workup of pts with prerenal AKI. In general, the BUN/Cr ratio tends to be high (>20:1), more so with volume depletion and CHF than with cirrhosis. The uric acid may also be disproportionately elevated in noncirrhotic prerenal states (due to increased proximal tubular absorption). Urine chemistries tend to show low urine [$Na^+$] (<10–20 mmol/L, <10 with hepatorenal syndrome) and a fractional excretion of sodium ($FE_{Na^+}$) of <1% (Table 138-2). The urinalysis (UA) typically shows hyaline and a few granular casts, without cells or cellular casts. Renal ultrasonography is usually normal.

Pts with *intrinsic renal disease* present with varying complaints. Glomerulonephritis (GN) is often accompanied by hypertension and mild to moderate edema (associated with Na retention and proteinuria, and sometimes with gross hematuria). An antecedent prodromal illness and/or prominent extrarenal symptoms and signs may occur if GN occurs in the context of a systemic illness, e.g., vasculitis or SLE; these may include hemoptysis or pulmonary hemorrhage (vasculitis and Goodpasture's syndrome), arthralgias/arthritis (vasculitis or SLE), serositis (SLE), and unexplained sinusitis (vasculitis). The urine chemistries may be indistinguishable from those in pts with prerenal failure; in fact, some pts with GN have renal hypoperfusion (due to glomerular inflammation and ischemia) with resultant hyperreninemia leading to acute volume expansion and hypertension. The urine sediment can be very helpful in these cases. Red blood cell (RBC), white blood cell (WBC), and cellular casts are characteristic of GN; RBC casts are rarely seen in other conditions (i.e., they are highly specific). In the setting of inflammatory nephritis (GN or interstitial

**TABLE 138-2 URINE DIAGNOSTIC INDICES IN DIFFERENTIATION OF PRERENAL VERSUS INTRINSIC RENAL AZOTEMIA**

| Diagnostic Index | Typical Findings | |
|---|---|---|
| | Prerenal Azotemia | Intrinsic Renal Azotemia |
| Fractional excretion of sodium (%)[a] $U_{Na} \times P_{Cr}/P_{Na} \times U_{Cr} \times 100$ | <1 | >1 |
| Urine sodium concentration (mmol/L) | <10 | >20 |
| Urine creatinine to plasma creatinine ratio | >40 | >20 |
| Urine urea nitrogen to plasma urea nitrogen ratio | >8 | <3 |
| Urine specific gravity | >1.018 | <1.015 |
| Urine osmolality (mosmol/kg $H_2O$) | >500 | <300 |
| Plasma BUN/creatinine ratio | >20 | <10–15 |
| Renal failure index $U_{Na}/U_{Cr}/P_{Cr}$ | <1 | >1 |
| Urinary sediment | Hyaline casts | Muddy brown granular casts |

[a]Most sensitive indices.

***Abbreviations:*** $P_{Cr}$, plasma creatinine concentration; $P_{Na}$, plasma sodium concentration; $U_{Cr}$, urine creatinine concentration; $U_{Na}$, urine sodium concentration.

nephritis, see below), there may be increased renal echogenicity on ultrasonography. Unlike pts with GN, pts with interstitial diseases are less likely to have hypertension or proteinuria; a notable exception is NSAID-associated acute interstitial nephritis, which can be accompanied by proteinuria due to an associated minimal-change glomerular lesion. Hematuria and pyuria may present on UA. The classic sediment finding in allergic interstitial nephritis is a predominance (>10%) of urinary eosinophils with Wright's or Hansel's stain; however, urinary eosinophils can be increased in several other causes of AKI, such that measurement of urine eosinophils has no diagnostic utility in renal disease. WBC casts may also be seen, particularly in cases of pyelonephritis.

The urinary sediment of pts with ischemic or toxic ATN will characteristically contain pigmented "muddy-brown" granular casts and casts containing tubular epithelial cells; free tubular epithelial cells can also be seen. The $FE_{Na}$ is typically >1% in ATN, but may be <1% in pts with milder, nonoliguric ATN (e.g., from rhabdomyolysis) and in pts with underlying "prerenal" disorders, such as CHF or cirrhosis.

Pts with *postrenal* AKI due to urinary tract obstruction are usually less severely ill than pts with prerenal or intrinsic renal disease, and their presentation may be delayed until azotemia is markedly advanced (BUN >54 μmol/L [150 mg/dL], Cr >1060–1325 μmol/L [12–15 mg/dL]). An associated impairment of urinary concentrating ability often "protects" the pt from complications of volume overload. Urinary electrolytes typically show an $FE_{Na}$ >1%, and microscopic examination of the urinary sediment is usually bland. Ultrasonography is the key initial diagnostic tool. More than 90% of pts with postrenal AKI show obstruction of the urinary collection system on ultrasound (e.g., dilated ureter, calyces); false negatives include hyperacute obstruction and encasement of the ureter and/or kidney by tumor or of the ureter by retroperitoneal fibrosis, functionally obstructing urinary outflow without structural dilation. Other imaging techniques, such as a furosemide renogram (MAG3 nuclear

medicine study), may be required to define better the presence or absence of obstructive uropathy.

## TREATMENT ACUTE RENAL FAILURE

Treatment should focus on providing etiology-specific supportive care. For example, pts with prerenal failure due to GI fluid loss may experience relatively rapid correction of AKI after the administration of IV fluid to expand volume. The same treatment in prerenal pts with CHF would be counterproductive; in this case, treatment of the underlying disease with vasodilators and/or inotropic agents would more likely be of benefit.

There are relatively few intrinsic renal causes of AKI for which there is safe and effective therapy. GN associated with vasculitis or SLE may respond to high-dose glucocorticoids and cytotoxic agents (e.g., cyclophosphamide); plasmapheresis and plasma exchange may be useful in other selected circumstances (e.g., Goodpasture's syndrome and HUS/TTP, respectively). Antibiotic therapy may be sufficient for the treatment of AKI associated with pyelonephritis or endocarditis. There are conflicting data regarding the utility of glucocorticoids in allergic interstitial nephritis. Many practitioners advocate their use with clinical evidence of progressive renal insufficiency despite discontinuation of the offending drug, or with biopsy evidence of potentially reversible, severe disease.

The treatment of urinary tract obstruction often involves consultation with a urologist. Interventions as simple as Foley catheter placement or as complicated as multiple ureteral stents and/or nephrostomy tubes may be required.

### DIALYSIS FOR AKI AND RECOVERY OF RENAL FUNCTION

Most cases of community- and hospital-acquired AKI resolve with conservative supportive measures, time, and patience. If nonprerenal AKI continues to progress, dialysis must be considered. The traditional indications for dialysis—volume overload refractory to diuretic agents; hyperkalemia; encephalopathy not otherwise explained; pericarditis, pleuritis, or other inflammatory serositis; and severe metabolic acidosis, compromising respiratory or circulatory function—can seriously compromise recovery from acute nonrenal illness. Therefore, dialysis should generally be provided in advance of these complications. The inability to provide requisite fluids for antibiotics, inotropes and other drugs, and/or nutrition should also be considered an indication for acute dialysis.

Dialytic options for AKI include (1) intermittent hemodialysis (IHD), (2) peritoneal dialysis (PD), and (3) continuous renal replacement therapy (CRRT, i.e., continuous arteriovenous or venovenous hemodiafiltration). Most pts are treated with IHD. It is unknown whether conventional thrice-weekly hemodialysis is sufficient or more frequent treatments are required. Few centers rely on PD for management of AKI (risks include infection associated with intraperitoneal catheter insertion and respiratory compromise due to abdominal distention). At some centers, CRRT is prescribed only in pts intolerant of IHD, usually because of hypotension; other centers use it as the modality of choice for pts in intensive care units. Hybrid hemodialysis techniques, such as slow low-efficiency dialysis (SLED), are equally effective and may be used in centers in which CRRT is not employed.

For a more detailed discussion, see Liu KD, Chertow GM: Dialysis in the Treatment of Acute Renal Failure, Chap. 336, p. 1822, in HPIM-19.

# 139 Chronic Kidney Disease and Uremia

## EPIDEMIOLOGY

The prevalence of chronic kidney disease (CKD), generally defined as a long-standing, irreversible impairment of kidney function, is substantially greater than the number of pts with end-stage renal disease (ESRD), now ≥500,000 in the United States. There is a spectrum of disease related to decrements in renal function; clinical and therapeutic issues differ greatly depending on whether the glomerular filtration rate (GFR) reduction is moderate (stage 3 CKD, 30–59 mL/min per 1.73 $m^2$) (see Table 46-1), severe (stage 4 CKD, 15–29 mL/min per 1.73 $m^2$), or "end-stage renal disease" (stage 5 CKD, <15 mL/min per 1.73 $m^2$). Dialysis is usually required once GFR <10 mL/min per 1.73 $m^2$. Common causes of CKD are outlined in Table 139-1.

## DIFFERENTIAL DIAGNOSIS

The first step in the differential diagnosis of CKD is establishing its chronicity, i.e., disproving a major acute component. The two most common means of determining disease chronicity are the history and prior laboratory data (if available) and the renal ultrasound, which is used to measure kidney size. In general, kidneys that have shrunk (<10–11.5 cm, depending on body size) are more likely affected by chronic disease. While reasonably specific (few false positives), reduced kidney size is only a moderately sensitive marker for CKD, i.e., there are several relatively common conditions in which kidney disease may be chronic without any reduction in renal size. Diabetic nephropathy, HIV-associated nephropathy, and infiltrative diseases such as multiple myeloma or amyloidosis may in fact be associated with relatively large kidneys despite chronicity. Renal biopsy, although rarely performed in pts with CKD, is a more reliable means of proving chronicity; a predominance of glomerulosclerosis or interstitial fibrosis argues strongly for chronic disease. Hyperphosphatemia, anemia, and other laboratory abnormalities are not reliable indicators in distinguishing acute from chronic disease.

Once chronicity has been established, clues from the physical examination, laboratory panel, and urine sediment evaluation can be used to determine etiology. A detailed history will identify important comorbid conditions, such as diabetes, HIV seropositivity, or peripheral vascular disease. The family history is paramount in the workup of autosomal dominant polycystic kidney disease or hereditary nephritis (Alport's syndrome). An occupational history may reveal exposure to environmental

**TABLE 139-1 COMMON CAUSES OF CHRONIC RENAL FAILURE**

| |
|---|
| Diabetic nephropathy |
| Hypertensive nephropathy[a] |
| Glomerulonephritis |
| Renovascular disease (ischemic nephropathy) |
| Polycystic kidney disease |
| Reflux nephropathy and other congenital renal diseases |
| Interstitial nephritis, including analgesic nephropathy |
| HIV-associated nephropathy |
| Transplant allograft failure ("chronic rejection") |

[a]Often diagnosis of exclusion; very few pts undergo renal biopsy; may be occult renal disease with hypertension.

toxins or culprit drugs (including over-the-counter agents, such as analgesics or Chinese herbs).

Physical examination may demonstrate abdominal masses (i.e., polycystic kidneys), diminished pulses or femoral/carotid bruits (i.e., atherosclerotic peripheral vascular disease), or abdominal or femoral bruits (i.e., renovascular disease). The history and examination may also yield important data regarding severity of disease. Excoriations (uremic pruritus), pallor (anemia), muscle wasting, and a nitrogenous fetor are all signs of advanced CKD, as are pericarditis, pleuritis, and asterixis, complications of particular concern that usually prompt the initiation of dialysis.

### Laboratory Findings

Serum and urine laboratory findings typically provide additional information useful in determining the etiology and severity of CKD; serial studies determine the pace of progression and/or whether the renal failure is in fact acute. Heavy proteinuria (>3.5 g/d), hypoalbuminemia, hypercholesterolemia, and edema suggest nephrotic syndrome (Chap. 142). Diabetic nephropathy, membranous nephropathy, focal segmental glomerulosclerosis, minimal change disease, amyloid, and HIV-associated nephropathy are principal causes. Proteinuria may decrease slightly with decreasing GFR, but rarely to normal levels. Hyperkalemia and metabolic acidosis may complicate all forms of CKD eventually, but can be more prominent in pts with interstitial renal diseases. Serum and urine protein electrophoresis, in addition to serum free light chains, should be obtained in all pts >35 years of age with CKD to exclude paraproteinemia-associated renal disease. If underlying glomerulonephritis is suspected, autoimmune disorders such as lupus and infectious etiologies such as hepatitis B and C should be assessed. Serum concentrations of calcium, phosphate, vitamin D, and parathyroid hormone (PTH) should be measured to evaluate metabolic bone disease. Hemoglobin, vitamin $B_{12}$, folate, and iron studies should be measured to evaluate anemia.

## THE UREMIC SYNDROME

The culprit toxin(s) responsible for the uremic syndrome remain elusive. The serum creatinine (Cr) is the most common laboratory surrogate of renal function. GFR can be estimated using serum Cr–based equations derived from the Modification of Diet in Renal Disease Study. This "eGFR" is now reported with serum Cr by most clinical laboratories in the United States and is the basis for the National Kidney Foundation classification of CKD (see Table 46-1).

Uremic symptoms tend to develop with serum Cr >530–710 μmol/L (>6–8 mg/dL) or $Cr_{Cl}$ <10 mL/min, although these values vary widely. Uremia is thus a clinical diagnosis made in pts with CKD. Symptoms of advanced uremia include anorexia, weight loss, dyspnea, fatigue, pruritus, sleep and taste disturbance, and confusion and other forms of encephalopathy. Key findings on physical examination include hypertension, jugular venous distention, pericardial and/or pleural friction rub, muscle wasting, asterixis, excoriations, and ecchymoses. Pts may suffer from excessive bleeding due to uremic platelet dysfunction. Laboratory abnormalities may include hyperkalemia, hyperphosphatemia, metabolic acidosis, hypocalcemia, hyperuricemia, anemia, and hypoalbuminemia. Most of these abnormalities eventually resolve with initiation of dialysis or renal transplantation (Chaps. 140 and 141) or with appropriate drug therapies (see below).

## TREATMENT CHRONIC KIDNEY DISEASE AND UREMIA

Hypertension complicates many forms of CKD and warrants aggressive treatment to reduce the risk of stroke and potentially to slow the progression of CKD (see below). Volume overload contributes to hypertension in many cases, and potent diuretic agents are frequently required. Anemia can be ameliorated

with recombinant human erythropoietin (rHuEPO); current practice is to target a hemoglobin concentration of 90–110 g/L. Iron deficiency and/or other causes of anemia can reduce the response to rHuEPO and should be investigated if present. Iron supplementation is often required; many pts require parenteral iron therapy, since intestinal iron absorption is reduced in CKD.

Hyperphosphatemia can be controlled with judicious restriction of dietary phosphorus and the use of postprandial phosphate binders, either calcium-based salts (calcium carbonate or acetate) or nonabsorbed agents (e.g., sevelamer). Hyperkalemia should be controlled with dietary potassium restriction. Dialysis should be considered if the potassium is >6 mmol/L on repeated occasions. If these conditions cannot be conservatively controlled, dialysis should be instituted (Chap. 140). It is also advisable to begin dialysis if severe anorexia, weight loss, and/or hypoalbuminemia develop, as it has been definitively shown that outcomes for dialysis pts with malnutrition are particularly poor.

**SLOWING PROGRESSION OF RENAL DISEASE** Prospective clinical trials have explored the roles of blood pressure control and dietary protein restriction on the rate of progression of renal failure. Control of hypertension is of benefit, although angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) may exert unique beneficial effects, most likely due to their effects on intrarenal hemodynamics. The effects of ACE inhibitors and ARBs are most pronounced in pts with diabetic nephropathy and in those without diabetes but with significant proteinuria (>1 g/d). Diuretics and other antihypertensive agents are often required, in addition to ACE inhibitors and ARBs, to optimize hypertension control and attenuate disease progression; diuretics may also help control serum [$K^+$].

For a more detailed discussion, see Bargman JM, Skorecki K: Chronic Kidney Disease, Chap. 335, p. 1811, in HPIM-19.

# 140 Dialysis

## OVERVIEW

The decision to initiate dialysis for the management of end stage renal disease (ESRD) usually depends on a combination of the pt's symptoms, comorbid conditions, and laboratory parameters. Unless a living donor is identified, transplantation is deferred by necessity, due to the scarcity of deceased donor organs (median waiting time, 3–6 years at most transplant centers). Dialytic options include hemodialysis and peritoneal dialysis (PD). Roughly 85% of U.S. pts are started on hemodialysis.

Absolute indications for dialysis include severe volume overload refractory to diuretic agents, severe hyperkalemia and/or acidosis, severe encephalopathy not otherwise explained, and pericarditis or other serositis. Additional indications for dialysis include symptomatic uremia (Chap. 139) (e.g., intractable fatigue, anorexia, dysgeusia,

**TABLE 140-1 COMPLICATIONS OF HEMODIALYSIS**

| | |
|---|---|
| Hypotension | Dialysis-related amyloidosis |
| Accelerated vascular disease | Protein-energy malnutrition |
| Rapid loss of residual renal function | Hemorrhage |
| Access thrombosis | Anaphylactoid reaction[a] |
| Access or catheter sepsis | Thrombocytopenia[b] |

[a]Primarily with first use of "bioincompatible" modified cellulosic dialyzer membranes.
[b]Associated with the use of dialyzers sterilized by e-beam treatment.

nausea, vomiting, pruritus, difficulty maintaining attention and concentration) and protein-energy malnutrition/failure to thrive without other overt cause. No absolute serum creatinine, blood urea nitrogen, creatinine or urea clearance, or glomerular filtration rate (GFR) is used as an absolute cutoff for requiring dialysis, although most individuals experience, or will soon develop, symptoms and complications when the GFR is below ~10 mL/min. However, the "pre-emptive" initiation of dialysis in such pts, prior to the onset of clinical indications, does not improve outcomes in ESRD.

## HEMODIALYSIS

This requires direct access to the circulation, either via a native arteriovenous fistula (the preferred method of vascular access), usually at the wrist (a "Brescia-Cimino" fistula); an arteriovenous graft, usually made of polytetrafluoroethylene; a large-bore intravenous catheter; or a subcutaneous device attached to intravascular catheters. Blood is pumped though hollow fibers of an artificial kidney (the "dialyzer") and bathed with a solution of favorable chemical composition (isotonic, free of urea and other nitrogenous compounds, and generally low in potassium). Dialysate [$K^+$] is varied from 1 to 4 mM, depending on predialysis [$K^+$] and the clinical setting. Dialysate [$Ca^{2+}$] is typically 2.5 mg/dL (1.25 mM), [$HCO_3^-$] typically 35 meq/L, and dialysate [$Na^+$] 140 mM; these can also be modified, depending on the clinical situation. Most pts undergo dialysis thrice weekly, usually for 3–4 h. The efficiency of dialysis is largely dependent on the duration of dialysis, blood flow rate, dialysate flow rate, and surface area of the dialyzer.

Complications of hemodialysis are outlined in Table 140-1. Many of these relate to the process of hemodialysis as an intense, intermittent therapy. In contrast to the native kidney or to PD, both major dialytic functions (i.e., clearance of solutes and fluid removal, or "ultrafiltration") are accomplished over relatively short time periods. The rapid flux of fluid can cause hypotension, even without a pt reaching "dry weight." Hemodialysis-related hypotension is common in diabetic pts whose neuropathy prevents the compensatory responses (vasoconstriction and tachycardia) to intravascular volume depletion. Occasionally, confusion or other central nervous system symptoms will occur. The dialysis "disequilibrium syndrome" refers to the development of headache, confusion, and rarely seizures, in association with rapid solute removal early in the pt's dialysis history, before adaptation to the procedure; this complication is largely avoided by an incremental induction of chronic dialytic therapy in uremic pts, starting with treatments of short duration, lower blood flows, and lower dialysate flow rates.

## PERITONEAL DIALYSIS

PD does not require direct access to the circulation; rather, it obligates placement of a peritoneal catheter that allows infusion of a dialysate solution into the abdominal cavity; this allows transfer of solutes (i.e., urea, potassium, other uremic molecules) across the peritoneal membrane, which serves as the "artificial kidney." This solution is similar to that used for hemodialysis, except that it must be sterile, and it uses

**TABLE 140-2 COMPLICATIONS OF PERITONEAL DIALYSIS**

| | |
|---|---|
| Peritonitis | Dialysis-related amyloidosis |
| Hyperglycemia<br>Hypertriglyceridemia<br>Obesity | Insufficient clearance due to vascular disease or other factors<br>Uremia secondary to loss of residual renal function |
| Hypoproteinemia | Pleural effusion due to pleuro-peritoneal leak |
| Gastroesophageal reflux disease | Delayed gastric emptying |

lactate, rather than bicarbonate, to provide base equivalents. PD is far less efficient at cleansing the bloodstream than hemodialysis and therefore requires a much longer duration of therapy. Pts generally have the choice of performing their own "exchanges" (2–3 L of dialysate, four to five times during daytime hours) or using an automated device at night. Compared with hemodialysis, PD offers the major advantages of (1) independence and flexibility, and (2) a more gentle hemodynamic profile, with better preservation of residual renal function.

Complications are outlined in Table 140-2. Peritonitis is the most important complication. The clinical presentation typically consists of abdominal pain and cloudy dialysate; peritoneal fluid leukocyte count is typically >100/μL, 50% neutrophils. In addition to the negative effects of the systemic inflammatory response, protein loss is magnified severalfold during the peritonitis episode. If severe or prolonged, an episode of peritonitis may prompt removal of the peritoneal catheter or even discontinuation of the modality (i.e., switch to hemodialysis). Gram-positive organisms (especially *Staphylococcus aureus* and other *Staphylococcus* spp.) predominate; *Pseudomonas* or fungal (usually *Candida*) infections tend to be more resistant to medical therapy and typically obligate catheter removal. Antibiotic administration may be intravenous or intraperitoneal when intensive therapy is required.

For a more detailed discussion, see Liu KD, Chertow GM: Dialysis in the Treatment of Renal Failure: Chap. 336, p. 1822, in HPIM-19.

# 141 Renal Transplantation

With the advent of more potent and well-tolerated immunosuppressive regimens and further improvements in short-term graft survival, renal transplantation remains the treatment of choice for most pts with end-stage renal disease. Results are best with living-related transplantation, in part because of optimized tissue matching and in part because waiting time and ischemic time can be minimized; ideally, these pts are transplanted prior to the onset of symptomatic uremia or indications for dialysis. Transplant centers now also perform living-unrelated donor (e.g., spousal) transplants, often in "chains" involving multiple donors to optimize tissue matching.

**TABLE 141-1 SOME FACTORS THAT INFLUENCE GRAFT SURVIVAL IN RENAL TRANSPLANTATION**

| | |
|---|---|
| HLA mismatch | ↓ |
| Presensitization (preformed antibodies) | ↓ |
| Very young or older donor age | ↓ |
| Female donor sex | ↓ |
| African-American donor race (compared with white) | ↓ |
| At-risk APOL1 donor genotype (two risk alleles for ESRD) | ↓ |
| Older recipient age | ↑ |
| African-American recipient race (compared with white) | ↓ |
| Recipient diabetes as the cause of end-stage renal disease | ↓ |
| Prolonged cold ischemia time | ↓ |
| Hepatitis C infection | ↓ |
| Large recipient body size | ↓ |

Graft survival in these cases is far superior to that observed with deceased donor transplants, although less favorable than with living-related transplants.

In 2011, there were 55,371 active adult candidates on the waiting list for deceased-donor kidneys, and less than 18,000 pts were transplanted. This imbalance is set to worsen over the coming years with the predicted increased rates of obesity and diabetes worldwide. In an attempt to increase utilization of deceased-donor kidneys and reduce discard rates of organs, criteria for the use of so-called expanded criteria donor (ECD) kidneys and kidneys from donors after cardiac death (DCD) have been developed. ECD kidneys are usually used for older pts who are expected to fare less well on dialysis.

Factors that influence graft survival are outlined in Table 141-1. Pretransplant blood transfusion should be avoided, so as to reduce the likelihood of sensitization to incompatible HLA antigens; if transfusion is necessary, leukocyte-reduced irradiated blood is preferred. Contraindications to renal transplantation are outlined in Table 141-2. Overall, the current standard of care is that the pt should have >5 years

**TABLE 141-2 CONTRAINDICATIONS TO RENAL TRANSPLANTATION**

| |
|---|
| **Absolute contraindications** |
| Active glomerulonephritis |
| Active bacterial or other infection |
| Active or very recent malignancy |
| Overt AIDS[a] |
| Active hepatitis |
| Severe degrees of comorbidity (e.g., advanced atherosclerotic vascular disease) |
| **Relative contraindications** |
| Severe psychiatric disease |
| Moderately severe degrees of comorbidity |
| Hepatitis C infection with chronic hepatitis or cirrhosis |
| Noncompliance with dialysis or other medical therapy |
| Primary renal diseases |
| Primary focal sclerosis with prior recurrence in transplant |
| Multiple myeloma |
| Amyloid |
| Oxalosis |

[a]Most centers consider overt AIDS a contraindication to transplantation; however, transplantation of HIV-positive pts is increasing in frequency.

of life expectancy to be eligible for a renal transplant, since the benefits of transplantation are only realized after a perioperative period in which the mortality rate is higher than in comparable pts on dialysis.

## REJECTION

Immunologic rejection is the major hazard to the short-term success of renal transplantation. Rejection may be (1) hyperacute (immediate graft dysfunction due to presensitization) or (2) acute (sudden change in renal function occurring within weeks to months). Rejection is usually detected by a rise in serum creatinine but may also lead to hypertension, fever, reduced urine output, and occasionally graft tenderness. A percutaneous renal transplant biopsy confirms the diagnosis. Treatment usually consists of a "pulse" of methylprednisolone (500–1000 mg/d for 3 days). In refractory or particularly severe cases, 7–10 days of a monoclonal antibody directed at human T lymphocytes may be given.

## IMMUNOSUPPRESSION

Maintenance immunosuppressive therapy usually consists of a three-drug regimen, with each drug targeted at a different stage in the immune response. The calcineurin inhibitors cyclosporine and tacrolimus are the cornerstones of immunosuppressive therapy. The most potent of orally available agents, calcineurin inhibitors have vastly improved short-term graft survival. Side effects of cyclosporine include hypertension, hyperkalemia, resting tremor, hirsutism, gingival hypertrophy, hyperlipidemia, hyperuricemia and gout, and a slowly progressive loss of renal function with characteristic histopathologic patterns (also seen in exposed recipients of heart and liver transplants). Recently, the U.S. Food and Drug Administration (FDA) approved a new costimulatory blocking antibody, belatacept, as a new strategy to prevent long-term calcineurin inhibitor toxicity. While the side effect profile of tacrolimus is generally similar to cyclosporine, there is a higher risk of hyperglycemia, a lower risk of hypertension, and occasional hair loss rather than hirsutism.

Prednisone is frequently used in conjunction with cyclosporine, at least for the first several months following successful graft function. Side effects of prednisone include hypertension, glucose intolerance, cushingoid features, osteoporosis, hyperlipidemia, acne, and depression and other mood disturbances. Some centers have adopted "steroid-free" immunosuppressive regimens to avoid prednisone-associated side-effects.

Mycophenolate mofetil has proved more effective than azathioprine in combination therapy with calcineurin inhibitors and prednisone. The major side effects of mycophenolate mofetil are gastrointestinal (diarrhea is most common); leukopenia (and thrombocytopenia to a lesser extent) develops in a fraction of pts.

Sirolimus is a newer immunosuppressive agent often used in combination with other drugs, particularly when calcineurin inhibitors are reduced or eliminated. Side effects include hyperlipidemia and oral ulcers.

## OTHER COMPLICATIONS

Infection and neoplasia are important complications of renal transplantation. Infection is common in the heavily immunosuppressed host (e.g., cadaveric transplant recipient with multiple episodes of rejection requiring steroid pulses or monoclonal antibody treatment). The culprit organism depends in part on characteristics of the donor and recipient and timing following transplantation (Table 141-3). In the first month, bacterial organisms predominate. After 1 month, there is a significant risk of systemic infection with cytomegalovirus (CMV), particularly in recipients without prior exposure whose donor was CMV positive. Prophylactic use of ganciclovir or

**TABLE 141-3 THE MOST COMMON OPPORTUNISTIC INFECTIONS IN RENAL TRANSPLANT RECIPIENTS**

| | |
|---|---|
| Peritransplant (<1 month) | Late (>6 months) |
| Wound infections | *Aspergillus* |
| Herpesvirus | *Nocardia* |
| Oral candidiasis | BK virus (polyoma) |
| Urinary tract infection | Herpes zoster |
| Early (1–6 months) | Hepatitis B |
| *Pneumocystis carinii* | Hepatitis C |
| Cytomegalovirus | |
| *Legionella* | |
| *Listeria* | |
| Hepatitis B | |
| Hepatitis C | |

valacyclovir can reduce the risk of CMV disease. Later on, there is a substantial risk of fungal and related infections, especially in pts who are unable to taper prednisone to <20–30 mg/d. Daily low-dose trimethoprim-sulfamethoxazole is effective at reducing the risk of *Pneumocystis carinii* infection.

The polyoma group of DNA viruses (BK, JC, SV40) can be activated by immunosuppression. Reactivation of BK is associated with a typical pattern of renal inflammation, BK nephropathy, which can lead to loss of the allograft; therapy typically involves reduction of immunosuppression to aid in clearance of the reactivated virus.

Epstein-Barr virus–associated lymphoproliferative disease is the most important neoplastic complication of renal transplantation, especially in pts who receive polyclonal (antilymphocyte globulin, used at some centers for induction of immunosuppression) or monoclonal antibody therapy. Non-Hodgkin's lymphoma and squamous cell carcinoma of the skin are also more common in this population.

For a more detailed discussion, see Azzi J, Milford EL, Sayegh MH, Chandraker A: Transplantation in the Treatment of Renal Failure, Chap. 337, p. 1825, in HPIM-19.

# 142 Glomerular Diseases

## ACUTE GLOMERULONEPHRITIS (GN)

Often called the "nephritic syndrome." Characterized by development, over days, of azotemia, hypertension, edema, hematuria, proteinuria, and sometimes oliguria. Salt and water retention are due to reduced glomerular filtration rate (GFR) and may result in circulatory congestion. Red blood cell (RBC) casts on urinalysis

**TABLE 142-1 CAUSES OF ACUTE GLOMERULONEPHRITIS**

I. Infectious diseases
   A. Poststreptococcal glomerulonephritis[a]
   B. Nonstreptococcal postinfectious glomerulonephritis
      1. Bacterial: infective endocarditis, "shunt nephritis," sepsis, pneumococcal pneumonia, typhoid fever, secondary syphilis, meningococcemia
      2. Viral: hepatitis B, infectious mononucleosis, mumps, measles, varicella, vaccinia, echovirus, and coxsackievirus
      3. Parasitic: malaria, toxoplasmosis
      4. IgA dominant postinfectious glomerulonephritis—usually poststaphylococcal
II. Multisystem diseases: SLE, vasculitis, Henoch-Schönlein purpura, Goodpasture's syndrome
III. Primary glomerular diseases: mesangiocapillary glomerulonephritis, Berger's disease (IgA nephropathy), "pure" mesangial proliferative glomerulonephritis
IV. Miscellaneous: Guillain-Barré syndrome, irradiation of Wilms' tumor, self-administered diphtheria-pertussis-tetanus vaccine, serum sickness

[a]Most common cause.
***Source:*** RJ Glassock, BM Brenner: HPIM-13.

confirm diagnosis. Proteinuria is usually <3 g/d. Most forms of acute GN are mediated by humoral immune mechanisms. Clinical course depends on underlying lesion (Table 142-1).

### Acute Poststreptococcal GN

This is the prototype of the nephritic syndrome and the most common cause in childhood. Nephritis develops 1–3 weeks after pharyngeal or cutaneous infection with "nephritogenic" strains of group A β-hemolytic streptococci. Diagnosis depends on a positive pharyngeal or skin culture (if available), positive titers for antistreptococcal antigens (ASO, anti-DNAse, or antihyaluronidase), and hypocomplementemia. Renal biopsy reveals diffuse proliferative GN. Treatment consists of correction of fluid and electrolyte imbalance. In most cases the disease is self-limited, although the prognosis is less favorable and urinary abnormalities are more likely to persist in adults.

### Postinfectious GN

May follow other bacterial, viral, and parasitic infections. Examples are bacterial endocarditis, sepsis, hepatitis B, and pneumococcal pneumonia. Features are milder than with poststreptococcal GN. A specific IgA-dominant acute postinfectious glomerulonephritis, with a dominance of IgA deposits on immunofluorescence, can be seen after staphylococcal infections. Control of primary infection usually produces resolution of postinfectious GN, but steroids are often administered in severe cases to avoid dialysis.

## RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS

Defined as a subacute reduction in GFR of >50%, with evidence of a proliferative GN; causes overlap with those of acute GN (Table 142-2). Broadly classified into three major subtypes on the basis of renal biopsy findings and pathophysiology: (1) immune complex–associated, e.g., in systemic lupus erythematosus (SLE); (2)

**TABLE 142-2 CAUSES OF RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS**

I. Infectious diseases
   A. Poststreptococcal glomerulonephritis[a]
   B. Infective endocarditis
   C. Occult visceral sepsis
   D. Hepatitis B infection (with vasculitis and/or cryoglobulinemia)
   E. HIV infection
   F. Hepatitis C infection (with cryoglobulinemia, membranoproliferative glomerulonephritis)
II. Multisystem diseases
   A. Systemic lupus erythematosus
   B. Henoch-Schönlein purpura
   C. Systemic necrotizing vasculitis (including granulomatosis with polyangiitis [Wegener's])
   D. Goodpasture's syndrome
   E. Essential mixed (IgG/IgM) cryoglobulinemia
   F. Malignancy
   G. Relapsing polychondritis
   H. Rheumatoid arthritis (with vasculitis)
III. Drugs
   A. Penicillamine
   B. Hydralazine
   C. Allopurinol (with vasculitis)
   D. Rifampin
   E. Cocaine adulterated with levamisole (ANCA-associated)
IV. Idiopathic or primary glomerular disease
   A. Idiopathic crescentic glomerulonephritis
      1. Type I—with linear deposits of Ig (anti-GBM antibody–mediated)
      2. Type II—with granular deposits of Ig (immune complex–mediated)
      3. Type III—with few or no immune deposits of Ig ("pauci-immune")
      4. Antineutrophil cytoplasmic antibody–induced, forme fruste of vasculitis
      5. Immunotactoid glomerulonephritis
      6. Fibrillary glomerulonephritis
   B. Superimposed on another primary glomerular disease
      1. Mesangiocapillary (membranoproliferative) glomerulonephritis (especially type II)
      2. Membranous glomerulonephritis
      3. Berger's disease (IgA nephropathy)

[a]Most common cause.
***Abbreviation:*** GBM, glomerular basement membrane.
***Source:*** RJ Glassock, BM Brenner: HPIM-13.

"pauci-immune," associated with antineutrophil cytoplasmic antibodies (ANCA); and (3) associated with anti–glomerular basement (anti-GBM) antibodies, e.g., in Goodpasture's syndrome. All three forms will typically have a proliferative, crescentic GN by light microscopy but differ in the results of the immunofluorescence and electron microscopy components of the renal biopsy.

## SLE (Lupus)

Renal involvement is due to deposition of circulating immune complexes. Clinical features of SLE with or without renal involvement include arthralgias, "butterfly" skin rash, serositis, alopecia (hair loss), and central nervous system disease. Nephrotic syndrome with renal insufficiency is common. Renal biopsy reveals mesangial, focal, or diffuse GN and/or membranous nephropathy. Diffuse GN, the most common finding in renal biopsy series, is typically characterized by an active sediment, severe proteinuria, and progressive renal insufficiency and may have an ominous prognosis. Pts have a positive antinuclear antibody test, anti-dsDNA antibodies, and hypocomplementemia. Treatment includes glucocorticoids and cytotoxic agents. Oral or IV monthly cyclophosphamide is most commonly employed, typically for a period of 6 months; pts of childbearing age should first bank sperm and eggs. Mycophenolate mofetil is an alternative.

## Antineutrophil Cytoplasmic Antibody (ANCA)–Associated, Pauci-Immune GN

May be renal-limited (idiopathic pauci-immune GN) or associated with systemic vasculitis (granulomatosis with polyangiitis [GPA, formerly known as Wegener's] or microscopic polyarteritis nodosa). Defining characteristic is the presence of circulating ANCA. These are detected by immunofluorescence of alcohol-fixed neutrophils; a "perinuclear" pattern (pANCA) is usually due to antibodies against myeloperoxidase (MPO), whereas a "cytoplasmic" pattern (cANCA) is almost always due to reactivity against proteinase-3 (PR3). Confirmatory enzyme-linked immunosorbent assay testing against the MPO and PR3 antigens is mandatory, since the pANCA pattern can be caused by antibodies against other neutrophil components, e.g., lactoferrin; these do not have the same consistent relationship to vasculitis and pauci-immune GN. The anti-MPO or anti-PR3 titer does not always correlate with disease activity.

Pts typically have a prodromal, "flulike" syndrome, which may encompass myalgias, fever, arthralgias, anorexia, and weight loss. There may be associated cutaneous, pulmonary, upper respiratory (sinusitis), or neurologic (mononeuritis monoplex) complications of associated systemic vasculitis. In particular, pulmonary necrotizing capillaritis can lead to hemoptysis and pulmonary hemorrhage.

Standard initial therapy for ANCA-associated rapidly progressive GN includes methylprednisolone and cyclophosphamide; more specific depletion of B cells by anti-CD20 antibody therapy with rituximab is an alternative. Most centers will also utilize plasmapheresis in the initial management of pts with a severe pulmonary-renal syndrome or to stave off dialysis in pts with severe renal impairment. Steroids are quickly tapered soon after the acute inflammation subsides; cyclophosphamide is continued until a stable remission is achieved, typically within 3–6 months. Pts must receive prophylaxis for *Pneumocystis carinii* (*jiroveci*) pneumonia (PCP) with trimethoprim-sulfamethoxazole, atovaquone, or dapsone. Some form of maintenance immunosuppression is standard, typically for 12–18 months after achievement of a stable remission; drugs include methotrexate, mycophenolate mofetil, and azathioprine. Notably, however, pts treated with rituximab do not require maintenance oral immunosuppression, but may require maintenance with regular rituximab infusions or repeated rituximab therapy after a recurrence.

## Anti–Glomerular Basement Membrane Disease

Caused by antibodies against the α3 NCI (noncollagenous) domain of type IV collagen; circulating anti-GBM antibody and linear immunofluorescence on renal biopsy

establish the diagnosis. Pts may have isolated GN; Goodpasture's syndrome encompasses GN and lung hemorrhage. Plasma exchange may produce remission; renal prognosis is worse in those who require dialytic support, with >50% crescents on renal biopsy, or creatinine >5–6 mg/dL. Severe lung hemorrhage is treated with IV glucocorticoids (e.g., 1 g/d × 3 days). Approximately 10–15% will also have ANCA against MPO, some with evidence of vasculitis, e.g., leukocytoclastic vasculitis in the skin.

### Henoch-Schönlein Purpura

A generalized vasculitis causing IgA nephropathy, purpura, arthralgias, and abdominal pain; occurs mainly in children. Renal involvement is manifested by hematuria and proteinuria. Serum IgA is increased in half of pts. Renal biopsy is useful for prognosis. Treatment is symptomatic.

## NEPHROTIC SYNDROME (NS)

Characterized by albuminuria (>3.5 g/d) and hypoalbuminemia (<30 g/L) and accompanied by edema, hyperlipidemia, and lipiduria. Protein excretion should be quantified by 24-h urine collection, but can be monitored by measurement of the urine protein:creatinine ratio or albumin:creatinine ratio on a random spot urine. The measurement of creatinine excretion helps define the adequacy of 24-h urine collections: daily creatinine excretion should be 20–25 mg/kg lean body weight in men and 15–20 mg/kg lean body weight in women. For random urine samples, the ratio of protein or albumin to creatinine in mg/dL approximates the 24-h urine protein excretion, since creatinine excretion is only slightly greater than 1000 mg/d per 1.73 $m^2$. A urine protein:creatinine ratio of 5 is thus consistent with 5 g/d per 1.73 $m^2$. Quantification of urine protein excretion on spot urines has largely supplanted formal 24-h urine collections for monitoring or screening, due to the greater ease and the need to verify a complete 24-h collection. The total protein:creatinine ratio does not detect microalbuminuria, a level of albumin excretion that is below the level of detection by tests for total protein; urine albumin:creatinine measurement is therefore preferred as a screening tool for lesser proteinuria.

In addition to edema, the complications of NS can include renal vein thrombosis and other thromboembolic events, infection, vitamin D deficiency, protein malnutrition, and drug toxicities due to decreased protein binding.

In adults, the most common cause of NS is diabetes. A minority of cases are secondary to SLE, amyloidosis, drugs, neoplasia, or other disorders (Table 142-3). By

**TABLE 142-3 CAUSES OF NEPHROTIC SYNDROME (NS)**

| Systemic Causes | Glomerular Disease |
|---|---|
| Diabetes mellitus, SLE, amyloidosis, HIV-associated nephropathy | Membranous<br>Minimal change disease |
| Drugs: gold, penicillamine, probenecid, street heroin, NSAIDs, pamidronate, interferons | Focal glomerulosclerosis |
| Infections: bacterial endocarditis, hepatitis B, shunt infections, syphilis, malaria, hepatic schistosomiasis | Membranoproliferative GN |
| Malignancy: multiple myeloma, light chain deposition disease, Hodgkin's and other lymphomas, leukemia, carcinoma of breast and GI tract | Mesangioproliferative GN<br>Immunotactoid and fibrillary GN |

***Abbreviations:*** GN, glomerulonephritis.
***Source:*** Modified from RJ Glassock, BM Brenner: HPIM-13.

exclusion, the remainder are idiopathic. With the exception of diabetic nephropathy, suggested by a compatible natural history of proteinuria in a diabetic pt, a renal biopsy is required to make the diagnosis and determine therapy in NS.

## Minimal Change Disease

Causes about 10–15% of idiopathic NS in adults, but 70–90% of NS in children. Blood pressure is normal; GFR is normal or slightly reduced; urinary sediment is benign or may show few RBCs. Protein selectivity is variable in adults. Recent upper respiratory infection, allergies, or immunizations are present in some cases; nonsteroidal anti-inflammatory drugs can cause minimal change disease with interstitial nephritis. Acute renal failure due to associated acute tubular necrosis may rarely occur, particularly among elderly persons. Renal biopsy shows only foot process fusion on electron microscopy. Remission of proteinuria with glucocorticoids carries a good prognosis; cytotoxic therapy or calcineurin inhibitor therapy may be required for relapse. Progression to renal failure is uncommon. Focal sclerosis should be suspected in cases that are refractory to steroid therapy; these pts are more likely to progress to end-stage renal disease (ESRD). Children with steroid-resistant MCD/FSGS are more likely to have an underlying genetic cause.

## Membranous GN

Characterized by subepithelial IgG deposits; accounts for ~30% of idiopathic adult NS. Pts present with edema and nephrotic proteinuria. Blood pressure, GFR, and urine sediment are usually normal at initial presentation. Hypertension, mild renal insufficiency, and abnormal urine sediment develop later. Renal vein thrombosis can occur, with low but greater frequency than with other forms of NS. Underlying diseases such as SLE, hepatitis B, and solid tumors and exposure to such drugs as high-dose captopril or penicillamine should be sought. The majority of pts with idiopathic membranous GN have detectable circulating autoantibodies to the M-type phospholipase $A_2$ ($PLA_2R$), which is expressed in glomerular podocytes; the PLA2R titre can be monitored during therapy or utilized as a screening tool for idiopathic membranous GN in nephrotic syndrome. Some pts progress to ESRD; however, 20–33% may experience a spontaneous remission. Male gender, older age, hypertension, and persistence of significant proteinuria (>6 g/d) are associated with a higher risk of progressive disease. Optimal immunosuppressive therapy is controversial. Glucocorticoids alone are ineffective. Cytotoxic agents may promote complete or partial remission in some pts, as may cyclosporine. Anti-CD20 antibody therapy with rituximab has recently shown considerable promise, consistent with a role for B cells and anti-$PLA_2R$ antibodies in the pathophysiology. Reduction of proteinuria with angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin receptor blockers (ARBs) is also an important mainstay of therapy. Venous thromboembolic events (DVTs, renal vein thrombosis, etc.) occur in about 7% of pts with membranous nephropathy; hypoalbuminemia is the most significant independent predictor of venous thrombotic risk. Prophylactic anticoagulation is not recommended for all pts, but should be considered in pts at very high risk for venous thrombosis (albumin <2.0 g/dL) with low or intermediate bleeding risk.

## Focal Glomerulosclerosis (FGS)

Can be primary or secondary. Primary tends to be more acute, similar to minimal change disease in abruptness of NS, but with added features of hypertension, renal insufficiency, and hematuria. Involves fibrosis of portions of some (primarily juxtamedullary) glomeruli and is found in ~35% of pts with NS. There are several different pathologic subtypes of idiopathic FGS, with prognostic implications. In particular, the "collapsing glomerulopathy" variant has pathologic similarity to HIV-associated nephropathy (HIVAN); both nephropathies cause rapidly progressive disease.

African Americans are disproportionately affected by FGS, HIVAN, and other nondiabetic renal disease, with higher incidence, greater susceptibility (HIVAN),

and a much higher risk of developing ESRD. "African-specific" variants in the *APOL1* gene, which encodes apolipoprotein L1 expressed in glomerular podocytes, have recently been implicated in this enhanced genetic risk.

Treatment of primary FGS typically begins with an extended course of steroids; fewer than half of pts undergo remission. Cyclosporine is an alternative therapy for maintenance of remission and for steroid-resistant pts. As in other glomerulopathies, reduction of proteinuria with ACE inhibitors and/or ARBs is also an important component of therapy. Finally, primary FGS may recur after renal transplant, when it may lead to loss of the allograft.

Secondary FGS can occur in the late stages of any form of kidney disease associated with nephron loss (e.g., remote GN, prior severe pyelonephritis, sickle cell disease, vesicoureteral reflux). Treatment includes anti-proteinuric therapy with ACE inhibition and blood pressure control. There is no benefit of glucocorticoids or other immunsuppressive agents in secondary FGS. Clinical history, kidney size, biopsy findings, and associated conditions usually allow differentiation of primary versus secondary causes.

## Membranoproliferative Glomerulonephritis (MPGN)

Mesangial expansion and proliferation extend into the capillary loop. Two ultrastructural variants exist. In MPGN I, subendothelial electron-dense deposits are present, C3 is deposited in a granular pattern indicative of immune-complex pathogenesis, and IgG and the early components of complement may or may not be present. In MPGN II, the lamina densa of the GBM is transformed into an electron-dense character, as is the basement membrane in Bowman's capsule and tubules. C3 is found irregularly in the GBM. Small amounts of Ig (usually IgM) are present, but early components of complement are absent.

Pts with MPGN may have associated genetic mutations in complement components or complement regulatory factors. MPGN has been proposed to be reclassified into immunoglobulin-mediated disease (driven by the classical complement pathway) and non-immunoglobulin-mediated disease (driven by the alternative complement pathway).

Serum complement levels are usually decreased. MPGN affects young adults. Blood pressure and GFR are abnormal, and the urine sediment is active. Some have acute nephritis or hematuria. Similar lesions occur in SLE and hemolytic-uremic syndrome. Infection with hepatitis C virus (HCV) has been linked to MPGN, often with associated cryoglobulinemia. Glucocorticoids, cytotoxic agents, antiplatelet agents, and plasmapheresis have been used with limited success in HCV-associated MPGN; rituximab is a newer therapy with greater evident efficacy. Therapy with a direct-acting, interferon-free antiviral regimen should be considered in pts with MPGN and/or cryoglobulinemic vasculitis associated with HCV infection, either as primary therapy or once the vasculitis and/or MPGN has been controlled with rituximab.

## Diabetic Nephropathy

The most common cause of NS. Although prior duration of diabetes mellitus (DM) is variable, in type 1 DM proteinuria may develop 10–15 years after onset of diabetes, progress to NS, and then lead to renal failure over 3–5 years. Retinopathy is nearly universal in type 1 diabetics with nephropathy, so much so that the absence of retinopathy should prompt consideration of another glomerular lesion (e.g., membranous nephropathy). In contrast, only ~60% of type 2 diabetics with diabetic nephropathy have retinopathy. Clinical features include proteinuria, progressive hypertension, and progressive renal insufficiency. Pathologic changes include mesangial sclerosis, diffuse, and/or nodular (Kimmelstiel-Wilson) glomerulosclerosis. However, pts rarely undergo renal biopsy; to the extent that yearly measurement of microalbuminuria is routine management for all diabetics, the natural history is an important component of the diagnosis. Pts typically demonstrate progression

**TABLE 142-4 EVALUATION OF NEPHROTIC SYNDROME**

| |
|---|
| Random spot urine for protein and creatinine |
| Serum albumin, cholesterol, complement |
| Urine protein electrophoresis |
| Rule out SLE, diabetes mellitus |
| Review drug exposure |
| Renal biopsy |
| Consider malignancy (in elderly pt with membranous GN or minimal change disease) |
| Consider renal vein thrombosis (if membranous GN or symptoms of pulmonary embolism are present) |

***Abbreviation:*** GN, glomerulonephritis.

from microalbuminuria (30–300 mg/24 h) to dipstick-positive proteinuria (>300 mg albuminuria) and then progressively overt proteinuria and chronic kidney disease. However, proteinuria can be quite variable in diabetic nephropathy, with as much as 25 g/24 h in the absence of profound renal insufficiency or alternatively with progressive renal insufficiency and stable, modest proteinuria.

Treatment with ACE inhibitors delays the onset of nephropathy and of ESRD in type 1 diabetics with microalbuminuria and/or declining renal function and should be instituted in all pts tolerant to that class of drug. If a cough develops in a pt treated with an ACE inhibitor, an ARB is the next best choice. Type 2 diabetics with microalbuminuria or proteinuria can be treated with ACE inhibitors or ARBs. Hyperkalemia, hypotension, and/or worsening GFR can limit single or combined therapy with renin-angiotensin-aldosterone (RAA) system inhibitors. If hyperkalemia develops and cannot be controlled with (1) optimizing glucose control, (2) loop diuretics (if otherwise appropriate), or (3) treatment of metabolic acidosis (if present), then tight control of blood pressure with alternative agents is warranted.

Evaluation of NS is shown in Table 142-4.

## ASYMPTOMATIC URINARY ABNORMALITIES

Proteinuria in the nonnephrotic range and/or hematuria unaccompanied by edema, reduced GFR, or hypertension can be due to multiple causes (Table 142-5).

### Thin Basement Membrane Nephropathy

Also known as benign familial hematuria, may cause up to 25% of isolated, sustained hematuria without proteinuria. Diffuse thinning of the glomerular basement membrane on renal biopsy, with minimal other changes. May be hereditary, caused in some instances by defects in type IV collagen. Pts have persistent glomerular hematuria, with minimal proteinuria. The renal prognosis is controversial but appears to be relatively benign.

### IgA Nephropathy

Another very common cause of recurrent hematuria of glomerular origin. Episodes of macroscopic hematuria are present with flulike symptoms, without skin rash, abdominal pain, or arthritis. Renal biopsy shows diffuse mesangial deposition of IgA, often with lesser amounts of IgG, nearly always by C3 and properdin but not by C1q or C4. Prognosis is variable; 50% develop ESRD within 25 years; men with hypertension and heavy proteinuria are at highest risk. Glucocorticoids and other

**TABLE 142-5 GLOMERULAR CAUSES OF ASYMPTOMATIC URINARY ABNORMALITIES**

I. Hematuria with or without proteinuria
   A. Primary glomerular diseases
      1. Berger's disease (IgA nephropathy)[a]
      2. Mesangiocapillary glomerulonephritis
      3. Other primary glomerular hematurias accompanied by "pure" mesangial proliferation, focal and segmental proliferative glomerulonephritis, or other lesions
      4. "Thin basement membrane" disease (? forme fruste of Alport's syndrome)
   B. Associated with multisystem or hereditary diseases
      1. Alport's syndrome and other "benign" familial hematurias
      2. Fabry's disease
      3. Sickle cell disease
   C. Associated with infections
      1. Resolving poststreptococcal glomerulonephritis
      2. Other postinfectious glomerulonephritides
II. Isolated nonnephrotic proteinuria
   A. Primary glomerular diseases
      1. "Orthostatic" proteinuria
      2. Focal and segmental glomerulosclerosis
      3. Membranous glomerulonephritis
   B. Associated with multisystem or heredofamilial diseases
      1. Diabetes mellitus
      2. Amyloidosis
      3. Nail-patella syndrome

[a]Most common.
***Source:*** RJ Glassock, BM Brenner: HPIM-13.

immunosuppressive agents have not proved successful, except in pts who present with rapidly progressive GN. A randomized clinical trial of fish oil supplementation suggested a modest therapeutic benefit. Rarely recurs in allografts.

## Glomerulopathies Associated with Multisystem Disease (Table 142-6)

For a more detailed discussion, see Lewis JB, Neilson EG: Glomerular Diseases, Chap. 338, p. 1831, in HPIM-19.

**TABLE 142-6 SEROLOGIC FINDINGS IN SELECTED MULTISYSTEM DISEASES CAUSING GLOMERULAR DISEASE**

| Disease | C3 | Ig | FANA | Anti-dsDNA | Anti-GBM | Cryo-Ig | CIC | ANCA |
|---|---|---|---|---|---|---|---|---|
| SLE | ↓ | ↑ IgG | +++ | ++ | – | ++ | +++ | ± |
| Goodpasture's syndrome | – | – | – | – | +++ | – | ± | + (10–15%) |
| Henoch-Schönlein purpura | – | ↑IgA | – | – | – | ± | ++ | – |
| Polyarteritis | ↓↑ | IgG | + | ± | – | ++ | +++ | +++ |
| Granulomatosis with polyangiitis (Wegener's) | ↓↑ | ↑ IgA, IgE | – | – | – | ± | ++ | +++ |
| Cryoglobulinemia | ↓ | ±<br>↓↑ IgG<br>IgA, IgD | – | | – | +++ | ++ | – |
| Multiple myeloma | – | IgE | – | | – | + | – | – |
| Waldenström's macroglobulinemia | – | ↑ IgM | – | – | – | – | – | – |
| Amyloidosis | – | ± Ig | – | – | – | – | – | – |

***Abbreviations:*** ANCA, antineutrophil cytoplasmic antibody; anti-dsDNA, antibody to double-stranded (native) DNA; anti-GBM, antibody to glomerular basement membrane antigens; CIC, circulating immune complexes; cryo-Ig, cryoimmunoglobulin; C3, complement component 3; FANA, fluorescent antinuclear antibody assay; Ig, immunoglobulin levels; SLE, systemic lupus erythematosus; –, normal; +, occasionally slightly abnormal; ++, often abnormal; +++, severely abnormal.

***Source:*** RJ Glassock, BM Brenner: HPIM-13.

# 143 Renal Tubular Disease

Tubulointerstitial diseases constitute a diverse group of acute and chronic, hereditary and acquired disorders involving the renal tubules and supporting structures (Table 143-1). Functionally, they may result in a wide variety of physiologic phenotypes, including nephrogenic diabetes insipidus (DI) with polyuria, non-anion-gap

**TABLE 143-1 PRINCIPAL CAUSES OF TUBULOINTERSTITIAL DISEASE OF THE KIDNEY**

| | |
|---|---|
| **Toxins** | |
| Exogenous toxins | Metabolic toxins |
| Analgesic nephropathy[a] | Acute uric acid nephropathy |
| Lead nephropathy | Gouty nephropathy[a] |
| Chinese herb nephropathy | Hypercalcemic nephropathy |
| Balkan endemic nephropathy | Hypokalemic nephropathy |
| Miscellaneous nephrotoxins (e.g., antibiotics, cyclosporine, radiographic contrast media, heavy metals)[a,b] | Miscellaneous metabolic toxins (e.g., hyperoxaluria, cystinosis, Fabry's disease) |
| **Neoplasia** | |
| Lymphoma | |
| Leukemia | |
| Multiple myeloma (cast nephropathy, AL amyloidosis) | |
| **Immune disorders** | |
| Acute (allergic) interstitial nephritis[a,b] | Transplant rejection |
| Sjögren's syndrome | HIV-associated nephropathy |
| Amyloidosis | |
| **Vascular disorders** | |
| Arteriolar nephrosclerosis[a] | Sickle cell nephropathy |
| Atheroembolic disease | Acute tubular necrosis[a,b] |
| **Hereditary renal diseases** | |
| Disorders associated with renal failure | Hereditary tubular disorders |
| Autosomal dominant polycystic kidney disease | Bartter's syndrome (hereditary hypokalemic alkalosis) |
| Autosomal recessive polycystic kidney disease | Gitelman's syndrome (hereditary hypokalemic alkalosis) |
| Medullary cystic kidney disease | Pseudohypoaldosteronism type I (hypotension/salt wasting and hyperkalemia) |
| Hereditary nephritis (Alport's syndrome) | Pseudohypoaldosteronism type II (hereditary hypertension and hyperkalemia) |
| | Liddle's syndrome (hypertension and hypokalemia) |
| | Hereditary hypomagnesemia |

(*Continued*)

**TABLE 143-1 PRINCIPAL CAUSES OF TUBULOINTERSTITIAL DISEASE OF THE KIDNEY (*CONTINUED*)**

| | |
|---|---|
| **Hereditary renal diseases** | |
| | Hereditary nephrogenic diabetes insipidus |
| | X-linked (AVP receptor dysfunction) |
| | Autosomal (aquaporin-2 dysfunction) |
| **Infectious injury** | |
| Acute pyelonephritis[a,b] | |
| Chronic pyelonephritis | |
| **Miscellaneous disorders** | |
| Chronic urinary tract obstruction[a] | |
| Vesicoureteral reflux[a] | |
| Radiation nephritis | |

[a]Common.
[b]Typically acute.

metabolic acidosis, salt wasting, and hypo- or hyperkalemia. Azotemia is common, owing to associated glomerular fibrosis and/or ischemia. Compared with glomerulopathies, proteinuria and hematuria are less dramatic, and hypertension is less common. The functional consequences of tubular dysfunction are outlined in Table 143-2.

**TABLE 143-2 TRANSPORT DYSFUNCTION IN TUBULOINTERSTITIAL DISEASE**

| Defect | Cause(s) |
|---|---|
| Reduced GFR[a] | Obliteration of microvasculature and obstruction of tubules |
| Fanconi syndrome | Damage to proximal tubular reabsorption of solutes, primarily glucose, amino acids, and phosphate; may also exhibit hypouricemia, proximal tubular acidosis, low-molecular-weight proteinuria |
| Hyperchloremic acidosis[a] | 1. Reduced ammonia production (CKD) or excretion (hyperkalemia)<br>2. Inability to acidify the collecting duct fluid (distal renal tubular acidosis)<br>3. Proximal bicarbonate wasting (proximal RTA) |
| Polyuria, isothenuria[a] | Damage to medullary tubules (thick ascending limb and/or collecting duct) and vasculature |
| Hypokalemic alkalosis | Damage or hereditary dysfunction of the thick ascending limb or distal convoluted tubule (Bartter's and Gitelman's syndromes) |
| Magnesium wasting | Damage or hereditary dysfunction of the thick ascending limb or distal convoluted tubules |
| Hyperkalemia[a] | Potassium secretory defects including aldosterone resistance |
| Salt wasting | Distal tubular damage with impaired sodium reabsorption |

[a]Common.
***Abbreviations:*** CKD, chronic kidney disease; RTA, renal tubular acidosis.

## ACUTE INTERSTITIAL NEPHRITIS (AIN)

Drugs are a leading cause of this type of renal failure, usually identified by a gradual rise in the serum creatinine at least several days after the institution of therapy, occasionally accompanied by fever, eosinophilia, rash, and arthralgias. The onset of renal dysfunction may be very rapid in pts who have previously been sensitized to the offending agent; this is particularly true for rifampin, for which intermittent or interrupted therapy appears to be associated with the development of AIN. In addition to azotemia, there may be evidence of tubular dysfunction (e.g., hyperkalemia, metabolic acidosis). Urinalysis may show hematuria, pyuria, white cell casts, and eosinophiluria on Hansel's or Wright's stain; notably, however, eosinophiluria is not specific for AIN, occurring in other causes of acute kidney injury (AKI), including atheroemboli; "urine for eosinophils" is not a diagnostically useful test.

Drugs that commonly cause AIN are listed in Table 143-3. Some drugs have a particular predilection for causing AIN, e.g., nafcillin; however, less frequent causes may be apparent only from case reports, such that a detailed history and literature review may be required to make the association with AIN. Many drugs, nonsteroidal anti-inflammatory drugs (NSAIDs) in particular, may elicit a glomerular lesion with similarity to minimal change disease, in addition to AIN; these pts typically have nephrotic-range proteinuria, versus the modest proteinuria typically associated with tubulointerstitial disease.

Renal dysfunction in drug-associated AIN usually improves after withdrawal of the offending drug, but complete recovery may be delayed and incomplete. In uncontrolled studies, glucocorticoids have been shown to promote earlier recovery of renal function and reduce fibrosis; this therapy is generally reserved to avoid or reduce the duration of dialytic therapy in pts who fail to respond to medication withdrawal.

AIN may also occur in the context of systemic infections, classically leptospirosis, *Legionella* infection, and streptococcal bacterial infection. Interstitial nephritis characterized by a dense infiltrate of IgG4-expressing plasma cells can occur as part of IgG4-related systemic disease; pancreatitis, retroperitoneal fibrosis, and a chronic

**TABLE 143-3 CAUSES OF ACUTE INTERSTITIAL NEPHRITIS**

| |
|---|
| Drugs (70%, antibiotics in one-third) |
| Antibiotics |
| Methicillin, nafcillin, oxacillin |
| Rifampin |
| Penicillins, cephalosporins |
| Ciprofloxacin |
| Sulfamethoxazole and other sulfonamides |
| Proton pump inhibitors, e.g., omeprazole |
| $H_2$ blockers, e.g., cimetidine |
| Allopurinol |
| 5-Aminosalicylates |
| NSAIDs, including COX-2 inhibitors |
| Infections (16%) |
| Leptospirosis, *Legionella*, streptococcal, tuberculosis |
| Tubulointerstitial nephritis and uveitis syndrome (TINU) (5%) |
| Idiopathic (8%) |
| Sarcoidosis (1%) |
| IgG4-related systemic disease |

***Abbreviation:*** COX-2, cyclooxygenase 2.

sclerosing sialadenitis may variably be present. Sjögren's syndrome can also be associated with acute tubulointerstitial nephritis. Finally, the tubulointerstitial nephritis and uveitis syndrome (TINU) is another increasingly recognized form of AIN. In addition to uveitis, which may precede or follow the AIN in pts with TINU, systemic symptoms and signs are common, e.g., weight loss, fever, malaise, arthralgias, and an elevated erythrocyte sedimentation rate. The renal disease is typically self-limited; those with progressive disease are often treated with prednisone.

## CHRONIC INTERSTITIAL NEPHRITIS (IN)

Analgesic nephropathy is an important cause of chronic kidney disease that results from the cumulative (in quantity and duration) effects of combination analgesic agents, usually phenacetin and aspirin. It is thought to be a more common cause of end-stage renal disease (ESRD) in Australia/New Zealand than elsewhere owing to the larger per capita ingestion of analgesic agents in that region of the world. Transitional cell carcinoma may develop. Analgesic nephropathy should be suspected in pts with a history of chronic headache or back pain with chronic kidney disease (CKD) that is otherwise unexplained. Manifestations include papillary necrosis, calculi, sterile pyuria, and azotemia.

A severe form of chronic tubulointerstitial fibrosis has been associated with the ingestion of Chinese herbal medicines, typically employed as part of a dieting regimen; Balkan endemic nephropathy (BEN), geographically restricted to pts from this region of southeastern Europe, shares many similarities with Chinese herbal nephropathy. These disorders are thought to be caused by exposure to aristolochic acid and/or other plant, endemic (in BEN), and medical toxins (the appetite suppressants fenfluramine and diethylpropion, in Chinese herbal nephropathy). Like analgesic nephropathies, these syndromes are both characterized by a high incidence of genitourinary malignancy.

Chronic therapy with lithium can also cause a chronic tubulointerstitial nephritis, often accompanied by nephrogenic DI that persists following discontinuation of the medication. If at all feasible, lithium-treated pts with evolving CKD should be transitioned to alternative medications for their psychiatric disease (e.g., valproic acid). Co-treatment with lithium and amiloride may prevent nephrogenic diabetes insipidus in these pts by blocking entry of lithium into principal cells via the amiloride-sensitive Na+ channel; however, there are no long-term studies on the effect of amiloride co-therapy on the development or progression of CKD.

Metabolic causes of chronic IN include hypercalcemia (with nephrocalcinosis), oxalosis (primary or secondary, e.g., with intestinal disease and hyperabsorption of dietary oxalate), hypokalemia, and hyperuricemia or hyperuricosuria. The renal pathology associated with chronic hypokalemia includes a relatively specific proximal tubular vacuolization, interstitial nephritis, and renal cysts; both chronic and acute renal failure have been described. Chronic IN can occur in association with several systemic diseases, including sarcoidosis, Sjögren's syndrome, and following radiation or chemotherapy exposure (e.g., ifosfamide, cisplatin).

## MONOCLONAL IMMUNOGLOBULINS AND RENAL DISEASE

Monoclonal immunoglobulins are associated with a wide variety of renal manifestations (Table 143-4), of which myeloma-associated cast nephropathy is the most common. The physiochemical characteristics of the monoclonal immunoglobulin, or more commonly the monoclonal light or heavy chains, determine the clinical phenotype in individual pts, most commonly cast nephropathy, light chain deposition disease, and AL amyloidosis. In cast nephropathy, filtered light chains aggregate and cause tubular obstruction, tubular damage, and interstitial inflammation. Pts can present with CKD or with AKI; important predisposing factors in acute cast nephropathy include hypercalcemia and volume depletion.

**TABLE 143-4 RENAL DISEASES ASSOCIATED WITH MONOCLONAL IMMUNOGLOBULINS**

| Disease | Notes |
|---|---|
| Cast nephropathy | Most common cause of CKD in myeloma<br>Tubular obstruction with light chains<br>Interstitial inflammation<br>Acute or chronic renal failure |
| Light chain deposition disease | Nephrotic syndrome, chronic renal failure, ~40% have associated myeloma |
| Heavy chain deposition disease | Nephrotic syndrome, chronic renal failure |
| Monoclonal immunoglobulin deposition disease | Nephrotic syndrome, chronic renal failure |
| AL amyloidosis | Nephrotic syndrome, cardiac/endocrine/neuropathic involvement<br>~10% have associated myeloma<br>Renal tubular dysfunction (RTA, nephrogenic DI, etc.) |
| Hypercalcemia | With myeloma |
| Hyperviscosity syndrome | With Waldenström's macroglobulinemia |
| Fanconi syndrome | Glucosuria, aminoaciduria, phosphaturia, ± hypouricemia, proximal RTA, etc. |

***Abbreviations:*** CKD, chronic kidney disease; DI, diabetes insipidus; RTA, renal tubular acidosis.

Diagnosis of cast nephropathy relies on the detection of monoclonal light chains in serum and/or urine, typically by protein electrophoresis and immunofixation. Dipstick analysis of the urine for protein is classically negative in cast nephropathy, despite the excretion of up to several grams a day of light chain protein; light chains are not detected by this screening test, which tests only for albuminuria. In contrast, the glomerular deposition of light chains in light chain deposition disease or AL amyloidosis can result in nephrotic-range proteinuria (Table 143-4), with strongly *positive* urine dipstick for protein.

Management of cast nephropathy encompasses aggressive hydration, treatment of hypercalcemia if present, and chemotherapy for the associated multiple myeloma. Some experts advocate the use of plasmapheresis for pts with severe AKI, high levels of serum monoclonal light chains, and a renal biopsy demonstrating cast nephropathy.

Filtered light chains and multiple other low-molecular-weight proteins are also endocytosed and metabolized by the proximal tubule. Rarely, specific light chains generate crystalline depositions within proximal tubule cells, causing a Fanconi syndrome; again, this property appears to be caused by the specific physicochemical characteristics of the associated light chains. Fanconi syndrome or dysfunction of the distal nephron (hyperkalemic acidosis or nephrogenic DI) may also complicate renal amyloidosis.

## POLYCYSTIC KIDNEY DISEASE

Autosomal dominant polycystic kidney disease (ADPKD) is the most common life-threatening monogenic genetic disorder, caused by autosomal dominant mutations in the *PKD1* and *PKD2* genes; it is a quantitatively important cause of ESRD.

Autosomal recessive polycystic disease is a less much common cause of renal failure, typically presenting in infancy; hepatic involvement is much more prominent. The massive renal cysts in ADPKD can lead to progressive CKD, episodic flank pain, hematuria (often gross), hypertension, and/or urinary tract infection. The kidneys are often palpable and occasionally of very large size. Hepatic cysts and intracranial aneurysms may also be present; pts with ADPKD and a family history of ruptured intracranial aneurysms should undergo presymptomatic screening. Other common extrarenal features include diverticulosis and mitral valve prolapse.

The expression of ADPKD is highly variable, even within individual families, with the age of onset of ESRD ranging from childhood to old age. The renal phenotype is more severe in pts with mutations in *PKD1*, who on average develop ESRD approximately 15 years earlier than those with *PKD2* mutations. Indeed, some pts with ADPKD discover the disease incidentally in late adult life, having had mild to moderate hypertension earlier.

The diagnosis is usually made by ultrasonography. In a 15- to 29-year-old at-risk individual from a family with ADPKD, the presence of at least two renal cysts (unilateral or bilateral) is sufficient for diagnosis. Notably, however, renal cysts are a common ultrasound finding in older pts without ADPKD, particularly those with CKD. Therefore, in at-risk individuals 30–59 years of age, the presence of at least two cysts in each kidney is required for the diagnosis; this increases to four cysts in each kidney for those older than 60. Conversely, the absence of at least two cysts in each kidney excludes the diagnosis of ADPKD in at-risk individuals between the ages of 30 and 59.

Hypertension is common in ADPKD, often in the absence of an apparent reduction in glomerular filtration rate. Activation of the renin-angiotensin system appears to play a dominant role; angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are the recommended antihypertensive agents, with a target blood pressure of <130/80 mmHg. Dual therapy with an angiotensin receptor blocker (ARB) and ACE inhibitor does not confer additional benefit in slowing progression of ADPKD to ESRD. Promising treatment modalities for halting progression of CKD in ADPKD include vasopressin antagonists, somatostatin analogues, and inhibitors of cell proliferation.

Urinary tract infections are also common in ADPKD. In particular, pts may develop cyst infections, often with negative urine cultures and an absence of pyuria. Pts with an infected cyst may have a discrete area of tenderness, as opposed to the more diffuse discomfort of pyelonephritis; however, clinical distinction between these two possibilities can be problematic. Many commonly used antibiotics, including penicillins and aminoglycosides, fail to penetrate cysts and are ineffective; therapy of kidney infections in ADPKD should use an antibiotic that is known to penetrate cysts (e.g., quinolones), guided initially by local antimicrobial susceptibility patterns.

## RENAL TUBULAR ACIDOSIS (RTA)

This describes a number of pathophysiologically distinct entities of tubular function whose common feature is the presence of a non-anion-gap metabolic acidosis. Diarrhea, CKD, and RTA together constitute the vast majority of cases of non-anion-gap metabolic acidosis. Pts with earlier stages of CKD (Table 46-1) typically develop a non-anion-gap acidosis, with a superimposed increase in the anion gap at later stages (Chap. 1). Acidosis may develop at an earlier stage of CKD in those with prominent injury to the distal nephron, as for example in reflux nephropathy.

### Distal Hypokalemic (Type I) RTA

Pts are unable to acidify the urine despite systemic acidosis; the urinary anion gap is positive, reflective of a decrease in ammonium excretion (Chap. 1). Distal hypokalemic RTA may be inherited (both autosomal dominant and autosomal recessive) or

acquired due to autoimmune and inflammatory diseases (e.g., Sjögren's syndrome, sarcoidosis), urinary tract obstruction, or amphotericin B therapy. Chronic type I RTA is typically associated with hypercalciuria and osteomalacia, a consequence of the long-term buffering of acidosis by bone.

### Proximal (Type II) RTA

There is a defect in bicarbonate reabsorption, usually associated with features of Fanconi syndrome, including glycosuria, aminoaciduria, phosphaturia, and uricosuria (indicating proximal tubular dysfunction). Isolated proximal RTA is caused by hereditary dysfunction of the basolateral sodium-bicarbonate cotransporter. Fanconi syndrome may be inherited or acquired due to myeloma, chronic IN (e.g., Chinese herbal nephropathy), or drugs (e.g., ifosfamide, tenofovir). Treatment requires large doses of bicarbonate (5–15 mmol/kg per day), which may aggravate hypokalemia.

### Type IV RTA

This may be due to hyporeninemic hypoaldosteronism or to resistance of the distal nephron to aldosterone. Hyporeninemic hypoaldosteronism is typically associated with volume expansion and most commonly seen in elderly and/or diabetic pts with CKD. The hyperkalemia associated with NSAIDs and cyclosporine is at least partially due to hyporeninemic hypoaldosteronism. Pts with hyporeninemic hypoaldosteronism are typically hyperkalemic; they may also exhibit a mild non-anion-gap acidosis, with urine pH <5.5 and a positive urinary anion gap. Acidosis often improves with reduction in serum [$K^+$]; hyperkalemia appears to interfere with medullary concentration of ammonium by the renal countercurrent mechanism. Should reduction in serum [$K^+$] not improve acidosis, pts should be treated with oral bicarbonate or citrate. Finally, various forms of distal tubular injury and tubulointerstitial disease, e.g., interstitial nephritis, are associated with distal insensitivity to aldosterone; urine pH is classically >5.5, again with a positive urinary anion gap.

For a more detailed discussion, see Beck LH, Salant DJ: Tubulointerstitial Diseases of the Kidney, Chap. 340, p. 1856, in HPIM-19.

# 144 Urinary Tract Infections and Interstitial Cystitis

## URINARY TRACT INFECTIONS

### Definitions

The term *urinary tract infection* encompasses a variety of clinical entities: *cystitis* (symptomatic disease of the bladder), *pyelonephritis* (symptomatic disease of the kidney), *prostatitis* (symptomatic disease of the prostate), and asymptomatic bacteriuria (ABU). *Uncomplicated UTI* refers to acute disease in nonpregnant outpatient women

without anatomic abnormalities or instrumentation of the urinary tract; *complicated UTI* refers to all other types of UTI.

## Epidemiology

UTI occurs far more commonly in females than in males, although obstruction from prostatic hypertrophy causes men >50 years old to have an incidence of UTI comparable to that among women of the same age.

- 50–80% of women have at least one UTI during their lifetime, and 20–30% of women have recurrent episodes.
- Risk factors for acute cystitis include recent use of a diaphragm with spermicide, frequent sexual intercourse, a history of UTI, diabetes mellitus, and incontinence; many of these factors also increase the risk of pyelonephritis.

## Microbiology

In the United States, *Escherichia coli* accounts for 75–90% of cystitis isolates; *Staphylococcus saprophyticus* for 5–15%; and *Klebsiella* spp., *Proteus* spp., *Enterococcus* spp., *Citrobacter* spp., and other organisms for 5–10%.

- The spectrum of organisms causing uncomplicated pyelonephritis is similar, with *E. coli* predominating.
- Gram-positive bacteria (e.g., enterococci and *Staphylococcus aureus*) and yeasts are also important pathogens in complicated UTI.

## Pathogenesis

In the majority of UTIs, bacteria establish infection by ascending from the urethra to the bladder. Continuing ascent up the ureter to the kidney is the pathway for most renal parenchymal infections.

- The pathogenesis of candiduria is distinct in that the hematogenous route is common.
- The presence of *Candida* in the urine of a noninstrumented immunocompetent pt implies either genital contamination or potentially widespread visceral dissemination.

## Clinical Manifestations

When a UTI is suspected, the most important issue is to classify it as ABU; as uncomplicated cystitis, pyelonephritis, or prostatitis; or as complicated UTI.

- *Asymptomatic bacteriuria* is diagnosed when a screening urine culture performed for a reason unrelated to the genitourinary tract is incidentally found to contain bacteria, but the pt has no local or systemic symptoms referable to the urinary tract.
- *Cystitis* presents as dysuria, urinary frequency, and urgency; nocturia, hesitancy, suprapubic discomfort, and gross hematuria are often noted as well. Unilateral back or flank pain and fever are signs that the upper urinary tract is involved.
- *Pyelonephritis* presents as fever, lower-back or costovertebral-angle pain, nausea, and vomiting. Bacteremia develops in 20–30% of cases.
  - *Papillary necrosis* can occur in pts with obstruction, diabetes, sickle cell disease, or analgesic nephropathy.
  - *Emphysematous pyelonephritis* is particularly severe, is associated with the production of gas in renal and perinephric tissues, and occurs almost exclusively in diabetic pts.
  - *Xanthogranulomatous pyelonephritis* occurs when chronic urinary obstruction (often by staghorn calculi), together with chronic infection, leads to suppurative destruction of renal tissue.
- *Prostatitis* can be either infectious or noninfectious; noninfectious cases are far more common. Acute bacterial prostatitis presents as dysuria, urinary frequency,

fever, chills, symptoms of bladder outlet obstruction, and pain in the prostatic, pelvic, or perineal area.

- *Complicated UTI* presents as symptomatic disease in a man or woman with an anatomic predisposition to infection, with a foreign body in the urinary tract, or with factors predisposing to a delayed response to therapy.

## Diagnosis

The clinical history itself has a high predictive value in diagnosing uncomplicated cystitis; the likelihood of UTI is 96% in a pt presenting with both dysuria and urinary frequency in the absence of vaginal discharge.

- A urine dipstick test positive for nitrite or leukocyte esterase can confirm the diagnosis of uncomplicated cystitis in pts with a high pretest probability of disease.
- The detection of bacteria in a urine culture is the diagnostic gold standard for UTI. A colony count threshold of $>10^2$ bacteria/mL is more sensitive (95%) and specific (85%) than a threshold of $10^5$/mL for the diagnosis of acute cystitis in women with symptoms of cystitis.

## TREATMENT URINARY TRACT INFECTIONS

- **Uncomplicated cystitis in women** See Table 144-1 for effective therapeutic regimens.
  - Trimethoprim-sulfamethoxazole (TMP-SMX) has been recommended as first-line treatment for acute cystitis but should be avoided in regions with resistance rates >20%.
  - Nitrofurantoin is another first-line agent with low rates of resistance.

**TABLE 144-1 TREATMENT STRATEGIES FOR ACUTE UNCOMPLICATED CYSTITIS**

| Drug and Dose | Estimated Clinical Efficacy, % | Estimated Bacterial Efficacy,[a] % | Common Side Effects |
|---|---|---|---|
| Nitrofurantoin, 100 mg bid × 5–7 d | 84–95 | 86–92 | Nausea, headache |
| TMP-SMX, 1 DS tablet bid × 3 d | 90–100 | 91–100 | Rash, urticaria, nausea, vomiting, hematologic abnormalities |
| Fosfomycin, 3-g single-dose sachet | 70–91 | 78–83 | Diarrhea, nausea, headache |
| Pivmecillinam, 400 mg bid × 3–7 d | 55–82 | 74–84 | Nausea, vomiting, diarrhea |
| Fluoroquinolones, dose varies by agent; 3-d regimen | 85–95 | 81–98 | Nausea, vomiting, diarrhea, headache, drowsiness, insomnia |
| β-Lactams, dose varies by agent; 5- to 7-d regimen | 79–98 | 74–98 | Diarrhea, nausea, vomiting, rash, urticaria |

[a]Microbial response as measured by reduction of bacterial counts in the urine.
***Note:*** Efficacy rates are averages or ranges calculated from the data and studies included in the 2010 Infectious Diseases Society of America/European Society of Clinical Microbiology and Infectious Diseases Guideline for Treatment of Uncomplicated UTI. TMP-SMX, trimethoprim-sulfamethoxazole; DS, double-strength.

- Fluoroquinolones should be used only when other antibiotics are not suitable because of increasing resistance or their role in prompting nosocomial outbreaks of *Clostridium difficile* infection.
- Except for pivmecillinam, β-lactam agents are associated with lower rates of pathogen eradication and higher rates of relapse.

- **Pyelonephritis** Given high rates of TMP-SMX-resistant *E. coli*, fluoroquinolones (e.g., ciprofloxacin, 500 mg PO bid for 7 days) are first-line agents for the treatment of acute uncomplicated pyelonephritis. Oral TMP-SMX (one double-strength tablet bid for 14 days) is effective against susceptible uropathogens.
- **UTI in pregnant women** Nitrofurantoin, ampicillin, and the cephalosporins are considered relatively safe in early pregnancy.
- **UTI in men** In men with apparently uncomplicated UTI, a 7- to 14-day course of a fluoroquinolone or TMP-SMX is recommended.
  - If acute bacterial prostatitis is suspected, antibiotics should be initiated after urine and blood are obtained for cultures.
  - Therapy can be tailored to urine culture results and should be continued for 2–4 weeks; a 4- to 6-week course is often necessary for chronic bacterial prostatitis.
- **Asymptomatic bacteriuria** ABU should be treated only in pregnant women, in pts undergoing urologic surgery, and perhaps in neutropenic pts and renal transplant recipients. Antibiotic choice is guided by culture results.
- **Catheter-associated UTI** Urine culture results are essential to guide therapy.
  - Replacing the catheter during treatment is generally necessary. Candiduria, a common complication of indwelling catheterization, resolves in ~1/3 of asymptomatic cases with catheter removal.
  - Treatment of candiduria (fluconazole, 200–400 mg/d for 14 days) is recommended for pts who have symptomatic cystitis or pyelonephritis and for those who are at high risk for disseminated disease.

### Prevention of Recurrent UTI

Women experiencing symptomatic UTIs ≥2 times a year are candidates for prophylaxis—either continuous or postcoital—or pt-initiated therapy. Continuous prophylaxis and postcoital prophylaxis usually entail low doses of TMP-SMX, a fluoroquinolone, or nitrofurantoin. Pt-initiated therapy involves supplying the pt with materials for urine culture and for self-medication with a course of antibiotics at the first symptoms of infection.

### Prognosis

In the absence of anatomic abnormalities, recurrent infection in children and adults does not lead to chronic pyelonephritis or to renal failure.

## INTERSTITIAL CYSTITIS

Interstitial cystitis (painful bladder syndrome) is a chronic condition characterized by pain perceived to be from the urinary bladder, urinary urgency and frequency, and nocturia.

### Epidemiology

In the United States, 3–6% of women and 2–4% of men have interstitial cystitis. Among women, the average age at onset is the early forties, but the range is from childhood through the early sixties.

### Etiology

The etiology remains unknown.

- Theoretical possibilities include chronic bladder infection, inflammatory factors such as mast cells, autoimmunity, increased permeability of the bladder mucosa, and unusual pain sensitivity.
- However, few data support any of these factors as an inciting cause.

## Clinical Manifestations

The cardinal symptoms of pain (often at ≥2 sites), urinary urgency and frequency, and nocturia occur in no consistent order. Symptoms can begin acutely or gradually.

- Unlike pelvic pain arising from other sources, pain caused by interstitial cystitis is exacerbated by bladder filling and relieved by bladder emptying.
- 85% of pts void >10 times per day; some do so as often as 60 times per day.
- Many pts with interstitial cystitis have comorbid functional somatic syndromes (e.g., fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, vulvodynia, migraine).

## Diagnosis

The diagnosis is based on the presence of appropriate symptoms and the exclusion of diseases with a similar presentation (e.g., diseases that manifest with pelvic pain and/or urinary symptoms; functional somatic syndromes with urinary symptoms); physical exam and laboratory findings are insensitive and/or nonspecific. Cystoscopy may reveal an ulcer (10% of pts) or petechial hemorrhages after bladder distension, but neither of these findings is specific.

**TREATMENT INTERSTITIAL CYSTITIS**

The goal of therapy is the relief of symptoms, which often requires a multifaceted approach (e.g., education, stress reduction, dietary changes, medications such as nonsteroidal anti-inflammatory drugs or amitriptyline, pelvic-floor physical therapy, and treatment of associated functional somatic syndromes).

For a more detailed discussion, see Warren JW: Dysuria, Bladder Pain, and the Interstitial Cystitis/Bladder Pain Syndrome, Chap. 60e; and Gupta K, Trautner BW: Urinary Tract Infections, Pyelonephritis, and Prostatitis, Chap. 162, p. 861, in HPIM-19.

# 145 Nephrolithiasis

Renal calculi are common, affecting ~1% of the population, and recurrent in more than half of pts. Stone formation begins when urine becomes supersaturated with insoluble components due to (1) low urinary volume, (2) excessive or insufficient excretion of selected compounds, or (3) other factors (e.g., urinary pH) that diminish

solubility. Approximately 75% of stones are Ca-based (the majority Ca oxalate; also Ca phosphate and other mixed stones), 15% struvite (magnesium-ammonium-phosphate), 5% uric acid, and 1% cystine, reflecting the metabolic disturbance(s) from which they arise.

## SIGNS AND SYMPTOMS

Stones in the renal pelvis may be asymptomatic or cause hematuria alone; with passage, obstruction may occur at any site along the collecting system. Obstruction related to the passing of a stone leads to severe pain, often radiating to the groin, sometimes accompanied by intense visceral symptoms (i.e., nausea, vomiting, diaphoresis, light-headedness), hematuria, pyuria, urinary tract infection (UTI), and, rarely, hydronephrosis. In contrast, staghorn calculi, associated with recurrent UTI with urea-splitting organisms (*Proteus*, *Klebsiella*, *Providencia*, *Morganella*, and others), may be completely asymptomatic, presenting with loss of renal function.

## STONE COMPOSITION

Most stones are composed of Ca oxalate. These may be associated with hypercalciuria and/or hyperoxaluria. Hypercalciuria can be seen in association with a very high-Na diet, loop diuretic therapy, distal (type I) renal tubular acidosis (RTA), sarcoidosis, Cushing's syndrome, aldosterone excess, or conditions associated with hypercalcemia (e.g., primary hyperparathyroidism, vitamin D excess, milk-alkali syndrome), or it may be idiopathic.

*Hyperoxaluria* may be seen with intestinal (especially ileal) malabsorption syndromes (e.g., inflammatory bowel disease, pancreatitis), due to reduced intestinal secretion of oxalate and/or the binding of intestinal Ca by fatty acids within the bowel lumen, with enhanced absorption of free oxalate and hyperoxaluria. Ca oxalate stones may also form due to (1) a deficiency of urinary citrate, an inhibitor of stone formation that is underexcreted with metabolic acidosis; and (2) hyperuricosuria (see below). Ca phosphate stones are much less common and tend to occur in the setting of an abnormally high urinary pH (7–8), usually in association with a complete or partial distal RTA.

*Struvite* stones form in the collecting system when infection with urea-splitting organisms is present. Struvite is the most common component of staghorn calculi and obstruction. Risk factors include previous UTI, nonstruvite stone disease, urinary catheters, neurogenic bladder (e.g., with diabetes or multiple sclerosis), and instrumentation.

*Uric acid* stones develop when the urine is saturated with uric acid in the presence of an acid urine pH; pts typically have underlying metabolic syndrome and insulin resistance, often with clinical gout, associated with a relative defect in ammoniagenesis and urine pH that is <5.4 and often <5.0. Pts with myeloproliferative disorders and other causes of secondary hyperuricemia and hyperuricosuria due to increased purine biosynthesis and/or urate production are at risk for stones if the urine volume diminishes. Hyperuricosuria without hyperuricemia may be seen in association with certain drugs (e.g., probenecid, high-dose salicylates).

*Cystine* stones are the result of a rare inherited defect in renal and intestinal transport of several dibasic amino acids; the overexcretion of cystine (cysteine disulfide), which is relatively insoluble, leads to nephrolithiasis. Stones begin in childhood and are a rare cause of staghorn calculi; they occasionally lead to end-stage renal disease. Cystine stones are more likely to form in acidic urinary pH.

## WORKUP

Although some have advocated a complete workup after a first stone episode, others would defer that evaluation until there has been evidence of recurrence or if

**TABLE 145-1 WORKUP FOR AN OUTPATIENT WITH A RENAL STONE**

1. Dietary and fluid intake history
2. Careful medical history and physical examination, focusing on systemic diseases
3. Noncontrast helical CT, with 5-mm CT cuts
4. Routine UA; presence of crystals, hematuria, measurement of urine pH
5. Serum chemistries: BUN, Cr, uric acid, calcium, phosphate, chloride, bicarbonate, PTH
6. Timed urine collections (at least 1 day during week, 1 day on weekend): Cr, Na, K, urea nitrogen, uric acid, calcium, phosphate, oxalate, citrate, pH

***Abbreviations:*** Cr, creatinine; PTH, parathyroid hormone.

there is no obvious cause (e.g., low fluid intake during the summer months with obvious dehydration). Table 145-1 outlines a reasonable workup for an outpatient with an uncomplicated kidney stone. On occasion, a stone is recovered and can be analyzed for content, yielding important clues to pathogenesis and management. For example, a predominance of Ca phosphate suggests underlying distal RTA or hyperparathyroidism.

## TREATMENT NEPHROLITHIASIS

Treatment of renal calculi is often empirical, based on odds (Ca oxalate stones most common), clinical history, and/or the metabolic workup. An increase in fluid intake to at least 2.5–3 L/d is perhaps the single most effective intervention, regardless of the type of stone. Con servative recommendations for pts with Ca oxalate stones (i.e., low-salt, low-fat, moderate-protein diet) are thought to be healthful in general and therefore advisable in pts whose condition is otherwise uncomplicated. In contrast to prior assumptions, dietary calcium intake does not contribute to stone risk; rather, dietary calcium may help to reduce oxalate absorption and reduce stone risk. Table 145-2 outlines stone-specific therapies for pts with complex or recurrent nephrolithiasis.

**TABLE 145-2 SPECIFIC THERAPIES FOR NEPHROLITHIASIS**

| Stone Type | Dietary Modifications | Other |
|---|---|---|
| Calcium oxalate | Increase fluid intake<br>Moderate sodium intake | Citrate supplementation (calcium or potassium salts > sodium) |
| | Moderate oxalate intake<br>Moderate protein intake<br>Moderate fat intake | Cholestyramine or other therapy for fat malabsorption<br>Thiazides if hypercalciuric<br>Allopurinol if hyperuricosuric |
| Calcium phosphate | Increase fluid intake | Thiazides if hypercalciuric |
| | Moderate sodium intake | Treat hyperparathyroidism if present<br>Alkali for distal renal tubular acidosis |

(*Continued*)

**TABLE 145-2 SPECIFIC THERAPIES FOR NEPHROLITHIASIS (*CONTINUED*)**

| | | |
|---|---|---|
| Struvite | Increase fluid intake; same as calcium oxalate if evidence of calcium oxalate nidus for struvite | Methenamine and vitamin C or daily suppressive antibiotic therapy (e.g., trimethoprim-sulfamethoxazole) |
| Uric acid | Increase fluid intake<br>Moderate dietary protein intake | Allopurinol<br>Alkali therapy ($K^+$ citrate) to raise urine pH to 6.0–6.5 |
| Cystine | Increase fluid intake | Alkali therapy<br>Penicillamine |

***Note:*** Sodium excretion correlates with calcium excretion.

For a more detailed discussion, see Curhan, GC: Nephrolithiasis, Chap. 342, p. 1866, in HPIM-19.

# 146 Urinary Tract Obstruction

Urinary tract obstruction (UTO), a potentially reversible cause of renal failure (RF), should be considered in all cases of acute or abrupt worsening of chronic RF. Consequences depend on duration and severity and whether the obstruction is unilateral or bilateral. UTO may occur at any level from collecting tubule to urethra. It is preponderant in women (pelvic tumors), elderly men (prostatic disease), diabetic pts (papillary necrosis), pts with neurologic diseases (spinal cord injury or multiple sclerosis, with neurogenic bladder), and individuals with retroperitoneal lymphadenopathy or fibrosis, vesicoureteral reflux, nephrolithiasis, or other causes of functional urinary retention (e.g., anticholinergic drugs).

## CLINICAL MANIFESTATIONS

Pain can occur in some settings (obstruction due to stones) but is not common. In men, there is frequently a history of lower urinary tract symptoms, e.g., hesitancy, urgency, or frequent nocturia. Physical examination may reveal an enlarged bladder by percussion over the lower abdominal wall; bedside ultrasound assessment ("bladder scan") can be helpful to assess the postvoid bladder volume. Other findings depend on the clinical scenario. Prostatic hypertrophy can be determined by digital rectal examination. A bimanual examination in women may show a pelvic or rectal mass. The workup of pts with RF suspected of having UTO is shown in Fig. 146-1. Laboratory studies may show marked elevations of blood urea nitrogen and creatinine; if the obstruction has been of sufficient duration, there may be evidence of tubulointerstitial disease (e.g., hyperkalemia, non-anion-gap metabolic acidosis, mild hypernatremia). Urinalysis is most often benign or with a small number of

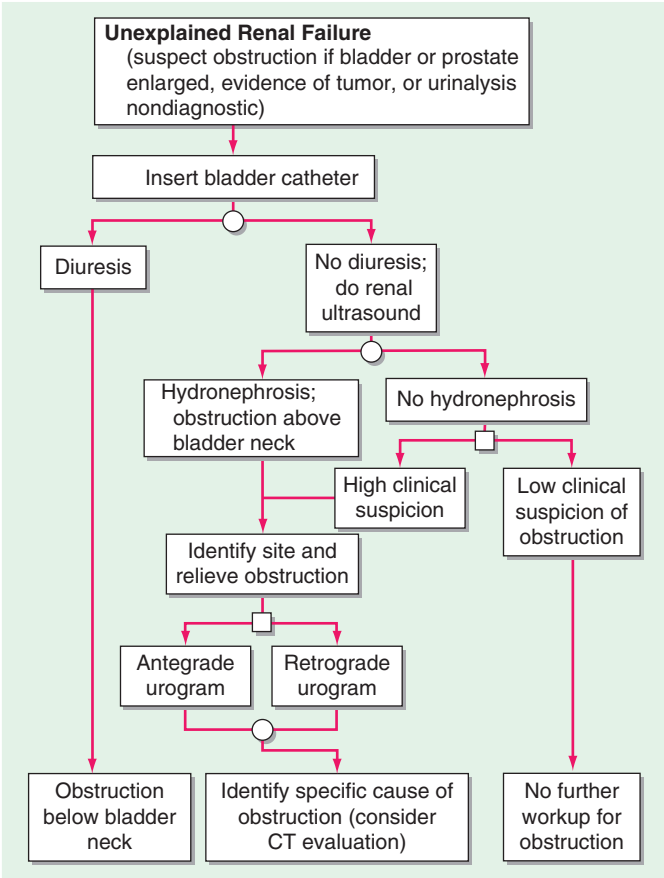


**FIGURE 146-1** Diagnostic approach for urinary tract obstruction in unexplained renal failure. Circles represent diagnostic procedures, and squares indicate clinical decisions based on available data.

cells; heavy proteinuria is rare. An obstructing stone may be visualized on abdominal radiography or helical noncontrast CT with 5-mm cuts.

Ultrasonography can be used to assess the degree of hydronephrosis and the integrity of the renal parenchyma; CT or IV urography may be required to localize the level of obstruction. Calyceal dilation is commonly seen; it may be absent with hyperacute obstruction, upper tract encasement by tumor or retroperitoneal fibrosis, or indwelling staghorn calculi. A nuclear renal scan to assess excretion of the radioisotope technetium Tc-99m mertiatide (Tc-99m MAG3), before and after administration of a loop diuretic may be helpful for functional assessment of obstruction; it can also identify a difference in function between the two kidneys. Imaging in retroperitoneal fibrosis with associated periaortitis classically reveals a periaortic, confluent mass encasing the anterior and lateral sides of the aorta. Kidney size may indicate the duration of obstruction. It should be noted that unilateral obstruction may be prolonged and severe (ultimately leading to loss of renal function in the obstructed kidney), with no hint of abnormality on physical examination and laboratory survey.

## TREATMENT URINARY TRACT OBSTRUCTION

Management of acute RF associated with UTO is dictated by (1) the level of obstruction (upper vs lower tract), and (2) the acuity of the obstruction and its clinical consequences, including renal dysfunction and infection. Benign causes of UTO, including bladder outlet obstruction and nephrolithiasis, should be ruled out because conservative management, including Foley catheter placement and IV fluids, respectively, will usually relieve the obstruction in most cases.

Among more seriously ill pts, ureteral obstruction due to tumor is the most common and concerning cause of UTO. If technically feasible, ureteral obstruction due to tumor is best managed by cystoscopic placement of a ureteral stent. Otherwise, the placement of nephrostomy tubes with external drainage may be required. IV antibiotics should also be given if there are signs of pyelonephritis or urosepsis. In addition to ureteral stenting, pts with idiopathic retroperitoneal fibrosis are typically treated with immunosuppression (prednisone, mycophenolate mofetil, and/or tamoxifen).

Fluid and electrolyte status should be carefully monitored after obstruction is relieved. There may be a physiologic natriuresis/diuresis related to volume overload. However, there may be an "inappropriate" natriuresis/diuresis related to (1) elevated urea nitrogen, leading to an osmotic diuresis; and (2) acquired nephrogenic diabetes insipidus. Hypernatremia, sometimes of a severe degree, may develop.

For a more detailed discussion, see Seifter JL: Urinary Tract Obstruction, Chap. 343, p. 1871, in HPIM-19.

# 147 Peptic Ulcer and Related Disorders

## PEPTIC ULCER DISEASE

Peptic ulcer disease (PUD) occurs most commonly in duodenal bulb (duodenal ulcer, DU) and stomach (gastric ulcer, GU). It may also occur in esophagus, pyloric channel, duodenal loop, jejunum, and Meckel's diverticulum. PUD results when "aggressive" factors (gastric acid, pepsin) overwhelm "defensive" factors involved in mucosal resistance (gastric mucus, bicarbonate, microcirculation, prostaglandins, mucosal "barrier") and from effects of *Helicobacter pylori*.

### CAUSES AND RISK FACTORS

#### General

*H. pylori* is a spiral urease-producing organism that colonizes gastric antral mucosa in up to 100% of persons with DU and 80% with GU. It is also found in normals (increasing prevalence with age) and in those of low socioeconomic status. *H. pylori* is invariably associated with histologic evidence of active chronic gastritis, which over years can lead to atrophic gastritis and gastric cancer. The other major cause of ulcers (those not due to *H. pylori*) is nonsteroidal anti-inflammatory drugs (NSAIDs). Fewer than 1% are due to gastrinoma (Zollinger-Ellison [Z-E] syndrome). Other risk factors and associations: hereditary (? increased parietal cell number), smoking, hypercalcemia, mastocytosis, blood group O (antigens may bind *H. pylori*). Unproven: stress, coffee, alcohol.

#### Duodenal Ulcer

Mild gastric acid hypersecretion resulting from (1) increased release of gastrin, presumably due to (a) stimulation of antral G cells by cytokines released by inflammatory cells and (b) diminished production of somatostatin by D cells, both resulting from *H. pylori* infection; and (2) an exaggerated acid response to gastrin due to an increased parietal cell mass resulting from gastrin stimulation. These abnormalities reverse rapidly with eradication of *H. pylori*. However, a mildly elevated maximum gastric acid output in response to exogenous gastrin persists in some pts long after eradication of *H. pylori*, suggesting that gastric acid hypersecretion may be, in part, genetically determined. *H. pylori* may also result in elevated serum pepsinogen levels. Mucosal defense in duodenum is compromised by toxic effects of *H. pylori* infection on patches of gastric metaplasia that result from gastric acid hypersecretion or rapid gastric emptying. Other risk factors include glucocorticoids, NSAIDs, chronic renal failure, renal transplantation, cirrhosis, and chronic lung disease.

#### Gastric Ulcer

*H. pylori* is also principal cause. Gastric acid secretory rates are usually normal or reduced, possibly reflecting earlier age of infection by *H. pylori* than in DU pts. Gastritis due to reflux of duodenal contents (including bile) may play a role. Chronic salicylate or NSAID use may account for 15–30% of GUs and increase risk of associated bleeding, perforation.

## CLINICAL FEATURES

### Duodenal Ulcer

Burning epigastric pain 90 min to 3 h after meals, often nocturnal, relieved by food.

### Gastric Ulcer

Burning epigastric pain made worse by or unrelated to food; anorexia, food aversion, weight loss (in 40%). Great individual variation. Similar symptoms may occur in persons without demonstrated peptic ulcers ("nonulcer dyspepsia"); less responsive to standard therapy.

## COMPLICATIONS

Bleeding, obstruction, penetration causing acute pancreatitis, perforation, intractability.

## DIAGNOSIS

### Duodenal Ulcer

Upper endoscopy or upper gastrointestinal (GI) barium radiography.

### Gastric Ulcer

Upper endoscopy preferable to exclude possibility that ulcer is malignant (brush cytology, ≥6 pinch biopsies of ulcer margin). Radiographic features suggesting malignancy: ulcer within a mass, folds that do not radiate from ulcer margin, a large ulcer (>2.5–3 cm).

## DETECTION OF *H. PYLORI*

Detection of antibodies in serum (inexpensive, preferred when endoscopy is not required); rapid urease test of antral biopsy (when endoscopy is required). Urea breath test generally used to confirm eradication of *H. pylori*, if necessary. The fecal antigen test is sensitive, specific, and inexpensive (Table 147-1).

**TABLE 147-1 TESTS FOR DETECTION OF *H. PYLORI***

| Test | Sensitivity/ Specificity, % | Comments |
|---|---|---|
| **Invasive (endoscopy/biopsy required)** | | |
| Rapid urease | 80–95/95–100 | Simple, false negative with recent use of PPIs, antibiotics, or bismuth compounds |
| Histology | 80–90/>95 | Requires pathology processing and staining; provides histologic information |
| Culture | —/— | Time consuming, expensive, dependent on experience; allows determination of antibiotic susceptibility |
| **Noninvasive** | | |
| Serology | >80/>90 | Inexpensive, convenient; not useful for early follow-up |
| Urea breath test | >90/>90 | Simple, rapid; useful for early follow-up; false negatives with recent therapy (see rapid urease test); exposure to low-dose radiation with $^{14}C$ test |
| Stool antigen | >90/>90 | Inexpensive, convenient; not established for eradication but promising |

***Abbreviation:*** PPIs, proton pump inhibitors.

## TREATMENT PEPTIC ULCER DISEASE

**MEDICAL** Objectives: pain relief, healing, prevention of complications, prevention of recurrences. For GU, exclude malignancy (follow endoscopically to healing). Dietary restriction unnecessary with contemporary drugs; discontinue NSAIDs; smoking may prevent healing and should be stopped. Eradication of *H. pylori* markedly reduces rate of ulcer relapse and is indicated for all DUs and GUs associated with *H. pylori* (Table 147-2). Acid suppression is generally included in regimen. Reinfection rates are <1%/year. Standard drugs ($H_2$ receptor blockers, sucralfate, antacids) heal 80–90% of DUs and 60% of GUs in 6 weeks; healing is more rapid with omeprazole (20 mg/d).

**SURGERY** Used for complications (persistent or recurrent bleeding, obstruction, perforation) or, uncommonly, intractability (first screen for surreptitious NSAID use and gastrinoma). For DU, see Table 147-3. For GU, perform subtotal gastrectomy.

**COMPLICATIONS OF SURGERY** (1) Obstructed afferent loop (Billroth II), (2) bile reflux gastritis, (3) dumping syndrome (rapid gastric emptying with abdominal distress + postprandial vasomotor symptoms), (4) postvagotomy diarrhea, (5) bezoar, (6) anemia (iron, $B_{12}$, folate malabsorption), (7) malabsorption (poor mixing of gastric contents, pancreatic juices, bile; bacterial overgrowth), (8) osteomalacia and osteoporosis (vitamin D and Ca malabsorption), (9) gastric remnant carcinoma.

## APPROACH TO THE PATIENT: Peptic Ulcer Disease

Optimal approach is uncertain. Serologic testing for *H. pylori* and treating, if present, may be cost-effective. Other options include trial of acid-suppressive therapy, endoscopy only in treatment failures, or initial endoscopy in all cases.

**TABLE 147-2 REGIMENS RECOMMENDED FOR ERADICATION OF *H. PYLORI* INFECTION**

| Drug | Dose |
|---|---|
| **Triple therapy** | |
| 1. Bismuth subsalicylate *plus* | 2 tablets qid |
| Metronidazole *plus* | 250 mg qid |
| Tetracycline[a] | 500 mg qid |
| 2. Ranitidine bismuth citrate *plus* | 400 mg bid |
| Tetracycline *plus* | 500 mg bid |
| Clarithromycin or metronidazole | 500 mg bid |
| 3. Omeprazole (lansoprazole) *plus* | 20 mg bid (30 mg bid) |
| Clarithromycin *plus* | 250 or 500 mg bid |
| Metronidazole[b] *or* | 500 mg bid |
| Amoxicillin[c] | 1 g bid |
| **Quadruple therapy** | |
| Omeprazole (lansoprazole) | 20 mg (30 mg) daily |
| Bismuth subsalicylate | 2 tablets qid |
| Metronidazole | 250 mg qid |
| Tetracycline | 500 mg qid |

[a]Alternative: use prepacked Helidac.
[b]Alternative: use prepacked Prevpac.
[c]Use either metronidazole or amoxicillin, not both.

**TABLE 147-3 SURGICAL TREATMENT OF DUODENAL ULCER**

| Operation | Recurrence Rate | Complication Rate |
|---|---|---|
| Vagotomy + antrectomy (Billroth I or II)[a] | 1% | Highest |
| Vagotomy and pyloroplasty | 10% | Intermediate |
| Parietal cell (proximal gastric, superselective) vagotomy | ≥10% | Lowest |

[a]Billroth I, gastroduodenostomy; Billroth II, gastrojejunostomy.

## GASTROPATHIES

### EROSIVE GASTROPATHIES

Hemorrhagic gastritis, multiple gastric erosions may be caused by aspirin and other NSAIDs (lower risk with newer agents, e.g., nabumetone and etodolac, which do not inhibit gastric mucosal prostaglandins) or severe stress (burns, sepsis, trauma, surgery, shock, or respiratory, renal, or liver failure). Pt may be asymptomatic or experience epigastric discomfort, nausea, hematemesis, or melena. Diagnosis is made by upper endoscopy.

**TREATMENT EROSIVE GASTROPATHIES**

Removal of offending agent and maintenance of $O_2$ and blood volume as required. For prevention of stress ulcers in critically ill pts, hourly oral administration of liquid antacids (e.g., Maalox 30 mL), IV $H_2$ receptor antagonist (e.g., cimetidine, 300-mg bolus + 37.5–50 mg/h IV), or both is recommended to maintain gastric pH > 4. Alternatively, sucralfate slurry, 1 g PO q6h, can be given; does not raise gastric pH and may thus avoid increased risk of aspiration pneumonia associated with liquid antacids. Pantoprazole can be administered IV to suppress gastric acid in the critically ill. Misoprostol, 200 μg PO qid, or profound acid suppression (e.g., famotidine, 40 mg PO bid) can be used with NSAIDs to prevent NSAID-induced ulcers.

### CHRONIC GASTRITIS

Identified histologically by an inflammatory cell infiltrate dominated by lymphocytes and plasma cells with scant neutrophils. In its early stage, the changes are limited to the lamina propria (*superficial gastritis*). When the disease progresses to destroy glands, it becomes *atrophic gastritis*. The final stage is *gastric atrophy*, in which the mucosa is thin and the infiltrate sparse. Chronic gastritis can be classified based on predominant site of involvement.

#### Type A Gastritis

This is the body-predominant and less common form. Generally asymptomatic, common in elderly; autoimmune mechanism may be associated with achlorhydria, pernicious anemia, and increased risk of gastric cancer (value of screening endoscopy uncertain). Antibodies to parietal cells present in >90%.

#### Type B Gastritis

This is antral-predominant disease and caused by *H. pylori*. Often asymptomatic but may be associated with dyspepsia. Atrophic gastritis, gastric atrophy, gastric lymphoid follicles, and gastric B cell lymphomas may occur. Infection early in life or in setting of malnutrition or low gastric acid output is associated with gastritis of entire stomach (including body) and increased risk of gastric cancer. Eradication of

*H. pylori* (Table 147-2) not routinely recommended unless PUD or gastric mucosa-associated lymphoid tissue (MALT) lymphoma is present.

### SPECIFIC TYPES OF GASTROPATHY OR GASTRITIS

Alcoholic gastropathy (submucosal hemorrhages), Ménétrier's disease (hypertrophic gastropathy), eosinophilic gastritis, granulomatous gastritis, Crohn's disease, sarcoidosis, infections (tuberculosis, syphilis, fungi, viruses, parasites), pseudolymphoma, radiation, corrosive gastritis.

## ZOLLINGER-ELLISON (Z-E) SYNDROME (GASTRINOMA)

Consider when ulcer disease is severe, refractory to therapy, associated with ulcers in atypical locations, or associated with diarrhea. Tumors are usually pancreatic or in duodenum (submucosal, often small), may be multiple, slowly growing; >60% malignant; 25% associated with MEN 1, i.e., multiple endocrine neoplasia type 1 (gastrinoma, hyperparathyroidism, pituitary neoplasm), often duodenal, small, multicentric, less likely to metastasize to liver than pancreatic gastrinomas but often metastasize to local lymph nodes.

### DIAGNOSIS

#### Suggestive

Basal acid output >15 mmol/h; basal/maximal acid output >60%; large mucosal folds on endoscopy or upper GI radiograph.

#### Confirmatory

Serum gastrin >1000 ng/L or rise in gastrin of 200 ng/L following IV secretin and, if necessary, rise of 400 ng/L following IV calcium (Table 147-4).

### DIFFERENTIAL DIAGNOSIS

#### Increased Gastric Acid Secretion

Z-E syndrome, antral G-cell hyperplasia or hyperfunction (? due to *H. pylori*), post-gastrectomy retained antrum, renal failure, massive small bowel resection, chronic gastric outlet obstruction.

#### Normal or Decreased Gastric Acid Secretion

Pernicious anemia, chronic gastritis, gastric cancer, vagotomy, pheochromocytoma.

### TREATMENT ZOLLINGER-ELLISON SYNDROME

Omeprazole (or lansoprazole), beginning at 60 mg PO q A.M. and increasing until maximal gastric acid output is <10 mmol/h before next dose, is drug of choice during evaluation and in pts who are not surgical candidates; dose can often be reduced over time. Radiolabeled octreotide scanning has emerged as the

**TABLE 147-4 DIFFERENTIAL DIAGNOSTIC TESTS**

| | | Gastrin Response to | |
|---|---|---|---|
| **Condition** | **Fasting Gastrin** | **IV Secretin** | **Food** |
| DU | N (≤150 ng/L) | NC | Slight ↑ |
| Z-E | ↑↑↑ | ↑↑↑ | NC |
| Antral G (gastrin) cell hyperplasia | ↑ | ↑, NC | ↑↑↑ |

***Abbreviations:*** DU, duodenal ulcer; N, normal; NC, no change; Z-E, Zollinger-Ellison syndrome.

most sensitive test for detecting primary tumors and metastases; may be supplemented by endoscopic ultrasonography. Exploratory laparotomy with resection of primary tumor and solitary metastases is done when possible. In pts with MEN 1, tumor is often multifocal and unresectable; treat hyperparathyroidism first (hypergastrinemia may improve). For unresectable tumors, parietal cell vagotomy may enhance control of ulcer disease by drugs. Chemotherapy is used for metastatic tumor to control symptoms (e.g., streptozocin, 5-fluorouracil, doxorubicin, or interferon α); 40% partial response rate. Newer agents effective in pancreatic neuroendocrine tumors have not been evaluated.

For a more detailed discussion, see Del Valle J: Peptic Ulcer Disease and Related Disorders, Chap. 348, p. 1911, in HPIM-19.

# 148 Inflammatory Bowel Diseases

Inflammatory bowel diseases (IBDs) are chronic inflammatory disorders of unknown etiology involving the gastrointestinal (GI) tract. Peak occurrence is between ages 15 and 30 and between ages 60 and 80, but onset may occur at any age. Epidemiologic features are shown in Table 148-1. Pathogenesis of IBD involves activation of immune cells by unknown inciting agent (? microorganism, dietary component, bacterial or self-antigen) leading to release of cytokines and inflammatory mediators. Genetic component suggested by increased risk in first-degree relatives of pts with IBD and concurrence of type of IBD, location of Crohn's disease (CD), and clinical

**TABLE 148-1 EPIDEMIOLOGY OF IBD**

| | Ulcerative Colitis | Crohn's Disease |
|---|---|---|
| Incidence (North America) per person-years | 0–19.2 per 100,000 | 0–20.2 per100,000 |
| Age of onset | 15–30 and 60–80 | 15–30 and 60–80 |
| Ethnicity | Jewish > non-Jewish white > African American > Hispanic > Asian | |
| Male/female ratio | 0.51–1.58 | 0.34–1.65 |
| Smoking | May prevent disease (OR 0.58) | May cause disease (OR 1.76) |
| Oral contraceptives | No increased risk | OR 1.4 |
| Appendectomy | Protective (risk 13–26% lower) | Not protective |
| Monozygotic twins | 6–18% concordance | 38–58% concordance |
| Dizygotic twins | 0–2% concordance | 4% concordance |

***Abbreviation:*** IBD, inflammatory bowel disease; OR, odds ratio.

course. Reported associations include HLA-DR2 in Japanese pts with ulcerative colitis (UC) and a CD-related gene called *CARD15* on chromosome 16p. *CARD15* mutations may account for 10% of CD risk. Other potential pathogenic factors include serum antineutrophil cytoplasmic antibodies (ANCA) in 70% of pts with UC (also in 5–10% of CD pts) and antibodies to *Saccharomyces cerevisiae* (ASCA) in 60–70% of CD pts (also in 10–15% of UC pts and 5% of normal controls). Granulomatous angiitis (vasculitis) may occur in CD. Acute flares may be precipitated by infections, nonsteroidal anti-inflammatory drugs (NSAIDs), and stress. Onset of UC often follows cessation of smoking.

## ULCERATIVE COLITIS (UC)

### PATHOLOGY

Colonic mucosal inflammation; rectum almost always involved, with inflammation extending continuously (no skip areas) proximally for a variable extent; histologic features include epithelial damage, inflammation, crypt abscesses, loss of goblet cells.

### CLINICAL MANIFESTATIONS

Bloody diarrhea, mucus, fever, abdominal pain, tenesmus, weight loss; spectrum of severity (majority of cases are mild, limited to rectosigmoid). In severe cases, dehydration, anemia, hypokalemia, hypoalbuminemia.

### COMPLICATIONS

Toxic megacolon, colonic perforation; cancer risk related to extent and duration of colitis; often preceded by or coincident with dysplasia, which may be detected on surveillance colonoscopic biopsies.

### DIAGNOSIS

Sigmoidoscopy/colonoscopy: mucosal erythema, granularity, friability, exudate, hemorrhage, ulcers, inflammatory polyps (pseudopolyps). Barium enema: loss of haustrations, mucosal irregularity, ulcerations.

## CROHN'S DISEASE (CD)

### PATHOLOGY

Any part of GI tract, usually terminal ileum and/or colon; transmural inflammation, bowel wall thickening, linear ulcerations, and submucosal thickening leading to cobblestone pattern; discontinuous (skip areas); histologic features include transmural inflammation, granulomas (often absent), fissures, fistulas.

### CLINICAL MANIFESTATIONS

Fever, abdominal pain, diarrhea (often without blood), fatigue, weight loss, growth retardation in children; acute ileitis mimicking appendicitis; anorectal fissures, fistulas, abscesses. Clinical course falls into three broad patterns: (1) inflammatory, (2) stricturing, and (3) fistulizing.

### COMPLICATIONS

Intestinal obstruction (edema vs. fibrosis); rarely toxic megacolon or perforation; intestinal fistulas to bowel, bladder, vagina, skin, soft tissue, often with abscess formation; bile salt malabsorption leading to cholesterol gallstones and/or oxalate kidney stones; intestinal malignancy; amyloidosis.

### DIAGNOSIS

Sigmoidoscopy/colonoscopy, barium enema, upper GI and small-bowel series: nodularity, rigidity, ulcers that may be deep or longitudinal, cobblestoning, skip areas, strictures, fistulas. CT may show thickened, matted bowel loops or an abscess.

## DIFFERENTIAL DIAGNOSIS

### INFECTIOUS ENTEROCOLITIS

*Shigella*, *Salmonella*, *Campylobacter*, *Yersinia* (acute ileitis), *Plesiomonas shigelloides*, *Aeromonas hydrophila*, *Escherichia coli* serotype O157:H7, *Gonorrhea*, *Lymphogranuloma venereum*, *Clostridium difficile* (pseudomembranous colitis), tuberculosis, amebiasis, cytomegalovirus, AIDS.

### OTHERS

Ischemic bowel disease, appendicitis, diverticulitis, radiation enterocolitis, bile salt–induced diarrhea (ileal resection), drug-induced colitis (e.g., NSAIDs), bleeding colonic lesion (e.g., neoplasm), irritable bowel syndrome (no bleeding), microscopic (lymphocytic) or collagenous colitis (chronic watery diarrhea)—normal colonoscopy, but biopsies show superficial colonic epithelial inflammation and, in collagenous colitis, a thick subepithelial layer of collagen; response to aminosalicylates and glucocorticoids variable.

## EXTRAINTESTINAL MANIFESTATIONS OF UC AND CD

1. *Joint:* peripheral arthritis—parallels activity of bowel disease; ankylosing spondylitis and sacroiliitis (associated with HLA-B27)—activity independent of bowel disease
2. *Skin:* erythema nodosum, aphthous ulcers, pyoderma gangrenosum, cutaneous CD
3. *Eye:* conjunctivitis, episcleritis, iritis, uveitis
4. *Liver:* fatty liver, "pericholangitis" (intrahepatic sclerosing cholangitis), primary sclerosing cholangitis, cholangiocarcinoma, chronic hepatitis
5. *Others:* autoimmune hemolytic anemia, phlebitis, pulmonary embolus (hypercoagulable state), kidney stones, metabolic bone disease

## TREATMENT INFLAMMATORY BOWEL DISEASES (FIG. 48-1)

**SUPPORTIVE** Antidiarrheal agents (diphenoxylate and atropine, loperamide) in mild disease; IV hydration and blood transfusions in severe disease; parenteral nutrition or defined enteral formulas—effective as primary therapy in CD, although high relapse rate when oral feeding is resumed; should not replace drug therapy; important role in preoperative preparation of malnourished pt; emotional support.

**SULFASALAZINE AND AMINOSALICYLATES** Active component of sulfasalazine is 5-aminosalicylic acid (5-ASA) linked to sulfapyridine carrier; useful in colonic disease of mild to moderate severity (1–1.5 g PO qid); efficacy in maintaining remission demonstrated only for UC (500 mg PO qid). Toxicity (generally due to sulfapyridine component): dose related—nausea, headache, rarely hemolytic anemia—may resolve when drug dose is lowered; idiosyncratic—fever, rash, neutropenia, pancreatitis, hepatitis, etc.; miscellaneous—oligospermia. Newer aminosalicylates are as effective as sulfasalazine but with fewer side effects. Enemas containing 4 g of 5-ASA (mesalamine) may be used in distal UC, one nightly retained qhs until remission, then q2hs or q3hs. Suppositories containing 500 mg of 5-ASA may be used in proctitis.

**GLUCOCORTICOIDS** Useful in severe disease and ileal or ileocolonic CD. Prednisone, 40–60 mg PO qd, then taper; IV hydrocortisone, 100 mg tid or equivalent, in hospitalized pts; IV adrenocorticotropic hormone drip (120 U qd) may be preferable in first attacks of UC. Nightly hydrocortisone retention enemas in proctosigmoiditis. Numerous side effects make long-term use problematic.

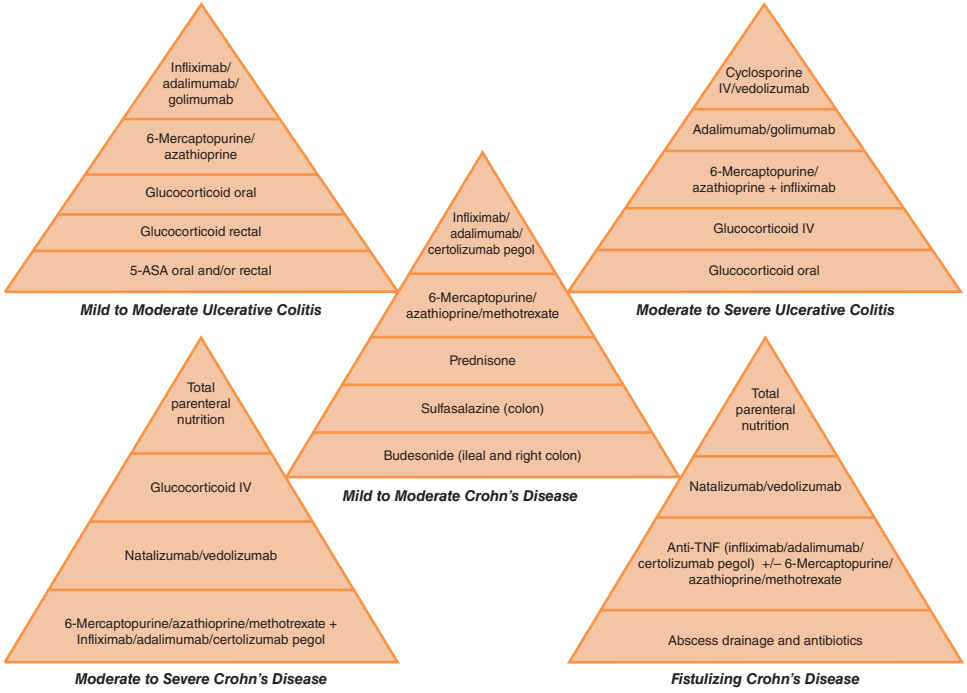


**FIGURE 148-1** Medical management of IBD. 5-ASA, 5-aminosalicylic acid.

**IMMUNOSUPPRESSIVE AGENTS** Azathioprine, 6-mercaptopurine—50 mg PO qd up to 2.0 or 1.5 mg/kg qd, respectively. Useful as steroid-sparing agents and in intractable or fistulous CD (may require 2- to 6-month trial before efficacy seen). Toxicity—immunosuppression, pancreatitis, ?carcinogenicity. Avoid in pregnancy.

**METRONIDAZOLE** Appears effective in colonic CD (500 mg PO bid) and refractory perineal CD (10–20 mg/kg PO qd). Toxicity—peripheral neuropathy, metallic taste, ?carcinogenicity. Avoid in pregnancy. Other antibiotics (e.g., ciprofloxacin 500 mg PO bid) may be of value in terminal ileal and perianal CD, and broad-spectrum IV antibiotics are indicated for fulminant colitis and abscesses.

**OTHERS** Cyclosporine (potential value in a dose of 4 [mg/kg]/d IV for 7–14 days in severe UC and possibly intractable Crohn's fistulas); experimental—tacrolimus, methotrexate, chloroquine, fish oil, nicotine, others. Infliximab (monoclonal antibody to tumor necrosis factor [TNF]) 5 mg/kg IV induces responses in 65% (complete in 33%) of CD pts refractory to 5-ASA, glucocorticoids, and 6-mercaptopurine. In UC, 27–49% of pts respond.

Adalimumab is a humanized version of the anti-TNF antibody that is less likely to elicit neutralizing antibodies in the pt. Pegylated versions of anti-TNF antibody may be used once monthly.

Natalizumab is an anti-integrin antibody with activity against CD, but some pts develop progressive multifocal leukoencephalopathy. Vedolizumab is specific for α4β7 integrin and is more gut selective in its effects.

**SURGERY** UC: Colectomy (curative) for intractability, toxic megacolon (if no improvement with aggressive medical therapy in 24–48 h), cancer, dysplasia. Ileal pouch—anal anastomosis is operation of choice in UC, but contraindicated in CD and in elderly. CD: Resection for fixed obstruction (or stricturoplasty), abscesses, persistent symptomatic fistulas, intractability.

For a more detailed discussion, see Friedman S, Blumberg RS: Inflammatory Bowel Disease, Chap. 351, p. 1947, in HPIM-19.

# 149 Colonic and Anorectal Diseases

## IRRITABLE BOWEL SYNDROME (IBS)

Characterized by altered bowel habits, abdominal pain, and absence of detectable organic pathology. Most common GI disease in clinical practice. Three types of clinical presentations: (1) spastic colon (chronic abdominal pain and constipation), (2) alternating constipation and diarrhea, or (3) chronic, painless diarrhea.

### PATHOPHYSIOLOGY

Visceral hyperalgesia to mechanoreceptor stimuli is common. Reported abnormalities include altered colonic motility at rest and in response to stress, cholinergic drugs, cholecystokinin; altered small-intestinal motility; enhanced visceral sensation

**TABLE 149-1 DIAGNOSTIC CRITERIA FOR IRRITABLE BOWEL SYNDROME[a]**

Recurrent abdominal pain or discomfort[b] at least 3 days per month in the last 3 months associated with *two or more* of the following:

1. Improvement with defecation
2. Onset associated with a change in frequency of stool
3. Onset associated with a change in form (appearance) of stool

[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.
[b]Discomfort means an uncomfortable sensation not described as pain. In pathophysiology research and clinical trials, a pain/discomfort frequency of at least 2 days a week during screening evaluation is required for subject eligibility.
***Source:*** Adapted from Longstreth GF et al: Functional bowel disorders. *Gastroenterology* 130:1480, 2006.

(lower pain threshold in response to gut distention); and abnormal extrinsic innervation of the gut. Pts presenting with IBS to a physician have an increased frequency of psychological disturbances—depression, hysteria, obsessive-compulsive disorder. Specific food intolerances and malabsorption of bile acids by the terminal ileum may account for a few cases.

## CLINICAL MANIFESTATIONS

Onset often before age 30; females:males = 2:1. Abdominal pain and irregular bowel habits. Additional symptoms often include abdominal distention, relief of abdominal pain with bowel movement, increased frequency of stools with pain, loose stools with pain, mucus in stools, and sense of incomplete evacuation. Associated findings include pasty stools, ribbony or pencil-thin stools, heartburn, bloating, back pain, weakness, faintness, palpitations, and urinary frequency.

## DIAGNOSIS

IBS is a diagnosis of exclusion. Rome criteria for diagnosis are shown in Table 149-1. Consider sigmoidoscopy and barium radiographs to exclude inflammatory bowel disease or malignancy; consider excluding giardiasis, intestinal lactase deficiency, and hyperthyroidism.

## TREATMENT IRRITABLE BOWEL SYNDROME (TABLE 149-2)

Reassurance and supportive physician-pt relationship, avoidance of stress or precipitating factors, dietary bulk (fiber, psyllium extract, e.g., Metamucil one tbsp daily or bid); for diarrhea, trials of loperamide (2-mg tabs PO q A.M. then 1 PO after each loose stool to a maximum of 8/d, then titrate), diphenoxylate (Lomotil) (up to 2-mg tabs PO qid), or cholestyramine (up to 1-g packet mixed in water PO qid); for pain, anticholinergics (e.g., dicyclomine HCl 10–40 mg PO qid) or hyoscyamine as Levsin 1–2 PO q4h prn. Amitriptyline 25–50 mg PO qhs or other antidepressants in low doses may relieve pain. Selective serotonin reuptake inhibitors such as paroxetine are being evaluated in constipation-dominant pts, and serotonin receptor antagonists such as alosetron are being evaluated in diarrhea-dominant pts. Altering gut flora with probiotics (*Bifidobacterium infantis* 35624) or oral nonabsorbable antibiotics (rifaximin) is being evaluated with some promising early results. Psychotherapy, hypnotherapy of possible benefit in severe refractory cases. Some pts respond to dietary changes to eliminate or severely reduce fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPS).

**TABLE 149-2 POSSIBLE DRUGS FOR A DOMINANT SYMPTOM IN IBS**

| Symptom | Drug | Dose |
|---|---|---|
| Diarrhea | Loperamide | 2–4 mg when necessary/ maximum 12 g/d |
| | Cholestyramine resin | 4 g with meals |
| | Alosetron[a] | 0.5–1 mg bid (for severe IBS, women) |
| Constipation | Psyllium husk | 3–4 g bid with meals, then adjust |
| | Methylcellulose | 2 g bid with meals, then adjust |
| | Calcium polycarbophil | 1 g qd to qid |
| | Lactulose syrup | 10–20 g bid |
| | 70% sorbitol | 15 mL bid |
| | Polyethylene glycol 3350 | 17 g in 250 mL water qd |
| | Lubiprostone (Amitiza) | 24 mg bid |
| | Magnesium hydroxide | 30–60 mL qd |
| Abdominal pain | Smooth-muscle relaxant | qd to qid ac |
| | Tricyclic antidepressants | Start 25–50 mg hs, then adjust |
| | Selective serotonin reuptake inhibitors | Begin small dose, increase as needed |

[a]Available only in the United States.
***Abbreviation:*** IBS, irritable bowel syndrome.
***Source:*** Adapted from Longstreth GF et al: Functional bowel disorders. *Gastroenterology* 130:1480, 2006.

## DIVERTICULAR DISEASE

Herniations or saclike protrusions of the mucosa through the muscularis at points of nutrient artery penetration; possibly due to increased intraluminal pressure, low-fiber diet; most common in sigmoid colon.

### CLINICAL PRESENTATION

1. *Asymptomatic* (detected by barium enema or colonoscopy).
2. *Pain*: recurrent left lower quadrant pain relieved by defecation; alternating constipation and diarrhea. Diagnosis by barium enema.
3. *Diverticulitis*: pain, fever, altered bowel habits, tender colon, leukocytosis. Best confirmed and staged by CT after opacification of bowel. (In pts who recover with medical therapy, perform elective barium enema or colonoscopy in 4–6 weeks to exclude cancer.) Complications: pericolic abscess, perforation, fistula (to bladder, vagina, skin, soft tissue), liver abscess, stricture. Frequently require surgery or, for abscesses, percutaneous drainage.
4. *Hemorrhage*: usually in absence of diverticulitis, often from ascending colon and self-limited. If persistent, manage with mesenteric arteriography and intra-arterial infusion of vasopressin, or surgery (Chap. 41).

### TREATMENT DIVERTICULAR DISEASE

**PAIN** High-fiber diet, psyllium extract (e.g., Metamucil 1 tbsp PO qd or bid), anticholinergics (e.g., dicyclomine HCl 10–40 mg PO qid).

**DIVERTICULITIS** NPO, IV fluids, antibiotics for 7–10 d (e.g., trimethoprim/sulfamethoxazole or ciprofloxacin and metronidazole; add ampicillin to cover enterococci in

nonresponders); for ambulatory pts, ampicillin/clavulanate (clear liquid diet); surgical resection in refractory or frequently recurrent cases, young persons (<age 50), immunosuppressed pts, or when there is inability to exclude cancer.

Pts who have had at least two documented episodes and those who respond slowly to medical therapy should be offered surgical options to achieve removal of the diseased colonic segment, controlling sepsis, eliminating obstructions or fistulas, and restoring intestinal continuity.

## INTESTINAL PSEUDOOBSTRUCTION

Recurrent attacks of nausea, vomiting, and abdominal pain and distention mimicking mechanical obstruction; may be complicated by steatorrhea due to bacterial overgrowth.

### CAUSES

*Primary:* Familial visceral neuropathy, familial visceral myopathy, idiopathic. *Secondary:* Scleroderma, amyloidosis, diabetes, celiac disease, parkinsonism, muscular dystrophy, drugs, electrolyte imbalance, postsurgical.

### TREATMENT INTESTINAL PSEUDOOBSTRUCTION

For acute attacks: intestinal decompression with long tube. Oral antibiotics for bacterial overgrowth (e.g., metronidazole 250 mg PO tid, tetracycline 500 mg PO qid, or ciprofloxacin 500 mg bid 1 week out of each month, usually in an alternating rotation of at least two antibiotics). Avoid surgery. In refractory cases, consider long-term parenteral hyperalimentation.

## VASCULAR DISORDERS (SMALL AND LARGE INTESTINE)

### MECHANISMS OF MESENTERIC ISCHEMIA

(1) Occlusive: embolus (atrial fibrillation, valvular heart disease); arterial thrombus (atherosclerosis); venous thrombosis (trauma, neoplasm, infection, cirrhosis, oral contraceptives, antithrombin-III deficiency, protein S or C deficiency, lupus anticoagulant, factor V Leiden mutation, idiopathic); vasculitis (systemic lupus erythematosus, polyarteritis, rheumatoid arthritis, Henoch-Schönlein purpura); (2) nonocclusive: hypotension, heart failure, arrhythmia, digitalis (vasoconstrictor).

### ACUTE MESENTERIC ISCHEMIA

Periumbilical pain out of proportion to tenderness; nausea, vomiting, distention, GI bleeding, altered bowel habits. Abdominal x-ray shows bowel distention, air-fluid levels, thumbprinting (submucosal edema), but may be normal early in course. Peritoneal signs indicate infarcted bowel requiring surgical resection. Early celiac and mesenteric arteriography is recommended in all cases following hemodynamic resuscitation (avoid vasopressors, digitalis). Intra-arterial vasodilators (e.g., papaverine) can be administered to reverse vasoconstriction. Laparotomy indicated to restore intestinal blood flow obstructed by embolus or thrombosis or to resect necrotic bowel. Postoperative anticoagulation indicated in mesenteric venous thrombosis, controversial in arterial occlusion.

### CHRONIC MESENTERIC INSUFFICIENCY

"Abdominal angina": dull, crampy periumbilical pain 15–30 min after a meal and lasting for several hours; weight loss; occasionally diarrhea. Evaluate with mesenteric arteriography for possible bypass graft surgery.

### ISCHEMIC COLITIS

Usually due to nonocclusive disease in pts with atherosclerosis. Severe lower abdominal pain, rectal bleeding, hypotension. Abdominal x-ray shows colonic dilation, thumbprinting. Sigmoidoscopy shows submucosal hemorrhage, friability, ulcerations; rectum often spared. Conservative management (NPO, IV fluids); surgical resection for infarction or postischemic stricture.

## COLONIC ANGIODYSPLASIA

In persons over age 60, vascular ectasias, usually in right colon, account for up to 40% of cases of chronic or recurrent lower GI bleeding. May be associated with aortic stenosis. Diagnosis is by arteriography (clusters of small vessels, early and prolonged opacification of draining vein) or colonoscopy (flat, bright red, fernlike lesions). For bleeding, treat by colonoscopic electro- or laser coagulation, band ligation, arteriographic embolization, or, if necessary, right hemicolectomy (Chap. 41).

## ANORECTAL DISEASES

### HEMORRHOIDS

Due to increased hydrostatic pressure in hemorrhoidal venous plexus (associated with straining at stool, pregnancy). May be external, internal, thrombosed, acute (prolapsed or strangulated), or bleeding. Treat pain with bulk laxative and stool softeners (psyllium extract, dioctyl sodium sulfosuccinate 100–200 mg/d), sitz baths one to four per day, witch hazel compresses, analgesics as needed. Bleeding may require rubber band ligation or injection sclerotherapy. Operative hemorrhoidectomy in severe or refractory cases.

### ANAL FISSURES

Medical therapy as for hemorrhoids. Relaxation of the anal canal with nitroglycerin ointment (0.2%) applied tid or botulinum toxin type A up to 20 U injected into the internal sphincter on each side of the fissure. Internal anal sphincterotomy in refractory cases.

### PRURITUS ANI

Often of unclear cause; may be due to poor hygiene, fungal or parasitic infection. Treat with thorough cleansing after bowel movement, topical glucocorticoid, and antifungal agent if indicated.

### ANAL CONDYLOMAS (GENITAL WARTS)

Wartlike papillomas due to sexually transmitted papillomavirus. Treat with cautious application of liquid nitrogen or podophyllotoxin or with intralesional interferon α. Tend to recur. May be prevented by vaccination with human papilloma virus (HPV) vaccine.

For a more detailed discussion, see Owyang C: Irritable Bowel Syndrome, Chap. 352, p. 1965; Ahmed R, Gearhart SL: Diverticular Disease and Common Anorectal Disorders, Chap. 353, p. 1971; Ahmed R, Malas M: Mesenteric Vascular Insufficiency, Chap. 354, p. 1978, in HPIM-19.

# 150 Cholelithiasis, Cholecystitis, and Cholangitis

## CHOLELITHIASIS

There are two major types of gallstones: cholesterol and pigment stones. Cholesterol gallstones contain >50% cholesterol monohydrate. Pigment stones have <20% cholesterol and are composed primarily of calcium bilirubinate. In the United States, 80% of stones are cholesterol and 20% are pigment.

### EPIDEMIOLOGY

One million new cases of cholelithiasis per year in the United States. Predisposing factors include demographic/genetics (increased prevalence in North American Indians), obesity, weight loss, female sex hormones, age, ileal disease, pregnancy, type IV hyperlipidemia, and cirrhosis.

### SYMPTOMS AND SIGNS

Many gallstones are "silent," i.e., present in asymptomatic pts. Symptoms occur when stones trigger inflammation or cause obstruction of the cystic or common bile ducts (CBDs). Major symptoms: (1) biliary colic—a severe steady ache in the RUQ or epigastrium that begins suddenly; often occurs 30–90 min after meals, lasts for several hours, and occasionally radiates to the right scapula or back; (2) nausea, vomiting. Physical examination may be normal or show epigastric or RUQ tenderness.

### LABORATORY

Occasionally, mild and transient elevations in bilirubin (<85 μmol/L [<5 mg/dL]) accompany biliary colic.

### IMAGING

Only 10% of cholesterol gallstones are radiopaque. Ultrasonography is best diagnostic test. The oral cholecystogram has been largely replaced by ultrasound, but may be used to assess the patency of the cystic duct and gallbladder emptying function (Table 150-1).

### DIFFERENTIAL DIAGNOSIS

Includes peptic ulcer disease (PUD), gastroesophageal reflux, irritable bowel syndrome, and hepatitis.

### COMPLICATIONS

Cholecystitis, pancreatitis, cholangitis.

## TREATMENT CHOLELITHIASIS

In asymptomatic pts, risk of developing complications requiring surgery is small. Elective cholecystectomy should be reserved for: (1) symptomatic pts (i.e., biliary colic despite low-fat diet); (2) persons with previous complications of cholelithiasis (see below); and (3) presence of an underlying condition predisposing to an increased risk of complications (calcified or porcelain gallbladder). Pts with gallstones >3 cm or with an anomalous gallbladder containing stones should also

**TABLE 150-1 DIAGNOSTIC EVALUATION OF THE BILE DUCTS**

| Diagnostic Advantages | Diagnostic Limitations |
|---|---|
| **Hepatobiliary ultrasound** | |
| Rapid | Bowel gas |
| Simultaneous scanning of GB, liver, bile ducts, pancreas | Massive obesity<br>Ascites |
| Accurate identification of dilated bile ducts | Barium |
| Not limited by jaundice, pregnancy | Partial bile duct obstruction |
| Guidance for fine-needle biopsy | Poor visualization of distal CBD |
| **Computed tomography** | |
| Simultaneous scanning of GB, liver, bile ducts, pancreas | Extreme cachexia<br>Movement artifact |
| Accurate identification of dilated bile ducts, masses | Ileus<br>Partial bile duct obstruction |
| Not limited by jaundice, gas, obesity, ascites | |
| High-resolution image | |
| Guidance for fine-needle biopsy | |
| **Magnetic resonance cholangiopancreatography** | |
| Useful modality for visualizing pancreatic and biliary ducts | Cannot offer therapeutic intervention |
| Has excellent sensitivity for bile duct dilation, biliary stricture, and intraductal abnormalities | High cost |
| Can identify pancreatic duct dilation or stricture, pancreatic duct stenosis, and pancreas divisum | |
| **Endoscopic retrograde cholangiopancreatography** | |
| Simultaneous pancreatography | Gastroduodenal obstruction |
| Best visualization of distal biliary tract | ?Roux-en-Y biliary-enteric anastomosis |
| Bile or pancreatic cytology | |
| Endoscopic sphincterotomy and stone removal | |
| Biliary manometry | |
| **Percutaneous transhepatic cholangiogram** | |
| Extremely successful when bile ducts dilated | Nondilated or sclerosed ducts |
| Best visualization of proximal biliary tract | |
| Bile cytology/culture | |
| Percutaneous transhepatic drainage | |
| **Endoscopic ultrasound** | |
| Most sensitive method to detect ampullary stones | |

***Abbreviations:*** CBD, common bile duct; GB, gallbladder.

be considered for surgery. Laparoscopic cholecystectomy is minimally invasive and is the procedure of choice for most pts undergoing elective cholecystectomy. Oral dissolution agents (ursodeoxycholic acid) partially or completely dissolve small radiolucent stones in 50% of selected pts within 6–24 months. Because of the frequency of stone recurrence and the effectiveness of laparoscopic surgery,

the role of oral dissolution therapy has been largely confined to pts who are not candidates for elective cholecystectomy.

## ACUTE CHOLECYSTITIS

Acute inflammation of the gallbladder is usually caused by cystic duct obstruction by an impacted stone. Inflammatory response is evoked by (1) mechanical inflammation from increased intraluminal pressure; (2) chemical inflammation from release of lysolecithin; (3) bacterial inflammation, which plays a role in 50–85% of pts with acute cholecystitis.

### ETIOLOGY

Approximately 90% calculous; 10% acalculous. Acalculous cholecystitis is associated with higher complication rate and acute illness (i.e., burns, trauma, major surgery), fasting, hyperalimentation leading to gallbladder stasis, vasculitis, carcinoma of gallbladder or CBD, some gallbladder infections (*Leptospira*, *Streptococcus*, *Salmonella*, or *Vibrio cholerae*), but in >50% of cases an underlying explanation is not found.

### SYMPTOMS AND SIGNS

(1) Biliary colic (RUQ or epigastric pain) that progressively worsens; (2) nausea, vomiting, anorexia; and (3) fever. Examination typically reveals RUQ tenderness; palpable RUQ mass found in 20% of pts. *Murphy's sign* is present when deep inspiration or cough during palpation of the RUQ produces increased pain or inspiratory arrest.

### LABORATORY

Mild leukocytosis; serum bilirubin, alkaline phosphatase, and aspartate aminotransferase (AST) may be mildly elevated.

### IMAGING

Ultrasonography is useful for demonstrating gallstones and occasionally a phlegmonous mass surrounding the gallbladder. Radionuclide scans (HIDA, DIDA, DISIDA, etc.) may identify cystic duct obstruction.

### DIFFERENTIAL DIAGNOSIS

Includes acute pancreatitis, appendicitis, pyelonephritis, PUD, hepatitis, and hepatic abscess.

### COMPLICATIONS

Empyema, hydrops, gangrene, perforation, fistulization, gallstone ileus, porcelain gallbladder.

### TREATMENT ACUTE CHOLECYSTITIS

No oral intake, nasogastric suction, IV fluids and electrolytes, analgesia (meperidine or NSAIDs), and antibiotics (ureidopenicillins, ampicillin sulbactam, ciprofloxacin, third-generation cephalosporins; anaerobic coverage should be added if gangrenous or emphysematous cholecystitis is suspected; imipenem/meropenem covers the spectrum of bacteria causing ascending cholangitis but should be reserved for the most life-threatening infections when other antibiotics have failed). Acute symptoms will resolve in 70% of pts. Optimal timing of surgery depends on pt stabilization and should be performed as soon as feasible. Urgent cholecystectomy is appropriate in most pts with a suspected or confirmed complication. Delayed surgery is reserved for pts with high risk of emergent surgery and where the diagnosis is in doubt.

## CHRONIC CHOLECYSTITIS

### ETIOLOGY

Chronic inflammation of the gallbladder; almost always associated with gallstones. Results from repeated acute/subacute cholecystitis or prolonged mechanical irritation of gallbladder wall.

### SYMPTOMS AND SIGNS

May be asymptomatic for years, may progress to symptomatic gallbladder disease or to acute cholecystitis, or present with complications.

### LABORATORY

Tests are usually normal.

### IMAGING

Ultrasonography preferred; usually shows gallstones within a contracted gallbladder (Table 150-1).

### DIFFERENTIAL DIAGNOSIS

PUD, esophagitis, irritable bowel syndrome.

**TREATMENT CHRONIC CHOLECYSTITIS**

Surgery indicated if pt is symptomatic.

## CHOLEDOCHOLITHIASIS/CHOLANGITIS

### ETIOLOGY

In pts with cholelithiasis, passage of gallstones into CBD occurs in 10–15%; increases with age. At cholecystectomy, undetected stones are left behind in 1–5% of pts.

### SYMPTOMS AND SIGNS

Choledocholithiasis may present as an incidental finding, biliary colic, obstructive jaundice, cholangitis, or pancreatitis. Cholangitis usually presents as fever, RUQ pain, and jaundice (*Charcot's triad*).

### LABORATORY

Elevations in serum bilirubin, alkaline phosphatase, and aminotransferases. Leukocytosis usually accompanies cholangitis; blood cultures are frequently positive. Amylase is elevated in 15% of cases.

### IMAGING

Diagnosis usually made by cholangiography either preoperatively by endoscopic retrograde cholangiopancreatography (ERCP) or intraoperatively at the time of cholecystectomy. Ultrasonography may reveal dilated bile ducts but is not sensitive for detecting CBD stones (Table 150-1).

### DIFFERENTIAL DIAGNOSIS

Acute cholecystitis, renal colic, perforated viscus, pancreatitis.

### COMPLICATIONS

Cholangitis, obstructive jaundice, gallstone-induced pancreatitis, and secondary biliary cirrhosis.

## TREATMENT CHOLEDOCHOLITHIASIS/CHOLANGITIS

Laparoscopic cholecystectomy and ERCP have decreased the need for choledocholithotomy and T-tube drainage of the bile ducts. When CBD stones are suspected prior to laparoscopic cholecystectomy, preoperative ERCP with endoscopic papillotomy and stone extraction is the preferred approach. CBD stones should be suspected in gallstone pts with (1) history of jaundice or pancreatitis, (2) abnormal LFT, and (3) ultrasound evidence of a dilated CBD or stones in the duct. Cholangitis treated like acute cholecystitis; no oral intake, hydration, analgesia, and antibiotics are the mainstays; stones should be removed surgically or endoscopically.

## PRIMARY SCLEROSING CHOLANGITIS (PSC)

PSC is a sclerosing, inflammatory, and obliterative process involving the biliary tree.

### ETIOLOGY

Associations: inflammatory bowel disease (75% of cases of PSC—especially ulcerative colitis), AIDS, rarely retroperitoneal fibrosis.

### SYMPTOMS AND SIGNS

Pruritus, RUQ pain, jaundice, fever, weight loss, and malaise. Approximately 44% may be asymptomatic at diagnosis. May progress to cirrhosis with portal hypertension.

### LABORATORY

Evidence of cholestasis (elevated bilirubin and alkaline phosphatase) common.

### RADIOLOGY/ENDOSCOPY

Transhepatic or endoscopic cholangiograms reveal stenosis and dilation of the intra- and extrahepatic bile ducts.

### DIFFERENTIAL DIAGNOSIS

Cholangiocarcinoma, Caroli disease (cystic dilation of bile ducts), *Fasciola hepatica* infection, echinococcosis, and ascariasis. IgG4-associated cholangitis.

## TREATMENT PRIMARY SCLEROSING CHOLANGITIS

No satisfactory therapy. Cholangitis should be treated as outlined above. Cholestyramine may control pruritus. Supplemental vitamin D and calcium may retard bone loss. Glucocorticoids, methotrexate, and cyclosporine have not been shown to be effective. Ursodeoxycholic acid improves liver tests but has not been shown to affect survival. Surgical relief of biliary obstruction may be appropriate but has a high complication rate. Liver transplantation should be considered in pts with end-stage cirrhosis. Median survival: 9–12 years after diagnosis, with age, bilirubin level, histologic stage, and splenomegaly being predictors of survival.

For a more detailed discussion, see Greenberger NJ, Paumgartner G: Diseases of the Gallbladder and Bile Ducts, Chap. 369, p. 2075, in HPIM-19.

# 151 Pancreatitis

## ACUTE PANCREATITIS

Any severe acute pain in the abdomen or back should suggest the possibility of acute pancreatitis. The diagnosis is established by two of the following three criteria: (1) typical abdominal pain in the epigastrium that may radiate to the back, (2) threefold or greater elevation in serum lipase and/or amylase, and (3) confirmatory findings of acute pancreatitis on cross-sectional abdominal imaging. The pathologic spectrum of acute pancreatitis varies from *interstitial pancreatitis*, which is usually a mild and self-limited disorder, to *necrotizing pancreatitis*, in which the degree of necrosis may correlate with the severity of the attack and its systemic manifestations.

### ETIOLOGY

Most common causes in the United States are cholelithiasis and alcohol. Others are listed in Table 151-1.

### CLINICAL FEATURES

Can vary from mild abdominal pain to shock. *Common symptoms:* (1) steady, boring pain in the epigastricand periumbilical region may radiate to the back, chest, flanks, and lower abdomen; (2) nausea, vomiting, abdominal distention.

*Physical examination:* (1) low-grade fever, tachycardia, hypotension; (2) erythematous skin nodules due to subcutaneous fat necrosis; (3) basilar rales, pleural effusion (often on the left); (4) abdominal tenderness and rigidity, diminished bowel sounds, palpable upper abdominal mass; (5) Cullen's sign: blue discoloration in the periumbilical area due to hemoperitoneum; (6) Turner's sign: blue-red-purple or green-brown discoloration of the flanks due to tissue catabolism of hemoglobin.

### LABORATORY

1. *Serum amylase:* Large elevations (>3 × normal) virtually assure the diagnosis if salivary gland disease and intestinal perforation/infarction are excluded. However, normal serum amylase does not exclude the diagnosis of acute pancreatitis, and the degree of elevation does not predict severity of pancreatitis. Amylase levels typically return to normal in 3–7 days.
2. *Serum lipase level:* Serum lipase is the preferred test for diagnosis of acute pancreatitis. Increases in parallel with amylase level and measurement of both tests increases the diagnostic yield.
3. *Other tests: Hypocalcemia* occurs in ~25% of pts. *Leukocytosis* (15,000–20,000/μL) occurs frequently. *Hypertriglyceridemia* occurs in 15–20% of cases and can cause a spuriously normal serum amylase level. *Hyperglycemia* is common. *Serum bilirubin, alkaline phosphatase*, and *aspartame aminotransferase* can be transiently elevated. *Hypoalbuminemia* and marked elevations of *serum lactic dehydrogenase* (LDH) are associated with an increased mortality rate. *Hypoxemia* is present in 25% of pts. Arterial pH <7.32 may spuriously elevate serum amylase.

### IMAGING

1. *Abdominal radiographs* can be abnormal but are not specific for pancreatitis and are infrequently used.
2. *Ultrasound* often fails to visualize the pancreas because of overlying intestinal gas but may detect gallstones, pseudocysts, mass lesions, or edema or enlargement of the pancreas.

**TABLE 151-1 CAUSES OF ACUTE PANCREATITIS**

| |
|---|
| **Common Causes** |
| Gallstones (including microlithiasis) |
| Alcohol (acute and chronic alcoholism) |
| Hypertriglyceridemia |
| Endoscopic retrograde cholangiopancreatography (ERCP), especially after biliary manometry |
| Drugs (azathioprine, 6-mercaptopurine, sulfonamides, estrogens, tetracycline, valproic acid, anti-HIV medications, 5-aminosalicylic acid [5-ASA]) |
| Trauma (especially blunt abdominal trauma) |
| Postoperative (abdominal and nonabdominal operations) |
| **Uncommon Causes** |
| Vascular causes and vasculitis (ischemic-hypoperfusion states after cardiac surgery) |
| Connective tissue disorders and thrombotic thrombocytopenic purpura (TTP) |
| Cancer of the pancreas |
| Hypercalcemia |
| Periampullary diverticulum |
| Pancreas divisum |
| Hereditary pancreatitis |
| Cystic fibrosis |
| Renal failure |
| Infections (mumps, coxsackievirus, cytomegalovirus, echovirus, parasites) |
| Autoimmune (e.g., type 1 and type 2) |
| **Causes to Consider in Pts with Recurrent Bouts of Acute Pancreatitis Without an Obvious Etiology** |
| Occult disease of the biliary tree or pancreatic ducts, especially microlithiasis, biliary sludge |
| Drugs |
| Alcohol abuse |
| Metabolic: Hypertriglyceridemia, hypercalcemia |
| Anatomic: Pancreas divisum |
| Pancreatic cancer |
| Intraductal papillary mucinous neoplasm (IPMN) |
| Hereditary pancreatitis |
| Cystic fibrosis |
| Autoimmune |
| Idiopathic |

3. *CT* can confirm the clinical impression of acute pancreatitis. It can also be helpful in evaluating the complications of acute pancreatitis.

## DIFFERENTIAL DIAGNOSIS

Intestinal perforation (especially peptic ulcer), cholecystitis, acute intestinal obstruction, mesenteric vascular occlusion, renal colic, inferior myocardial infarction, aortic dissection, connective tissue disorders, pneumonia, and diabetic ketoacidosis.

## TREATMENT ACUTE PANCREATITIS

Most (90%) cases subside over a period of 3–7 days. Severity should be assessed to determine if ICU care is required. The most important treatment is safe, aggressive IV fluid resuscitation. Other conventional measures: no oral alimentation and analgesics for abdominal pain. Precipitating factors (alcohol, medications) must be eliminated. In mild or moderate pancreatitis, a clear liquid diet can usually be started after 3–6 days.

## COMPLICATIONS

Risk factors and markers of severe acute pancreatitis are listed in Table 151-2. The median prevalence of organ failure is 54% in necrotizing pancreatitis. With single-organ system failure, the mortality is 3–10% but increases to 47% with multisystem organ failure.

**TABLE 151-2 SEVERE ACUTE PANCREATITIS**

| |
|---|
| **Risk Factors for Severity** |
| • Age >60 years |
| • Obesity, BMI >30 |
| • Comorbid disease (Charlson Comorbidity Index) |
| **Markers of Severity at Admission or Within 24 h** |
| • SIRS—defined by presence of 2 or more criteria: |
| • Core temperature <36° or>38°C |
| • Heart rate >90 beats/min |
| • Respirations >20/min or $Pco_2$ <32 mmHg |
| • White blood cell count >12,000/μL, <4000/μL, or 10% bands |
| • APACHE II |
| • Hemoconcentration (hematocrit >44%) |
| • Admission BUN (>22 mg/dL) |
| • BISAP Score |
| – (B) BUN >25 mg/dL |
| – (I) Impaired mental status |
| – (S) SIRS: ≥2 of 4 present |
| – (A) Age >60 years |
| – (P) Pleural effusion |
| • Organ failure (Modified Marshall Score) |
| • Cardiovascular: systolic bp <90 mmHg, heart rate >130 beats/min |
| • Pulmonary: $Pao_2$ <60 mmHg |
| • Renal: serum creatinine >2.0 mg% |
| **Markers of Severity During Hospitalization** |
| • Persistent organ failure |
| • Pancreatic necrosis |

***Abbreviations:*** APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; BISAP, Bedside Index of Severity in Acute Pancreatitis; SIRS, systemic inflammatory response syndrome.

### Systemic

Shock, GI bleeding, common duct obstruction, ileus, splenic infarction or rupture, disseminated intravascular coagulation, subcutaneous fat necrosis, acute respiratory distress syndrome, pleural effusion, acute renal failure, sudden blindness.

### Local

1. Sterile or infected *pancreatic necrosis*—necrosis may become secondarily infected in 40–60% of pts, typically within 1–2 weeks after the onset of pancreatitis. Percutaneous aspiration of necrosis with Gram stain and culture should be performed if there are ongoing signs of possible pancreatic infection such as sustained leukocytosis, fever, or organ failure. Repeated fine-needle aspiration and Gram stain with culture of pancreatic necrosis may be done every 5–7 days in the presence of persistent fever. Repeated CT or MRI imaging should also be considered with any change in clinical course to monitor for complications. *Sterile necrosis* is most often managed conservatively unless complications arise. Once a diagnosis of *infected necrosis* is established and an organism identified, targeted antibiotics should be instituted. Pancreatic debridement (necrosectomy) should be considered for definitive management of *infected necrosis*, but clinical decisions are generally influenced by response to antibiotic treatment and overall clinical condition. A step-up approach (percutaneous or endoscopic transgastric drainage followed, if necessary, by open necrosectomy) has been successfully reported by some pancreatic centers.
2. *Pancreatic pseudocysts* develop over 1–4 weeks in 15% of pts. Abdominal pain is the usual complaint, and a tender upper abdominal mass may be present. Can be detected by abdominal ultrasound or CT. In pts who are stable and uncomplicated, treatment is supportive; pseudocysts that are >5 cm in diameter and persist for >6 weeks should be considered for drainage. In pts with an expanding pseudocyst or one complicated by hemorrhage, rupture, or abscess, surgery should be performed.
3. *Pancreatic ascites* and *pancreatic duct disruption*. Diagnosis can be confirmed on MRCP or ERCP. Placement of a bridging pancreatic stent for at least 6 weeks is >90% effective at resolving the leak.

## CHRONIC PANCREATITIS

Chronic pancreatitis is a disease process characterized by irreversible damage to the pancreas.

### ETIOLOGY

Alcoholism is most frequent cause of clinically apparent chronic pancreatitis; in 25% of adults, etiology is unknown. Other causes are listed in Table 151-3.

### SYMPTOMS AND SIGNS

*Pain* is cardinal symptom. Weight loss, steatorrhea, and other signs and symptoms of malabsorption common. Physical examination often unremarkable.

### LABORATORY

No specific laboratory test for chronic pancreatitis. Serum amylase and lipase levels are often normal. Serum bilirubin and alkaline phosphatase may be elevated. The fecal elastase-1 and small-bowel biopsy are useful in the evaluation of pts with suspected pancreatic steatorrhea. Impaired glucose tolerance is present in >50% of pts. Secretin stimulation test is a relatively sensitive test for pancreatic exocrine deficiency and becomes abnormal when ≥60% of the pancreatic exocrine function has been lost.

### IMAGING

*Plain films* of the abdomen reveal pancreatic calcifications in 30–60%. *CT scan* is the imaging modality of choice followed by MRI, endoscopic ultrasound, and pancreas function testing.

**TABLE 151-3 CHRONIC PANCREATITIS AND PANCREATIC EXOCRINE INSUFFICIENCY: TIGAR-O CLASSIFICATION SYSTEM**

| | |
|---|---|
| **Toxic-metabolic** | **Autoimmune** |
| Alcoholic | Type 1 autoimmune chronic pancreatitis |
| Tobacco smoking | IgG4 systemic |
| Hypercalcemia | Type 2 autoimmune chronic pancreatitis |
| Hyperlipidemia | **Recurrent and severe acute pancreatitis** |
| Chronic renal failure | Postnecrotic (severe acute pancreatitis) |
| Medications—phenacetin abuse | Recurrent acute pancreatitis |
| Toxins—organotin compounds (e.g., dibutylin dichloride, DBTC) | Vascular diseases/ischemia |
| **Idiopathic** | Radiation induced |
| Early onset | **Obstructive** |
| Late onset | Pancreas divisum |
| Tropical | Duct obstruction (e.g., tumor) |
| **Genetic** | Preampullary duodenal wall cysts |
| Cationic trypsinogen (*PRSS1*) | Posttraumatic pancreatic duct scars |
| Cystic fibrosis transmembrane conductance regulator gene (*CFTR*) | |
| Calcium-sensing receptor (*CASR*) | |
| Chymotrypsin C gene (*CTRC*) | |
| Pancreatic secretory trypsin inhibitor gene (*SPINK1*) | |

***Abbreviations:*** DBTC, dibutylin dichloride; TIGAR-O, toxic-metabolic, idiopathic, genetic, autoimmune, recurrent and severe acute pancreatitis, obstructive.

## DIFFERENTIAL DIAGNOSIS

Important to distinguish from pancreatic carcinoma; may require radiographically guided biopsy.

## TREATMENT CHRONIC PANCREATITIS

Aimed at controlling pain and malabsorption. The management of pain in pts with chronic pancreatitis is problematic. Recent meta-analyses have shown no consistent benefit of enzyme therapy at reducing pain in chronic pancreatitis. A recent prospective study reported that pregabalin can improve pain in chronic pancreatitis and lower pain medication requirement. Surgery with ductal decompression may control pain if there is a large-duct disease. Subtotal pancreatectomy may also control pain but at the cost of exocrine insufficiency and diabetes. Malabsorption is managed with a low-fat diet and pancreatic enzyme replacement. Because pancreatic enzymes are inactivated by acid, agents that reduce acid production (e.g., omeprazole or sodium bicarbonate) may improve their efficacy (but should not be given with enteric-coated preparations). Insulin may be necessary to control serum glucose.

### COMPLICATIONS

Chronic abdominal pain, gastroparesis, malabsorption/maldigestion, impaired glucose tolerance. Nondiabetic retinopathy due to vitamin A and/or zinc deficiency. GI bleeding, icterus, effusions, subcutaneous fat necrosis, and metabolic bone disease. Increased risk for pancreatic carcinoma. Narcotic addiction common.

For a more detailed discussion, see Conwell DL, Greenberger NJ, Banks PA: Approach to the Patient with Pancreatic Disease, Chap. 370, p. 2086; Conwell DL, Banks PA, Greenberger NJ: Acute and Chronic Pancreatitis, Chap. 371, p. 2090, in HPIM-19.

# 152 Acute Hepatitis

## VIRAL HEPATITIS

*Acute viral hepatitis* is a systemic infection predominantly affecting the liver. Clinically characterized by malaise, nausea, vomiting, diarrhea, and low-grade fever followed by dark urine, jaundice, and tender hepatomegaly; may be subclinical and detected on basis of elevated aspartate and alanine aminotransferase (AST and ALT) levels. Hepatitis B may be associated with immune-complex phenomena, including arthritis, serum sickness-like illness, glomerulonephritis, and a polyarteritis nodosa–like vasculitis. Hepatitis-like illnesses may be caused not only by hepatotropic viruses (A, B, C, D, E) but also by other viruses (Epstein-Barr, CMV, coxsackievirus, etc.), alcohol, drugs, hypotension and ischemia, and biliary tract disease (Table 152-1).

### HEPATITIS A (HAV)

27-nm picornavirus (hepatovirus) with single-stranded RNA genome.

#### Clinical Course See Fig. 152-1.

#### Outcome

Recovery within 6–12 months, usually with no clinical sequelae; a small proportion will have one or two apparent clinical and serologic relapses; in some cases, pronounced cholestasis suggesting biliary obstruction may occur; rare fatalities (fulminant hepatitis), no chronic carrier state.

#### Diagnosis

IgM anti-HAV in acute or early convalescent serum sample.

#### Epidemiology

Fecal-oral transmission; endemic in underdeveloped countries; food-borne and waterborne epidemics; outbreaks in day-care centers, residential institutions.

**TABLE 152-1 CLINICAL AND EPIDEMIOLOGIC FEATURES OF VIRAL HEPATITIS**

| Feature | HAV | HBV | HCV | HDV | HEV |
|---|---|---|---|---|---|
| Incubation (days) | 15–45, mean 30 | 30–180, mean 60–90 | 15–160, mean 50 | 30–180, mean 60–90 | 14–60, mean 40 |
| Onset | Acute | Insidious or acute | Insidious | Insidious or acute | Acute |
| Age preference | Children, young adults | Young adults (sexual and percutaneous), babies, toddlers | Any age, but more common in adults | Any age (similar to HBV) | Epidemic cases: young adults (20–40 years); sporadic cases: older adults (>60) |
| Transmission | | | | | |
| Fecal-oral | +++ | – | – | – | +++ |
| Percutaneous | Unusual | +++ | +++ | +++ | – |
| Perinatal | – | +++ | ±[a] | + | – |
| Sexual | ± | ++ | ±[a] | ++ | – |
| Clinical | | | | | |
| Severity | Mild | Occasionally severe | Moderate | Occasionally severe | Mild |
| Fulminant | 0.1% | 0.1–1% | 0.1% | 5–20%[b] | 1–2%[e] |
| Progression to chronicity | None | Occasional (1–10%) (90% of neonates) | Common (85%) | Common[d] | None[f] |
| Carrier | None | 0.1–30%c | 1.5–3.2% | Variable[g] | None |
| Cancer | None | + (neonatal infection) | + | ± | None |
| Prognosis | Excellent | Worse with age, debility | Moderate | Acute good, Chronic poor | Good |

| | | | | | |
|---|---|---|---|---|---|
| Prophylaxis | Ig, inactivated vaccine | HBIG, recombinant vaccine | None | HBV vaccine (none for HBV carriers) | Vaccine |

[a]Primarily with HIV co-infection and high-level viremia in index case; risk ~5%.
[b]Up to 5% in acute HBV/HDV co-infection; up to 20% in HDV superinfection of chronic HBV infection.
[c]Varies considerably throughout the world and in subpopulations within countries; see text.
[d]In acute HBV/HDV co-infection, the frequency of chronicity is the same as that for HBV; in HDV superinfection, chronicity is invariable.
[e]10–20% in pregnant women.
[f]Except as observed in immunosuppressed liver allograft recipients or other immunosuppressed hosts.
[g]Common in Mediterranean countries; rare in North America and western Europe.
***Abbreviation:*** HBIG, hepatitis B immunoglobulin. See text for other abbreviations.

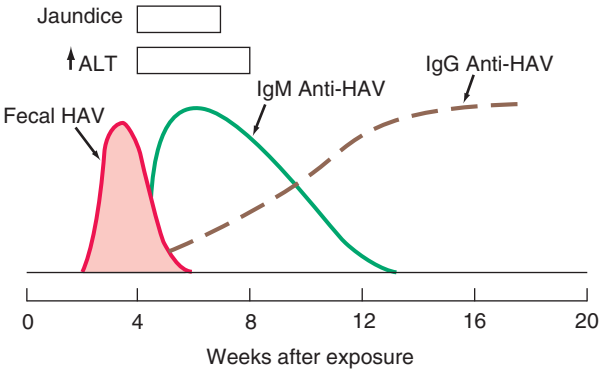


**FIGURE 152-1** Scheme of typical clinical and laboratory features of HAV. ALT, alanine aminotransferase.

## Prevention

*After exposure*: immune globulin 0.02 mL/kg IM within 2 weeks to household and institutional contacts (not casual contacts at work). *Before exposure*: inactivated HAV vaccine 1 mL IM (unit dose depends on formulation); half dose to children; repeat at 6–12 months; target travelers, military recruits, animal handlers, day-care personnel, laboratory workers, and pts with chronic liver disease (especially hepatitis C).

### HEPATITIS B (HBV)

42-nm hepadnavirus with outer surface coat (HBsAg), inner nucleocapsid core (HBcAg), DNA polymerase, and partially double-stranded DNA genome of 3200 nucleotides. Circulating form of HBcAg is HBeAg, a marker of viral replication and infectivity. Multiple serotypes and genetic heterogeneity.

## Clinical Course See Fig. 152-2.

## Outcome

Recovery >90%, fulminant hepatitis (<1%), chronic hepatitis or carrier state (only 1–2% of immunocompetent adults; higher in neonates, elderly, immunocompromised), cirrhosis, and hepatocellular carcinoma (especially following chronic infection beginning in infancy or early childhood) (Chap. 154). Reactivation of HBV has been observed with immunosuppression, particularly with rituximab.

## Diagnosis

HBsAg in serum (acute or chronic infection); IgM anti-HBc (early anti-HBc indicative of acute or recent infection). Most sensitive test is detection of HBV DNA in serum; not generally required for routine diagnosis.

## Epidemiology

Percutaneous (needle stick), sexual, or perinatal transmission. Endemic in sub-Saharan Africa and Southeast Asia, where up to 20% of population acquire infection, usually early in life.

## Prevention

*After exposure in unvaccinated persons:* hepatitis B immune globulin (HBIG) 0.06 mL/kg IM immediately after needle stick to within 14 days of sexual exposure in

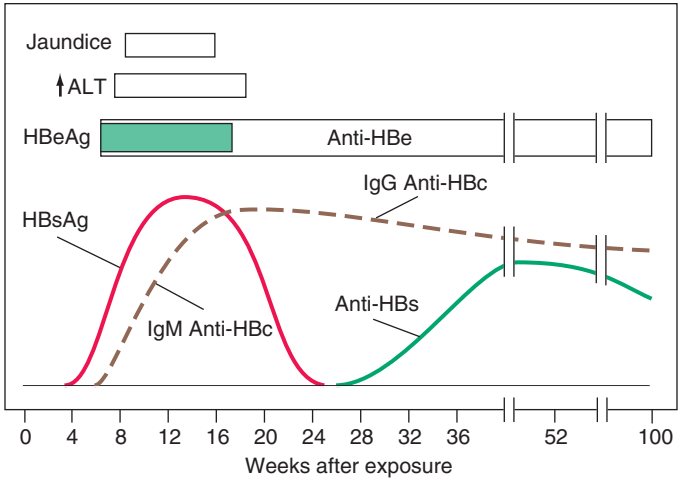


**FIGURE 152-2** Scheme of typical clinical and laboratory features of HBV. ALT, alanine aminotransferase.

combination with vaccine series. For perinatal exposure (HbsAg+ mother) HBIG 0.05 mL in the thigh immediately after birth with the vaccine series started within the first 12 h of life. *Before exposure*: recombinant hepatitis B vaccine IM (dose depends on formulation as well as adult or pediatric and hemodialysis); at 0, 1, and 6 months; deltoid, not gluteal injection. Has been targeted to high-risk groups (e.g., health workers, persons with multiple sexual partners, IV drug users, hemodialysis pts, hemophiliacs, household and sexual contacts of HBsAg carriers, persons traveling in endemic areas, unvaccinated children <18). Universal vaccination of all children is now recommended in the United States.

## HEPATITIS C (HCV)

Caused by flavi-like virus in the genus Hepacivirus with RNA genome of >9000 nucleotides; genetic heterogeneity. Incubation period 7–8 weeks.

### Clinical Course

Often clinically mild and marked by fluctuating elevations of serum aminotransferase levels; >50% likelihood of chronicity, leading to cirrhosis in >20%.

### Diagnosis

Anti-HCV in serum. Current third-generation immunoassay incorporates proteins from the core, NS3, and NS5 regions. The most sensitive indicator of HCV infection is HCV RNA (Fig. 152-3).

### Epidemiology

HCV accounts for >90% of transfusion-associated hepatitis cases. IV drug use accounts >50% of reported cases of hepatitis C. Little evidence for frequent sexual or perinatal transmission.

### Prevention

Exclusion of paid blood donors, testing of donated blood for anti-HCV. Anti-HCV detected by enzyme immunoassay in blood donors with normal ALT is often falsely positive (30%); result should be confirmed by HCV RNA in serum.

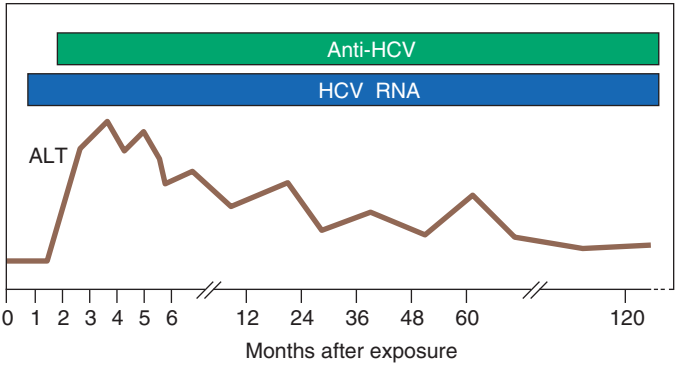


**FIGURE 152-3** Scheme of typical laboratory features during acute hepatitis C progressing to chronicity. HCV RNA is the first detectable event, preceding alanine aminotransferase (ALT) elevation and the appearance of anti-HCV.

### HEPATITIS D (HDV, DELTA AGENT)

Defective 37-nm RNA virus that requires HBV for its replication; either co-infects with HBV or superinfects a chronic HBV carrier. Enhances severity of HBV infection (acceleration of chronic hepatitis to cirrhosis, occasionally fulminant acute hepatitis).

#### Diagnosis

Anti-HDV in serum (acute hepatitis D—often in low titer, is transient; chronic hepatitis D—in higher titer, is sustained).

#### Epidemiology

Endemic among HBV carriers in Mediterranean Basin, where it is spread predominantly by nonpercutaneous means. In nonendemic areas (e.g., northern Europe, United States) HDV is spread percutaneously among HBSAg+ IV drug users or by transfusion in hemophiliacs.

#### Prevention

Hepatitis B vaccine (noncarriers only).

### HEPATITIS E (HEV)

Caused by 29- to 32-nm agent resembling caliciviruses but considered within its own genus, Hepevirus. Enterically transmitted and responsible for waterborne epidemics of hepatitis in India, parts of Asia and Africa, and Central America. Self-limited illness with high (10–20%) mortality rate in pregnant women.

## TREATMENT VIRAL HEPATITIS

Activity as tolerated, high-calorie diet (often tolerated best in morning), IV hydration for severe vomiting, cholestyramine up to 4 g PO four times daily for severe pruritus, avoid hepatically metabolized drugs; no role for glucocorticoids. Liver transplantation for fulminant hepatic failure. In rare instances of severe acute HBV, treatment with a nucleoside analogue has been used successfully. Most authorities would recommend antiviral therapy for severe acute HBV (Chap. 153). For acute HCV, in places where directly acting antivirals are available, delay in treatment initiation for up to 6 months with counseling and monitoring of HCV RNA levels are recommended. The same regimens that are recommended for

treatment naïve pts with chronic HCV infection can then be used for acute infection (Chap. 153).

## TOXIC AND DRUG-INDUCED HEPATITIS

### DOSE-DEPENDENT (DIRECT HEPATOTOXINS)

Onset is within 48 h, predictable, necrosis around terminal hepatic venule–e.g., carbon tetrachloride, benzene derivatives, mushroom poisoning, acetaminophen, or microvesicular steatosis (e.g., tetracyclines, valproic acid).

### IDIOSYNCRATIC

Variable dose and time of onset; small number of exposed persons affected; may be associated with fever, rash, arthralgias, eosinophilia. In many cases, mechanism may actually involve toxic metabolite, possibly determined on genetic basis—e.g., isoniazid, halothane, phenytoin, methyldopa, carbamazepine, diclofenac, oxacillin, sulfonamides.

### TREATMENT TOXIC AND DRUG-INDUCED HEPATITIS

Supportive as for viral hepatitis; withdraw suspected agent, and include use of gastric lavage and oral administration of charcoal or cholestyramine. Liver transplantation if necessary. In acetaminophen overdose, more specific therapy is available in the form of sulfhydryl compounds (e.g., *N*-acetylcysteine). These agents appear to act by providing a reservoir of sulfhydryl groups to bind the toxic metabolites or by stimulating synthesis of hepatic glutathione. Therapy should be begun within 8 h of ingestion but may be effective even if given as late as 24–36 h after overdose.

## FULMINANT HEPATITIS

Massive hepatic necrosis with impaired consciousness occurring within 8 weeks of the onset of illness.

### CAUSES

Infections (viral, including HAV, HBV, HCV [rarely], HDV, HEV; bacterial, rickettsial, parasitic), drugs and toxins, ischemia (shock), Budd-Chiari syndrome, idiopathic chronic active hepatitis, acute Wilson's disease, microvesicular fat syndromes (Reye's syndrome, acute fatty liver of pregnancy).

### CLINICAL MANIFESTATIONS

Pts usually present with signs and symptoms of encephalopathy that may evolve to deep coma. The combination of rapidly shrinking liver size, rapidly rising bilirubin level, and marked prolongation of the PT, even as aminotransferase levels fall, together with clinical signs of confusion, disorientation, somnolence, ascites, and edema, indicates that the pt has hepatic failure with encephalopathy. Cerebral edema is common; brainstem compression, gastrointestinal bleeding, sepsis, respiratory failure, cardiovascular collapse, and renal failure are terminal events. The mortality rate is exceedingly high (>80% in pts with deep coma).

### TREATMENT FULIMINANT HEPATITIS

The goal of therapy is to support the pt by maintenance of fluid balance, support of circulation and respiration, control of bleeding, correction of hypoglycemia, and treatment of other complications of the comatose state in anticipation of liver

regeneration and repair. Protein intake should be restricted, and oral lactulose or neomycin administered. Meticulous intensive care that includes prophylactic antibiotic coverage is the one factor that does appear to improve survival. Liver transplantation should be considered.

For a more detailed discussion, see Dienstag JL: Acute Viral Hepatitis, Chap. 360, p.2004, and Lee WM, Dienstag JL: Toxic and Drug-Induced Hepatitis, Chap. 361, p. 2023, in HPIM-19.

# 153 Chronic Hepatitis

A group of disorders characterized by a chronic inflammatory reaction in the liver for at least 6 months.

## OVERVIEW

### ETIOLOGY

Hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV, delta agent), drugs (methyldopa, nitrofurantoin, isoniazid, dantrolene), autoimmune hepatitis, Wilson's disease, hemochromatosis, $\alpha_1$-antitrypsin deficiency.

### HISTOLOGIC CLASSIFICATION

Chronic hepatitis can be classified by *grade* and *stage*. The grade is a histologic assessment of necrosis and inflammatory activity and is based on examination of the liver biopsy. The stage of chronic hepatitis reflects the level of disease progression and is based on the degree of fibrosis (see Table 362-2, p. 2032, HPIM-19).

### PRESENTATION

Wide clinical spectrum ranging from asymptomatic serum aminotransferase elevations to apparently acute, even fulminant, hepatitis. Common symptoms include fatigue, malaise, anorexia, low-grade fever; jaundice is frequent in severe disease. Some pts may present with complications of cirrhosis: ascites, variceal bleeding, encephalopathy, coagulopathy, and hypersplenism. In chronic HBV or HCV and autoimmune hepatitis, extrahepatic features may predominate.

## CHRONIC HEPATITIS B

Follows up to 1–2% of cases of acute hepatitis B in immunocompetent hosts; more frequent in immunocompromised hosts. Spectrum of disease: asymptomatic antigenemia, chronic hepatitis, cirrhosis, hepatocellular cancer; early phase often

associated with continued symptoms of hepatitis, elevated aminotransferase levels, presence in serum of HBeAg and HBV DNA, and presence in liver of replicative form of HBV; later phase in some pts may be associated with clinical and biochemical improvement, disappearance of HBeAg and HBV DNA and appearance of anti-HBeAg in serum, and integration of HBV DNA into host hepatocyte genome. In Mediterranean and European countries as well as in Asia, a frequent variant is characterized by readily detectable HBV DNA, but without HBeAg (anti-HBeAg-reactive). Most of these cases are due to a mutation in the pre-C region of the HBV genome that prevents HBeAg synthesis (may appear during course of chronic wild-type HBV infection as a result of immune pressure and may also account for some cases of fulminant hepatitis B). Chronic hepatitis B ultimately leads to cirrhosis in 25–40% of cases (particularly in pts with HDV superinfection or the pre-C mutation) and hepatocellular carcinoma in many of these pts (particularly when chronic infection is acquired early in life).

### EXTRAHEPATIC MANIFESTATIONS (IMMUNE COMPLEX–MEDIATED)

Rash, urticaria, arthritis, polyarteritis nodosa–like vasculitis, polyneuropathy, glomerulonephritis.

### TREATMENT CHRONIC HEPATITIS B

There are currently seven approved drugs for the treatment of chronic HBV: interferon α (IFN-α), pegylated interferon (PEG IFN), lamivudine, adefovir dipivoxil, entecavir, telbivudine, and tenofovir (see Table 153-1).Use of IFN-α has been supplanted by PEG-IFN. Table 153-2 summarizes recommendations for treatment of chronic HBV.

## CHRONIC HEPATITIS C

Follows 50–70% of cases of transfusion-associated and sporadic hepatitis C. Clinically mild, often waxing and waning aminotransferase elevations; mild chronic hepatitis on liver biopsy. Extrahepatic manifestations include cryoglobulinemia, porphyria cutanea tarda, membranoproliferative glomerulonephritis, and lymphocytic sialadenitis. Diagnosis confirmed by detecting anti-HCV in serum. May lead to cirrhosis in ≥20% of cases after 20 years.

### TREATMENT CHRONIC HEPATITIS C

Therapy for chronic HCV is currently stratified based on HCV genotype and the presence of treatment naïve or treatment experienced disease in addition to pt-specific factors (see Tables 153-3 and Table 153-4). Therapeutic options for chronic HCV have evolved rapidly such that current recommendations as established by leading expert panels should be reviewed prior to deciding on the most appropriate treatment regimen.

## HEPATITIS A

Although hepatitis A rarely causes fulminant hepatic failure, it may do so more frequently in pts with chronic liver disease—especially those with chronic hepatitis B or C. The hepatitis A vaccine is immunogenic and well tolerated in pts with chronic hepatitis. Thus, pts with chronic liver disease, especially those with chronic hepatitis B or C, should be vaccinated against hepatitis A.

**TABLE 153-1 COMPARISON OF PEGYLATED INTERFERON (PEG IFN), LAMIVUDINE, ADEFOVIR, ENTECAVIR, TELBIVUDINE, AND TENOFOVIR THERAPY FOR CHRONIC HEPATITIS B[a]**

| Feature | PEG IFN[b] | Lamivudine | Adefovir | Entecavir | Telbivudine | Tenofovir |
|---|---|---|---|---|---|---|
| Route of administration | Subcutaneous injection | Oral | Oral | Oral | Oral | Oral |
| Duration of therapy[c] | 48–52 weeks | ≥52 weeks | ≥48 weeks | ≥48 weeks | ≥52 weeks | ≥48 weeks |
| Tolerability | Poorly tolerated | Well tolerated | Well tolerated; creatinine monitoring recommended | Well tolerated | Well tolerated | Well tolerated; creatinine monitoring recommended |
| HBeAg seroconversion | | | | | | |
| 1 yr Rx | 18–20% | 16–18% | 12% | 21% | 22% | 21% |
| >1 yr Rx | NA | up to 50% @ 5 yrs | 43% @ 3 yrs[d] | 31% @ 2 yrs<br>44% @ 6 yrs | 30% @ 2 yrs | 40% @ 5 yrs |
| $Log_{10}$ HBV DNA reduction (mean copies/mL) | | | | | | |
| HBeAg-reactive | 4.5 | 5.5 | median 3.5–5 | 6.235.0 | 6.4 | 6.2 |
| HBeAg-negative | 4.1 | 4.4–4.7 | median 3.5–3.9 | | 5.2 | 4.6 |
| HBV DNA PCR negative (<300–400 copies/mL; <1000 copies/mL for adefovir) at end of yr 1 | | | | | | |
| HBeAg-reactive | 10–25% | 36–44% | 13–21% | 67% (91% @ 4 yrs) | 60% | 76% |
| HBeAg-negative | 63% | 60–70% | 48–77% | 90% | 88% | 93% |
| ALT normalization at end of yr 1 | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| HBeAg-reactive | 39% | 41–75% | 48–61% | 68% | 77% | 68% |
| HBeAg-negative | 34–38% | 62–79% | 48–77% | 78% | 74% | 76% |
| HBsAg loss yr 1 | 3–4% | ≤1% | 0% | 2% | <1% | 3% |
| >yr 1 | 12% 5 yr after 1 yr of Rx | No data | 5% at yr 5 | 6% at yr 6 | No data | 8% at yr 5 |
| Histologic improvement (≥2 point reduction in HAI) at yr 1 | | | | | | |
| HBeAg-reactive | 38% 6 months after | 49–56% | 53–68% | 72% | 65% | 74% |
| HBeAg-negative | 48% 6 months after | 61–66% | 64% | 70% | 67% | 72% |
| Viral resistance | None | 15–30% @ 1 yr | None @ 1 yr | ≤1% @ 1 yr[e] | Up to 5% @ yr 1 | 0% @ yr 1 |
| | | 70% @ 5 yrs | 29% @ 5 yrs | 1.2% @ 6 yrs[e] | Up to 22% @ yr 2 | 0% through yr 5 |
| Pregnancy category | C | C[f] | C | C | B | B |
| Cost (US$) for 1 yr | ~$18,000 | ~$2,500 | ~$6,500 | ~$8,700[g] | ~$6,000 | ~$6,000 |

[a]Generally, these comparisons are based on data on each drug tested individually versus placebo in registration clinical trials; because, with rare exception, these comparisons are not based on head-to-head testing of these drugs, relative advantages and disadvantages should be interpreted cautiously.
[b]Although standard interferon α administered daily or three times a week is approved as therapy for chronic hepatitis B, it has been supplanted by PEG IFN, which is administered once a week and is more effective. Standard interferon has no advantages over PEG IFN.
[c]Duration of therapy in clinical efficacy trials; use in clinical practice may vary.
[d]Because of a computer-generated randomization error that resulted in misallocation of drug versus placebo during the second year of clinical trial treatment, the frequency of HBeAg seroconversion beyond the first year is an estimate (Kaplan-Meier analysis) based on the small subset in whom adefovir was administered correctly.
[e]7% during a year of therapy (43% at year 4) in lamivudine-resistant pts.
[f]Despite its Class C designation, lamivudine has an extensive pregnancy safety record in women with HIV/AIDS.
[g]Approximately $17,400 for lamivudine-refractory pts.
***Abbreviations:*** ALT, alanine aminotransferase; HAI, histologic activity index; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; NA, not applicable; PEG IFN, pegylated interferon; Rx, therapy; yr, year.

**TABLE 153-2 RECOMMENDATIONS FOR TREATMENT OF CHRONIC HEPATITIS B[a]**

| HBeAg status | Clinical | HBV DNA (IU/mL) | ALT | Recommendation |
|---|---|---|---|---|
| HBeAg-reactive | [b] | $>2 \times 10^4$ | $\leq 2 \times$ ULN[c,d] | No treatment; monitor. In pts >40, with family history of hepatocellular carcinoma, and/or ALT persistently at the high end of the twofold range, liver biopsy may help in decision to treat |
| | Chronic hepatitis | $>2 \times 10^4$[d] | $>2 \times$ ULN[d] | Treat[e] |
| | Cirrhosis compensated | $>2 \times 10^3$ | < or > ULN | Treat[e] with oral agents, not PEG IFN |
| | Cirrhosis decompensated | $<2 \times 10^3$ | >ULN | Consider treatment[f] |
| | | Detectable | < or > ULN | Treat[e] with oral agents[g], not PEG IFN; refer for liver transplantation |
| | | Undetectable | < or > ULN | Observe; refer for liver transplantation |
| HBeAg-negative | [b] | $\leq 2 \times 10^3$ | ≤ULN | Inactive carrier; treatment not necessary |
| | Chronic hepatitis | $>10^3$ | 1 to $>2 \times$ ULN[d] | Consider liver biopsy; treat[h] if biopsy shows moderate to severe inflammation or fibrosis |
| | Chronic hepatitis | $>10^4$ | $>2 \times$ ULN[d] | Treat[h,i] |
| | Cirrhosis compensated | $>2 \times 10^3$ | < or > ULN | Treat[e] with oral agents, not PEG IFN |
| | | $<2 \times 10^3$ | >ULN | Consider treatment[f] |
| | Cirrhosis decompensated | Detectable | < or > ULN | Treat[h] with oral agents[g], not PEG IFN; refer for liver transplantation |
| | | Undetectable | < or > ULN | Observe; refer for liver transplantation |

[a]Based on practice guidelines of the American Association for the Study of Liver Diseases (AASLD). Except as indicated in footnotes, these guidelines are similar to those issued by the European Association for the Study of the Liver (EASL).
[b]Liver disease tends to be mild or inactive clinically; most such pts do not undergo liver biopsy.
[c]This pattern is common during early decades of life in Asian pts infected at birth.
[d]According to the EASL guidelines, treat if HBV DNA is $>2 \times 10^3$ IU/mL and ALT >ULN.
[e]One of the potent oral drugs with a high barrier to resistance (entecavir or tenofovir) or PEG IFN can be used as first-line therapy (see text). These oral agents, but not PEG IFN, should be used for interferon-refractory/intolerant and immunocompromised pts. PEG IFN is administered weekly by subcutaneous injection for a year; the oral agents are administered daily for at least a year and continued indefinitely or until at least 6 months after HBeAg seroconversion.
[f]According to EASL guidelines, pts with compensated cirrhosis and detectable HBV DNA at any level, even with normal ALT, are candidates for therapy. Most authorities would treat indefinitely, even in HBeAg-positive disease after HBeAg seroconversion.
[g]Because the emergence of resistance can lead to loss of antiviral benefit and further deterioration in decompensated cirrhosis, a low-resistance regimen is recommended—entecavir or tenofovir monotherapy or combination therapy with the more resistance-prone lamivudine (or telbivudine) plus adefovir. Therapy should be instituted urgently.
[h]Because HBeAg seroconversion is not an option, the goal of therapy is to suppress HBV DNA and maintain a normal ALT. PEG IFN is administered by subcutaneous injection weekly for a year; caution is warranted in relying on a 6-month posttreatment interval to define a sustained response, because the majority of such responses are lost thereafter. Oral agents, entecavir or tenofovir, are administered daily, usually indefinitely or until, as very rarely occurs, virologic and biochemical responses are accompanied by HBsAg seroconversion.
[i]For older pts and those with advanced fibrosis, consider lowering the HBV DNA threshold to $>2 \times 10^3$ IU/mL.
***Abbreviations:*** AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; EASL, European Association for the Study of the Liver; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; PEG IFN, pegylated interferon; ULN, upper limit of normal.

**TABLE 153-3 PEGYLATED INTERFERON (PEG IFN) α2a AND α2b FOR CHRONIC HEPATITIS C**

| | PEG IFN-α2b | PEG IFN-α2a |
|---|---|---|
| PEG size | 12 kD linear | 40 kD branched |
| Elimination half-life | 54 h | 65 h |
| Clearance | 725 mL/h | 60 mL/h |
| Dose | 1.5 μg/kg (weight-based) | 180 μg |
| Storage | Room temperature | Refrigerated |
| Ribavirin dose | | |
| Genotype 1 | 800–1400 mg[a] | 1000–1200 mg[b] |
| Genotype 2/3 | 800 mg | 800 mg |
| Duration of therapy | | |
| Genotype 1 | 48 weeks | 48 weeks |
| Genotype 2/3 | 48 weeksc | 24 weeks |
| Efficacy of combination therapy[d] | 54% | 56% |
| Genotype 1 | 40–42% | 41–51% |
| Genotype 2/3 | 82% | 76–78% |

[a]In the registration trial for PEG IFN-α2b plus ribavirin, the optimal regimen was 1.5 μg of PEG IFN plus 800 mg of ribavirin; however, a post hoc analysis of this study suggested that higher ribavirin doses are better. In subsequent trials of PEG IFN-α2b with ribavirin in pts with genotype 1, the following daily ribavirin doses have been validated: 800 mg for pts weighing <65 kg, 1000 mg for pts weighing >65–85 kg, 1200 for pts weighing >85–105 kg, and 1400 mg for pts weighing >105 kg.
[b]1000 mg for pts weighing <75 kg; 1200 mg for pts weighing ≥75 kg.
[c]In the registration trial for PEG IFN-α2b plus ribavirin, all pts were treated for 48 weeks; however, data from other trials of standard interferons and the other PEG IFN demonstrated that 24 weeks suffices for pts with genotypes 2 and 3. For pts with genotype 3 who have advanced fibrosis/cirrhosis and/or high-level HCV RNA, a full 48 weeks is preferable.
[d]Attempts to compare the two PEG IFN preparations based on the results of registration clinical trials are confounded by differences between trials of the two agents in methodologic details (different ribavirin doses, different methods for recording depression, and other side effects) and study-population composition (different proportion with bridging fibrosis/cirrhosis, proportion from the United States versus international, mean weight, proportion with genotype 1, and proportion with high-level HCV RNA). In the head-to-head comparison of the two PEG IFN preparations in the IDEAL trial reported in 2009, the two drugs were comparable in tolerability and efficacy. PEG IFN-α2b was administered at a weekly weight-based dose of 1.0 μg/kg or 1.5 μg/kg, and PEG IFN-α2a at a weekly fixed dose of 180 μg. For PEG IFN-α2b, daily ribavirin weight-based doses ranged between 800 and 1400 mg based on weight criteria (see footnote [a], above), whereas for PEG IFN-α2a, daily ribavirin weight-based doses ranged between 1000 and 1200 mg (see footnote [b], above). For the two PEG IFN-α2b study arms, ribavirin dose reductions for ribavirin-associated adverse effects were done in 200- to 400-mg decrements; for PEG IFN-α2a, the ribavirin dose was reduced to 600 mg for intolerability. Sustained virologic responses occurred in 38.0% of the low-dose PEG IFN-α2b group, 39.8% of the standard, full-dose PEG IFN-α2b group, and 40.9% of the PEG IFN-α2a group.
***Abbreviations:*** HCV RNA, hepatitis C virus RNA; PEG, polyethylene glycol.

**TABLE 153-4 INDICATIONS AND RECOMMENDATIONS FOR ANTIVIRAL THERAPY OF CHRONIC HEPATITIS C[a]**

**Standard Indications for Therapy[a]**

AASLD and EASL 2015 Guidelines recommend treatment for all with advanced fibrosis and differ regarding therapy for those with earlier stage fibrosis as follows:

AASLD

- Treatment is recommended for all pts with chronic HCV infection, except those with short life expectancies owing to comorbid conditions.
- Immediate treatment is assigned the highest priority for those pts with advanced fibrosis (Metavir stage F3), those with compensated cirrhosis (Metavir stage F4), liver transplant recipients, and pts with severe extrahepatic hepatitis C.

EASL

- All treatment-naïve and treatment-experienced pts with compensated and decompensated liver disease.
- Treatment should be prioritized for pts with significant fibrosis (METAVIR score F3 or F4)
- In pts with less severe disease, the indication for and timing of therapy can be individualized.

**Antiviral Therapy Management Decisions Made on an Individual Basis**

Children (age <18 years)—protease inhibitors not recommended.

Age >70 (in protease inhibitor trials, telaprevir trials included pts age 18–70; boceprevir trials included pts >18 years of age [no upper age cutoff])

Mild hepatitis on liver biopsy

Persons with severe renal insufficiency (require reduced doses of PEG IFN and ribavirin)

Concurrent HIV treated similarly, but with extra attention to interactions.

**Long-Term Maintenance Therapy Recommended: None**

**Long-Term Maintenance Therapy in Nonresponders: Not Recommended**

**Antiviral Therapy Not Recommended**

Decompensated cirrhosis (contraindicated with IFN based regimens)

Pregnancy (teratogenicity of ribavirin, unknown effects DAAs)

Contraindications to use of antiviral medications

**Therapeutic Regimens**

**TREATMENT-NAÏVE**

Genotype 1a:

- Daclatasvir 60 mg and sofosbuvir 400 mg daily for 12 (no cirrhosis) or 24 weeks +/- weight-based ribavirin (cirrhosis)
- Ledipasvir 90 mg and sofosbuvir 400 mg daily for 12 weeks
- Daily paritaprevir 150mg and ritonavir 100mg/ombitasvir 25mg + twice daily dasabuvir 250mg + weight-based ribavirin for 12 (no cirrhosis) or 24 weeks (cirrhosis)
- Simepravir 150 mg and sofosbuvir 400 mg daily for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis without q80K mutation) +/- weight-based ribavirin

(*Continued*)

**TABLE 153-4 INDICATIONS AND RECOMMENDATIONS FOR ANTIVIRAL THERAPY OF CHRONIC HEPATITIS C[a] (*CONTINUED*)**

Genotype 1b:

- Same as genotype 1a with the exception of daily paritaprevir 150 mg/ritonavir 100mg/ombitasvir 25 mg + twice daily dasabuvir 250 mg is used without ribavirin

Genotype 2:

- Daclatasvir 60 mg and sofosbuvir 400 mg daily for 12 weeks in pts who cannot tolerate ribavirin
- Sofosbuvir 400 mg daily + weight-based ribavirin for 12 weeks in noncirrhotic pts, 16 weeks if cirrhotic.

Genotype 3:

- Daclatasvir 60 mg and sofosbuvir 400 mg daily for 12 weeks (no cirrhosis) or 24 weeks +/- weight-based ribavirin (cirrhosis).
- Sofosbuvir 400 mg daily and weight-based ribavirin + weekly PEG-IFN for IFN eligible pts
- Alternative: sofosbuvir 400 mg daily and weight-based ribavirin for 24 weeks

Genotype 4:

- Ledipasvir 90 mg and sofosbuvir 400 mg daily for 12 weeks
- Daily paritaprevir 150mg/ritonavir 100mg/ombitasvir 25mg + weight-based ribavirin for 12 weeks
- Sofosbuvir 400 mg daily + weight-based ribavirin for 24 weeks
- Alternative: sofosbuvir 400 mg daily + weight-based ribavirin + weekly PEG-IFN for 12 weeks

Genotype 5 and 6:

- Ledipasvir 90 mg/sofosbuvir 400 mg daily for 12 weeks
- Alternative: sofosbuvir 400 mg + weight-based ribavirin + weekly PEG-IFN for 12 weeks

**TREATMENT-EXPERIENCED**

For the latest guidelines:

- AASLD Guidelines; http://www.hcvguidelines.org
- EASL guidelines: http://www.easl.eu/research/our-contributions/clinical-practice-guidelines/detail/recommendations-on-treatment-of-hepatitis-c-2015

**Features Associated with Reduced Responsiveness**

Genotype and subtype

Treatment experience

Extent of fibrosis

[a]Recommendations for the treatment of hepatitis C are rapidly evolving and new recommendations continue to supplant those listed in this table. Before making any therapeutic decisions, the most recent guidelines should be reviewed which can be found at the website locations provided within the table.

***Abbreviations:*** AASLD, American Society for the Study of Liver Diseases; ALT, alanine aminotransferase; DAA, directly acting antivirals; EASL, European Association for the Study of the Liver; HCV, hepatitis C virus; IFN, interferon; PEG IFN, pegylated interferon; IU, international units (1 IU/mL is equivalent to ~2.5 copies/mL).

## AUTOIMMUNE HEPATITIS

### CLASSIFICATION

*Type I:* classic autoimmune hepatitis, anti–smooth-muscle and/or antinuclear antibodies (ANA). *Type II:* associated with anti-liver/kidney microsomal (anti-LKM) antibodies, which are directed against cytochrome P450IID6 (seen primarily in southern Europe). *Type III* pts lack ANA and anti-LKM, have antibodies reactive with hepatocyte cytokeratins; clinically similar to type I. Criteria have been suggested by an international group for establishing a diagnosis of autoimmune hepatitis.

### CLINICAL MANIFESTATIONS

Classic autoimmune hepatitis (type I): 80% women, third to fifth decades. Abrupt onset (acute hepatitis) in a third. Insidious onset in two-thirds: progressive jaundice, anorexia, hepatomegaly, abdominal pain, epistaxis, fever, fatigue, amenorrhea. Leads to cirrhosis; >50% 5-year mortality if untreated.

### EXTRAHEPATIC MANIFESTATIONS

Rash, arthralgias, keratoconjunctivitis sicca, thyroiditis, hemolytic anemia, nephritis.

### SEROLOGIC ABNORMALITIES

Hypergammaglobulinemia, positive rheumatoid factor, smooth-muscle antibody (40–80%), ANA (20–50%), antimitochondrial antibody (10–20%), false-positive anti-HCV enzyme immunoassay but usually not HCV RNA, atypical p-ANCA. Type II: anti-LKM antibody.

### TREATMENT AUTOIMMUNE HEPATITIS

Indicated for symptomatic disease with biopsy evidence of severe chronic hepatitis (bridging necrosis), marked aminotransferase elevations (5- to 10-fold), and hypergammaglobulinemia. Prednisone or prednisolone 30–60 mg/d PO tapered to 10–15 mg/d over several weeks; often azathioprine 50 mg/d PO is also administered to permit lower glucocorticoid doses and avoid steroid side effects. Monitor liver function tests monthly. Symptoms may improve rapidly, but biochemical improvement may take weeks or months and subsequent histologic improvement (to lesion of mild chronic hepatitis or normal biopsy) up to 18–24 months. Therapy should be continued for at least 12–18 months. Relapse occurs in at least 50% of cases (re-treat). For frequent relapses, consider maintenance therapy with low-dose glucocorticoids or azathioprine 2 (mg/kg)/d.

For a more detailed discussion, see Dienstag JL: Chronic Hepatitis, Chap. 362, p. 2031, in HPIM-19.

# 154 Cirrhosis and Alcoholic Liver Disease

## CIRRHOSIS

*Cirrhosis* is defined histopathologically and has a variety of causes, clinical features, and complications. In cirrhosis, there is the development of liver fibrosis to the point that there is architectural distortion with the formation of regenerative nodules, which results in decreased liver function.

### CAUSES (SEE TABLE 154-1)

### CLINICAL MANIFESTATIONS

May be absent, with cirrhosis being incidentally found at surgery.

#### Symptoms

Anorexia, nausea, vomiting, diarrhea, vague RUQ pain, fatigue, weakness, fever, jaundice, amenorrhea, impotence, infertility.

#### Signs

Spider telangiectases, palmar erythema, jaundice, scleral icterus, parotid and lacrimal gland enlargement, clubbing, Dupuytren's contracture, gynecomastia, testicular atrophy, hepatosplenomegaly, ascites, gastrointestinal bleeding (e.g., varices), hepatic encephalopathy.

#### Laboratory Findings

Anemia (microcytic due to blood loss, macrocytic due to folate deficiency; hemolytic called *Zieve's syndrome*), pancytopenia (hypersplenism), prolonged PT, rarely overt DIC; hyponatremia, hypokalemic alkalosis, glucose disturbances, hypoalbuminemia.

### DIAGNOSTIC STUDIES

Depend on clinical setting. Serum: HBsAg, anti-HBc, anti-HBs, anti-HCV, anti-HDV, Fe, total iron-binding capacity, ferritin, antimitochondrial antibody (AMA), smooth-muscle antibody (SMA), anti-liver/kidney microsomal (anti-LKM) antibody, ANA, ceruloplasmin, $\alpha_1$ antitrypsin (and phenotyping); abdominal ultrasound with Doppler study, CT or MRI (may show cirrhotic liver, splenomegaly, collaterals, venous thrombosis). Definitive diagnosis often depends on liver biopsy (percutaneous, transjugular, or open).

**TABLE 154-1 CAUSES OF CIRRHOSIS**

| | |
|---|---|
| Alcoholism | Cardiac cirrhosis |
| Chronic viral hepatitis | Inherited metabolic liver disease |
| Hepatitis B | Hemochromatosis |
| Hepatitis C | Wilson's disease |
| Autoimmune hepatitis | $\alpha_1$-Antitrypsin deficiency |
| Nonalcoholic steatohepatitis | Cystic fibrosis |
| Biliary cirrhosis | Cryptogenic cirrhosis |
| Primary biliary cirrhosis | |
| Primary sclerosing cholangitis | |
| Autoimmune cholangiopathy | |

**TABLE 154-2 COMPLICATIONS OF CIRRHOSIS**

| | |
|---|---|
| Portal hypertension | Coagulopathy |
| Gastroesophageal varices | Factor deficiency |
| Portal hypertensive gastropathy | Fibrinolysis |
| Splenomegaly, hypersplenism | Thrombocytopenia |
| Ascites | Bone disease |
| Spontaneous bacterial peritonitis | Osteopenia |
| Hepatorenal syndrome | Osteoporosis |
| Type 1 | Osteomalacia |
| Type 2 | Hematologic abnormalities |
| Hepatic encephalopathy | Anemia |
| Hepatopulmonary syndrome | Hemolysis |
| Portopulmonary hypertension | Thrombocytopenia |
| Malnutrition | Neutropenia |

### COMPLICATIONS (SEE TABLE 154-2 AND CHAPS. 42, 43, AND 155)

The Child-Pugh scoring system has been used to predict the severity of cirrhosis and the risk of complications (Table 154-3).

## ALCOHOLIC LIVER DISEASE

Excessive alcohol use can cause fatty liver, alcoholic hepatitis, cirrhosis. Alcoholic cirrhosis accounts for about 40% of the deaths due to cirrhosis. History of excessive alcohol use often denied. Severe forms (hepatitis, cirrhosis) associated with ingestion of 160 g/d for 10–20 years; women more susceptible than men and develop advanced liver disease with less alcohol intake. Hepatitis B and C may be cofactors in the development of liver disease. Malnutrition may contribute to development of cirrhosis.

### FATTY LIVER

Often presents as asymptomatic hepatomegaly and mild elevations in biochemical liver tests. Reverses on withdrawal of ethanol; does not lead to cirrhosis.

**TABLE 154-3 CHILD-PUGH CLASSIFICATION OF CIRRHOSIS**

| Factor | Units | 1 | 2 | 3 |
|---|---|---|---|---|
| Serum bilirubin | μmol/L | <34 | 34–51 | >51 |
| | mg/dL | <2.0 | 2.0–3.0 | >3.0 |
| Serum albumin | g/L | >35 | 30–35 | <30 |
| | g/dL | >3.5 | 3.0–3.5 | <3.0 |
| Prothrombin time | Seconds prolonged | 0–4 | 4–6 | >6 |
| | INR | <1.7 | 1.7–2.3 | >2.3 |
| Ascites | | None | Easily controlled | Poorly controlled |
| Hepatic encephalopathy | | None | Minimal | Advanced |

***Note:*** The Child-Pugh score is calculated by adding the scores of the five factors and can range from 5–15. Child-Pugh class is either A (a score of 5–6), B (7–9), or C (10 or above). Decompensation indicates cirrhosis with a Child-Pugh score of 7 or more (class B). This level has been the accepted criterion for listing for liver transplantation.

### ALCOHOLIC HEPATITIS

Clinical presentation ranges from asymptomatic to severe liver failure with jaundice, ascites, GI bleeding, and encephalopathy. Typically anorexia, nausea, vomiting, fever, jaundice, tender hepatomegaly. Occasional cholestatic picture mimicking biliary obstruction. Aspartate aminotransferase (AST) usually <400 U/L and more than twofold higher than alanine aminotransferase (ALT). Bilirubin and WBC may be elevated. Diagnosis defined by liver biopsy findings: hepatocyte swelling, alcoholic hyaline (Mallory-Denk bodies), infiltration of PMNs, necrosis of hepatocytes, pericentral venular fibrosis.

### OTHER METABOLIC CONSEQUENCES OF ALCOHOLISM

Increased NADH/NAD ratio leads to lactic acidemia, ketoacidosis, hyperuricemia, hypoglycemia, hypomagnesemia, hypophosphatemia. Also mitochondrial dysfunction, induction of microsomal enzymes resulting in altered drug metabolism, lipid peroxidation leading to membrane damage, hypermetabolic state; many features of alcoholic hepatitis are attributable to toxic effects of acetaldehyde and cytokines (interleukins 1 and 6, and TNF, released because of impaired detoxification of endotoxin).

### ADVERSE PROGNOSTIC FACTORS

Critically ill pts with alcoholic hepatitis have 30-day mortality rates >50%. Severe alcoholic hepatitis characterized by PT >5 × above control, bilirubin >137 μmol/L (>8 mg/dL), hypoalbuminemia, azotemia. A discriminant function can be calculated as 4.6 × (pt's PT in seconds) (control PT in seconds) + serum bilirubin (mg/dL). Values ≥32 are associated with poor prognosis. A Model for End-Stage Liver Disease (MELD) score > 21 is also associated with significant mortality in alcoholic hepatitis. Ascites, variceal hemorrhage, encephalopathy, hepatorenal syndrome predict a poor prognosis.

### TREATMENT ALCOHOLIC LIVER DISEASE

Abstinence is essential; 8500- to 12,500-kJ (2000- to 3000-kcal) diet with 1 g/kg protein (less if encephalopathy). Daily multivitamin, thiamine 100 mg, folic acid 1 mg. Correct potassium, magnesium, and phosphate deficiencies. Transfusions of packed red cells, plasma as necessary. Monitor glucose (hypoglycemia in severe liver disease). Pts with severe alcoholic hepatitis defined as a discriminant function >32 or MELD >20 should be given prednisone 40 mg/d or prednisolone 32 mg/d PO for 4 weeks followed by a taper. Pentoxifylline demonstrated improved survival, primarily due to a decrease in hepatorenal syndrome and led to the inclusion of this agent as an alternative to glucocorticoids in the treatment of severe alcoholic hepatitis. Liver transplantation may be an option in carefully selected pts with end-stage cirrhosis.

## PRIMARY BILIARY CIRRHOSIS (PBC)

PBC is a progressive nonsuppurative destructive intrahepatic cholangitis. Strong female predominance, median age of 50 years. Presents as asymptomatic elevation in alkaline phosphatase (better prognosis) or with pruritus, progressive jaundice, consequences of impaired bile excretion, and ultimately cirrhosis and liver failure.

### CLINICAL MANIFESTATIONS

Pruritus, fatigue, jaundice, xanthelasma, xanthomata, osteoporosis, steatorrhea, skin pigmentation, hepatosplenomegaly, portal hypertension; elevations in serum alkaline phosphatase, bilirubin, cholesterol, and IgM levels.

### ASSOCIATED DISEASES

Sjögren's syndrome, collagen vascular diseases, thyroiditis, glomerulonephritis, pernicious anemia, renal tubular acidosis.

### DIAGNOSIS

Antimitochondrial antibodies (AMA) in 90% (directed against enzymes of the pyruvate dehydrogenase complex and other 2-oxo-acid dehydrogenase mitochondrial enzymes). Liver biopsy most important in AMA-negative PBC. Biopsies identify 4 stages: stage 1—destruction of interlobular bile ducts, granulomas; stage 2—ductular proliferation; stage 3—fibrosis; stage 4—cirrhosis.

### PROGNOSIS

Correlates with age, serum bilirubin, serum albumin, prothrombin time, edema.

### TREATMENT PRIMARY BILIARY CIRRHOSIS

Ursodeoxycholic acid 13–15 mg/kg per day has been shown to improve the biochemical and histologic features of disease. Response is greatest when given early. Cholestyramine 4 g PO with meals for pruritus; in refractory cases consider rifampin, naltrexone, plasmapheresis. Calcium, vitamin D, and bisphosphonates are given for osteoporosis. Liver transplantation for end-stage disease.

## LIVER TRANSPLANTATION

Consider in the absence of contraindications for chronic, irreversible, progressive liver disease or fulminant hepatic failure when no alternative therapy is available (Table 154-4).

**TABLE 154-4 INDICATIONS FOR LIVER TRANSPLANTATION**

| Children | Adults |
|---|---|
| Biliary atresia | Primary biliary cirrhosis |
| Neonatal hepatitis | Secondary biliary cirrhosis |
| Congenital hepatic fibrosis | Primary sclerosing cholangitis |
| Alagille syndrome[a] | Autoimmune hepatitis |
| Byler disease[b] | Caroli disease[c] |
| $\alpha_1$-Antitrypsin deficiency | Cryptogenic cirrhosis |
| Inherited disorders of metabolism | Chronic hepatitis with cirrhosis |
| Wilson's disease | Hepatic vein thrombosis |
| Tyrosinemia | Fulminant hepatitis |
| Glycogen storage diseases | Alcoholic cirrhosis |
| Lysosomal storage diseases | Chronic viral hepatitis |
| Protoporphyria | Primary hepatocellular malignancies |
| Crigler-Najjar disease type I | Hepatic adenomas |
| Familial hypercholesterolemia | Nonalcoholic steatohepatitis |
| Primary hyperoxaluria type I | Familial amyloid polyneuropathy |
| Hemophilia | |

[a]Arteriohepatic dysplasia, with paucity of bile ducts, and congenital malformations, including pulmonary stenosis.
[b]Intrahepatic cholestasis, progressive liver failure, mental and growth retardation.
[c]Multiple cystic dilatations of the intrahepatic biliary tree.

**TABLE 154-5 CONTRAINDICATIONS TO LIVER TRANSPLANTATION**

| Absolute | Relative |
|---|---|
| Uncontrolled extrahepatobiliary infection | Age >70 |
| Active, untreated sepsis | Prior extensive hepatobiliary surgery |
| Uncorrectable, life-limiting congenital anomalies | Portal vein thrombosis |
| Active substance or alcohol abuse | Renal failure not attributable to liver disease |
| Advanced cardiopulmonary disease | Previous extrahepatic malignancy (not including nonmelanoma skin cancer) |
| Extrahepatobiliary malignancy (not including nonmelanoma skin cancer) | Severe obesity |
| Metastatic malignancy to the liver | Severe malnutrition/wasting |
| Cholangiocarcinoma | Medical noncompliance |
| AIDS | HIV seropositivity with failure to control HIV viremia or CD4 <100/μL |
| Life-threatening systemic diseases | Intrahepatic sepsis |
| | Severe hypoxemia secondary to right-to-left intrapulmonary shunts ($Po_2$<50 mmHg) |
| | Severe pulmonary hypertension (mean pulmonary artery pressure >35 mmHg) |
| | Uncontrolled psychiatric disorder |

## CONTRAINDICATIONS (SEE TABLE 154-5)

## SELECTION OF DONOR

Matched for ABO blood group compatibility and liver size (reduced-size grafts may be used, esp. in children). Should be negative for HIV, HBV, and HCV. Living-donor transplant has gained increased popularity with transplantation of the right hepatic lobe from a healthy adult donor to an adult. Living-donor transplant of the left lobe accounts for one-third of all liver transplants in children.

## IMMUNOSUPPRESSION

Various combinations of tacrolimus or cyclosporine and glucocorticoids, sirolimus, everolimus, mycophenolate mofetil, or OKT3 (monoclonal antithymocyte globulin).

## MEDICAL COMPLICATIONS AFTER TRANSPLANTATION

Liver graft dysfunction (primary nonfunction, acute or chronic rejection, ischemia, hepatic artery thrombosis, biliary obstruction or leak, recurrence of primary disease); infections (bacterial, viral, fungal, opportunistic); renal dysfunction; neuropsychiatric disorders, cardiovascular instability, pulmonary compromise.

## SUCCESS RATE

Currently, 5-year survival rates exceed 60%; less for certain conditions (e.g., chronic hepatitis B, hepatocellular carcinoma).

For a more detailed discussion, see Mailliard ME, Sorrell MF: Alcoholic Liver Disease, Chap. 363, p. 2052; Bacon BR: Cirrhosis and Its Complications, Chap. 365, p. 2058; Chung RT, Dienstag JL,: Liver Transplantation, Chap. 368, p. 2067, in HPIM-19.

# 155 Portal Hypertension

Portal hypertension is defined as elevation of the hepatic venous pressure gradient to >5 mmHg, which occurs as a consequence of cirrhosis (Chap. 154). It is caused by increased intrahepatic resistance to the passage of blood flow through the liver due to cirrhosis together with increased splanchnic blood flow due to vasodilatation within the splanchnic vascular bed.

## CLASSIFICATION (SEE TABLE 155-1)

## CONSEQUENCES

The primary complications of portal hypertension are gastroesophageal varices with hemorrhage, ascites (Chap. 43), hypersplenism, hepatic encephalopathy,

**TABLE 155-1 CLASSIFICATION OF PORTAL HYPERTENSION**

| |
|---|
| Prehepatic |
| Portal vein thrombosis |
| Splenic vein thrombosis |
| Massive splenomegaly (Banti's syndrome) |
| Hepatic |
| Presinusoidal |
| Schistosomiasis |
| Congenital hepatic fibrosis |
| Sinusoidal |
| Cirrhosis—many causes |
| Alcoholic hepatitis |
| Postsinusoidal |
| Hepatic sinusoidal obstruction (venoocclusive syndrome) |
| Posthepatic |
| Budd-Chiari syndrome |
| Inferior vena caval webs |
| Cardiac causes |
| Restrictive cardiomyopathy |
| Constrictive pericarditis |
| Severe congestive heart failure |

spontaneous bacterial peritonitis (Chap. 43), hepatorenal syndrome (Chap. 43), hepatocellular carcinoma (Chap. 71).

## ESOPHAGOGASTRIC VARICES

About one-third of pts with cirrhosis have varices, and one-third of pts with varices will develop bleeding. Bleeding is a life-threatening complication; risk of bleeding correlates with variceal size and location, the degree of portal hypertension (portal venous pressure >12 mmHg), and the severity of cirrhosis, e.g., Child-Pugh classification (see Table 154-3).

### DIAGNOSIS

*Esophagogastroscopy*: procedure of choice for evaluation of upper GI hemorrhage in pts with known or suspected portal hypertension. *Celiac* and *mesenteric arteriography* are alternatives when massive bleeding prevents endoscopy and to evaluate portal vein patency (portal vein may also be studied by ultrasound with Doppler and MRI).

## TREATMENT ESOPHAGOGASTRIC VARICES

See Chap. 41 for general measures to treat GI bleeding.

### CONTROL OF ACUTE BLEEDING

Choice of approach depends on clinical setting and availability.

1. Endoscopic intervention is employed as first-line treatment to control bleeding acutely. Endoscopic variceal ligation (EVL) is used to control acute bleeding in >90% of cases. EVL is less successful when varices extend into proximal stomach. Some endoscopists will use variceal injection (sclerotherapy) as initial therapy, particularly when bleeding is vigorous.
2. Vasoconstricting agents: somatostatin or octreotide (50–100 μg/h by continuous infusion).
3. Balloon tamponade (Sengstaken-Blakemore- or Minnesota tube). Can be used when endoscopic therapy is not immediately available or in pts who need stabilization prior to endoscopic therapy. Complications—obstruction of pharynx, asphyxiation, aspiration, esophageal ulceration. Generally reserved for massive bleeding, failure of vasopressin and/or endoscopic therapy.
4. Transjugular intrahepatic portosystemic shunt (TIPS)—portacaval shunt placed by interventional radiologic technique, reserved for failure of other approaches; risk of hepatic encephalopathy (20–30%), shunt stenosis or occlusion, infection.

### PREVENTION OF RECURRENT BLEEDING

1. EVL should be repeated until obliteration of all varices is accomplished.
2. Propranolol or nadolol—nonselective beta blockers that act as portal venous antihypertensives; may decrease the risk of variceal hemorrhage and mortality due to hemorrhage.
3. TIPS—regarded as useful "bridge" to liver transplantation in pt who has failed pharmacologic therapy and is awaiting a donor liver.
4. Portosystemic shunt surgery used less commonly with the advent of TIPS; could be considered for pts with good hepatic synthetic function.

### PREVENTION OF INITIAL BLEED

For pts at high risk of variceal bleeding, consider prophylaxis with EVL and/or nonselective beta blockers.

## HEPATIC ENCEPHALOPATHY

An alteration in mental status and cognitive function occurring in the presence of liver failure; may be acute and reversible or chronic and progressive.

### CLINICAL FEATURES

Confusion, slurred speech, change in personality that can include being violent and hard to manage, being sleepy and difficult to arouse, asterixis (flapping tremor). Can progress to coma; initially responsive to noxious stimuli, later unresponsive.

### PATHOPHYSIOLOGY

Gut-derived neurotoxins that are not removed by the liver because of vascular shunting and decreased hepatic mass reach the brain and cause the symptoms of hepatic encephalopathy. Ammonia levels are typically elevated in encephalopathy, but the correlation between the severity of liver disease and height of ammonia levels is often poor. Other compounds that may contribute include false neurotransmitters and mercaptans.

### PRECIPITANTS

GI bleeding, azotemia, constipation, high-protein meal, hypokalemic alkalosis, CNS depressant drugs (e.g., benzodiazepines and barbiturates), hypoxia, hypercarbia, sepsis.

### TREATMENT HEPATIC ENCEPHALOPATHY

Remove precipitants; correct electrolyte imbalances. Lactulose (nonabsorbable disaccharide) results in colonic acidification and diarrhea and is the mainstay of treatment; goal is to produce 2–3 soft stools per day. Poorly absorbed antibiotics are often used in pts who do not tolerate lactulose, with alternating administration of neomycin and metronidazole being used to reduce the individual side effects of each. Rifaximin has recently also been used; zinc supplementation is sometimes helpful. Liver transplantation when otherwise indicated.

For a more detailed discussion, see Bacon BR: Cirrhosis and Its Complications, Chap. 365, p. 2058; in HPIM-19.

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# 156 Diseases of Immediate-Type Hypersensitivity

## DEFINITION

These diseases result from IgE-dependent release of mediators from sensitized basophils and mast cells upon contact with an offending antigen (allergen). Associated disorders include anaphylaxis, allergic rhinitis, urticaria, asthma, and eczematous (atopic) dermatitis.

## PATHOPHYSIOLOGY

IgE binds to the surface of mast cells and basophils through a high-affinity receptor. Cross-linking of this IgE by antigen causes cellular activation with subsequent release of preformed and newly synthesized mediators (Fig. 156-1). These mediators have been implicated in many pathophysiologic events associated with immediate-type hypersensitivity, such as vasodilation, increased vasopermeability, smooth-muscle contraction, and chemotaxis of neutrophils and other inflammatory cells. The clinical manifestations of each allergic reaction depend largely on the anatomic site(s) and time course of mediator release.

## URTICARIA AND ANGIOEDEMA

### DEFINITION

May occur together or separately. *Urticaria* involves only the superficial dermis and presents as circumscribed wheals with raised serpiginous borders and blanched

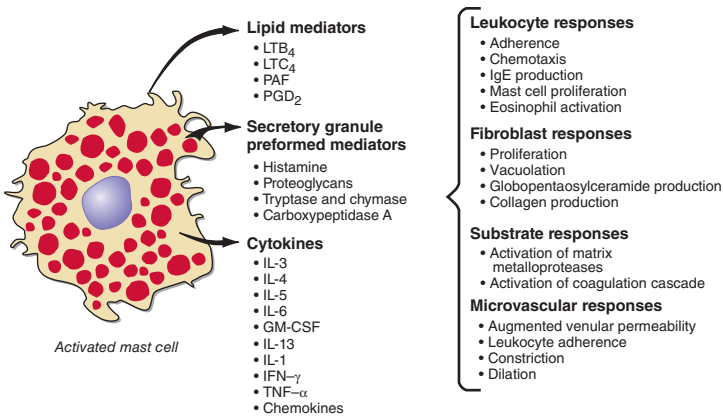


**FIGURE 156-1** Bioactive mediators of three categories generated by IgE-dependent activation of murine mast cells can elicit common but sequential target cell effects leading to acute and sustained inflammatory responses. GM-CSF, granulocyte-macrophage colony-stimulating factor; LT, leukotriene; PAF, platelet-activating factor; $PGD_2$, prostaglandin $D_2$.

**TABLE 156-1 CLASSIFICATION OF URTICARIA AND/OR ANGIOEDEMA**

1. IgE-dependent
   a. Specific antigen sensitivity (pollens, foods, drugs, fungi, molds, Hymenoptera venom, helminths)
   b. Physical: dermographism, cold, solar, pressure, cholinergic
   c. Autoimmune
2. Bradykinin-mediated
   a. Hereditary angioedema: C1 inhibitor deficiency: null (type 1) and dysfunctional (type 2), mutated factor XII (type 3)
   b. Acquired angioedema: C1 inhibitor deficiency: anti-idiotype and anti-C1 inhibitor
   c. Angiotensin-converting enzyme inhibitors
3. Complement-mediated
   a. Necrotizing vasculitis
   b. Serum sickness
   c. Reactions to blood products
4. Nonimmunologic
   a. Direct mast cell–releasing agents (opiates, antibiotics, curare, D-tubocurarine, radiocontrast media)
   b. Agents that alter arachidonic acid metabolism (aspirin and nonsteroidal anti-inflammatory agents, azo dyes, and benzoates)
5. Idiopathic

centers; wheals may coalesce. *Angioedema* involves deeper layers of skin and may include subcutaneous tissue. Recurrent episodes of urticaria and/or angioedema of <6 weeks duration are considered acute, whereas attacks persisting beyond this period are chronic.

## CLASSIFICATION AND ETIOLOGY

The classification of urticaria-angioedema focuses on mechanisms that elicit clinical disease and can be useful for differential diagnosis, but most cases of chronic urticaria are idiopathic (Table 156-1).

Urticaria-angioedema can occur secondary to inhalation, physical contact, or more commonly ingestion (fruits, shellfish, fish, milk products, chocolate, legumes including peanuts, drugs) that may elicit urticaria alone or the anaphylactic syndrome (Chap. 26).

## PATHOPHYSIOLOGY

Characterized by edema in the superficial dermis in urticaria and subcutaneous tissue and deep dermis in angioedema. Up to 40% of pts with chronic urticaria have an autoimmune cause including autoantibodies to IgE (5–10%) or, more commonly, to the α chain of FcεRI (35–45%).

## DIAGNOSIS

History, with special attention to possible offending exposures and/or ingestion as well as the duration of lesions. Urticarial vasculitis typically persists >72 h, whereas conventional urticaria often lasts <48 h.

- Skin testing to food and/or inhalant antigens.
- Physical provocation, e.g., challenge with vibratory or cold stimuli.

- Laboratory examination: complement levels, erythrocyte sedimentation rate (ESR) (neither an elevated ESR nor hypocomplementemia is observed in IgE-mediated urticaria or angioedema); C1 inhibitor (C1INH) testing for deficiency of C1INH antigen (type 1) or a nonfunctional protein (type 2) if history suggests hereditary angioedema; cryoglobulins, hepatitis B antigen, and antibody studies; autoantibody screen.
- Skin biopsy may be necessary.

### DIFFERENTIAL DIAGNOSIS

Atopic dermatitis, contact sensitivity, cutaneous mastocytosis (urticaria pigmentosa), systemic mastocytosis.

### PREVENTION

Identification and avoidance of offending agent(s), if possible.

### TREATMENT URTICARIA AND ANGIOEDEMA

- $H_1$ antihistamines may be helpful: e.g., chlorpheniramine up to 24 mg PO daily; diphenhydramine 25–50 mg PO qid; hydroxyzine 40–200 mg PO daily; cyproheptadine 8–32 mg PO daily; or the low or nonsedating class, e.g., loratidine 10 mg PO daily; desloratidine 5 mg PO daily; fexofenadine up to 180 mg PO daily; cetirizine 5–10 mg PO daily; levocetirizine 5 mg PO daily.
- $H_2$ antihistamines: e.g., ranitidine 150 mg PO bid may add benefit.
- Doxepin, a tricyclic compound with $H_1$ and $H_2$ receptor antagonist activity, has been used.
- Leukotriene receptor antagonists can be add-on therapy: e.g., montelukast 10 mg daily or zafirlukast 20 mg bid.
- Topical glucocorticoids are of no value in the management of urticaria and/or angioedema. Systemic glucocorticoids should not be used in the treatment of idiopathic, allergen-induced, or physical urticaria because of their long-term toxicity.

## ALLERGIC RHINITIS

### DEFINITION

Characterized by sneezing; rhinorrhea; obstruction of the nasal passages; conjunctival, nasal, and pharyngeal itching; and lacrimation, all occurring in a temporal relationship to allergen exposure. Prevalence in North America is ~20% with a peak prevalence ~40% occurring in childhood and adolescence. Perennial allergic rhinitis occurs in response to allergens that are present throughout the year such as house dust (containing dust mite antigens) and animal danders.

### PATHOPHYSIOLOGY

Deposition of pollens and other allergens on nasal mucosa of sensitized individuals results in IgE-dependent triggering of mast cells with subsequent release of mediators that cause development of mucosal hyperemia, swelling, and fluid transudation.

### DIAGNOSIS

Accurate history of symptoms correlated with time of seasonal pollination of plants in a given locale; special attention must be paid to other potentially sensitizing antigens such as materials associated with pets, e.g., dander.

- Physical examination: nasal mucosa may be boggy or erythematous; nasal polyps may be present; conjunctivae may be inflamed or edematous; manifestations of other allergic conditions (e.g., asthma, eczema) may be present.
- Skin tests to inhalant and/or food antigens.
- Nasal smear may reveal large numbers of eosinophils; presence of neutrophils may suggest infection.
- Total and specific serum IgE (as assessed by immunoassay) may be elevated.

### DIFFERENTIAL DIAGNOSIS

Vasomotor rhinitis, upper respiratory infection (URI), irritant exposure, pregnancy with nasal mucosal edema, rhinitis medicamentosa, nonallergic rhinitis with eosinophilia, rhinitis due to α-adrenergic agents.

### PREVENTION

Identification and avoidance of offending antigen(s).

### TREATMENT ALLERGIC RHINITIS

- Older antihistamines (e.g., chlorpheniramine, diphenhydramine) are effective but cause sedation and psychomotor impairment including reduced hand-eye coordination and impaired automobile driving skills. Newer antihistamines (e.g., fexofenadine, loratadine, desloratadine, cetirizine, levocetirizine, olopatadine, bilastine, and azelastine) are equally effective but are less sedating and more $H_1$ specific.
- Oral sympathomimetics, e.g., pseudoephedrine 30–60 mg PO qid; may aggravate hypertension; combination antihistamine/decongestant preparations may balance side effects and provide improved pt convenience.
- Topical vasoconstrictors—should be used sparingly due to rebound congestion and chronic rhinitis associated with prolonged use.
- Topical nasal glucocorticoids, e.g., beclomethasone, two sprays in each nostril bid, or fluticasone, two sprays in each nostril once daily.
- Topical nasal cromolyn sodium, one to two sprays in each nostril qid.
- Montelukast 10 mg PO daily is approved for seasonal and perennial rhinitis.
- Hyposensitization therapy, if more conservative therapy is unsuccessful.

## SYSTEMIC MASTOCYTOSIS

### DEFINITION

A systemic disorder defined by a clonal expansion of mast cells that in most instances is indolent and nonmalignant. Generally involves bone marrow, skin, gastrointestinal (GI) mucosa, liver, and spleen. Classified as cutaneous mastocytosis with variants and four systemic forms: indolent, associated with concomitant hematologic disorder, aggressive, and mast cell leukemia. Mast cell sarcoma and extracutaneous mastocytomas are rare solid mast cell tumors.

### PATHOPHYSIOLOGY AND CLINICAL MANIFESTATIONS

The clinical manifestations of systemic mastocytosis are due to tissue occupancy by the mast cell mass, the tissue response to that mass (fibrosis), and the release of bioactive substances acting both locally (urticaria pigmentosa, crampy abdominal pain, gastritis, peptic ulcer) and at distal sites (headache, pruritus, flushing, vascular

**TABLE 156-2 DIAGNOSTIC CRITERIA FOR SYSTEMIC MASTOCYTOSIS[a]**

| |
|---|
| Major: Multifocal dense infiltrates of mast cells in bone marrow or other extracutaneous tissues with confirmation by immunodetection of tryptase or metachromasia |
| Minor: Abnormal mast cell morphology with a spindle shape and/or multilobed or eccentric nucleus |
| Aberrant mast cell surface phenotype with expression of CD25 and CD2 (IL-2 receptor) in addition to C117 (*c-kit*) |
| Detection of codon 816 mutation in peripheral blood cells, bone marrow cells, or lesional tissue |
| Total serum tryptase (mostly alpha) >20 ng/mL |

[a]Diagnosis requires either the major and one minor or three minor criteria.

collapse). Clinical manifestations may be aggravated by alcohol, use of narcotics (e.g., codeine), and ingestion of nonsteroidal anti-inflammatory drugs (NSAIDs).

## DIAGNOSIS

Although the diagnosis of mastocytosis may be suspected on the basis of clinical and laboratory findings, it can be established only by tissue biopsy (usually bone marrow biopsy). The diagnostic criteria for systemic mastocytosis are shown in Table 156-2. Laboratory studies that can help support a diagnosis of systemic mastocytosis include measurement of urinary or blood levels of mast cell products such as histamine, histamine metabolites, prostaglandin $D_2$ ($PGD_2$) metabolites, or mast cell tryptase. Other studies including bone scan, skeletal survey, and GI contrast studies may be helpful. Other flushing disorders (e.g., carcinoid syndrome, pheochromocytoma) should be excluded.

## TREATMENT SYSTEMIC MASTOCYSTOSIS

- $H_1$ and $H_2$ antihistamines.
- Proton pump inhibitors for gastric hypersecretion.
- Oral cromolyn sodium for diarrhea and abdominal pain.
- Aspirin for severe flushing to block $PGD_2$.
- Systemic glucocorticoids may help, but frequently are associated with complications.
- Mast cell cytoreductive therapy with interferon α (IFN-α) or cladribine is generally reserved for advanced, nonindolent variants of systemic mastocytosis.
- Chemotherapy for frank leukemias.

For a more detailed discussion, see Boyce JA, Austen KF: Allergies, Anaphylaxis, and Systemic Mastocytosis, Chap. 376, p. 2113, in HPIM-19.

# 157 Primary Immune Deficiency Diseases

## DEFINITION

Primary immunodeficiencies are genetic diseases that can involve all possible aspects of immune responses, from innate through adaptive, as well as cell differentiation, effector function, and immune regulation (Table 157-1). The consequences of primary immunodeficiencies vary widely as a function of the molecules that are defective and include vulnerability to infection by pathogenic and opportunistic infection, immunopathologic responses such as allergy, lymphoproliferations, and autoimmunity, and increased risk of cancers. The locations and sites of infection and the causal microorganisms often aid the physician in diagnosis.

## DIAGNOSIS (SEE TABLE 157-2)

## CLASSIFICATION (TABLE 157-1)

### DEFICIENCIES OF THE INNATE IMMUNE SYSTEM

Account for ~10% of all primary immunodeficiencies (Table 157-1).

### DEFICIENCES OF THE ADAPTIVE IMMUNE SYSTEM

#### T-Lymphocyte Deficiency Syndromes

**Severe Combined Immunodeficiency (SCID)** Group of rare primary immunodeficiencies characterized by a profound block in T-cell development as a consequence of an intrinsic deficiency. Clinical consequences occur within 3–6 months following birth. The most frequent clinical manifestations are recurrent oral candidiasis, failure to thrive, protracted diarrhea, *Pneumocystis jirovecii* infections. Six distinct causative mechanisms have been identified:

- *Cytokine signaling deficiency:* Most frequent SCID accounting for 40–50% of cases with the absence of T and NK cells. These pts have a deficiency in the gamma chain receptor shared by several cytokine receptors (interleukins 2, 4, 7, 9, 15, 21). The same phenotype seen in X-linked SCID can be inherited as an autosomal recessive disease due to mutations in the JAK3 protein kinase gene.
- *Purine metabolism deficiency:* About 20% of SCID pts are deficient in adenosine deaminase (ADA) due to mutations in the *ADA* gene.
- *Defective rearrangements of T- and B-cell receptors:* Account for ~20–30% of SCID cases. Main deficiencies involve recombinase activating genes (RAG-1, RAG-2) DNA-dependent protein kinase, DNA ligase 4, and Cernunnos deficiencies.
- *Defective (pre-) T-cell receptor signaling in the thymus:* Rare deficiencies in CD3 subunits associated with the (pre) TCR and CD45.
- *Reticular dysgenesis:* Extremely rare. Results from adenylate kinase 2 deficiency.
- *Defective egress of lymphocytes:* Defective egress of T cells from the thymus resulting from deficiency in coronin-1A.

**TREATMENT SEVERE COMBINED IMMUNODEFICIENCY**

Curative treatment relies on hematopoietic stem cell transplant (HSCT).

**TABLE 157-1 CLASSIFICATION OF PRIMARY IMMUNE DEFICIENCY DISEASES**

| | |
|---|---|
| **Deficiencies of the Innate Immune System** | |
| • Phagocytic cells | |
| – Impaired production: SCN | |
| – Asplenia | |
| – Impaired adhesion: LAD | |
| – Impaired killing: CGD | |
| • Innate immunity receptors and signal transduction | |
| – Defects in toll-like receptor signaling | |
| – Mendelian susceptibility to mycobacterial disease | |
| • Complement deficiencies | |
| – Classical, alternative, and lectin pathways | |
| – Lytic phase | |
| **Deficiencies of the Adaptive Immune System** | |
| • T lymphocytes | |
| – Impaired development | SCIDs, DiGeorge syndrome |
| – Impaired survival, migration, function | Severe combined immunodeficiencies |
| | Hyper-IgE syndrome (autosomal dominant) |
| | DOK8 deficiency |
| | CD40 ligand deficiency |
| | Wiskott-Aldrich syndrome |
| | Ataxia-telangiectasia and other DNA repair deficiencies |
| • B lymphocytes | |
| – Impaired development | XL and AR agammaglobulinemia |
| – Impaired function | Hyper-IgM syndrome |
| | CVID |
| | IgA deficiency |
| **Regulatory Defects** | |
| • Innate immunity | Autoinflammatory syndromes (outside the scope of this chapter) |
| | Severe colitis |
| • Adaptive immunity | HLH |
| | ALPS |
| | Autoimmunity and inflammatory diseases (IPEX, APECED) |

***Abbreviations:*** ALPS, autoimmune lymphoproliferation syndrome; APECED, autoimmune polyendocrinopathy candidiasis ectodermal dysplasia; AR, autosomal recessive; CGD, chronic granulomatous disease; CVID, common variable immunodeficiency; HLH, hemophagocytic lymphohistiocytosis; IPEX, immunodysregulation polyendocrinopathy enteropathy X-linked syndrome; LAD, leukocyte adhesion deficiency; SCIDs, severe combined immune deficiencies; SCN, severe congenital neutropenia; XL, X-linked.

**TABLE 157-2 TEST MOST FREQUENTLY USED TO DIAGNOSE A PRIMARY IMMUNE DEFICIENCY**

| Test | Information | PID Disease |
|---|---|---|
| Blood cell counts and cell morphology | Neutrophil counts | ↓Severe congenital neutropenia, ↑↑ LAD |
| | Lymphocyte counts[a] | T-cell ID |
| | Eosinophilia | WAS, hyper-IgE syndrome |
| | Howell-Jolly bodies | Asplenia |
| Chest x-ray | Thymic shadow | SCID, DiGeorge syndrome |
| | Costochondral junctions | Adenosine deaminase deficiency |
| Bone x-ray | Metaphyseal ends | Cartilage hair hypoplasia |
| Immunoglobulin serum levels | IgG, IgA, IgM | B-cell ID |
| | IgE | Hyper-IgE syndrome, WAS, T-cell ID |
| Lymphocyte phenotype | T-, B-lymphocyte counts | T-cell ID, agammaglobulinemia |
| DHR assay | Reactive oxygen species production by PMN | Chronic granulomatous disease |
| NBT assay | | |
| CH50, AP50 | Classic and alternative complement pathways | Complement deficiencies |
| Ultrasonography of the abdomen | Spleen size | Asplenia |

[a]Normal counts vary with age. For example, the lymphocyte count is between 3000 and 9000/μL of blood below the age of 3 months and between 1500 and 2500/μL in adults.
***Abbreviations:*** DHR, dihydrorhodamine fluorescence; ID, immunodeficiency; LAD, leukocyte adhesion deficiency; NBT, nitroblue tetrazolium; PID, primary immune deficiency; PMNs, polymorphonuclear leukocytes; SCID, severe combined immunodeficiency; WAS, Wiskott-Aldrich syndrome.

## Other T Cell–Related Primary Immunodeficiencies

- *DiGeorge syndrome:* Maldevelopment of the thymus
- *Hyper-IgE syndrome*
- *CD40 ligand deficiency*
- *Wiskott-Aldrich syndrome*
- *Ataxia-telangiectasia and other DNA repair deficiencies*

### TREATMENT OTHER T CELL–RELATED PRIMARY IMMUNODEFICIENCIES

Treatment is complex and largely investigational. HSCT plays a role in some diseases. Live vaccines and blood transfusions containing viable T cells should be strictly avoided. Prophylaxis for *P. jirovecii* pneumonia should be considered in selected pts with severe T-cell deficiency.

## B-Lymphocyte Deficiency Syndromes

Deficiencies that affect B cells are the most common primary immunodeficiencies and account for ~60–70% of all cases. Defective antibody production predisposes to invasive pyogenic bacterial infections as well as recurrent sinus and pulmonary infections. Complete lack of antibody production (agammaglobulinemia) predisposes to disseminated enteroviral infections causing meningoencephalitis, hepatitis, and a dermatomyositis-like disease. Diagnosis relies on the determination of serum Ig level.

- *Agammaglobulinemia:* Due to an X-linked mutation in the Bruton's tyrosine kinase (Btk) gene in 85% of cases.
- *Hyper IgM:* In most pts this syndrome results from an X-linked defect in the gene encoding CD40 ligand. Pts exhibit normal or increased serum IgM with low or absent IgG and IgA.
- *Common variable immunodeficiency (CVID):* Heterogeneous group of syndromes characterized by low serum levels of one or more Ig isotypes. Prevalence estimated to be 1 in 20,000. Besides infections, pts may develop lymphoproliferation, granulomatous lesions, colitis, antibody-mediated autoimmune diseases, and lymphomas.
- *Isolated IgA deficiency:* Most common immunodeficiency; affects 1 in 600 people. The majority of affected individuals do not have increased infections; antibodies against IgA may lead to anaphylaxis during transfusion of blood or plasma; may progress to CVID.
- *Selective antibody deficiency to polysaccharide antigens.*

**TREATMENT B CELL/IMMUNOGLOBULIN DEFICIENCY SYNDROMES**

IV immunoglobulin administration (only for pts who have recurrent bacterial infections and are deficient in IgG):

- Starting dose 400–500 mg/kg given every 3–4 weeks
- Adjust dose to keep trough IgG level 800 mg/dL
- SC administration usually once a week can be considered in selected pts.

### REGULATORY DEFECTS

Rare but increasingly described primary immunodeficiencies that cause homeostatic dysregulation of the immune system either alone or in association with increased vulnerability to infection (Table 157-1).

For a more detailed discussion, see Fischer A: Primary Immune Deficiency Diseases, Chap. 374, p. 2103, in HPIM-19.

# 158 Systemic Lupus Erythematosus, Rheumatoid Arthritis, and Other Connective Tissue Diseases

## CONNECTIVE TISSUE DISEASE

### DEFINITION

Heterogeneous disorders that share certain common features, including inflammation of skin, joints, and other structures rich in connective tissue; as well as altered patterns of immunoregulation, including production of autoantibodies and abnormalities of cell-mediated immunity. While distinct clinical entities can be defined,

manifestations may vary considerably from one pt to the next, and overlap of clinical features between and among specific diseases can occur.

## SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

### DEFINITION AND PATHOGENESIS

Disease of unknown etiology in which tissues and cells undergo damage mediated by tissue-binding autoantibodies and immune complexes. Genetic, environmental, and sex hormonal factors are likely of pathogenic importance. T- and B-cell hyperactivity, production of autoantibodies with specificity for nuclear antigenic determinants, and abnormalities of T-cell function occur.

### CLINICAL MANIFESTATIONS

Approximately 90% of pts are women, usually of child-bearing age; more common in blacks than whites. Course of disease is often characterized by periods of exacerbation and relative quiescence. May involve virtually any organ system and have a wide range of disease severity. Common features include:

- *Constitutional:* fatigue, fever, malaise, weight loss
- *Cutaneous:* rashes (especially malar "butterfly" rash), photosensitivity, vasculitis, alopecia, oral ulcers
- *Arthritis:* inflammatory, symmetric, nonerosive
- *Hematologic:* anemia (may be hemolytic), neutropenia, thrombocytopenia, lymphadenopathy, splenomegaly, venous or arterial thrombosis
- *Cardiopulmonary:* pleuritis, pericarditis, myocarditis, endocarditis. Pts are also at increased risk of myocardial infarction usually due to accelerated atherosclerosis.
- *Nephritis:* classification is primarily histologic (Table 378-2, p. 2127, in HPIM-19)
- *GI:* peritonitis, vasculitis
- *Neurologic:* organic brain syndromes, seizures, psychosis, cerebritis

### Drug-Induced Lupus

A clinical and immunologic picture similar to spontaneous SLE may be induced by drugs; in particular: procainamide, hydralazine, isoniazid, chlorpromazine, methyldopa, minocycline, anti-TNF agents. Features are predominantly constitutional, joint, and pleuropericardial; CNS and renal disease are rare. All pts have ANAs; antihistone antibodies may be present, but antibodies to dsDNA and hypocomplementemia are uncommon. Most pts improve following withdrawal of offending drug.

### EVALUATION

- History and physical examination
- Presence of ANA is a cardinal feature, but a (+) ANA is not specific for SLE. Laboratory assessment should include: CBC, ESR, ANA and ANA subtypes (antibodies to dsDNA, ssDNA, Sm, anti-Ro/SS-A, anti-La/SS-B, histone), complement levels (C3, C4, CH50), serum immunoglobulins, VDRL, PT, PTT, anticardiolipin antibody, lupus anticoagulant, urinalysis.
- Appropriate radiographic studies
- ECG
- Consideration of renal biopsy if evidence of glomerulonephritis

### DIAGNOSIS

Classification criteria used to confirm SLE in studies can provide a basis in individual patients for estimating the probability that a disease is SLE. Four or more published criteria carry a 93% specificity and 92% sensitivity for SLE (Table 378-3, p. 2127, in HPIM-19).

## TREATMENT SYSTEMIC LUPUS ERYTHEMATOSUS

Choice of therapy is based on type and severity of disease manifestations. Goals are to control acute, severe flares and to develop maintenance strategies whereby symptoms are suppressed to an acceptable level. Treatment choices depend on (1) whether disease is life threatening or likely to cause organ damage; (2) whether manifestations are reversible; and (3) the best approach to prevent complications of disease and treatment (**Fig. 378-2**, p. 2128, and **Table 378-5**, p. 2130, in HPIM-19).

### Conservative Therapies for Non-Life-Threatening Disease

- *NSAIDs* (e.g., ibuprofen 400–800 mg three to four times a day). Must consider renal, GI, and cardiovascular complications.
- *Antimalarials* (hydroxychloroquine 400 mg/d): may improve constitutional, cutaneous, articular manifestations. Ophthalmologic evaluation required before and during treatment to rule out ocular toxicity.
- *Belimumab* (10 mg/kg IV at weeks 0, 2, 4 then monthly). B-lymphocyte stimulator (BLyS)-specific inhibitor. Should not be used in severe SLE such as nephritis or CNS disease and limited to pts with mild to moderate active disease.

### Treatments for Life-Threatening SLE

- *Systemic glucocorticoids*.
- *Cytotoxic/immunosuppressive agents:* added to glucocorticoids to treat serious SLE.
  1. Cyclophosphamide: administered as IV pulse 500–1000 mg/M$^2$ IV × 6 months followed by maintenance with mycophenolate mofetil or azathioprine. European studies have found cyclophosphamide 500 mg every 2 weeks for 6 doses may be effective, but it remains unclear whether these data will apply to U.S. populations.
  2. Mycophenolate mofetil: 2–3 g/d; efficacy data limited to nephritis. A higher proportion of African-American pts appear to respond to mycophenolate mofetil compared with cyclophosphamide.
  3. Azathioprine: may be effective but is slower in inducing therapeutic response.

## RHEUMATOID ARTHRITIS (RA)

### DEFINITION AND PATHOGENESIS

A chronic multisystem disease of unknown etiology characterized by persistent inflammatory synovitis, usually involving peripheral joints symmetrically. Although cartilaginous destruction, bony erosions, and joint deformity are hallmarks, the course of RA can be quite variable. An association with HLA-DR4 has been noted; both genetic and environmental factors may play a role in initiating disease. The propagation of RA is an immunologically mediated event in which joint injury occurs from synovial hyperplasia; lymphocytic infiltration of synovium; and local production of cytokines and chemokines by activated lymphocytes, macrophages, and fibroblasts.

### CLINICAL MANIFESTATIONS

RA occurs in 0.5–1.0% of the population; women affected three times more often than men; prevalence increases with age, onset most frequent in fourth and fifth decades.

## Articular Manifestations

Typically a symmetric polyarthritis of peripheral joints with pain, tenderness, and swelling of affected joints; morning stiffness is common; proximal interphalangeal (PIP) and metacarpophalangeal (MCP) joints frequently involved; joint deformities may develop after persistent inflammation.

## Extraarticular Manifestations

*Cutaneous:* rheumatoid nodules, vasculitis
*Pulmonary:* nodules, interstitial disease, bronchiolitis obliterans–organizing pneumonia (BOOP), pleural disease, Caplan's syndrome [sero (+) RA associated with pneumoconiosis]
*Ocular:* keratoconjunctivitis sicca (KCS), episcleritis, scleritis
*Hematologic:* anemia, Felty's syndrome (splenomegaly and neutropenia)
*Cardiac:* pericarditis, myocarditis
*Neurologic:* myelopathies secondary to cervical spine disease, entrapment, vasculitis

### EVALUATION

- History and physical examination with careful examination of all joints.
- Rheumatoid factor (RF) is present in >66% of pts; its presence correlates with severe disease, nodules, extra-articular features.
- Antibodies to cyclic citrullinated protein (anti-CCP) have similar sensitivity but higher specificity than RF; may be most useful in early RA; presence most common in pts with aggressive disease with a tendency for developing bone erosions.
- Other laboratory data: CBC, ESR.
- Synovial fluid analysis: useful to rule out crystalline disease, infection.
- Radiographs: juxta-articular osteopenia, joint space narrowing, marginal erosions. CXR should be obtained.

### DIAGNOSIS

Not difficult in pts with typical established disease. May be confusing early. Classification criteria were updated in 2010 (Table 380-1, p. 2143, in HPIM-19).

### DIFFERENTIAL DIAGNOSIS

Gout, SLE, psoriatic arthritis, infectious arthritis, osteoarthritis, sarcoid.

## TREATMENT RHEUMATOID ARTHRITIS

Goals: lessen pain, reduce inflammation, improve/maintain function, prevent long-term joint damage, control of systemic involvement. Increasing trend to treat RA more aggressively earlier in disease course (Table 380-2, HPIM-19, pp. 2146–2147). All RA therapies have individual toxicities, with many requiring pretreatment screening and monitoring.

- Pt education on disease, joint protection.
- Physical and occupational therapy: strengthen periarticular muscles, consider assistive devices.
- Aspirin or NSAIDs.
- Intra-articular glucocorticoids.
- Systemic glucocorticoids.
- Disease-modifying antirheumatic drugs (DMARDs): e.g., methotrexate, hydroxychloroquine, sulfasalazine, leflunomide.
- Biologic therapies.
- TNF-modulatory agents (etanercept, infliximab, adalimumab, golimumab, certolizumab): effective at controlling RA in many pts and can slow the rate of

progression of radiographic joint damage and decrease disability; carry potential for serious infection and individual toxicities.

- Abatacept (CTLA4-Ig): inhibits T-cell activation, can be given with or without methotrexate.
- Rituximab: a chimeric antibody directed to CD20 that depletes mature B cells and is approved for refractory RA.
- Tocilizumab: humanized monoclonal antibody directed against the IL-6 receptor.
- Tofacitinib: oral small molecule inhibitor that primarily inhibits JAK1 and JAK3.
- Anakinra: an IL-1 receptor antagonist approved for RA but rarely used in RA due to only modest clinical efficacy.
- Surgery: may be considered for severe functional impairment due to deformity.

## SYSTEMIC SCLEROSIS (SCLERODERMA, SSC)

### DEFINITION AND PATHOGENESIS

Systemic sclerosis (SSc) is a multisystem disorder characterized by thickening of the skin (scleroderma) and distinctive involvement of multiple internal organs (chiefly GI tract, lungs, heart, and kidney). Pathogenesis unclear; involves immunologic mechanisms leading to vascular endothelial damage and activation of fibroblasts.

### CLINICAL MANIFESTATIONS

- *Cutaneous:* edema followed by fibrosis of the skin (chiefly extremities, face, trunk); telangiectasis; calcinosis; Raynaud's phenomenon
- *Arthralgias and/or arthritis*
- *GI:* esophageal hypomotility; intestinal hypofunction, gastric antral vascular ectasia (GAVE)
- *Pulmonary:* interstitial lung disease, pulmonary arterial hypertension, alveolitis
- *Cardiac:* pericarditis, cardiomyopathy, conduction abnormalities
- *Renal:* hypertension; renal crisis/failure

Two distinct subsets can be identified:

1. *Diffuse cutaneous SSc:* rapid development of symmetric skin thickening of proximal and distal extremity, face, and trunk. At high risk for development of visceral disease early in course.
2. *Limited cutaneous SSc:* often have long-standing Raynaud's phenomenon before other features appear; skin involvement limited to fingers (sclerodactyly), extremity distal to elbows, and face; generally associated with better prognosis but can be associated with pulmonary arterial hypertension; a subset of limited SSc has features of *CREST syndrome* (*c*alcinosis, *R*aynaud's, *e*sophageal dysmotility, *s*clerodactyly, *t*elangiectasias).

### EVALUATION

- History and physical examination with particular attention to blood pressure (heralding feature of renal disease).
- Laboratories: ESR, ANA (anticentromere pattern associated with limited SSc), specific antibodies may include antitopoisomerase I (Scl-70), (UA). An increased range of autoantibodies correlating with specific clinical features have become recognized (Table 382-3, HPIM-19, p. 2157).
- Radiographs: CXR, barium swallow if indicated, hand x-rays may show distal tuft resorption and calcinosis.
- Additional studies: ECG, echo, PFT, consider skin biopsy.

**TREATMENT SYSTEMIC SCLEROSIS**

- Education regarding warm clothing, smoking cessation, antireflux measures.
- Calcium channel blockers (e.g., nifedipine) useful for Raynaud's phenomenon. Other agents with potential benefit include sildenafil, losartan, nitroglycerin paste, fluoxetine, bosentan, digital sympathectomy.
- ACE inhibitors: particularly important for controlling hypertension and limiting progression of renal disease.
- Antacids, $H_2$ antagonists, omeprazole, and metoclopramide may be useful for esophageal reflux.
- D-Penicillamine: controversial benefit to reduce skin thickening and prevent organ involvement; no advantages to using doses >125 mg every other day.
- Glucocorticoids: no efficacy in slowing progression of SSc; indicated for inflammatory myositis or pericarditis; high doses may be associated with development of renal crisis.
- Cyclophosphamide: improves lung function and survival in pts with alveolitis.
- Epoprostenol or treprostinil (prostacyclin), bosentan (endothelin-1 receptor antagonist), sildenafil (phosphodiesterase type 5 inhibitor): may improve cardiopulmonary hemodynamics in pts with pulmonary hypertension.

## MIXED CONNECTIVE TISSUE DISEASE (MCTD)

### DEFINITION

Syndrome characterized by a combination of clinical features similar to those of SLE, SSc, polymyositis, and RA; unusually high titers of circulating antibodies to a nuclear ribonucleoprotein (RNP) are found. It is controversial whether MCTD is a truly distinct entity or a subset of SLE or SSc.

### CLINICAL MANIFESTATIONS

Raynaud's phenomenon, polyarthritis, swollen hands or sclerodactyly, esophageal dysfunction, pulmonary fibrosis, inflammatory myopathy. Renal involvement occurs in about 25%. Laboratory abnormalities include high-titer ANAs, very high titers of antibody to RNP, positive RF in 50% of pts.

### EVALUATION

Similar to that for SLE and SSc.

**TREATMENT MIXED CONNECTIVE TISSUE DISEASE**

Few published data. Treat based on manifestations with similar approach to that used if feature occurred in SLE/SSc/polymyositis/RA.

## SJÖGREN'S SYNDROME

### DEFINITION

An immunologic disorder characterized by progressive lymphocytic destruction of exocrine glands most frequently resulting in symptomatic eye and mouth dryness; can be associated with extraglandular manifestations; predominantly affects middle-age females; may be primary or secondary when it occurs in association with other

autoimmune diseases. Lymphoma can occur in 6% with glandular MALT being most common.

### CLINICAL MANIFESTATIONS

- *Constitutional:* fatigue
- *Sicca symptoms:* KCS and xerostomia
- *Dryness of other surfaces:* nose, vagina, trachea, skin
- *Extraglandular features:* arthralgia/arthritis, Raynaud's, lymphadenopathy, interstitial pneumonitis, vasculitis (usually cutaneous), nephritis, lymphoma

### EVALUATION

- History and physical examination: with special attention to oral, ocular, lymphatic examination and presence of other autoimmune disorders.
- Presence of autoantibodies is a hallmark of disease (ANA, RF, anti-Ro/SS-A, anti-La/SS-B).
- Other laboratory tests: ESR; CBC; renal, liver, and thyroid function tests; serum protein electrophoresis (SPEP) (hypergammaglobulinemia or monoclonal gammopathy common); UA.
- Ocular studies: to diagnose and quantitate KCS; Schirmer's test, Rose bengal staining.
- Oral examination: unstimulated salivary flow, dental examination.
- Labial salivary gland biopsy: demonstrates lymphocytic infiltration and destruction of glandular tissue.

### DIAGNOSIS

International classification criteria based on clinical and laboratory features have been established (Table 383-5, HPIM-19, p. 2168).

**TREATMENT SJÖGREN'S SYNDROME**

- Regular follow-up with dentist and ophthalmologist.
- Dry eyes: artificial tears, ophthalmic lubricating ointments, local stimulation with cyclic adenosine monophosphate or cyclosporine drops.
- Xerostomia: frequent sips of water, sugarless candy.
- Pilocarpine or cevimeline: may help sicca manifestations.
- Hydroxychloroquine: may help arthralgias.
- Glucocorticoids: not effective for sicca symptoms but may have role in treatment of extraglandular manifestations.

## ANTIPHOSPHOLIPID SYNDROME (APS)

### DEFINITION

Autoantibody-mediated acquired thrombophilia characterized by recurrent arterial or venous thromboses and/or pregnancy morbidity in the presence of autoantibodies against phospholipid (PL)-binding plasma proteins. Can occur alone (primary) or in association with another autoimmune disease (secondary).

### CLINICAL MANIFESTATIONS

Consist of vascular thrombotic features and pregnancy morbidity (Table 379-2 in HPIM-19, p. 2135). Catastrophic APS (CAPS) is rapidly progressive thromboembolic disease involving three or more organ systems that can be life threatening.

### EVALUATION

Laboratory examination of clotting parameters to include PTT, kaolin clotting time, dilute Russell viper venom test, antibodies directed against cardiolipin, $\beta_2$ glycoprotein, prothrombin. Antibodies should be measured on two occasions 12 weeks apart.

### DIAGNOSIS

Suggested by the presence of at least one clinical and one laboratory feature.

### TREATMENT ANTIPHOSPHOLIPID SYNDROME

- After first thrombotic event, warfarin for life to achieve an international normalized ratio (INR) 2.5–3.5.
- Pregnancy morbidity prevented by heparin with aspirin 80 mg daily. IV immunoglobulins (IVIG) may also prevent pregnancy loss. Glucocorticoids are ineffective.
- For CAPS, consider anticoagulation, glucocorticoids, plasma exchange, and IVIG.

For a more detailed discussion, see Hahn BH: Systemic Lupus Erythematosus, Chap. 378, p. 2124; Shah A, St. Clair EW: Rheumatoid Arthritis, Chap. 380, p. 2136; Varga J: Systemic Sclerosis (Scleroderma) and Related Disorders, Chap. 382, p. 2154; Moutsopoulos HM, Tzioufas AG: Sjögren's Syndrome, Chap. 383, p. 2166; Moutsopoulos HM, Vlachoyiannopoulos PG: Antiphospholipid Syndrome, Chap. 379, p. 2134, in HPIM-19.

## 159 Vasculitis

### DEFINITION AND PATHOGENESIS

A clinicopathologic process characterized by inflammation of and damage to blood vessels, compromise of vessel lumen, and resulting ischemia. Clinical manifestations depend on size and location of affected vessel. Most vasculitic syndromes appear to be mediated by immune mechanisms. May be primary or sole manifestation of a disease or secondary to another disease process. Unique vasculitic syndromes can differ greatly with regards to clinical features, disease severity, histology, and treatment.

## PRIMARY VASCULITIS SYNDROMES

### Granulomatosis with Polyangiitis (Wegener's)

Granulomatous vasculitis of upper and lower respiratory tracts together with glomerulonephritis; upper airway lesions affecting the nose and sinuses can cause purulent or bloody nasal discharge, mucosal ulceration, septal perforation, and cartilaginous destruction (saddlenose deformity). Lung involvement may be asymptomatic or cause cough, hemoptysis, dyspnea; eye involvement may occur; glomerulonephritis can be rapidly progressive and asymptomatic and can lead to renal failure.

### Microscopic Polyangiitis

Small-vessel vasculitis that can affect the glomerulus and lungs; medium-sized vessels also may be affected.

### Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss)

Granulomatous vasculitis of multiple organ systems, particularly the lung; characterized by asthma, peripheral eosinophilia, eosinophilic tissue infiltration; glomerulonephritis can occur.

### Polyarteritis Nodosa

Medium-sized muscular arteries involved; frequently associated with arteriographic aneurysms; commonly affects renal arteries, liver, GI tract, peripheral nerves, skin, heart; can be associated with hepatitis B and C.

### Giant Cell Arteritis

Inflammation of medium- and large-sized arteries; primarily involves temporal artery but systemic and large vessel involvement may occur; symptoms include headache, jaw/tongue claudication, scalp tenderness, fever, musculoskeletal symptoms (*polymyalgia rheumatica*); sudden blindness from involvement of optic vessels is a dreaded complication.

### Takayasu Arteritis

Vasculitis of the large arteries with strong predilection for aortic arch and its branches; most common in young women; presents with inflammatory or ischemic symptoms in arms and neck, systemic inflammatory symptoms, aortic regurgitation.

### IgA Vasculitis (Henoch-Schönlein)

Characterized by involvement of skin, GI tract, kidneys; more common in children; may recur after initial remission.

### Cryoglobulinemic Vasculitis

Majority of cases are associated with hepatitis C where an aberrant immune response leads to formation of cryoglobulin; characterized by cutaneous vasculitis, arthritis, peripheral neuropathy, and glomerulonephritis.

### Idiopathic Cutaneous Vasculitis

Cutaneous vasculitis is defined broadly as inflammation of the blood vessels of the dermis; due to underlying disease in >70% of cases (see "Secondary Vasculitis Syndromes" below) with 30% occurring idiopathically.

### Miscellaneous Vasculitic Syndromes

- Kawasaki disease
- Primary central nervous system vasculitis
- Behçet's disease
- Cogan's syndrome
- Polyangiitis overlap syndrome

## SECONDARY VASCULITIS SYNDROMES

- Drug-induced vasculitis
- Serum sickness
- Vasculitis associated with infection, malignancy, rheumatic disease

## EVALUATION (FIG. 159-1)

- Thorough history and physical examination: special reference to ischemic manifestations and systemic inflammatory signs/symptoms.
- Laboratories: important in assessing organ involvement: CBC with differential, ESR, renal function tests, UA. Should also be obtained to rule out other diseases: ANA, rheumatoid factor, anti-GBM, hepatitis B/C serologies, HIV.
- Antineutrophil cytoplasmic autoantibodies (ANCA): associated with granulomatosis with polyangiitis (Wegener's), microscopic polyangiitis, and some pts with eosinophilic granulomatosis with polyangiitis (Churg-Strauss); presence of ANCA is adjunctive and should not be used in place of biopsy as a means of diagnosis or to guide treatment decisions.
- Radiographs: CXR should be performed even in the absence of symptoms in small-vessel vasculitides.
- Diagnosis: can usually be made only by arteriogram or biopsy of affected organ(s).

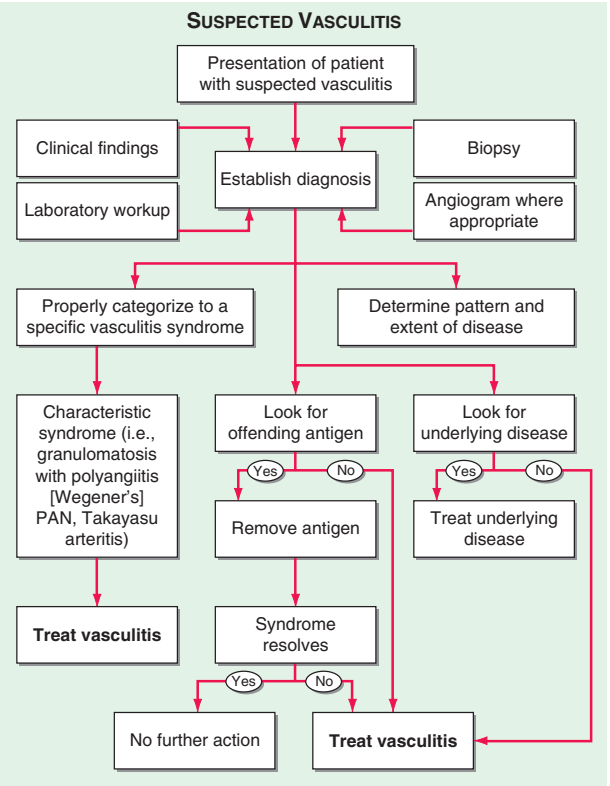


**FIGURE 159-1** Algorithm for the approach to a pt with suspected diagnosis of vasculitis. PAN, polyarteritis nodosa.

**TABLE 159-1 CONDITIONS THAT CAN MIMIC VASCULITIS**

| |
|---|
| Infectious diseases |
| Bacterial endocarditis |
| Disseminated gonococcal infection |
| Pulmonary histoplasmosis |
| Coccidioidomycosis |
| Syphilis |
| Lyme disease |
| Rocky Mountain spotted fever |
| Whipple's disease |
| Coagulopathies/thrombotic microangiopathies |
| Antiphospholipid syndrome |
| Thrombotic thrombocytopenic purpura |
| Neoplasms |
| Atrial myxoma |
| Lymphoma |
| Carcinomatosis |
| Drug toxicity |
| Cocaine/Levamisole |
| Amphetamines |
| Ergot alkaloids |
| Methysergide |
| Arsenic |
| Sarcoidosis |
| Atheroembolic disease |
| Anti–glomerular basement membrane antibody disease (Goodpasture's syndrome) |
| Amyloidosis |
| Migraine |
| Collagen vascular disorders |
| Ehlers-Danlos type IV |
| Marfan syndrome |
| Loey-Dietz syndrome |
| Vasospastic disorders |
| Reversible cerebral vasoconstrictive syndrome |

## DIFFERENTIAL DIAGNOSIS

Guided by organ manifestations. In many instances includes infections and neoplasms, which must be ruled out prior to beginning immunosuppressive therapy. Consideration must also be given for diseases that can mimic vasculitis (Table 159-1).

## TREATMENT VASCULITIS

Therapy is based on the specific vasculitic syndrome and the severity of its manifestations. Immunosuppressive therapy should be avoided in disease that

rarely results in irreversible organ system dysfunction or that usually does not respond to such agents (e.g., isolated cutaneous vasculitis). Antiviral agents play an important role in treating vasculitis occurring with hepatitis B or C. Glucocorticoids alone may control giant cell arteritis and Takayasu arteritis. Therapy that combines glucocorticoids with another immunosuppressive agent is particularly important in syndromes with life-threatening organ system involvement, especially active glomerulonephritis. Frequently used agents:

- Prednisone 1 (mg/kg)/d initially, then tapered.
- Cyclophosphamide 2 (mg/kg)/d, adjusted to avoid severe leukopenia. Morning administration with a large amount of fluid is important in minimizing bladder toxicity. IV cyclophosphamide (15 mg/kg every 2 weeks for three doses then every 3 weeks thereafter) can also induce remission but may be associated with a higher relapse rate. Treatment should be limited to 3–6 months followed by transition to maintenance therapy with methotrexate or azathioprine.
- Rituximab 375 (mg/m$^2$)/week for 4 weeks. As effective as cyclophosphamide to induce remission of granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis.
- Methotrexate in weekly doses up to 25 mg/week may be used to induce remission in granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis pts who do not have immediately life-threatening disease or cannot tolerate cyclophosphamide. It may also be used for maintaining remission after induction with cyclophosphamide. Cannot be used in renal insufficiency or chronic liver disease.
- Azathioprine 2 (mg/kg)/d. Less effective in treating active disease but useful in maintaining remission after induction with cyclophosphamide.
- Mycophenolate mofetil 1000 mg bid. Less effective than azathioprine to maintain remission but an option in pts who cannot take or who have relapsed with methotrexate and azathioprine.
- Plasmapheresis may have an adjunctive role in rapidly progressive glomerulonephritis.

For a more detailed discussion, see Langford CA, Fauci AS: The Vasculitis Syndromes, Chap. 385, p. 2179; in HPIM-19.

# 160 Ankylosing Spondylitis

## DEFINITION

Ankylosing spondylitis (AS) belongs to the family of *spondyloarthritides* that also includes reactive arthritis (Chap. 162), psoriatic arthritis (Chap. 161), enteropathic arthritis (Chap. 165) juvenile-onset spondyloarthritis, and undifferentiated spondyloarthritis. Classification criteria based on their main clinical features of axial spondyloarthritis (Table 160-1) and peripheral spondyloarthritis (Table 160-2) have been

**TABLE 160-1 ASAS CRITERIA FOR CLASSIFICATION OF AXIAL SPONDYLOARTHRITIS (TO BE APPLIED FOR PATIENTS WITH BACK PAIN ≥3 MONTHS AND AGE OF ONSET <45 YEARS)[a]**

| Sacroiliitis on Imaging Plus ≥1 SpA Feature | or | HLA-B27 Plus ≥ 2 Other SpA Features |
|---|---|---|
| Sacroiliitis on imaging<br>• Active (acute) inflammation on MRI highly suggestive of SpA-associated sacroiliitis[b]<br>*and/or*<br>• Definite radiographic sacroiliitis according to modified New York criteria[c] | | SpA features<br>• Inflammatory back pain[d]<br>• Arthritis[e]<br>• Enthesitis (heel)[f]<br>• Anterior uveitis[g]<br>• Dactylitis[e]<br>• Psoriasis[e]<br>• Crohn's disease or ulcerative colitis[e]<br>• Good response to NSAIDs[h]<br>• Family history of SpA[i]<br>• HLA-B27<br>• Elevated CRP[j] |

[a]Sensitivity 83%, specificity 84%. The imaging arm (sacroiliitis) alone has a sensitivity of 66% and a specificity of 97%.
[b]Bone marrow edema and/or osteitis on short tau inversion recovery (STIR) or gadolinium-enhanced T1 image.
[c]Bilateral grade ≥2 or unilateral grade 3 or 4.
[d]See text for criteria.
[e]Past or present, diagnosed by a physician.
[f]Past or present pain or tenderness on examination at calcaneus insertion of Achilles tendon or plantar fascia.
[g]Past or present, confirmed by an ophthalmologist.
[h]Substantial relief of back pain at 24–48 h after a full dose of NSAID.
[i]First- or second-degree relatives with ankylosing spondylitis (AS), psoriasis, uveitis, reactive arthritis (ReA), or inflammatory bowel disease (IBD).
[j]After exclusion of other causes of elevated CRP.
***Abbreviations:*** ASAS, Assessment of Spondyloarthritis International Society; CRP, C-reactive protein; SpA, spondyloarthritis.
***Source:*** From M Rudwaleit et al: *Ann Rheum Dis* 68:777, 2009. Copyright 2009, with permission from BMJ Publishing Group Ltd.

developed that aide in early identification. AS is a chronic and progressive inflammatory disease of the axial skeleton with sacroiliitis (usually bilateral) as its hallmark. Peripheral joints and extra-articular structures may also be affected. Most frequently presents in second or third decade more commonly in men; strong association with histocompatibility antigen HLA-B27.

## CLINICAL MANIFESTATIONS

- *Back pain and stiffness:* not relieved by lying down, often present at night forcing pt to leave bed, worse in the morning, improves with activity, insidious onset, duration >3 months (often called symptoms of "inflammatory" back pain).

**TABLE 160-2 ASAS CRITERIA FOR PERIPHERAL SPONDYLOARTHRITIS[a]**

| Arthritis[b] | *or* ***plus*** | Enthesitis |
|---|---|---|
| One or more of the following:<br>• Uveitis<br>• Psoriasis<br>• Crohn's disease or ulcerative colitis | | |
| *OR* two or more of the following:<br>• Arthritis<br>• Enthesitis<br>• Dactylitis<br>• Inflammatory back pain ever<br>• Family history for SpA | | |

[a]Sensitivity 79.5%, specificity 83.3%.
[b]Peripheral arthritis, usually predominantly lower limb and/or asymmetric.
***Abbreviations:*** ASAS, Assessment of Spondyloarthritis International Society; SpA, spondyloarthritis.
***Source:*** M Rudawaleit et al: *Ann Rheum Dis* 70:25, 2011.

- *Extra-axial arthritis:* hip and shoulders 25–35%, other peripheral joint involvement up to 30%, usually asymmetric.
- *Chest pain:* from involvement of thoracic skeleton and muscular insertions.
- *Extra/juxta-articular pain:* due to "enthesitis": inflammation at insertion of tendons and ligaments into bone; frequently affects greater trochanter, iliac crests, ischial tuberosities, tibial tubercles, heels.
- *Extra-articular findings*—include acute anterior uveitis in up to 40% of pts, aortitis, aortic insufficiency, GI inflammation, cardiac conduction defects, amyloidosis, bilateral upper lobe pulmonary fibrosis.
- *Constitutional symptoms:* fever, fatigue, weight loss may occur.
- *Neurologic complications:* related to spinal fracture/dislocation (can occur with even minor trauma), atlantoaxial subluxation (can lead to spinal cord compression), cauda equina syndrome.

## PHYSICAL EXAMINATION

- Tenderness over involved joints
- Diminished chest expansion
- Diminished anterior flexion of lumbar spine (Schober test)

## EVALUATION

- ESR and C-reactive protein elevated in majority.
- Mild anemia.
- Rheumatoid factor and ANA negative.
- HLA-B27 may be helpful in pts with inflammatory back symptoms but negative x-rays.
- Radiographs: early may be normal. Sacroiliac joints: usually symmetric; bony erosions with "pseudowidening" followed by fibrosis and ankylosis. Spine: squaring of vertebrae; syndesmophytes; ossification of annulus fibrosis and anterior longitudinal ligament causing "bamboo spine." Sites of enthesitis may ossify and be visible on x-ray. MRI is procedure of choice when plain radiographs do not reveal sacroiliac abnormalities and can show early intra-articular inflammation, cartilage changes, and bone marrow edema.

## DIAGNOSIS (TABLE 160-1)

### Differential Diagnosis

Osteoarthritis/spondylosis, degenerative disk disease, muscular strain, fibromyalgia; metabolic, infectious, or malignant causes of back pain; diffuse idiopathic skeletal hyperostosis.

## TREATMENT ANKYLOSING SPONDYLITIS

- Exercise program to maintain posture and mobility is important.
- NSAIDs first-line treatment, useful in most pts.
- TNF-modulatory agents (etanercept, infliximab, adalimumab, golimumab, certolizumab pegol) have been found to improve disease activity and function and reduce bone marrow edema on MRI. Generally used in active disease with failure of at least two NSAIDs.
- Secukinumab, an IL-17A antagonist, has been found to reduce signs and symptoms of active disease.
- Sulfasalazine 2–3 g/d is of modest benefit, primarily for peripheral arthritis.
- Methotrexate, widely used but has not been of proven benefit.
- No documented therapeutic role for systemic glucocorticoids.
- Intra-articular glucocorticoids for persistent enthesitis or peripheral synovitis; ocular glucocorticoids for uveitis with systemic immunosuppression required in some cases; surgery for severely affected or deformed joints.

For a more detailed discussion, see Taurog JD, Carter JD: The Spondyloarthritides, Chap. 384, p. 2169, in HPIM-19.

# 161 Psoriatic Arthritis

## DEFINITION

Psoriatic arthritis is a chronic inflammatory arthritis that affects 5–42% of persons with psoriasis. Some pts, especially those with spondylitis, will carry the HLA-B27 histocompatibility antigen. Onset of psoriasis usually precedes development of joint disease; approximately 15–20% of pts develop arthritis prior to onset of skin disease. Nail changes are seen in 90% of pts with psoriatic arthritis.

## PATTERNS OF JOINT INVOLVEMENT

There are five patterns of joint involvement in psoriatic arthritis.

- Asymmetric oligoarthritis: often involves distal interphalangeal/proximal interphalangeal (DIP/PIP) joints of hands and feet, knees, wrists, ankles; "sausage digits" may be present, reflecting tendon sheath inflammation.
- Symmetric polyarthritis (40%): resembles rheumatoid arthritis except rheumatoid factor is negative, absence of rheumatoid nodules.

- Predominantly DIP joint involvement (15%): high frequency of association with psoriatic nail changes.
- "Arthritis mutilans" (3–5%): aggressive, destructive form of arthritis with severe joint deformities and bony dissolution.
- Spondylitis and/or sacroiliitis: axial involvement is present in 20–40% of pts with psoriatic arthritis; may occur in absence of peripheral arthritis.

## EVALUATION

- Negative tests for rheumatoid factor.
- Hypoproliferative anemia, elevated ESR.
- Hyperuricemia may be present.
- HIV infection should be suspected in fulminant disease.
- Inflammatory synovial fluid and biopsy without specific findings.
- Radiographic features include erosion at joint margin, bony ankylosis, tuft resorption of terminal phalanges, "pencil-in-cup" deformity (bone proliferation at base of distal phalanx with tapering of proximal phalanx), axial skeleton with asymmetric sacroiliitis, asymmetric nonmarginal syndesmophytes.

## DIAGNOSIS (TABLE 161-1)

## TREATMENT PSORIATIC ARTHRITIS

- Coordinated therapy is directed at the skin and joints.
- Pt education, physical and occupational therapy.
- TNF modulatory agents (etanercept, infliximab, adalimumab, golimumab, certolizumab pegol) can improve joint disease and delay radiographic progression.

**TABLE 161-1 THE CASPAR (CLASSIFICATION CRITERIA FOR PSORIATIC ARTHRITIS) CRITERIA[a]**

**To meet the CASPAR criteria, a pt must have inflammatory articular disease (joint, spine, or entheseal) with ≥3 points from any of the following five categories:**

1. Evidence of current psoriasis,[b, c] a personal history of psoriasis, or a family history of psoriasis[d]
2. Typical psoriatic nail dystrophy[e] observed on current physical examination
3. A negative test result for rheumatoid factor
4. Either current dactylitis[f] or a history of dactylitis recorded by a rheumatologist
5. Radiographic evidence of juxtaarticular new bone formation[g] in the hand or foot

[a]Specificity of 99% and sensitivity of 91%.
[b]Current psoriasis is assigned 2 points; all other features are assigned 1 point.
[c]Psoriatic skin or scalp disease present at the time of examination, as judged by a rheumatologist or dermatologist.
[d]History of psoriasis in a first- or second-degree relative.
[e]Onycholysis, pitting, or hyperkeratosis.
[f]Swelling of an entire digit.
[g]III-defined ossification near joint margins, excluding osteophyte formation.
***Source:*** From Taylor W et al: Classification criteria for psoriatic arthritis. Development of new criteria from a large international study. *Arthritis Rheum*, 54:2665, 2006.

- Ustekinumab (anti-IL-12/23 p40 monoclonal antibody) has efficacy for both skin and joint disease.
- Apremilast (phosphodiesterase 4 inhibitor) benefit skin and joint involvement.
- Secukinumab, an IL-17A antagonist, has been found to improve disease activity and can also be used for moderate to severe plaque psoriasis.
- NSAIDs.
- Intraarticular steroid injections—useful in some settings. Systemic glucocorticoids should rarely be used as may induce rebound flare of skin disease upon tapering.
- Efficacy of gold salts and antimalarials controversial.
- Sulfasalazine 2–3 g/d has clinical efficacy but do not halt joint erosion.
- Methotrexate 15 mg/week had no improvement in synovitis but it improved skin scores and may have symptom-modifying effects.
- Leflunomide may be of benefit for skin and joint disease.

For a more detailed discussion, see Taurog JD, Carter JD: The Spondyloarthritides, Chap. 384, p. 2169, in HPIM-19.

# 162 Reactive Arthritis

## DEFINITION

*Reactive arthritis* (ReA) refers to acute nonpurulent arthritis complicating an infection elsewhere in the body. The term has been used primarily to refer to spondyloarthritides following enteric or urogenital infections

## PATHOGENESIS

The bacteria identified as being definitive triggers of ReA include enteric organisms *Shigella*, *Salmonella*, *Yersinia*, *Campylobacter* species; and genitourinary infection with *Chlamydia trachomatis*; there is also evidence implicating *Clostridium difficile*, certain toxigenic *Escherichia coli*, and possibly other agents.

## CLINICAL MANIFESTATIONS

Average age 18–40 years. The male:female ratio following enteric infection is 1:1; however, genitourinary-acquired reactive arthritis is predominantly seen in young males. In a majority of cases, history will elicit symptoms of genitourinary or enteric infection 1–4 weeks prior to onset of other features.

*Constitutional:* fatigue, malaise, fever, weight loss.

*Arthritis:* usually acute, asymmetric, oligoarticular, involving predominantly lower extremities; sacroiliitis may occur.

*Enthesitis:* inflammation at insertion of tendons and ligaments into bone; dactylitis or "sausage digit," plantar fasciitis, and Achilles tendinitis are common.

*Ocular features:* conjunctivitis, usually minimal; uveitis, keratitis, and optic neuritis rarely present.

*Urethritis:* discharge intermittent and may be asymptomatic.

*Other urogenital manifestations:* prostatitis, cervicitis, salpingitis.

*Mucocutaneous lesions:* painless lesions on glans penis (circinate balanitis) and oral mucosa in approximately a third of pts; *keratoderma blennorrhagica*: cutaneous vesicles that become hyperkeratotic, most common on soles and palms.

*Uncommon manifestations:* pleuropericarditis, aortic regurgitation, neurologic manifestations, secondary amyloidosis.

Reactive arthritis is associated with and may be the presenting sign and symptom of HIV.

## EVALUATION

- Pursuit of triggering infection by culture, serology, or molecular methods as clinically suggested.
- Rheumatoid factor and ANA negative.
- Mild anemia, leukocytosis, elevated ESR may be seen.
- HLA-B27 association was initially overestimated with recent studies showing a prevalence <50%. May be helpful in atypical cases and may have prognostic significance.
- HIV screening should be performed in all pts.
- Synovial fluid analysis—often very inflammatory; negative for crystals or infection.
- Radiographs—erosions may be seen with new periosteal bone formation, ossification of entheses, sacroiliitis (often unilateral).

## DIFFERENTIAL DIAGNOSIS

Includes septic arthritis (gram +/–), gonococcal arthritis, crystalline arthritis, psoriatic arthritis.

## TREATMENT REACTIVE ARTHRITIS

- Controlled trials have failed to demonstrate any benefit of antibiotics in reactive arthritis. Prompt antibiotic treatment of acute chlamydial urethritis may prevent subsequent reactive arthritis.
- NSAIDs (e.g., indomethacin 25–50 mg PO tid) benefit most pts.
- Intra-articular glucocorticoids.
- Sulfasalazine up to 3 g/d in divided doses may help some pts with persistent arthritis.
- Immunosuppressive agents, such as azathioprine (1–2 [mg/kg]/d) or methotrexate (7.5–15 mg/week) may be considered for debilitating disease refractory to other modalities; contraindicated in HIV disease.
- Anti-TNF agents can be considered in severe chronic cases.
- Uveitis may require therapy with ocular or systemic glucocorticoids.

## OUTCOME

Arthritis typically persists for 3–5 months; recurrence of the acute syndrome is common. Chronic joint symptoms persist in 15% with associated disability.

For a more detailed discussion, see Taurog JD, Carter JD: The Spondyloarthritides, Chap. 384, p. 2169, in HPIM-19.

# 163 Osteoarthritis

## DEFINITION

Osteoarthritis (OA) is a disorder characterized by progressive joint failure in which all structures of the joint have undergone pathologic change. The pathologic sine qua non of OA is hyaline articular cartilage loss accompanied by increasing thickness and sclerosis of the subchondral bone plate, outgrowth of osteophytes at the joint margin, stretching of the articular capsule, and weakness of the muscles bridging the joint. There are numerous pathways that lead to OA, but the initial step is often joint injury in the setting of a failure of protective mechanisms.

## EPIDEMIOLOGY

OA is the most common type of arthritis. The prevalence of OA correlates strikingly with age, and it is much more common in women than in men. Joint vulnerability and joint loading are the two major risk factors contributing to OA. These are influenced by factors that include age, female sex, race, genetic factors, nutritional factors, joint trauma, previous damage, malalignment, proprioceptive deficiencies, and obesity.

## PATHOGENESIS

The earliest changes of OA may begin in cartilage. The two major components of cartilage are type 2 collagen, which provides tensile strength, and aggrecan, a proteoglycan. OA cartilage is characterized by gradual depletion of aggrecan, unfurling of the collagen matrix, and loss of type 2 collagen, which leads to increased vulnerability.

## CLINICAL MANIFESTATIONS

OA can affect almost any joint but usually occurs in weight-bearing and frequently used joints such as the knee, hip, spine, and hands. The hand joints that are typically affected are the distal interphalangeal (DIP), proximal interphalangeal (PIP), or first carpometacarpal (thumb base); metacarpophalangeal joint involvement is rare.

### Symptoms

- Use-related pain affecting one or a few joints (rest and nocturnal pain less common)
- Stiffness after rest or in morning may occur but is usually brief (<30 min)
- Loss of joint movement or functional limitation
- Joint instability
- Joint deformity
- Joint crepitation ("crackling")

### Physical Examination

- Chronic monarthritis or asymmetric oligo/polyarthritis
- Firm or "bony" swellings of the joint margins, e.g., Heberden's nodes (hand DIP) or Bouchard's nodes (hand PIP)
- Mild synovitis with a cool effusion can occur but is uncommon
- Crepitance—audible creaking or crackling of joint on passive or active movement
- Deformity, e.g., OA of knee may involve medial, lateral, or patellofemoral compartments resulting in varus or valgus deformities
- Restriction of movement, e.g., limitation of internal rotation of hip
- Objective neurologic abnormalities may be seen with spine involvement (may affect intervertebral disks, apophyseal joints, and paraspinal ligaments)

## EVALUATION

- Routine lab work usually normal.
- ESR usually normal but may be elevated in pts who have synovitis.
- Rheumatoid factor, ANA studies negative.
- Joint fluid is straw-colored with good viscosity; fluid WBCs <1000/μL; of value in ruling out crystal-induced arthritis, inflammatory arthritis, or infection.
- Radiographs may be normal at first but as disease progresses may show joint space narrowing, subchondral bone sclerosis, subchondral cysts, and osteophytes. Erosions are distinct from those of rheumatoid and psoriatic arthritis as they occur subchondrally along the central portion of the joint surface.

## DIAGNOSIS

Usually established on basis of pattern of joint involvement. Radiographic features, normal laboratory tests, and synovial fluid findings can be helpful if signs suggest an inflammatory arthritis.

### Differential Diagnosis

Osteonecrosis, Charcot joint, rheumatoid arthritis, psoriatic arthritis, crystal-induced arthritides.

## TREATMENT OSTEOARTHRITIS

- Treatment goal—alleviate pain and minimize loss of physical function.
- Nonpharmacotherapy strategies aimed at altering loading across the painful joint—include pt education, weight reduction, appropriate use of cane and other supports, isometric exercises to strengthen muscles around affected joints, bracing/orthotics to correct malalignment.
- Topical capsaicin cream may help relieve hand or knee pain.
- Acetaminophen—commonly used analgesic, caution regarding hepatic toxicity.
- NSAIDs, COX-2 inhibitors—GI, renal, cardiovascular toxicity, must weigh individual risks and benefits.
- Topical NSAIDs—fewer GI and systemic side effects; can cause skin irritation
- Opioid analgesics—may be considered in selected pts whose symptoms are inadequately controlled with other measures and who cannot undergo surgery; habituation is a potential concern.
- Intraarticular glucocorticoids—may provide symptomatic relief but typically short-lived.
- Intraarticular hyaluronan—can be given for symptomatic knee and hip OA, but it is controversial whether it has efficacy beyond placebo.
- Glucosamine and chondroitin—large scale trials have failed to show efficacy for pain relief; recent guidelines recommend against use.
- Systemic glucocorticoids have no place in the treatment of OA.
- Arthroscopic debridement and lavage—randomized trials have shown no greater effect on pain relief or disability compared to sham procedure or no treatment.
- Joint replacement surgery may be considered in pts with advanced OA who have intractable pain and loss of function in whom aggressive medical management has failed.

For a more detailed discussion, see Felson DT: Osteoarthritis, Chap. 394, p. 2226, in HPIM-19.

# 164 Gout, Pseudogout, and Related Diseases

## GOUT

### DEFINITION

*Gout* is a metabolic disease most often affecting middle-aged to elderly men and postmenopausal women. Hyperuricemia is the biologic hallmark of gout. When present, plasma and extracellular fluids become supersaturated with uric acid, which, under the right conditions, may crystallize and result in a spectrum of clinical manifestations that may occur singly or in combination.

### PATHOGENESIS

Uric acid is the end product of purine nucleotide degradation; its production is closely linked to pathways of purine metabolism, with the intracellular concentration of 5-phosphoribosyl-1-pyrophosphate (PRPP) being the major determinant of the rate of uric acid biosynthesis. Uric acid is excreted primarily by the kidney through mechanisms of glomerular filtration, tubular secretion, and reabsorption. Hyperuricemia may thus arise in a wide range of settings that cause overproduction or reduced excretion of uric acid or a combination of the two.

### ACUTE GOUTY ARTHRITIS

Monosodium urate (MSU) crystals present in the joint are phagocytosed by leukocytes; release of inflammatory mediators and lysosomal enzymes leads to recruitment of additional phagocytes into the joint and to synovial inflammation.

### CLINICAL MANIFESTATIONS

**Acute arthritis:** most frequent early clinical manifestation of gout. Usually initially affects one joint, but may be polyarticular in later episodes. The first metatarsophalangeal joint (*podagra)* is often involved. Acute gout frequently begins at night with dramatic pain, swelling, warmth, and tenderness. Attack will generally subside spontaneously after 3–10 days. Although some pts may have a single attack, most pts have recurrent episodes with intervals of varying length with no symptoms between attacks. Acute gout may be precipitated by dietary excess, trauma, surgery, excessive ethanol ingestion, hypouricemic therapy, and serious medical illnesses such as myocardial infarction and stroke.

**Chronic arthritis:** a proportion of gout pts may have a chronic nonsymmetric synovitis; may rarely be the only manifestation. Can also present with periarticular *tophi* (aggregates of MSU crystals surrounded by a giant cell inflammatory reaction). Occurs in the setting of long-standing gout.

**Extraarticular tophi:** often occur in olecranon bursa, helix and anthelix of ears, ulnar surface of forearm, Achilles tendon.

**Tenosynovitis**

**Urate nephropathy:** deposition of MSU crystals in renal interstitium and pyramids. Can cause chronic renal insufficiency.

**Acute uric acid nephropathy:** reversible cause of acute renal failure due to precipitation of urate in the tubules; pts receiving cytotoxic treatment for neoplastic disease are at risk.

**Uric acid nephrolithiasis:** responsible for 10% of renal stones in the United States.

### DIAGNOSIS

- Synovial fluid analysis: should be performed to confirm gout even when clinical appearance is strongly suggestive; joint aspiration and demonstration of both intracellular and extracellular needle-shaped negatively birefringent MSU crystals by polarizing microscopy. Gram stain and culture should be performed on all fluid to rule out infection. MSU crystals can also be demonstrated in chronically involved joints or tophaceous deposits.
- Serum uric acid: normal levels do not rule out gout.
- Urine uric acid: excretion of >800 mg/d on regular diet in the absence of drugs suggests overproduction.
- Screening for risk factors or sequelae: urinalysis; serum creatinine, liver function tests, glucose and lipids; complete blood counts.
- If overproduction is suspected, measurement of erythrocyte hypoxanthine guanine phosphoribosyl transferase (HGPRT) and PRPP levels may be indicated.
- Joint x-rays: may demonstrate cystic changes, erosions with sclerotic margins in advanced chronic arthritis.
- If renal stones suspected, abdominal flat plate (stones often radiolucent), possibly IVP.
- Chemical analysis of renal stones.

## Differential Diagnosis

Septic arthritis, reactive arthritis, calcium pyrophosphate dihydrate (CPPD) deposition disease, rheumatoid arthritis.

## TREATMENT GOUT

### ASYMPTOMATIC HYPERURICEMIA

As only ~5% of hyperuricemic pts develop gout, treatment of asymptomatic hyperuricemia is not indicated. Exceptions are pts about to receive cytotoxic therapy for neoplasms.

### ACUTE GOUTY ARTHRITIS

Treatment is given for symptomatic relief only since attacks are self-limited and will resolve spontaneously. Toxicity of therapy must be considered in each pt.

- Analgesia
- NSAIDs: Treatment of choice when not contraindicated.
- Colchicine: generally only effective within first 24 h of attack; overdose has potentially life-threatening side effects; use is contraindicated in pts with renal insufficiency, cytopenias, LFTs >2 × normal, sepsis. PO—0.6 mg every 8 h with tapering or 1.2 mg followed by 0.6 mg in 1 h with subsequent day dosing depending on response.
- Intraarticular glucocorticoids: septic arthritis must be ruled out prior to injection.
- Systemic glucocorticoids: brief taper may be considered in pts with a polyarticular gouty attack for whom other modalities are contraindicated and where articular or systemic infection has been ruled out.
- Anakinra and other inhibitors of interleukin-1β have been studied, but are not widely used in clinical practice.

### URIC ACID–LOWERING AGENTS

Indications for initiating uric acid–lowering therapy include recurrent frequent acute gouty arthritis, polyarticular gouty arthritis, tophaceous gout, renal stones, prophylaxis during cytotoxic therapy. Should not start during an acute attack. Initiation of such therapy can precipitate an acute flare; in pts without contraindications consider concomitant PO colchicine 0.6 mg qd until uric acid <5.0 mg/dL, then discontinue.

1. *Xanthine oxidase inhibitors* (allopurinol, febuxostat): Decrease uric acid synthesis. Allopurinol must be dose-reduced in renal insufficiency. Both have side effects and drug interactions.
2. *Uricosuric drugs* (probenecid, sulfinpyrazone): Increases uric acid excretion by inhibiting its tubular reabsorption; ineffective in renal insufficiency; should not be used in these settings: age >60, renal stones, tophi, increased urinary uric acid excretion, prophylaxis during cytotoxic therapy.
3. *Pegloticase*: Recombinant uricase that lowers uric acid by oxidizing urate to allantoin. Risk of severe infusion reactions. Should be used only in selected pts with chronic tophaceous gout refractory to conventional therapy.

## CALCIUM PYROPHOSPHATE DIHYDRATE (CPPD) DEPOSITION DISEASE (PSEUDOGOUT)

### DEFINITION AND PATHOGENESIS

CPPD disease is characterized by acute and chronic inflammatory joint disease, usually affecting older individuals. The knee and other large joints are most commonly affected. Calcium deposits in articular cartilage (*chondrocalcinosis*) may be seen radiographically; these are not always associated with symptoms.

CPPD is most often idiopathic but can be associated with other conditions (Table 164-1).

Crystals are thought not to form in synovial fluid but are probably shed from articular cartilage into joint space, where they are phagocytosed by neutrophils and incite an inflammatory response.

### CLINICAL MANIFESTATIONS

- *Acute CPPD arthritis ("pseudogout"):* knee is most frequently involved, but polyarticular in two-thirds of cases; involved joint is erythematous, swollen, warm, and painful. Most pts have evidence of chondrocalcinosis.
- *Chronic arthropathy:* progressive degenerative changes in multiple joints; can resemble osteoarthritis (OA). Joint distribution may suggest CPPD with common sites including knee, wrist, metacarpophalangeal (MCP), hips, and shoulders.
- *Symmetric proliferative synovitis:* seen in familial forms with early onset; clinically similar to RA.

**TABLE 164-1 CONDITIONS ASSOCIATED WITH CPPD DEPOSITION DISEASE**

| |
|---|
| Aging |
| Disease-associated |
| Primary hyperparathyroidism |
| Hemochromatosis |
| Hypophosphatasia |
| Hypomagnesemia |
| Chronic gout |
| Postmeniscectomy |
| Gitelman's syndrome |
| Epiphyseal dysplasias |

- *Intervertebral disk and ligament calcification*
- *Spinal stenosis*

### DIAGNOSIS

- Synovial fluid analysis—demonstration of CPPD crystals that appear as short blunt rods, rhomboids, and cuboids with weak positive birefringence by polarizing microscopy.
- Radiographs may demonstrate chondrocalcinosis and degenerative changes (joint space narrowing, subchondral sclerosis/cysts).
- Secondary causes of CPPD deposition disease should be considered in pts <50 years old.

### Differential Diagnosis

OA, RA, gout, septic arthritis.

**TREATMENT PSEUDOGOUT**

- NSAIDs—when not contraindicated.
- Intraarticular injection of glucocorticoids.
- Colchicine (variably effective).

## CALCIUM APATITE DEPOSITION DISEASE

Apatite is the primary mineral of normal bone and teeth. Abnormal accumulation can occur in a wide range of clinical settings (Table 164-2). Apatite is an important factor in *Milwaukee shoulder*, a destructive arthropathy of the elderly that occurs in the shoulders and knees. Apatite crystals are small; clumps may stain purplish on Wright's stain and bright red with alizarin red S. Definitive identification requires electron microscopy or x-ray diffraction studies. Radiographic appearance resembles CPPD disease. *Treatment*: NSAIDs, repeated aspiration, and rest of affected joint.

**TABLE 164-2 CONDITIONS ASSOCIATED WITH APATITE DEPOSITION DISEASE**

| |
|---|
| Aging |
| Osteoarthritis |
| Hemorrhagic shoulder effusions in the elderly (Milwaukee shoulder) |
| Destructive arthropathy |
| Tendinitis, bursitis |
| Tumoral calcinosis (sporadic cases) |
| Disease-associated |
| Hyperparathyroidism |
| Milk-alkali syndrome |
| Renal failure/long-term dialysis |
| Connective tissue diseases (e.g., systemic sclerosis, idiopathic myositis, SLE) |
| Heterotopic calcification following neurologic catastrophes (e.g., stroke, spinal cord injury) |
| Heredity |
| Bursitis, arthritis |
| Tumoral calcinosis |
| Fibrodysplasia ossificans progressiva |

## CALCIUM OXALATE DEPOSITION DISEASE

CaOx crystals may be deposited in joints in primary oxalosis (rare) or secondary oxalosis (a complication of end-stage renal disease). Clinical syndrome similar to gout and CPPD disease. *Treatment*: marginally effective.

For a more detailed discussion, see Schumacher HR, Chen LX: Gout and Other Crystal-Associated Arthropathies, Chap. 395, p. 2233 and Burns CM, Wortmann RL: Disorders of Purine and Pyrimidine Metabolism, Chap. 431e, in HPIM-19.

# 165 Other Musculoskeletal Disorders

## ENTEROPATHIC ARTHRITIS

Both peripheral and axial arthritis may be associated with the inflammatory bowel diseases (IBD) of ulcerative colitis or Crohn's disease. The arthritis can occur after or before the onset of intestinal symptoms. Peripheral arthritis is episodic and asymmetric; it most frequently affects knee and ankle. Attacks usually subside within several weeks and characteristically resolve completely without residual joint damage. Enthesitis (inflammation at insertion of tendons and ligaments into bone) can occur with manifestations of "sausage digit," Achilles tendinitis, and plantar fasciitis. Axial involvement can manifest as spondylitis and/or sacroiliitis (often symmetric). Laboratory findings are nonspecific; rheumatoid factor (RF) absent; HLA-B27 is positive in 70% with IBD and axial disease but <15% with IBD and peripheral arthritis; radiographs of peripheral joints usually normal; axial involvement is often indistinguishable from ankylosing spondylitis.

**TREATMENT ENTEROPATHIC ARTHRITIS**

Directed at underlying IBD; treatment of Crohn's disease with anti-TNF agents has improved arthritis; NSAIDs may alleviate joint symptoms but can precipitate flares of IBD; sulfasalazine may benefit peripheral arthritis.

## WHIPPLE'S DISEASE

Characterized by arthritis in up to 75% of pts that usually precedes appearance of other symptoms. Usually oligo- or polyarticular, symmetric, transient but may become chronic. Joint manifestations respond to antibiotic therapy.

## NEUROPATHIC JOINT DISEASE

Also known as *Charcot's joint*, this is a severe destructive arthropathy that occurs in joints deprived of pain and position sense; may occur in diabetes mellitus, tabes dorsalis, syringomyelia, amyloidosis, spinal cord or peripheral nerve injury. Distribution depends on the underlying joint disease. Joint effusions are usually noninflammatory

but can be hemorrhagic. Radiographs can reveal either bone resorption or new bone formation with bone dislocation and fragmentation.

**TREATMENT NEUROPATHIC JOINT DISEASE**

Stabilization of joint; surgical fusion may improve function.

## RELAPSING POLYCHONDRITIS

An idiopathic disorder characterized by recurrent inflammation of cartilaginous structures. Cardinal manifestations include ear and nose involvement with floppy ear and saddlenose deformities, inflammation and collapse of tracheal and bronchial cartilaginous rings, and asymmetric episodic nondeforming polyarthritis. Other features can include scleritis, conjunctivitis, iritis, keratitis, aortic regurgitation, glomerulonephritis, and other features of systemic vasculitis. Onset is frequently abrupt, with the appearance of 1–2 sites of cartilaginous inflammation. Diagnosis is made clinically and may be confirmed by biopsy of affected cartilage.

**TREATMENT RELAPSING POLYCHONDRITIS**

Glucocorticoids (prednisone 40–60 mg/d with subsequent taper) may suppress acute features and reduce the severity/frequency of recurrences. Cytotoxic agents should be reserved for unresponsive disease or for pts who require high glucocorticoid doses. When airway obstruction is severe, tracheostomy is required.

## HYPERTROPHIC OSTEOARTHROPATHY

Syndrome consisting of periosteal new bone formation, digital clubbing, and arthritis. Most commonly seen in association with lung carcinoma but, also occurs with selected chronic lung or liver disease; congenital heart, lung, or liver disease in children; and idiopathic and familial forms. Symptoms include burning and aching pain most pronounced in distal extremities. Radiographs show periosteal thickening with new bone formation of distal ends of long bones.

**TREATMENT HYPERTROPHIC OSTEOARTHROPATHY**

Identify and treat associated disorder; aspirin, NSAIDs, other analgesics, vagotomy, or percutaneous nerve block may help to relieve symptoms.

## FIBROMYALGIA

A common disorder characterized by chronic widespread musculoskeletal pain, aching, stiffness, paresthesia, disturbed sleep, and easy fatigability along with multiple tender points. More common in women than in men. Diagnosis is made clinically; evaluation reveals soft tissue tender points but no objective joint abnormalities by examination, laboratory, or radiograph.

**TREATMENT FIBROMYALGIA**

Pregabalin, duloxetine, and milnacipran have shown benefit for fibromyalgia. Tricyclics for sleep disorder, local measures (heat, massage), physical conditioning, and cognitive-behavioral strategies to improve sleep hygiene.

## POLYMYALGIA RHEUMATICA (PMR)

Clinical syndrome characterized by aching and morning stiffness in the shoulder girdle, hip girdle, or neck for >1 month, elevated ESR, and rapid response to low-dose prednisone (10–20 mg qd). Rarely occurs before age 50; more common in women. PMR can occur in association with giant cell arteritis, which requires treatment with higher doses of prednisone. Evaluation should include a careful history to elicit symptoms suggestive of giant cell arteritis (Chap. 159); ESR; laboratory test results to rule out other processes usually include RF, ANA, CBC, CPK, serum protein electrophoresis; and renal, hepatic, and thyroid function tests.

**TREATMENT PMR**

Pts rapidly improve on prednisone, 10–20 mg qd, but may require treatment over months to years.

## OSTEONECROSIS (AVASCULAR NECROSIS)

Caused by death of cellular elements of bone, believed to be due to impairment in blood supply. Frequent associations include glucocorticoid treatment, connective tissue disease, trauma, sickle cell disease, embolization, alcohol use, and HIV disease. Commonly involved sites include femoral and humeral heads, femoral condyles, and proximal tibia. Hip disease is bilateral in >50% of cases. Clinical presentation is usually the abrupt onset of articular pain. Early changes are not visible on plain radiograph and are best seen by MRI; later stages demonstrate bone collapse ("crescent sign"), flattening of articular surface with joint space loss. Osteonecrosis of the jaw is a rare occurrence associated with cancer treatments (including radiation), infection, glucocorticoids, or bone antiresorptive therapies.

**TREATMENT OSTEONECROSIS**

Limited weight-bearing of unclear benefit; NSAIDs for symptoms. Surgical procedures to enhance blood flow may be considered in early-stage disease but are of controversial efficacy; joint replacement may be necessary in late-stage disease for pain unresponsive to other measures.

## PERIARTICULAR DISORDERS

### BURSITIS

Inflammation of the thin-walled bursal sac surrounding tendons and muscles over bony prominences. The subacromial and greater trochanteric bursae are most commonly involved.

**TREATMENT BURSITIS**

Prevention of aggravating conditions, rest, NSAIDs, and local glucocorticoid injections.

### TENDINITIS

May involve virtually any tendon but frequently affects tendons of the rotator cuff around shoulder, especially the supraspinatus. Pain is dull and aching but becomes acute and sharp when tendon is squeezed below acromion.

**TREATMENT** TENDINITIS

NSAIDs, glucocorticoid injection, and physical therapy may be beneficial. The rotator cuff tendons or biceps tendon may rupture acutely, frequently requiring surgical repair.

### CALCIFIC TENDINITIS

Results from deposition of calcium salts (primarily hydroxyapatite) in tendon, usually supraspinatus. The resulting pain may be sudden and severe.

**TREATMENT** CALCIFIC TENDINITIS

Most are self-limited and respond to physical therapy, NSAIDs. Refractory disease treated with ultrasound-guided needle aspiration and lavage or surgery.

### ADHESIVE CAPSULITIS ("FROZEN SHOULDER")

Results from conditions that enforce prolonged immobility of shoulder joint. Shoulder is painful and tender to palpation, and both active and passive range of motion is restricted.

**TREATMENT** ADHESIVE CAPSULITIS

Spontaneous improvement may occur; physical therapy is the foundation; NSAIDs, local injections of glucocorticoids may be helpful.

For a more detailed discussion, see Taurog JD, Carter JD: The Spondyloarthritides, Chap. 384, p. 2169; Crofford LJ: Fibromyalgia, Chap. 396, p. 2238; Langford CA, Mandell BF: Arthritis Associated with Systemic Disease, and Other Arthritides, Chap. 397, p. 2240; Langford CA: Periarticular Disorders of the Extremities, Chap. 398, p. 2247; Langford CA: Relapsing Polychondritis, Chap. 389, p. 2202, in HPIM-19.

# 166 Sarcoidosis

### DEFINITION

An inflammatory multisystem disease characterized by the presence of noncaseating granulomas of unknown etiology.

### PATHOPHYSIOLOGY

The cause of sarcoid is unknown, and current evidence suggests that the triggering of an inflammatory response by an unidentified antigen in a genetically susceptible host is

involved. The granuloma is the pathologic hallmark of sarcoidosis. The initial inflammatory response is an influx of CD4+ (helper) T cells and an accumulation of activated monocytes. This leads to an increased release of cytokines and the formation of a granuloma. The granuloma may resolve or lead to chronic disease, including fibrosis.

## CLINICAL MANIFESTATIONS

Up to one-third of sarcoidosis patients are asymptomatic with 20–30% of pulmonary sarcoidosis being detected by CXR in asymptomatic individuals. Sarcoid manifests symptomatically in organs where it affects function or where it is readily observed. *Löfgren's syndrome* consists of hilar adenopathy, erythema nodosum, often with uveitis and acute arthritis presenting in one or both ankles spreading to involve other joints.

Disease manifestations of sarcoid include:

- *Lung:* >90% of pts with sarcoidosis will have lung involvement. Features include hilar adenopathy, infiltrates, interstitial pneumonitis, and fibrosis; airways may be involved and cause obstruction to airflow; pulmonary hypertension from direct vascular involvement or lung fibrosis.
- *Lymph nodes:* intrathoracic nodes enlarged in 75–90% of pts. Extrathoracic lymph nodes affected in up to 20%.
- *Skin:* >33% will have skin involvement; lesions include erythema nodosum, maculopapular lesions, subcutaneous nodules, and *lupus pernio* (indurated blue-purple shiny lesions around nasal bridge, eyes, cheeks).
- *Eye:* uveitis 30% in the United States (higher in other countries); may progress to blindness.
- *Bone marrow and spleen*—lymphopenia, anemia 20%, splenomegaly 5–10%.
- *Liver:* involved on biopsy in >50%; 20–30% abnormal liver function studies.
- *Kidney*—parenchymal disease <5%, nephrolithiasis, acute renal failure due to hypercalcemia 1–2%.
- *Nervous system:* occurs in 5–10%; cranial/peripheral neuropathy, chronic meningitis, pituitary involvement, space-occupying lesions, seizures.
- *Heart:* disturbances of rhythm and/or contractility, pericarditis.
- *Musculoskeletal:* involvement of bone or muscle occurs in 10%, bone lesions consist of cysts in areas of expanded bone or lattice-like changes; joint involvement includes acute arthropathy often of the ankles and chronic mono- or oligoarthritis of knee, ankle, proximal interphalangeal (PIP) joints.
- *Constitutional symptoms*—fever, weight loss, anorexia, fatigue.
- *Other organ systems*—hypercalcemia 10%, endocrine/reproductive, exocrine glands, GI, upper respiratory tract.

## EVALUATION

- History and physical examination.
- CBC, $Ca^{2+}$, LFTs, ACE, tuberculosis screening.
- CXR and/or chest CT, ECG, PFTs.
- Biopsy of lung or other affected organ.
- Positron emission tomography (PET) has increasingly replaced gallium-67 scanning to identify areas of granulomatous disease. Both can be used to identify potential areas for biopsy.
- MRI can assess extrapulmonary sarcoidosis.

## DIAGNOSIS

Made on basis of clinical, radiographic, and histologic findings. Biopsy of lung or other affected organs is helpful in supporting the diagnosis and ruling out other diseases. Pulmonary involvement can be approached by bronchoscopy with transbronchial lung biopsy. Differential diagnosis includes neoplasms, infections including HIV, and other granulomatous processes.

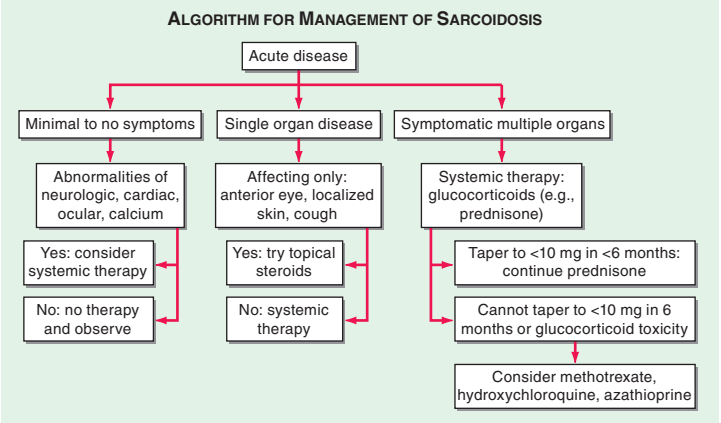


**FIGURE 166-1** The management of acute sarcoidosis is based on level of symptoms and extent of organ involvement. In pts with mild symptoms, no therapy may be needed unless specified manifestations are noted.

## TREATMENT SARCOIDOSIS

As sarcoidosis may remit spontaneously, treatment is based largely on the level of symptoms and extent of organ involvement (Figs. 166-1 and 166-2). When systemic therapy is indicated, glucocorticoids are the mainstay of therapy. Other immunomodulatory agents have been used in refractory or severe cases or when prednisone cannot be tapered.

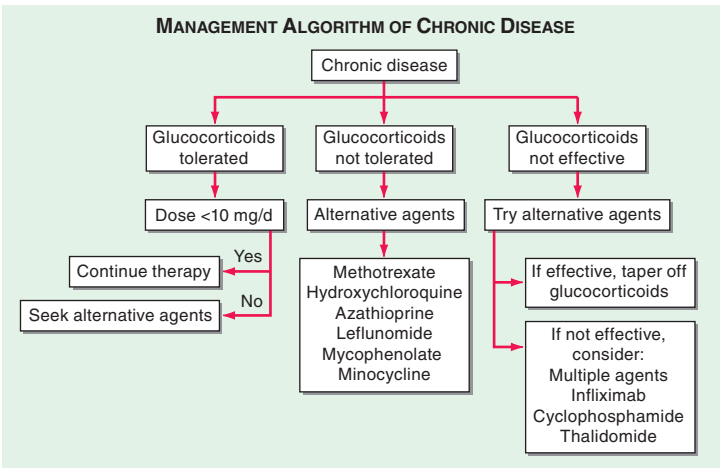


**FIGURE 166-2** Approach to chronic disease is based on whether glucocorticoid therapy is tolerated.

## OUTCOME

Sarcoidosis is usually a self-limited, non-life-threatening disease. Remission occurs in >50% within 2–5 years of diagnosis with 20–50% developing chronic disease Death directly due to disease occurs in 5% of cases usually related to lung, cardiac, neurologic, or liver involvement.

For a more detailed discussion, see Baughman RP, Lower EE: Sarcoidosis, Chap. 390, p. 2205, in HPIM-19.

# 167 Amyloidosis

## DEFINITION

*Amyloidosis* is a term for a group of protein folding disorders characterized by the extracellular deposition of insoluble polymeric protein fibrils in organs and tissues. Clinical manifestations depend on anatomic distribution and intensity of amyloid protein deposition; they range from local deposition with little significance to involvement of virtually any organ system with severe pathophysiologic consequences.

## CLASSIFICATION

Amyloid diseases are defined by the biochemical nature of the protein in the fibril deposits and are classified according to whether they are systemic or localized, acquired or inherited, and their clinical patterns. The accepted nomenclature is *AX* where *A* indicates amyloidosis and *X* is the protein in the fibril (Table 137-1, p. 720, in HPIM-19).

- AL (immunoglobulin light chains): *primary amyloidosis*; most common form of systemic amyloidosis; arises from a clonal B-cell disorder, usually multiple myeloma.
- AA (serum amyloid A): *secondary amyloidosis*; can occur in association with almost any chronic inflammatory state (e.g., RA, SLE, periodic fever syndromes such as familial Mediterranean fever [FMF], Crohn's disease) or chronic infections.
- AF (familial amyloidoses): number of different types that are dominantly transmitted in association with a mutation that enhances protein misfolding and fibril formation; most commonly due to transthyretin.
- $A\beta_2M$: composed of $\beta_2$ microglobulin; occurs in end-stage renal disease of long duration.
- Localized or organ-limited amyloidoses: most common form is Aβ found in Alzheimer's disease derived from abnormal proteolytic processing of the amyloid precursor protein.

## CLINICAL MANIFESTATIONS

Clinical features are varied and depend entirely on biochemical nature of the fibril protein. Frequent sites of involvement:

- *Kidney:* seen with AA and AL; proteinuria, nephrosis, azotemia.
- *Liver:* occurs in AA, AL, and AF; hepatomegaly.

- *Skin:* characteristic of AL but can be seen in AA; raised waxy papules.
- *Heart:* common in AL and AF; CHF, cardiomegaly, arrhythmias.
- *GI:* common in all types; GI obstruction or ulceration, hemorrhage, protein loss, diarrhea, macroglossia, disordered esophageal motility.
- *Joints:* usually AL, frequently with myeloma; periarticular amyloid deposits, "shoulder pad sign": firm amyloid deposits in soft tissue around the shoulder, symmetric arthritis of shoulders, wrists, knees, hands.
- *Nervous system:* prominent in AF; peripheral neuropathy, postural hypotension, dementia. Carpal tunnel syndrome may occur in AL and A$\beta_2$M.
- *Respiratory:* lower airways can be affected in AL; localized amyloid can cause obstruction along upper airways.

## DIAGNOSIS

Diagnosis relies on the identification of fibrillar deposits in tissues and typing of the amyloid (Fig. 167-1). Congo red staining of abdominal fat will demonstrate amyloid deposits in >80% of pts with systemic amyloid.

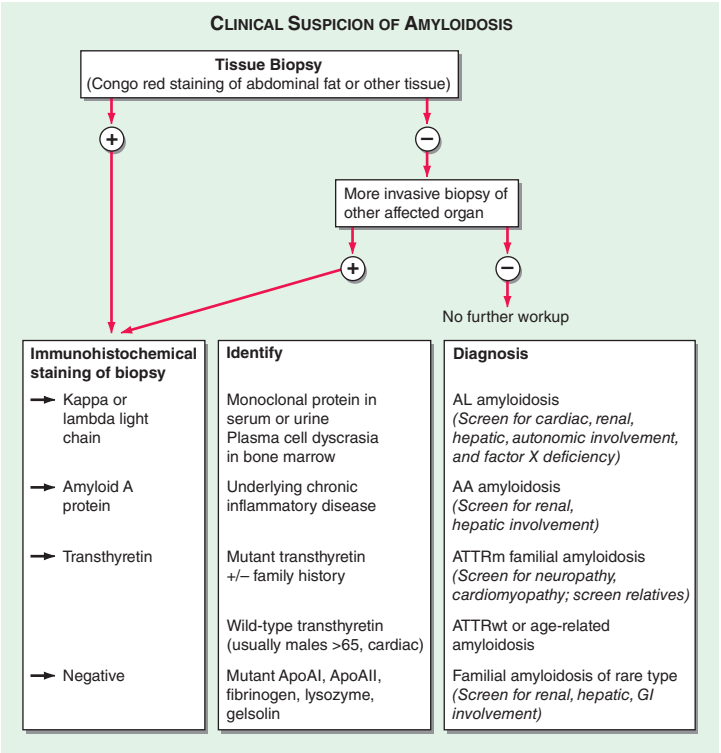


**FIGURE 167-1** Algorithm for the diagnosis of amyloidosis and determination of type. Clinical suspicion: unexplained nephropathy, cardiomyopathy, neuropathy, enteropathy, arthropathy, and macroglossia. ApoAI, apolipoprotein AI; ApoAII, apolipoprotein AII.

## PROGNOSIS

Outcome is variable and depends on type of amyloidosis and organ involvement. Average survival of AL amyloid without treatment is ~1–2 years; cardiac involvement is the leading cause of death with a median survival of ~6 months without treatment.

## TREATMENT AMYLOIDOSIS

For AL, current therapies target the clonal bone-marrow plasma cells using approaches used for multiple myeloma. High-dose IV melphalan followed by autologous stem-cell transplantation produces complete hematologic responses in ~40% but only 50% are eligible for such aggressive treatment, and peritransplant mortality is higher than for other hematologic diseases because of impaired organ function. Treatment of AA is directed toward controlling the underlying inflammatory condition. Colchicine (1.2–1.8 mg/d) is the standard treatment for FMF but has not been helpful for AA of other causes. TNF inhibitors and interleukin-1 antagonists can be effective in syndromes related to cytokine elevation. Eprodisate designed to disrupt fibril formation is being studied. In certain forms of AF, genetic counseling is important and liver transplantation is a successful form of therapy.

For a more detailed discussion, see Seldin DC, Berk JL: Amyloidosis, Chap. 137, p. 719, in HPIM-19.

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# 168 Disorders of the Anterior Pituitary and Hypothalamus

The anterior pituitary is often referred to as the "master gland" because, together with the hypothalamus, it orchestrates the complex regulatory functions of multiple other glands (Fig. 168-1). The anterior pituitary produces six major hormones: (1) prolactin (PRL), (2) growth hormone (GH), (3) adrenocorticotropin hormone (ACTH), (4) luteinizing hormone (LH), (5) follicle-stimulating hormone (FSH), and (6) thyroid-stimulating hormone (TSH). Pituitary hormones are secreted in a pulsatile manner, reflecting intermittent stimulation by specific hypothalamic-releasing factors. Each of these pituitary hormones elicits specific responses in peripheral target glands. The hormonal products of these peripheral glands, in turn, exert feedback control at the level of the hypothalamus and pituitary to modulate pituitary function. Disorders of the pituitary include neoplasms or other lesions (granulomas, hemorrhage) that lead to mass effects and clinical syndromes due to excess or deficiency of one or more pituitary hormones.

## PITUITARY TUMORS

Pituitary adenomas are benign monoclonal tumors that arise from one of the five anterior pituitary cell types and may cause clinical effects from either overproduction of a pituitary hormone or compressive/destructive effects on surrounding structures, including the hypothalamus, pituitary, optic chiasm, and cavernous sinus. About one-third of all adenomas are clinically nonfunctioning and produce no distinct clinical hypersecretory syndrome. Among hormonally functioning neoplasms, tumors secreting PRL is the most common (~50%); they have a greater prevalence in women than in men. GH- and ACTH-secreting tumors each account for about 10–15% of functioning pituitary tumors. Adenomas are classified as microadenomas (<10 mm) or macroadenomas (≥10 mm). Pituitary adenomas (especially PRL- and GH-producing tumors) may be part of genetic familial syndromes such as MEN 1, Carney syndrome, or mutant aryl hydrocarbon receptor inhibitor protein (AIP) syndrome. Other entities that can present as a sellar mass include craniopharyngiomas, Rathke's cleft cysts, sella chordomas, meningiomas, pituitary metastases, gliomas, and granulomatous disease (e.g., histiocytosis X, sarcoidosis).

### Clinical Features

Symptoms from mass effects include headache; visual loss through compression of the optic chiasm superiorly (classically a bitemporal hemianopia); and diplopia, ptosis, ophthalmoplegia, and decreased facial sensation from cranial nerve compression laterally. Pituitary stalk compression from the tumor may also result in mild hyperprolactinemia. Symptoms of hypopituitarism or hormonal excess may be present as well (see below).

Pituitary apoplexy, typically resulting from hemorrhage into a preexisting adenoma or post-partum as Sheehan's syndrome, is an endocrine emergency that typically presents with features that include severe headache, bilateral visual changes, ophthalmoplegia, and, in severe cases, cardiovascular collapse and loss of consciousness. It may result in hypotension, severe hypoglycemia, CNS hemorrhage, and death. Pts with no evident visual loss or impaired consciousness can usually

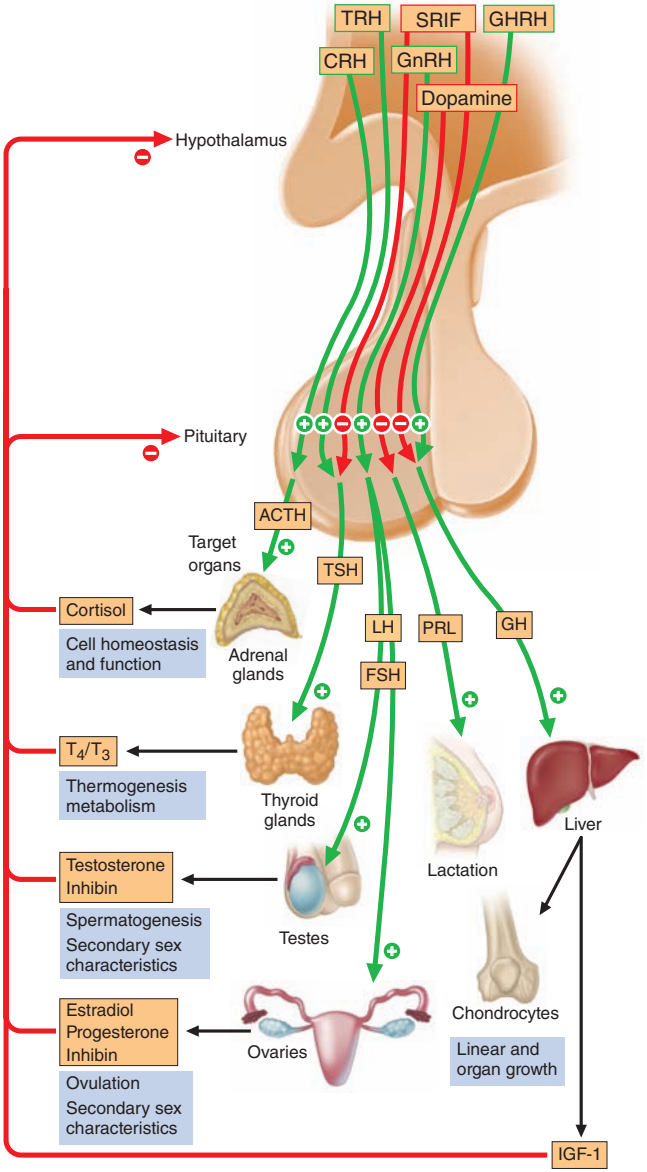



**FIGURE 168-1** Diagram of pituitary axes. Hypothalamic hormones regulate anterior pituitary tropic hormones that, in turn, determine target gland secretion. Peripheral hormones feedback to regulate hypothalamic and pituitary hormones. ACTH, adrenocorticotropin hormone; CRH, corticotropin-releasing hormone; FSH, follicle-stimulating hormone; GH, growth hormone; GHRH, growth hormone–releasing hormone; GnRH, gonadotropin-releasing hormone; IGF, insulin-like growth factor; LH, luteinizing hormone; PRL, prolactin; SRIF, somatostatin, somatotropin release–inhibiting factor; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

be observed and managed conservatively with high-dose glucocorticoids; surgical decompression should be considered when visual or neurologic symptoms/signs are present.

### Diagnosis

Sagittal and coronal T1-weighted MRI images with specific pituitary cuts should be obtained before and after administration of gadolinium. In pts with lesions close to the optic chiasm, visual field assessment that uses perimetry techniques should be performed. In pituitary apoplexy, CT or MRI of the pituitary may reveal signs of sellar hemorrhage, with deviation of the pituitary stalk and compression of pituitary tissue.

**TREATMENT PITUITARY TUMORS**

Pituitary surgery is indicated for mass lesions that impinge on surrounding structures or to correct hormonal hypersecretion, except in the case of prolactinoma, where medical treatment is usually effective (see below). Transsphenoidal surgery, rather than transfrontal resection, is the desired surgical approach for most pts. The goal is selective resection of the pituitary mass lesion without damage to the normal pituitary tissue, to decrease the likelihood of hypopituitarism. Transient or permanent diabetes insipidus, hypopituitarism, CSF rhinorrhea, visual loss, and oculomotor palsy may occur postoperatively. Tumor invasion outside of the sella is rarely amenable to surgical cure, but debulking procedures may relieve tumor mass effects and reduce hormonal hypersecretion. Radiation may be used as an adjunct to surgery, but efficacy is delayed and >50% of pts develop hormonal deficiencies within 10 years, usually due to hypothalamic damage. GH- and TSH-secreting tumors may also be amenable to medical therapy; in PRL-secreting tumors, medical therapy is the initial treatment of choice.

## PITUITARY HORMONE HYPERSECRETION SYNDROMES

### HYPERPROLACTINEMIA

Prolactin is unique among the pituitary hormones in that the predominant central control mechanism is inhibitory, reflecting dopamine-mediated suppression of PRL release. Prolactin acts to induce and maintain lactation and decrease reproductive function and drive (via suppression of gonadotropin-releasing hormone [GnRH], gonadotropins, and gonadal steroidogenesis).

### Etiology

Physiologic elevation of PRL occurs in pregnancy and lactation. Otherwise, PRL-secreting pituitary adenomas (prolactinomas) are the most common cause of PRL levels >100 μg/L. Less pronounced hyperprolactinemia is commonly caused by medications (risperidone, chlorpromazine, perphenazine, haloperidol, metoclopramide, opiates, $H_2$ antagonists, amitriptyline, selective serotonin reuptake inhibitors [SSRIs], verapamil, estrogens), pituitary stalk damage (tumors, lymphocytic hypophysitis, granulomas, trauma, irradiation), primary hypothyroidism, or renal failure. Nipple stimulation may also cause acute PRL increases.

### Clinical Features

In women, amenorrhea, galactorrhea, and infertility are the hallmarks of hyperprolactinemia. In men, symptoms of hypogonadism (Chap. 174) or mass effects are the usual presenting symptoms, and galactorrhea is rare.

### Diagnosis

Fasting, morning PRL levels should be measured; when clinical suspicion is high, measurement of levels on several different occasions may be required. If

hyperprolactinemia is present, nonneoplastic causes should be excluded (e.g., pregnancy test, hypothyroidism, medications).

## TREATMENT HYPERPROLACTINEMIA

If the pt is taking a medication that is known to cause hyperprolactinemia, the drug should be withdrawn, if possible. A pituitary MRI should be performed if the underlying cause of PRL elevation is unknown. Resection of hypothalamic or sellar mass lesions can reverse hyperprolactinemia due to stalk compression. Medical therapy with a dopamine agonist is indicated in microprolactinomas for control of symptomatic galactorrhea, for restoration of gonadal function, or when fertility is desired. Alternatively, estrogen replacement may be indicated if fertility is not desired, but tumor size should be carefully monitored. Dopamine agonist therapy for macroprolactinomas generally results in both adenoma shrinkage and reduction of PRL levels. Cabergoline (initial dose 0.5 mg a week, usual dose 0.5–1 mg twice a week) and bromocriptine (initial dose 0.625–1.25 mg qhs, usual dose 2.5 PO three times a day) are the two most frequently used dopamine agonists. Cabergoline is the more effective and better-tolerated drug. These medications should initially be taken at bedtime with food, followed by gradual dose increases, to reduce the side effects of nausea and postural hypotension. Other side effects include constipation, nasal stuffiness, dry mouth, nightmares, insomnia, or vertigo; decreasing the dose usually alleviates these symptoms. Dopamine agonists may also precipitate or worsen underlying psychiatric conditions. Cardiac echocardiography is prudent before starting cabergoline therapy as there has been concern about an association with valvular heart disease. In pts with microadenomas successfully treated (normal PRL, full tumors shrinkage), therapy may be withdrawn after 2 years, followed by careful monitoring for tumor recurrence. Spontaneous remission of microadenomas, presumably caused by infarction, occurs in some pts. Surgical debulking may be required for macroprolactinomas that do not adequately respond to medical therapy.

Women with microprolactinomas who become pregnant should discontinue dopaminergic therapy, as the risk for significant tumor growth during pregnancy is low. In those with macroprolactinomas, visual field testing should be performed at each trimester. A pituitary MRI should be performed if severe headache and/or visual defects occur.

## ACROMEGALY

### Etiology

GH hypersecretion is primarily the result of pituitary somatotrope adenomas, mostly sporadic, but also in conjunction with MEN 1, Carney syndrome, McCune-Albright syndrome, and familial AIP mutations. Extrapituitary causes of acromegaly (ectopic growth hormone–releasing hormone [GHRH] production) are very rare.

### Clinical Features

The peak occurrence of acromegaly is at age 40–45. In children, GH hypersecretion prior to long bone epiphyseal closure results in gigantism. The presentation of acromegaly in adults is usually indolent, and diagnosis is typically delayed by up to a decade. Pts may note a change in facial features, widened teeth spacing, deepening of the voice, snoring, increased shoe or glove size, ring tightening, hyperhidrosis, oily skin, arthropathy, and carpal tunnel syndrome. Frontal bossing, mandibular enlargement with prognathism, macroglossia, an enlarged thyroid, skin tags, thick heel pads, and hypertension may be present on examination. Associated conditions include cardiomyopathy, left ventricular hypertrophy, diastolic dysfunction, sleep

apnea, glucose intolerance, diabetes mellitus, colon polyps, and colonic malignancy. Overall mortality is increased approximately threefold.

### Diagnosis

Insulin-like growth factor type I (IGF-I) levels are a useful screening measure, with elevation suggesting acromegaly. Due to the pulsatility of GH, measurement of a single random GH level is not useful for screening. The diagnosis of acromegaly is confirmed by demonstrating the failure of GH suppression to <0.4 μg/L within 1–2 h of a 75-g oral glucose load. MRI of the pituitary usually reveals a macroadenoma.

**TREATMENT ACROMEGALY**

The primary treatment modality for acromegaly is transsphenoidal surgery. GH levels are not normalized by surgery alone in many pts with macroadenomas; in those, somatostatin analogues provide adjunctive medical therapy that suppresses GH secretion with modest to no effect on tumor size. Octreotide (50 μg SC three times a day) is used for initial therapy to determine response. Once a positive response and tolerance of side effects (nausea, abdominal discomfort, diarrhea, flatulence) are established, pts are changed to long-acting depot formulations (octreotide LAR 20–30 mg IM every 2–4 weeks or lanreotide autogel 90–120 mg IM once a month). Dopamine agonists (bromocriptine, cabergoline) can be used as adjunctive therapy but are generally not very effective. The GH receptor antagonist pegvisomant (10–30 mg SC daily) can be added in pts who do not respond to somatostatin analogues. Pegvisomant is highly effective in lowering IGF-I levels but does not lower GH levels or decrease tumor size. Pituitary irradiation may also be required as adjuvant therapy but has a slow therapeutic onset and a high rate of late hypopituitarism.

### CUSHING'S DISEASE (SEE CHAP. 171)

### NONFUNCTIONING AND GONADOTROPIN-PRODUCING ADENOMAS

These tumors are the most common type of pituitary neoplasm and usually present with symptoms of one or more hormonal deficiencies or mass effect. They typically produce small amounts of intact gonadotropins (usually FSH) as well as uncombined α-subunit and LHβ and FSHβ subunits. Surgery is indicated for mass effects or hypopituitarism; asymptomatic small adenomas may be followed with regular MRI and visual field testing. Diagnosis is based on immunohistochemical analysis of resected tumor tissue. Medical therapy is usually ineffective in shrinking these tumors.

### TSH-SECRETING ADENOMAS

TSH-producing adenomas are rare but often large and locally invasive when they occur. Pts present with goiter and hyperthyroidism, and/or sella mass effects. Diagnosis is based on elevated serum free $T_4$ levels in the setting of inappropriately normal or high TSH secretion and MRI evidence of a pituitary adenoma. Surgery is indicated and is usually followed by somatostatin analogue therapy to treat residual tumor. Somatostatin analogue therapy (see above) leads to normalization of TSH and euthyroidism in most and tumor shrinkage in 50–75% of pts. If necessary, thyroid ablation or antithyroid drugs can be used to reduce thyroid hormone levels.

## HYPOPITUITARISM

### Etiology

A variety of disorders may cause deficiencies of one or more pituitary hormones. These disorders may be genetic, congenital, traumatic (pituitary surgery, cranial

irradiation, head injury), neoplastic (large pituitary adenoma, parasellar mass, craniopharyngioma, metastases, meningioma), infiltrative (hemochromatosis, lymphocytic hypophysitis, sarcoidosis, histiocytosis X), vascular (pituitary apoplexy, postpartum necrosis, sickle cell disease), or infectious (tuberculous, fungal, parasitic). The most common cause of hypopituitarism is neoplastic in origin (macroadenomatous destruction, or following hypophysectomy or radiation therapy). Pituitary hormone failure due to compression, destruction, or radiation therapy typically follows a sequential pattern: GH>FSH>LH>TSH>ACTH. Genetic causes of hypopituitarism may affect several hormones (e.g., pituitary dysplasia, PROP-1 and PIT-1 mutations) or be restricted to single pituitary hormones or axes (e.g., isolated GH deficiency, Kallmann syndrome, isolated ACTH deficiency). Hypopituitarism following cranial irradiation develops over 5–15 years. Varying degrees of partial to complete hormone deficiencies occur during evolution of pituitary destruction.

## Clinical Features

Each hormone deficiency is associated with specific findings:

- *GH:* growth disorders in children; increased intraabdominal fat, reduced lean body mass, hyperlipidemia, reduced bone mineral density, decreased stamina, and social isolation in adults
- *FSH/LH:* menstrual disorders and infertility in women (Chap. 175); hypogonadism in men (Chap. 174)
- *ACTH:* features of hypocortisolism (Chap. 171) without mineralocorticoid deficiency
- *TSH:* growth retardation in children; features of hypothyroidism in children and adults (Chap. 170)
- *PRL:* failure to lactate postpartum

## Diagnosis

Biochemical diagnosis of pituitary insufficiency is made by demonstrating low or inappropriately normal levels of pituitary hormones in the setting of low target hormone levels. Initial testing should include an 8 A.M. cortisol level, TSH and free $T_4$, IGF-I, testosterone in men, assessment of menstrual cycles in women, and PRL level. Provocative tests are required for definitive diagnosis of GH and ACTH deficiency. Adult GH deficiency is diagnosed by demonstrating a subnormal GH response to a standard provocative test (insulin tolerance test, L-arginine + GHRH). Acute ACTH deficiency may be diagnosed by a subnormal response in an insulin tolerance test, metyrapone test, or corticotropin-releasing hormone (CRH) stimulation test. Standard ACTH (cosyntropin) stimulation tests may be normal in acute ACTH deficiency; with adrenal atrophy, the cortisol response to cosyntropin is blunted.

## TREATMENT HYPOPITUITARISM

Hormonal replacement should aim to mimic physiologic hormone production. Effective dose schedules are outlined in Table 168-1. Doses should be individualized, particularly for GH, glucocorticoids, and L-thyroxine. GH therapy, particularly when excessive, may be associated with fluid retention, joint pain, and carpal tunnel syndrome. Glucocorticoid replacement should always precede L-thyroxine therapy to avoid precipitation of adrenal crisis. Pts requiring glucocorticoid replacement should wear a medical alert bracelet and should be instructed to take additional doses during stressful events such as acute illness, dental procedures, trauma, and acute hospitalization.

**TABLE 168-1 HORMONE REPLACEMENT THERAPY FOR ADULT HYPOPITUITARISM[a]**

| Trophic Hormone Deficit | Hormone Replacement |
|---|---|
| ACTH | Hydrocortisone (10–20 mg A.M.; 5–10 mg P.M.) |
| | Cortisone acetate (25 mg A.M.; 12.5 mg P.M.) |
| | Prednisone (5 mg A.M.) |
| TSH | L-Thyroxine (0.075–0.15 mg daily) |
| FSH/LH | Males |
| | Testosterone enanthate (200 mg IM every 2 weeks) |
| | Testosterone gel (5–10 g/d applied to skin) |
| | Females |
| | Conjugated estrogen (0.625–1.25 mg qd for 25 days) |
| | Estradiol skin patch (0.025–0.1 mg, every week) |
| | Progesterone (5–10 mg qd) on days 16–25 |
| | For fertility: Menopausal or biosynthetic gonadotropins, human chorionic gonadotropins |
| GH | Adults: Somatotropin (0.1–1.25 mg SC qd) |
| | Children: Somatotropin (0.02–0.05 [mg/kg per day]) |
| Vasopressin | Intranasal desmopressin (5–20 μg twice daily) |
| | Oral desmopressin (300–600 μg qd) |

[a]All doses shown should be individualized for specific pts and should be reassessed during stress, surgery, or pregnancy. Male and female fertility requirements should be managed as discussed in Chaps. 174 and 175.
***Abbreviations:*** ACTH, adrenocorticotropin hormone; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone.

For a more detailed discussion, see Melmed S, Jameson JL: Anterior Pituitary: Physiology of Pituitary Hormones, Chap 401e; Hypopituitarism, Chap 402, p. 2255; Anterior Pituitary Tumor Syndromes, Chap 403, p. 2261, in HPIM-19.

# 169 Diabetes Insipidus and Syndrome of Inappropriate Antidiuretic Hormone

The neurohypophysis, or posterior pituitary gland, produces two hormones: (1) arginine vasopressin (AVP), also known as antidiuretic hormone (ADH), and (2) oxytocin. AVP acts on the renal tubules to induce water retention, leading to concentration of the urine. Oxytocin stimulates postpartum milk letdown in response to suckling. Clinical syndromes may result from deficiency or excess of AVP.

## DIABETES INSIPIDUS

### Etiology

Diabetes insipidus (DI) results from insufficient AVP production by the hypothalamus or from impaired AVP action in the kidney. AVP deficiency is characterized by production of large amounts of dilute urine. In *central DI*, insufficient AVP is released in response to physiologic stimuli. Causes include acquired (head trauma; neoplastic or inflammatory conditions affecting the hypothalamus/posterior pituitary), congenital, and genetic disorders, but almost half of cases are idiopathic. In *gestational DI*, increased metabolism of plasma AVP by an aminopeptidase (vasopressinase) produced by the placenta leads to a relative deficiency of AVP during pregnancy. *Primary polydipsia* results in secondary insufficiency of AVP due to physiologic inhibition of AVP secretion by excessive fluid intake. *Nephrogenic DI* is caused by AVP resistance at the level of the kidney; it can be genetic or acquired from drug exposure (lithium, demeclocycline, amphotericin B), metabolic conditions (hypercalcemia, hypokalemia), or renal damage.

### Clinical Features

Symptoms include polyuria, excessive thirst, and polydipsia, with a 24-h urine output of >50 mL/kg per day and a urine osmolality that is less than that of serum (<300 mosmol/kg; specific gravity <1.010). DI can be partial or complete; in the latter case the urine is maximally diluted (<100 mosmol/kg) and the daily urine output can reach 10–20 L. Clinical or laboratory signs of dehydration, including hypernatremia, occur only if the pt simultaneously has a thirst defect (not uncommon in pts with CNS disease) or does not have access to water. Other etiologies of hypernatremia are described in Chap. 1.

### Diagnosis

DI must be differentiated from other etiologies of polyuria (Chap. 46). Unless an inappropriately dilute urine is present in the setting of serum hyperosmolality, a fluid deprivation test is used to make the diagnosis of DI. This test should be started in the morning with careful supervision to avoid dehydration. Body weight, plasma osmolality, serum sodium, and urine volume and osmolality should be measured hourly. The test should be stopped when body weight decreases by 5% or plasma osmolality/sodium exceeds the upper limit of normal. If the urine osmolality is <300 mosmol/kg with serum hyperosmolality, desmopressin (0.03 μg/kg SC) should be administered with repeat measurement of urine osmolality 1–2 h later. An increase of >50% indicates severe pituitary DI, whereas a smaller or absent response suggests nephrogenic DI. Measurement of AVP levels before and after fluid deprivation may be helfpul to distinguish central and nephrogenic DI. Occasionally, hypertonic saline infusion may be required if fluid deprivation does not achieve the requisite level of hypertonic dehydration, but this should be administered with caution.

**TREATMENT DIABETES INSIPIDUS**

Pituitary DI can be treated with desmopressin (DDAVP) subcutaneously (1–2 μg once or twice per day), via nasal spray (10–20 μg two or three times a day), or orally (100–400 μg two or three times a day), with recommendations to drink to thirst. Symptoms of nephrogenic DI may be ameliorated by treatment with a thiazide diuretic and/or amiloride in conjunction with a low-sodium diet, or with prostaglandin synthesis inhibitors (e.g., indomethacin).

## SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE (SIADH)

### Etiology

Excessive or inappropriate production of AVP predisposes to hyponatremia, reflecting water retention. The evaluation of hyponatremia is described in Chap. 1. Etiologies of SIADH include neoplasms, lung infections, CNS disorders, and drugs (Table 169-1).

### Clinical Features

If hyponatremia develops gradually, it may be asymptomatic until it reaches a severe stage. However, if it develops acutely, symptoms of water intoxication may include mild headache, confusion, anorexia, nausea, vomiting, coma, and convulsions. Laboratory findings include low BUN, creatinine, uric acid, and albumin; serum Na <130 meq/L and plasma osmolality <270 mosmol/kg; urine is not maximally diluted and frequently hypertonic to plasma, and urinary $Na^+$ is usually >20 mmol/L.

**TABLE 169-1 CAUSES OF SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE (SIADH)**

| | |
|---|---|
| Neoplasms | Neurologic |
| Carcinomas | Guillain-Barré syndrome |
| Lung | Multiple sclerosis |
| Duodenum | Delirium tremens |
| Pancreas | Amyotrophic lateral sclerosis |
| Ovary | Hydrocephalus |
| Bladder, ureter | Psychosis |
| Other neoplasms | Peripheral neuropathy |
| Thymoma | Congenital malformations |
| Mesothelioma | Agenesis corpus callosum |
| Bronchial adenoma | Cleft lip/palate |
| Carcinoid | Other midline defects |
| Gangliocytoma | Metabolic |
| Ewing's sarcoma | Acute intermittent porphyria |
| Head trauma | Pulmonary |
| Infections | Asthma |
| Pneumonia, bacterial or viral | Pneumothorax |
| Abscess, lung or brain | Positive-pressure respiration |
| Cavitation (aspergillosis) | Drugs |
| Tuberculosis, lung or brain | Vasopressin or desmopressin |
| Meningitis, bacterial or viral | Chlorpropamide |
| Encephalitis | Oxytocin, high dose |
| AIDS | Vincristine |
| Vascular | Carbamazepine |
| Cerebrovascular occlusions, hemorrhage | Nicotine |
| Cavernous sinus thrombosis | Phenothiazines |
| Genetic | Cyclophosphamide |
| X-linked recessive | Tricyclic antidepressants |
| ($V_2$ receptor gene) | Monoamine oxidase inhibitors |
| | Serotonin reuptake inhibitors |

**TREATMENT SIADH**

Fluid intake should be restricted to 500 mL less than urinary output. In pts with severe symptoms or signs, hypertonic (3%) saline can be infused at ≤0.05 mL/kg body weight IV per minute, with hourly sodium levels measured until Na increases by 12 meq/L or to 130 meq/L, whichever occurs first. However, if the hyponatremia has been present for >24–48 h and is corrected too rapidly, saline infusion has the potential to produce central pontine myelinolysis, a serious, potentially fatal neurologic complication caused by osmotic fluid shifts. Vasopressin antagonists (conivaptan, tolvaptan) are now available, but experience with these agents in SIADH treatment is limited. Oral vaptan (tolvaptan), a selective $V_2$ antagonist increases urinary water excretion by blocking the antidiuretic effect of AVP. It should be initiated in the hospital (typically 15 mg PO qd) to evaluate the clinical response and avoid excessive diuresis. Other options include demeclocycline, 150–300 mg PO tid or qid, or fludrocortisone, 0.05–0.2 mg PO bid. The effect of the demeclocycline manifests in 7–14 days and is due to induction of a reversible form of nephrogenic DI. The effect of fludrocortisone also requires 1–2 weeks and is partly due to increased retention of sodium and possibly inhibition of thirst. It also increases urinary potassium excretion, which may require replacement through dietary adjustments or supplements and may induce hypertension.

For a more detailed discussion, see Robertson GL: Disorders of the Neurohypophysis, Chap. 404, p. 2274, in HPIM-19.

# 170 Thyroid Gland Disorders

Disorders of the thyroid gland result primarily from autoimmune processes that stimulate the overproduction of thyroid hormones (*thyrotoxicosis*) or cause glandular destruction and underproduction of thyroid hormones (*hypothyroidism*). *Neoplastic processes* in the thyroid gland can lead to benign nodules or thyroid cancer.

Thyroidal production of the hormones thyroxine ($T_4$) and triiodothyronine ($T_3$) is controlled via a classic endocrine feedback loop (see Fig. 168-1). Some $T_3$ is secreted by the thyroid, but most is produced by deiodination of $T_4$ in peripheral tissues. Both $T_4$ and $T_3$ are bound to carrier proteins (thyroid-binding globulin [TBG], transthyretin [binds $T_4$], and albumin) in the circulation. Increased levels of total $T_4$ and $T_3$ with normal free levels are seen in states of increased carrier proteins (pregnancy, estrogens, cirrhosis, hepatitis, and inherited disorders). Conversely, decreased total $T_4$ and $T_3$ levels with normal free levels are seen in severe systemic illness, chronic liver disease, and nephrosis.

## HYPOTHYROIDISM

### Etiology

Deficient thyroid hormone production can be due to thyroid failure (primary hypothyroidism) or, less commonly, pituitary or hypothalamic disease (secondary

**TABLE 170-1 CAUSES OF HYPOTHYROIDISM**

| |
|---|
| **Primary** |
| Autoimmune hypothyroidism: Hashimoto's thyroiditis, atrophic thyroiditis |
| Iatrogenic: $^{131}$I treatment, subtotal or total thyroidectomy, external irradiation of neck for lymphoma or cancer |
| Drugs: iodine excess (including iodine-containing contrast media and amiodarone), lithium, antithyroid drugs, *p*-aminosalicylic acid, interferon α and other cytokines, aminoglutethimide, sunitinib |
| Congenital hypothyroidism: absent or ectopic thyroid gland, dyshormonogenesis, TSH-R mutation |
| Iodine deficiency |
| Infiltrative disorders: amyloidosis, sarcoidosis, hemochromatosis, scleroderma, cystinosis, Riedel's thyroiditis |
| Overexpression of type 3 deiodinase in infantile hemangioma |
| **Transient** |
| Silent thyroiditis, including postpartum thyroiditis |
| Subacute thyroiditis |
| Withdrawal of thyroxine treatment in individuals with an intact thyroid |
| After $^{131}$I treatment or subtotal thyroidectomy for Graves' disease |
| **Secondary** |
| Hypopituitarism: tumors, pituitary surgery or irradiation, infiltrative disorders, Sheehan's syndrome, trauma, genetic forms of combined pituitary hormone deficiencies |
| Isolated TSH deficiency or inactivity |
| Bexarotene treatment |
| Hypothalamic disease: tumors, trauma, infiltrative disorders, idiopathic |

***Abbreviations:*** TSH, thyroid-stimulating hormone; TSH-R, TSH receptor.

hypothyroidism) (Table 170-1). Congenital hypothyroidism is present in 1 of 4000 newborns; the importance of its recognition and prompt treatment for child development has led to the adoption of neonatal screening programs. Transient hypothyroidism may occur in silent or subacute thyroiditis. *Subclinical* (or *mild*) *hypothyroidism* is a state of normal free thyroid hormone levels and mild elevation of thyroid-stimulating hormone (TSH); despite the name, some pts may have minor symptoms. With higher TSH levels and low free $T_4$ levels, symptoms become more readily apparent in *clinical* (or *overt*) *hypothyroidism*. In areas of iodine sufficiency, autoimmune disease and iatrogenic causes are the most common etiologies of hypothyroidism. The peak age of occurrence is around 60 years, and prevalence increases with age.

## Clinical Features

Symptoms of hypothyroidism include lethargy, dry hair and skin, cold intolerance, hair loss, difficulty concentrating, poor memory, constipation, mild weight gain with poor appetite, dyspnea, hoarse voice, muscle cramping, and menorrhagia. Cardinal features on examination include bradycardia, mild diastolic hypertension, prolongation of the relaxation phase of deep tendon reflexes, and cool peripheral extremities. Goiter may be palpated, or the thyroid may be atrophic and nonpalpable. Carpal tunnel syndrome may be present. Cardiomegaly may be present due to pericardial effusion. The most extreme presentation is a dull, expressionless face, sparse hair, periorbital puffiness, large tongue, and pale, doughy, cool skin. The condition may

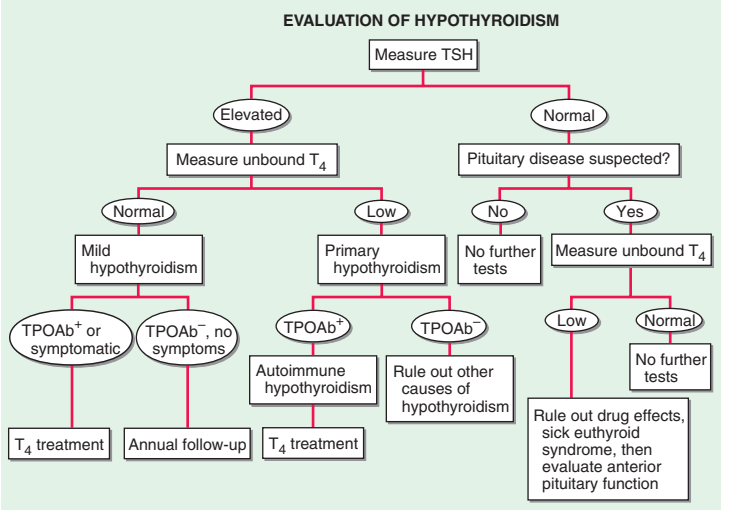



**FIGURE 170-1** Evaluation of hypothyroidism. $TPOAb^+$, thyroid peroxidase antibodies present; $TPOAb^-$, thyroid peroxidase antibodies not present; TSH, thyroid-stimulating hormone.

progress into a hypothermic, stuporous state (*myxedema coma*) with respiratory depression. Factors that predispose to myxedema coma include cold exposure, trauma, infection, and administration of narcotics. In mild hypothyroidism, the classic findings of overt hypothyroidism may not be present, and the clinical picture may be dominated by fatigue and ill-defined symptoms.

## Diagnosis

Decreased serum free $T_4$ is common to all varieties of hypothyroidism. An elevated serum TSH is a sensitive marker of primary hypothyroidism but is not found in secondary hypothyroidism. A summary of the investigations used to determine the existence and cause of hypothyroidism is provided in Fig. 170-1. Thyroid peroxidase (TPO) antibodies are increased in >90% of pts with autoimmune-mediated hypothyroidism. Elevated cholesterol, increased creatine phosphokinase, and anemia may be present; bradycardia, low-amplitude QRS complexes, and flattened or inverted T waves may be present on ECG.

## TREATMENT HYPOTHYROIDISM

Adult pts <60 years without evidence of heart disease may be started on 50–100 μg of levothyroxine ($T_4$) daily. In the elderly or in pts with known coronary artery disease, the starting dose of levothyroxine is 12.5–25 μg/d. The dose should be adjusted in 12.5- to 25-μg increments every 6–8 weeks on the basis of TSH levels, until a normal TSH level is achieved. The average daily replacement dose is 1.6 μg/kg per day, but dosing should be individualized and guided by TSH measurement. In *secondary* hypothyroidism, TSH levels cannot be used, and therapy needs to be guided by free $T_4$ measurement. Women on levothyroxine replacement should have a TSH level checked as soon as pregnancy is diagnosed, as the replacement dose typically increases by 30–50% during pregnancy. Failure to recognize and treat maternal hypothyroidism may

adversely affect fetal neural development. Therapy for myxedema coma should include levothyroxine (500 μg) as a single IV bolus followed by daily treatment with levothyroxine (50–100 μg/d), along with hydrocortisone (50 mg every 6 h) for impaired adrenal reserve, ventilatory support, space blankets, and treatment of precipitating factors.

## THYROTOXICOSIS

### Etiology

Causes of thyroid hormone excess include primary hyperthyroidism (Graves' disease, toxic multinodular goiter [MNG], toxic adenoma, iodine excess); thyroid destruction (subacute thyroiditis, silent thyroiditis, amiodarone, radiation); extrathyroidal sources of thyroid hormone (thyrotoxicosis factitia, struma ovarii, functioning follicular carcinoma); and secondary hyperthyroidism (TSH-secreting pituitary adenoma, thyroid hormone resistance syndrome, human chorionic gonadotropin [hCG]-secreting tumors, gestational thyrotoxicosis). Graves' disease, caused by activating TSH-receptor antibodies, is the most common cause of thyrotoxicosis and accounts for 60–80% of cases. Its prevalence in women is 10-fold higher than in men; its peak occurrence is at age 20–50 years.

### Clinical Features

Symptoms include nervousness, irritability, heat intolerance, excessive sweating, palpitations, fatigue and weakness, weight loss with increased appetite, frequent bowel movements, and oligomenorrhea. Pts are anxious, restless, and fidgety. Skin is warm and moist, and fingernails may separate from the nail bed (Plummer's nails). Eyelid retraction and lid lag may be present. Cardiovascular findings include tachycardia, systolic hypertension, systolic murmur, and atrial fibrillation. A fine tremor, hyperreflexia, and proximal muscle weakness also may be present. Long-standing thyrotoxicosis may lead to osteopenia. In the elderly, the classic signs of thyrotoxicosis may not be apparent, the main manifestations being weight loss and fatigue ("apathetic thyrotoxicosis").

In Graves' disease, the thyroid is usually diffusely enlarged to two to three times its normal size, and a bruit or thrill may be present. Infiltrative ophthalmopathy (with variable degrees of proptosis, periorbital swelling, and ophthalmoplegia) and dermopathy (pretibial myxedema) also may be found; these are extrathyroidal manifestations of the autoimmune process. In subacute thyroiditis, the thyroid is exquisitely tender and enlarged with referred pain to the jaw or ear, and sometimes accompanied by fever and preceded by an upper respiratory tract infection. Solitary or multiple nodules may be present in toxic adenoma or toxic MNG.

*Thyrotoxic crisis*, or thyroid storm, is rare, presents as a life-threatening exacerbation of hyperthyroidism, and can be accompanied by fever, delirium, seizures, arrhythmias, coma, vomiting, diarrhea, and jaundice.

### Diagnosis

Investigations used to determine the existence and causes of thyrotoxicosis are summarized in Fig. 170-2. Serum TSH is a sensitive marker of thyrotoxicosis caused by Graves' disease, autonomous thyroid nodules, thyroiditis, and exogenous levothyroxine treatment. Associated laboratory abnormalities include elevation of bilirubin, liver enzymes, and ferritin. Thyroid radioiodine uptake may be required to distinguish the various etiologies: high uptake in Graves' disease and nodular disease versus low uptake in thyroid destruction, iodine excess, and extrathyroidal sources of thyroid hormone. (***Note:*** Radioiodine is the nuclide required for quantitative thyroid uptake, whereas technetium is sufficient for imaging purposes.) The ESR is elevated in subacute thyroiditis.

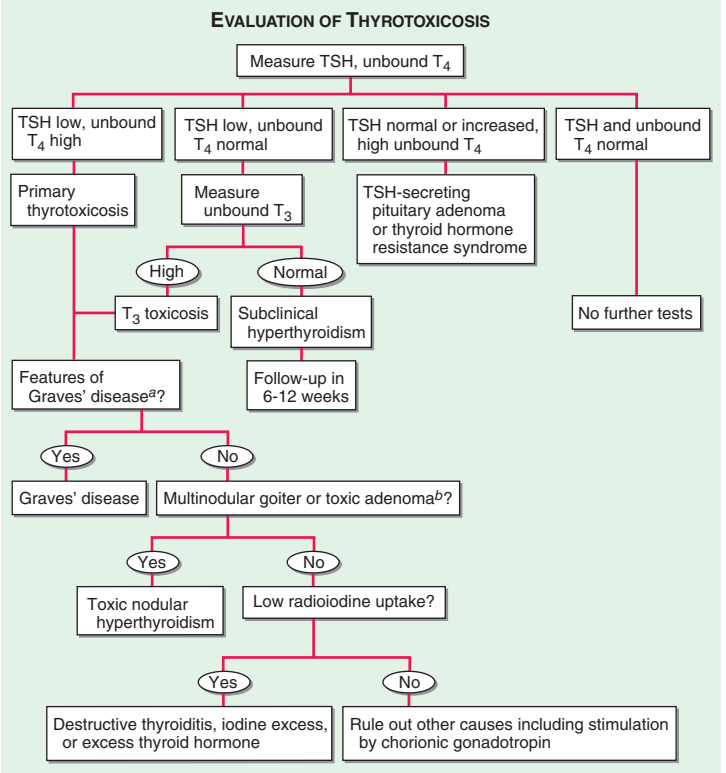



**FIGURE 170-2** Evaluation of thyrotoxicosis. [a]Diffuse goiter, positive TPO antibodies, ophthalmopathy, dermopathy; [b]can be confirmed by radionuclide scan. TSH, thyroid-stimulating hormone.

## TREATMENT THYROTOXICOSIS

Graves' disease may be treated with antithyroid drugs or radioiodine; subtotal thyroidectomy is rarely indicated. The main antithyroid drugs are methimazole or carbimazole (10–20 mg two to three times a day initially, titrated to 2.5–10 mg/d) and propylthiouracil (PTU) (100–200 mg every 8 h initially, titrated to 50 mg once or twice a day). Methimazole is preferred in most pts because of easier dosing. Thyroid function tests should be checked 3–4 weeks after initiation of treatment, with adjustments to maintain a normal free $T_4$ level. Since TSH recovery from suppression is delayed, serum TSH levels should not be used for dose adjustment in the first few months. The common side effects are rash, urticaria, fever, and arthralgia (1–5% of pts). Uncommon but major side effects include hepatitis, an SLE-like syndrome, and, rarely, agranulocytosis (<1%). All pts should be given written instructions regarding the symptoms of possible agranulocytosis (sore throat, fever, mouth ulcers) and the need to stop treatment pending a complete blood count to confirm that agranulocytosis is not present. Propranolol (20–40 mg every 6 h) or longer-acting beta blockers such as atenolol (50 mg/d) may be useful at the start of treatment to control adrenergic symptoms until euthyroidism is reached. Anticoagulation with warfarin

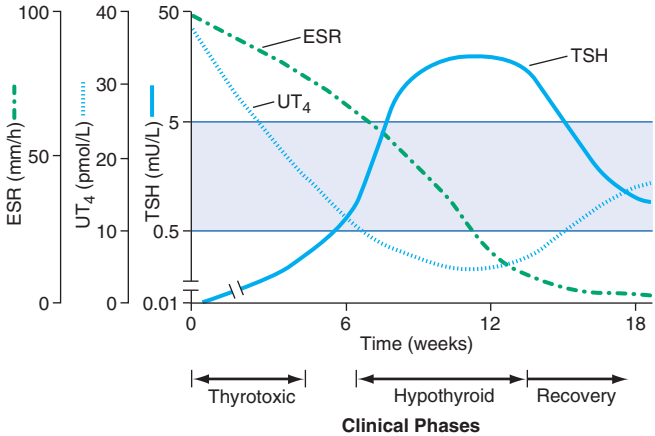



**FIGURE 170-3** Clinical course of subacute thyroiditis. The release of thyroid hormones is initially associated with a thyrotoxic phase and suppressed TSH levels. A hypothyroid phase then ensues, with $T_4$ and TSH levels that are initially low but gradually increase. During the recovery phase, increased TSH levels combined with resolution of thyroid follicular injury leads to normalization of thyroid function, often several months after the beginning of the illness. ESR, erythrocyte sedimentation rate; TSH, thyroid-stimulating hormone; $UT_4$, unbound $T_4$.

should be considered in pts with atrial fibrillation. Radioiodine can also be used as initial treatment or in pts who do not undergo remission after a 1- to 2-year trial of antithyroid drugs. Antecedent treatment with antithyroid drugs should be considered in elderly pts and those with cardiac problems, with cessation of antithyroid drugs 3–5 days prior to radioiodine administration. Radioiodine treatment is contraindicated in pregnancy; instead, symptoms should be controlled with the lowest effective dose of PTU. (Methimazole is not recommended in pregnancy because of reports of fetal agenesis cutis.) Corneal drying may be relieved with artificial tears and taping the eyelids shut during sleep. Progressive exophthalmos with chemosis, ophthalmoplegia, or vision loss is treated with large doses of prednisone (40–80 mg/d) and ophthalmologic referral; orbital decompression may be required.

In thyroid storm, large doses of PTU (600-mg loading dose) should be administered orally, per nasogastric tube, or per rectum, followed 1 h later by five drops saturated solution of KI (SSKI) q6h. PTU (200–300 mg every 6 h) should be continued, along with propranolol (40–60 mg PO q4h or 2 mg IV every 4 h) and dexamethasone (2 mg every 6 h). Any underlying precipitating cause should be identified and treated.

Radioiodine is the treatment of choice for toxic nodules. Subacute thyroiditis in its thyrotoxic phase should be treated with NSAIDs and beta blockade to control symptoms, with monitoring of the TSH and free $T_4$ levels every 4 weeks. Antithyroid drugs are not effective in thyroiditis. The clinical course of subacute thyroiditis is summarized in Fig. 170-3. Transient levothyroxine replacement (50–100 μg/d) may be required if the hypothyroid phase is prolonged. Silent thyroiditis (or postpartum thyroiditis if within 3–6 months of delivery) should be treated with beta blockade during the thyrotoxic phase and levothyroxine in the hypothyroid phase, with withdrawal after 6–9 months to assess recovery.

## SICK EUTHYROID SYNDROME

Any acute, severe illness can cause abnormalities of circulating thyroid hormone levels or TSH, even in the absence of underlying thyroid disease. Therefore, the routine testing of thyroid function should be avoided in acutely ill pts unless a thyroid disorder is strongly suspected. The most common pattern in sick euthyroid syndrome is a decrease in total and free $T_3$ levels, with normal levels of TSH and $T_4$. This is considered an adaptive response to a catabolic state. More ill pts may additionally have a fall in total $T_4$ levels, with normal free $T_4$ levels. TSH levels may range from <0.1 to >20 mU/L, with normalization after recovery from illness. The pathogenesis of this condition is not fully understood but may involve altered binding of $T_4$ to TBG and effects of high glucocorticoid and cytokine levels. Unless there is historic or unequivocal clinical evidence of hypothyroidism, thyroid hormone should not be administered and thyroid function tests should be repeated after recovery.

## AMIODARONE

Amiodarone is a type III antiarrhythmic agent that has some structural similarity to thyroid hormone and has a high iodine content. Amiodarone treatment leads to substantial iodine overload and is associated with (1) acute, transient suppression of thyroid function, (2) hypothyroidism, or (3) thyrotoxicosis. These effects are only partially attributable to iodine overload. Hypothyroidism can occur in pts with preexisting thyroid disease, with an inability to escape from the suppressive effect of excess iodine. Pts with hypothyroidism can be easily managed with levothyroxine replacement therapy, without a need to stop amiodarone. There are two major forms of amiodarone-induced thyrotoxicosis (AIT). Type 1 AIT is associated with an underlying thyroid abnormality (preclinical Graves' disease or nodular goiter). Thyroid hormone synthesis becomes excessive as a result of increased iodine exposure. Type 2 AIT occurs in pts with no intrinsic thyroid abnormalities and is the result of destructive thyroiditis. Differentiation between type 1 and type 2 AIT may be difficult as the high iodine load interferes with thyroid scans. The drug should be stopped, if possible, although this is often difficult to achieve without compromising the arrhythmia management. Amiodarone has a long biologic half-life, and its effects persist for weeks following discontinuation. Therapy of type 1 AIT consists of high-dose antithyroid drugs, but efficacy may be limited. In type 2 AIT, sodium ipodate (500 mg/d) or sodium tyropanoate (500 mg, 1–2 doses/d) can be used to rapidly lower thyroid hormone levels. Potassium perchlorate (200 mg every 6 h) can be used to deplete the thyroid of iodine, but long-term use carries a risk of agranulocytosis. Glucocorticoids in high doses are partially effective. Lithium can be used to block thyroid hormone release. In some cases, subacute thyroidectomy may be necessary to control thyrotoxicosis.

## NONTOXIC GOITER

*Goiter* refers to an enlarged thyroid gland (>20–25 g), which can be diffuse or nodular. Goiter is more common in women than men. Biosynthetic defects, iodine deficiency, autoimmune disease, dietary goitrogens (cabbage, cassava root), and nodular diseases can lead to goiter. Worldwide, iodine deficiency is the most common etiology of goiter. Nontoxic MNG is common in both iodine-deficient and iodine-replete populations, with a prevalence of up to 12%. The etiology, other than iodine deficiency, is usually not known and may be multifactorial. If thyroid function is preserved, most goiters are asymptomatic. Substernal goiter may obstruct the thoracic inlet and should be evaluated with respiratory flow measurements and CT or MRI in pts with obstructive signs or symptoms (difficulty swallowing, tracheal compression, or plethora). Thyroid function tests should be performed in all pts with goiter to exclude thyrotoxicosis or hypothyroidism. Ultrasound is not generally

indicated in the evaluation of diffuse goiter, unless a nodule is palpable on physical examination.

Iodine or thyroid hormone replacement induces variable regression of goiter in iodine deficiency. Thyroid hormone replacement is rarely effective in significantly shrinking a nontoxic goiter that is not due to iodine deficiency or a biosynthetic defect. Radioiodine reduces goiter size by about 50% in the majority of pts. Surgery is rarely indicated for diffuse goiter but may be required to alleviate compression in pts with nontoxic MNG.

## TOXIC MULTINODULAR GOITER AND TOXIC ADENOMA

### TOXIC MULTINODULAR GOITER (MNG)

In addition to features of goiter, the clinical presentation of toxic MNG includes subclinical hyperthyroidism or mild thyrotoxicosis. The pt is usually elderly and may present with atrial fibrillation or palpitations, tachycardia, nervousness, tremor, or weight loss. Recent exposure to iodine, from contrast dyes or other sources, may precipitate or exacerbate thyrotoxicosis; this may be prevented by prior administration of an antithyroid drug. The TSH level is low. $T_4$ may be normal or minimally increased; $T_3$ is often elevated to a greater degree than $T_4$. Thyroid scan shows heterogeneous uptake with multiple regions of increased and decreased uptake; 24-h uptake of radioiodine may not be increased. Cold nodules in a MNG should be evaluated in the same way as solitary nodules (see below). Antithyroid drugs, often in combination with beta blockers, can normalize thyroid function and improve clinical features of thyrotoxicosis but do not induce remission. A trial of radioiodine should be considered before subjecting pts, many of whom are elderly, to surgery. Subtotal thyroidectomy provides definitive treatment of goiter and thyrotoxicosis. Pts should be rendered euthyroid with antithyroid drugs before surgical intervention.

### TOXIC ADENOMA

A solitary, autonomously functioning thyroid nodule is referred to as *toxic adenoma*. Most cases are cause by somatic activating mutations of the TSH receptor. Thyrotoxicosis is typically mild. A thyroid scan provides a definitive diagnostic test, demonstrating focal uptake in the hyperfunctioning nodule and diminished uptake in the remainder of the gland, as activity of the normal thyroid is suppressed. Radioiodine ablation with relatively large doses (e.g., 10–29.9 mCi $^{131}$I) is usually the treatment of choice.

## THYROID NEOPLASMS

### Etiology

Thyroid neoplasms may be benign (adenomas) or malignant (carcinomas). Carcinomas of the follicular epithelium include papillary, follicular, and anaplastic thyroid cancer. Thyroid cancer incidence is ~12/100,000 per year and increases with age. Papillary thyroid cancer is the most common type of thyroid cancer (70–90%). It tends to be multifocal and to invade locally. Follicular thyroid cancer is difficult to diagnose via fine-needle aspiration (FNA) because the distinction between benign and malignant follicular neoplasms rests largely on evidence of invasion into vessels, nerves, or adjacent structures. It tends to spread hematogenously, leading to bone, lung, and CNS metastases. Anaplastic carcinoma is rare, highly malignant, and rapidly fatal. Thyroid lymphoma may arise in the background of Hashimoto's thyroiditis and occurs in the setting of a rapidly expanding thyroid mass. Medullary thyroid carcinoma arises from parafollicular (C) cells producing calcitonin and may occur sporadically or as a familial disorder, sometimes in association with multiple endocrine neoplasia type 2.

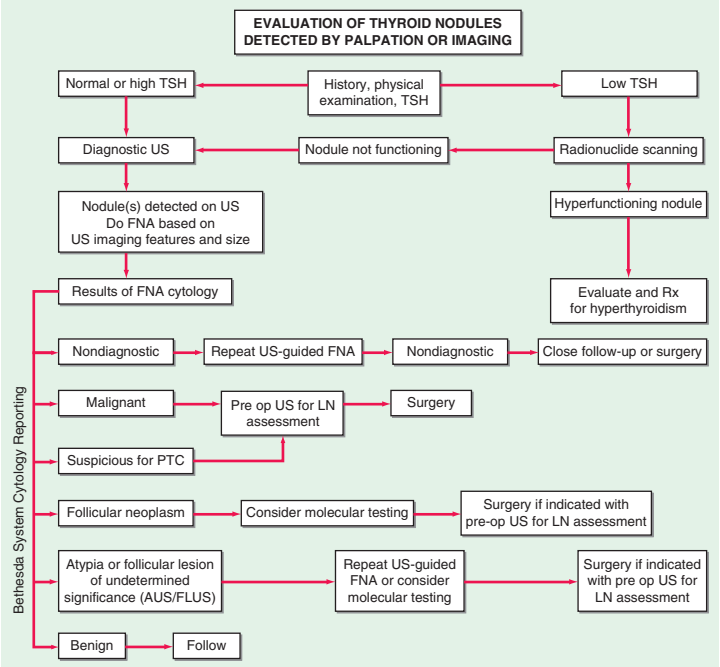



**FIGURE 170-4** Approach to the patient with a thyroid nodule. FNA, fine-needle aspiration; LN, lymph node; PTC, papillary thyroid cancer; TSH, thyroid-stimulating hormone; US, ultrasound.

## Clinical Features

Features suggesting carcinoma include recent or rapid growth of a nodule or mass, history of neck irradiation, lymph node involvement, hoarseness, and fixation to surrounding tissues. Glandular enlargement may result in compression and displacement of the trachea or esophagus and obstructive symptoms. Age <20 or >45, male sex, and larger nodule size are associated with a worse prognosis.

## Diagnosis

An approach to the evaluation of a solitary nodule is outlined in Fig. 170-4.

## TREATMENT THYROID NEOPLASMS

Benign nodules should be monitored via serial examination. TSH suppression with levothyroxine results in decreased nodule size in about 30% of pts. Suppressive therapy should not exceed 6–12 months if unsuccessful.

Follicular adenomas cannot be distinguished from follicular carcinomas on the basis of cytologic analysis of FNA specimens. The extent of surgical resection (lobectomy vs. near-total thyroidectomy) should be discussed prior to surgery.

Near-total thyroidectomy is required for papillary and follicular carcinoma and should be performed by a surgeon who is highly experienced in the procedure. If risk factors and pathologic features indicate the need for radioiodine treatment, the pt should be treated for several weeks postoperatively with liothyronine

($T_3$, 25 μg two to three times a day), followed by withdrawal for an additional 2 weeks, in preparation for postsurgical radioablation of remnant tissue. A therapeutic dose of $^{131}I$ is administered when the TSH level is >25 IU/L. Alternatively, recombinant TSH (0.9 mg) is administered as two daily consecutive injections followed by $^{131}I$ 24 h after the second injection. This appears to be equally effective as thyroid hormone withdrawal for radioablation therapy. Subsequent levothyroxine suppression of TSH to a low, but detectable, level (0.1–0.5 IU/L) should be attempted in pts with a low risk of recurrence, and to a completely suppressed level in those with a high risk of recurrence. In the latter case, free $T_4$ should be monitored to avoid overtreatment. Follow-up scans and serum thyroglobulin levels (acting as a tumor marker in an athyreotic pt) should be performed at regular intervals after either thyroid hormone withdrawal or administration of recombinant human TSH.

The management of medullary thyroid carcinoma is surgical, as these tumors do not take up radioiodine. Testing for *RET* mutations should be performed to assess for the presence of MEN 2, and the family should be screened if testing is positive. Following surgery, serum calcitonin provides a marker of residual or recurrent disease.

For a more detailed discussion, see Jameson JL, Mandel SJ, Weetman AP: Disorders of the Thyroid Gland, Chap. 405, p. 2283, in HPIM-19.

# 171 Adrenal Gland Disorders

The adrenal cortex produces three major classes of steroids: (1) glucocorticoids, (2) mineralocorticoids, and (3) adrenal androgens. Clinical syndromes may result from deficiency or excess of these hormones. The adrenal medulla produces catecholamines, with excess being caused by a pheochromocytoma (Chap. 117).

## HYPERFUNCTION OF THE ADRENAL GLAND

### CUSHING'S SYNDROME

#### Etiology

The most common cause of Cushing's syndrome is iatrogenic, due to administration of glucocorticoids for therapeutic reasons. Endogenous Cushing's syndrome results from production of excess cortisol (and other steroid hormones) by the adrenal cortex. The major cause is bilateral adrenal hyperplasia secondary to hypersecretion of adrenocorticotropic hormone (ACTH) by the pituitary (Cushing's disease) or from ectopic sources such as small cell carcinoma of the lung; carcinoids of the bronchus, thymus, gut and ovary, medullary carcinoma of the thyroid; or pheochromocytoma. Adenomas or carcinoma of the adrenal gland account for about 15–20% of endogenous Cushing's syndrome cases. There is a female preponderance in endogenous Cushing's syndrome except for the ectopic ACTH syndrome.

## Clinical Features

Some common manifestations (central obesity, hypertension, osteoporosis, psychological disturbances, acne, hirsutism, amenorrhea, and diabetes mellitus) are relatively nonspecific. More specific findings include easy bruising, purple striae, proximal myopathy, fat deposition in the face and nuchal areas (moon facies and buffalo hump), and rarely virilization. Thin, fragile skin and plethoric moon facies also may be found. Hypokalemia and metabolic alkalosis are prominent, particularly with ectopic production of ACTH.

## Diagnosis

The diagnosis of Cushing's syndrome requires demonstration of increased cortisol production and abnormal cortisol suppression in response to dexamethasone. For initial screening, measurement of 24-h urinary free cortisol, the 1-mg overnight dexamethasone test [8:00 A.M. plasma cortisol <1.8 μg/dL (50 nmol/L)], or late-night salivary cortisol measurement is appropriate. Repeat testing or performance of more than one screening test may be required. Definitive diagnosis is established in equivocal cases by inadequate suppression of urinary cortisol [<10 μg/d (25 nmol/d)] or plasma cortisol [<5 μg/dL (140 nmol/L)] after 0.5 mg dexamethasone every 6 h for 48 h. Once the diagnosis of Cushing's syndrome is established, further biochemical testing is required to localize the source. This evaluation is best performed by an experienced endocrinologist. Low levels of plasma ACTH levels suggest an adrenal adenoma or carcinoma; inappropriately normal or high plasma ACTH levels suggest a pituitary or ectopic source. In 95% of ACTH-producing pituitary microadenomas, cortisol production is suppressed by high-dose dexamethasone (2 mg every 6 h for 48 h). MRI of the pituitary should be obtained but may not reveal a microadenoma because these tumors are typically very small. Furthermore, because up to 10% of ectopic sources of ACTH may also suppress after high-dose dexamethasone testing, inferior petrosal sinus sampling may be required to distinguish pituitary from peripheral sources of ACTH. Testing with corticotropin-releasing hormone (CRH) also may be helpful in determining the source of ACTH. Imaging of the chest and abdomen is required to localize the source of ectopic ACTH production; small bronchial carcinoids may escape detection by conventional CT. Pts with chronic alcoholism, depression, or obesity may have false-positive results in testing for Cushing's syndrome—a condition named pseudo-Cushing's syndrome. Similarly, pts with acute illness may have abnormal laboratory test results, since major stress alters the normal regulation of ACTH secretion. The management of Cushing's syndrome is summarized in Fig. 171-1.

## TREATMENT CUSHING'S SYNDROME

Uncontrolled hypercorticism carries a poor prognosis, and treatment of Cushing's syndrome is therefore necessary. Transsphenoidal surgery for pituitary ACTH-secreting microadenomas is curative in 70–80% when performed by a highly experienced surgeon, but long-term follow-up is required because these tumors may recur. Radiation therapy may be used when a surgical cure is not achieved (Chap. 168). Therapy of adrenal adenoma or carcinoma requires surgical excision; stress doses of glucocorticoids must be given pre- and postoperatively. Metastatic and unresectable adrenal carcinomas are treated with mitotane in doses gradually increased to 6 g/d in three or four divided doses. On occasion, debulking of lung carcinoma or resection of carcinoid tumors can result in remission of ectopic Cushing's syndrome. If the source of ACTH cannot be resected, medical management with ketoconazole (600–1200 mg/d), metyrapone (2–3 g/d), or mitotane (2–3 mg/d) may relieve manifestations of cortisol excess. In some cases, bilateral total adrenalectomy is required to control hypercorticism. Pts with unresectable pituitary adenomas who have had bilateral adrenalectomy are at risk for Nelson's syndrome (aggressive pituitary adenoma enlargement).

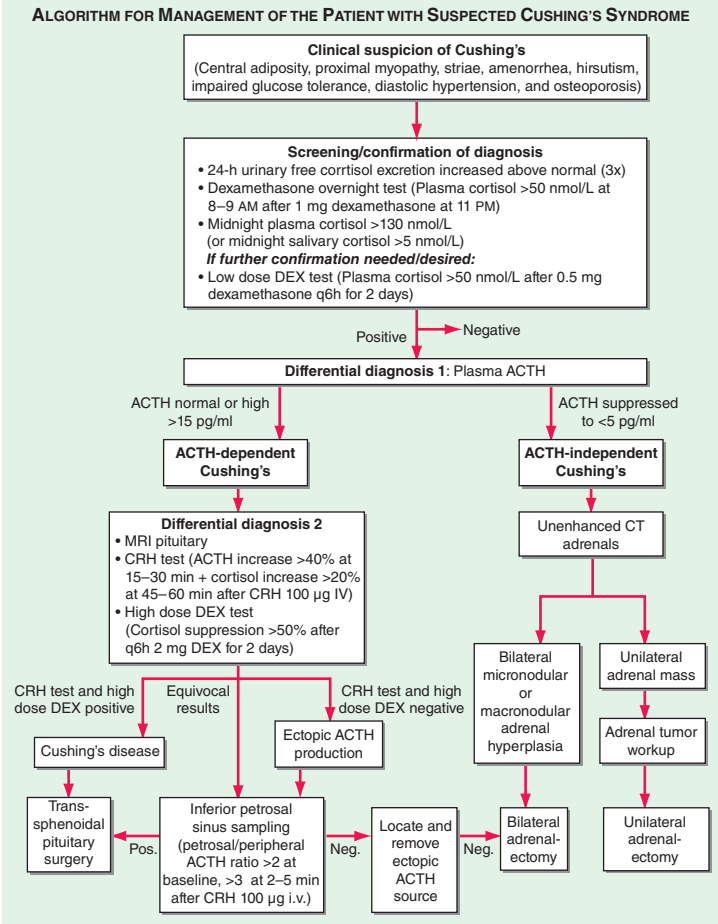



**FIGURE 171-1** Management of the patient with suspected Cushing's syndrome. ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; DEX, dexamethasone.

## HYPERALDOSTERONISM

### Etiology

Aldosteronism is caused by hypersecretion of the adrenal mineralocorticoid aldosterone. *Primary hyperaldosteronism* refers to an adrenal cause and can be due to either an adrenal adenoma or bilateral adrenal hyperplasia. Rare causes include glucocorticoid-remediable hyperaldosteronism, some forms of congenital adrenal hyperplasia, and other disorders of true or apparent mineralocorticoid excess (see Table 406-3, HPIM-19). The term *secondary hyperaldosteronism* is used when an extraadrenal stimulus for renin secretion is present, as in renal artery stenosis, decompensated liver cirrhosis, or diuretic therapy.

## Clinical Features

Most pts with primary hyperaldosteronism have difficult to control hypertension (especially diastolic) and hypokalemia. Headaches are common. Edema is characteristically absent, unless congestive heart failure or renal disease is present. Hypokalemia, caused by urinary potassium losses, may cause muscle weakness, fatigue, and polyuria, although potassium levels may be normal in mild primary hyperaldosteronism. Metabolic alkalosis is a typical feature.

## Diagnosis

The diagnosis is suggested by treatment-resistant hypertension that is associated with persistent hypokalemia in a nonedematous pt who is not receiving potassium-wasting diuretics. In pts receiving potassium-wasting diuretics, the diuretic should be discontinued and potassium supplements should be administered for 1–2 weeks. If hypokalemia persists after supplementation, screening using a serum aldosterone and plasma renin activity should be performed. Ideally, antihypertensives should be stopped before testing, but that is often impractical. Aldosterone receptor antagonists, beta-adrenergic blockers, ACE inhibitors, and angiotensin receptor blockers interfere with testing and should be substituted with other antihypertensives if possible. A ratio of serum aldosterone (in ng/dL) to plasma renin activity (in ng/mL per hour) >30 and an absolute level of aldosterone >15 ng/dL suggest primary aldosteronism. Failure to suppress plasma aldosterone (to <5 ng/dL after 500 mL/h of normal saline × 4 h) or urinary aldosterone after saline or sodium loading (to <10 μg/d on day 3 of 200 mmol/d oral NaCl + fludrocortisone 0.2 mg twice daily × 3 days) confirms primary hyperaldosteronism. Caution should be used with sodium loading in a hypertensive pt. Localization should then be undertaken with a high-resolution CT scan of the adrenal glands. If the CT scan is negative, bilateral adrenal vein sampling may be required to diagnose a unilateral aldosterone-producing adenoma. Secondary hyperaldosteronism is associated with elevated plasma renin activity.

### TREATMENT HYPERALDOSTERONISM

Surgery can be curative in pts with adrenal adenoma but is not effective for adrenal hyperplasia, which is managed with sodium restriction and spironolactone (25–100 mg twice daily) or eplerenone (25–50 mg twice daily). The sodium channel blocker amiloride (5–10 mg twice a day) also can be used. Secondary hyperaldosteronism is treated with salt restriction and correction of the underlying cause.

## SYNDROMES OF ADRENAL ANDROGEN EXCESS

See Chap. 175 for discussion of hirsutism and virilization.

## HYPOFUNCTION OF THE ADRENAL GLAND

*Primary adrenal insufficiency* is due to failure of the adrenal gland, whereas *secondary adrenal insufficiency* is due to failure of ACTH production or release.

### ADDISON'S DISEASE

## Etiology

Addison's disease occurs when >90% of adrenal tissue is destroyed. The most common cause is autoimmune destruction (alone, or as part of type I or type II polyglandular autoimmune syndromes). Tuberculosis used to be the leading etiology. Other granulomatous diseases (histoplasmosis, coccidioidomycosis, cryptococcosis, sarcoidosis), bilateral adrenalectomy, bilateral tumor metastases, bilateral hemorrhage, CMV, HIV, amyloidosis, and congenital diseases (some types of congenital

adrenal hypoplasia, adrenal hypoplasia congenita, and adrenoleukodystrophy) are additional etiologies.

## Clinical Features

Manifestations include fatigue, weakness, anorexia, nausea and vomiting, weight loss, abdominal pain, cutaneous and mucosal pigmentation, salt craving, hypotension (especially orthostatic), and, occasionally, hypoglycemia. Routine laboratory parameters may be normal, but typically serum Na is reduced and serum K increased. Extracellular fluid depletion accentuates hypotension. In secondary adrenal insufficiency, pigmentation is diminished and serum potassium is not elevated. Serum Na tends to be low because of hemodilution stemming from excess vasopressin secreted in the setting of cortisol deficiency.

## Diagnosis

The best screening test is the cortisol response 60 min after 250 μg ACTH (cosyntropin) IV or IM. Cortisol levels should exceed 18 μg/dL 30–60 min after the ACTH. If the response is abnormal, then primary and secondary deficiency may be distinguished by measurement of aldosterone from the same blood samples. In secondary, but not primary, adrenal insufficiency, the aldosterone increment from baseline will be normal (≥5 ng/dL). Furthermore, in primary adrenal insufficiency, plasma ACTH is elevated, whereas in secondary adrenal insufficiency, plasma ACTH values are low or inappropriately normal. Pts with recent onset or partial pituitary insufficiency may have a normal response to the rapid ACTH stimulation test. In these pts, alternative testing (metyrapone test or insulin tolerance testing) can be used for diagnosis.

### TREATMENT ADDISON'S DISEASE

Hydrocortisone, at 15–25 mg/d divided into $^{2}/_{3}$ in the morning and $^{1}/_{3}$ in the afternoon, is the mainstay of glucocorticoid replacement. Some pts benefit from doses administered three times daily, and other glucocorticoids may be given at equivalent doses. Mineralocorticoid supplementation is usually needed for primary adrenal insufficiency, with administration of 0.05–0.1 mg fludrocortisone PO qd and maintenance of adequate Na intake. Doses should be titrated to normalize Na and K levels and to maintain normal blood pressure without postural changes. Measurement of plasma renin levels may also be useful in titrating the dose. Mineralocorticoid replacement is not needed in pts with secondary adrenal insufficiency. All pts with adrenal insufficiency should be instructed in the parenteral self-administration of steroids and should be registered with a medical alert system. During periods of intercurrent illness, the dose of hydrocortisone should be doubled. During adrenal crisis, high-dose hydrocortisone (10 mg/h continuous IV or 100-mg bolus IV three times a day) should be administered along with normal saline. Thereafter, if the pt is improving and is afebrile, the dose can be tapered by 20–30% daily to usual replacement doses.

## HYPOALDOSTERONISM

Isolated aldosterone deficiency accompanied by normal cortisol production occurs with hyporeninism, as an inherited aldosterone synthase deficiency, postoperatively following removal of aldosterone-secreting adenomas (transient), and during protracted heparin therapy. Hyporeninemic hypoaldosteronism is seen most commonly in adults with diabetes mellitus and mild renal failure; it is characterized by mild to moderate hyperkalemia. This is usually a benign condition that can be managed by observation. If needed, oral fludrocortisone (0.05–0.15 mg/d PO) restores electrolyte balance if salt intake is adequate. In pts with hypertension, mild renal insufficiency,

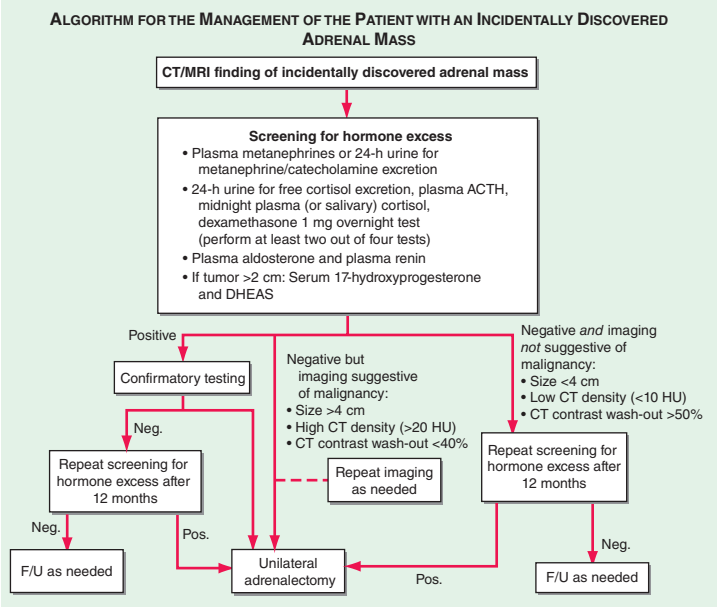



**FIGURE 171-2** Management of the patient with an incidentally discovered adrenal mass. F/U, follow-up.

or congestive heart failure, an alternative approach is to reduce salt intake and to administer furosemide.

## INCIDENTAL ADRENAL MASSES

Adrenal masses are common findings on abdominal CT or MRI scans (1–7% prevalence with increasing age). The majority (70–80%) of such "incidentalomas" are clinically nonfunctional, and the probability of an adrenal carcinoma is low (<0.01%). Genetic syndromes such as MEN 1, MEN 2, Carney syndrome, and McCune-Albright syndrome are all associated with adrenal masses. The first step in evaluation is to determine the functional status by measurement of plasma free metanephrines to screen for pheochromocytoma (Fig. 171-2). In a pt with a known extraadrenal malignancy, there is a 30–50% chance that the incidentaloma is a metastasis. Additional hormonal evaluation should include 24-h urine for urinary free cortisol or overnight 1-mg dexamethasone suppression testing, plasma renin activity/aldosterone ratio in hypertensives, DHEAS in women with signs of androgen excess, and estradiol in males with feminization. Fine-needle aspiration is rarely indicated and absolutely contraindicated if a pheochromocytoma is suspected. Adrenocortical cancer is suggested by large size (>4–6 cm), irregular margins, tumor inhomogeneity, soft tissue calcifications, and high unenhanced CT attenuation values (>10 HU).

For a more detailed discussion, see Arlt W: Disorders of the Adrenal Cortex, Chap. 406, p. 2309, in HPIM-19.

# 172 Obesity

*Obesity* is a state of excess adipose tissue mass. Obesity should not be defined by body weight alone, as muscular individuals may be overweight by arbitrary standards without having increased adiposity. The most widely used method to classify weight status and risk of disease is the *body mass index* (BMI), which is equal to weight/height$^2$ in kg/m$^2$ (Table 172-1). At a similar BMI, women have more body fat than men. Furthermore, regional fat distribution may influence the risks associated with obesity. Central (primarily visceral) obesity (high ratio of the circumference of the waist to the circumference of the hips [waist-to-hip ratio], >0.9 in women and 1.0 in men) is independently associated with a higher risk for metabolic syndrome, diabetes mellitus, hyperandrogenism in women, and cardiovascular disease. The prevalence of obesity has increased dramatically over the past 3 decades. In the United States, about 34% of adults age >20 are obese (BMI >30), and another 34% are overweight (BMI 25–30). Most alarming is a similar trend among children, where about 16% of adolescents are obese. This has led to an epidemic of type 2 diabetes in children, a condition almost never seen until recently. These trends to increased obesity are not limited to Western societies but are occurring worldwide.

## ETIOLOGY

Obesity can result from increased energy intake, decreased energy expenditure, or a combination of the two. Excess accumulation of body fat is the consequence of environmental and genetic factors; social factors and economic conditions also represent important influences. The recent increase in obesity can be attributed to a combination of excess caloric intake and decreasing physical activity. Poorly understood reasons for increased food assimilation due to dietary composition have also been postulated, as have sleep deprivation and an unfavorable gut flora. The susceptibility to obesity is polygenic in nature, and 30–50% of the variability in total fat stores is believed to be genetically determined. Among monogenic causes, mutations in the melanocortin receptor 4 are most common and account for ~1% of obesity in the general population and ~6% in severe, early-onset obesity. Syndromic obesity forms include Prader-Willi syndrome and Laurence-Moon-Biedl syndrome. Other monogenetic or syndromic causes are extremely rare. Secondary causes of obesity include hypothalamic injury, hypothyroidism, Cushing's syndrome, and hypogonadism. Drug-induced weight gain is also common in those who use

**TABLE 172-1 CLASSIFICATION OF WEIGHT STATUS AND RISK OF DISEASE**

| | BMI (kg/m$^2$) | Obesity Class | Risk of Disease |
|---|---|---|---|
| Underweight | <18.5 | | |
| Healthy weight | 18.5–24.9 | | |
| Overweight | 25.0–29.9 | | Increased |
| Obesity | 30.0–34.9 | I | High |
| Obesity | 35.0–39.9 | II | Very high |
| Extreme obesity | ≥40 | III | Extremely high |

***Source:*** Adapted from National Institutes of Health, National Heart, Lung, and Blood Institute: *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults*. U.S. Department of Health and Human Services, Public Health Service, 1998.

antidiabetes agents (insulin, sulfonylureas, thiazolidinediones), glucocorticoids, psychotropic agents, mood stabilizers (lithium), antidepressants (tricyclics, monoamine oxidase inhibitors, paroxetine, mirtazapine), or antiepileptic drugs (valproate, gabapentin, carbamazepine). Insulin-secreting tumors can cause overeating and weight gain.

## CLINICAL FEATURES

Obesity has major adverse effects on health. Increased mortality from obesity is primarily due to cardiovascular disease, hypertension, gall bladder disease, diabetes mellitus, and several types of cancer, such as cancer of the esophagus, colon, rectum, pancreas, liver, and prostate, and gallbladder, bile ducts, breasts, endometrium, cervix, and ovaries in women. Sleep apnea in severely obese individuals poses serious health risks. Obesity is also associated with an increased incidence of steatohepatitis, gastroesophageal reflux, osteoarthritis, gout, back pain, skin infections, and depression. Hypogonadism in men and infertility in both sexes are prevalent in obesity; in women this may be associated with hyperandrogenism (polycystic ovarian syndrome).

## TREATMENT OBESITY

Obesity is a chronic medical condition that requires ongoing treatment and lifestyle modifications. Treatment is important because of the associated health risks, but is made difficult by a limited repertoire of effective therapeutic options. Weight regain after weight loss is common with all forms of therapy. The urgency and selection of treatment modalities should be based on BMI and a risk assessment.

Diet, exercise, and behavior therapy are recommended for all pts with a BMI ≥25 kg/m$^2$. Behavior modification including group counseling, diet diaries, and changes in eating patterns should be initiated. Food-related behaviors should be monitored carefully (avoid cafeteria-style settings, eat small and frequent meals, eat breakfast). A deficit of 7500 kcal will produce a weight loss of approximately 1 kg. Therefore, eating 100 kcal/d less for a year should cause a 5-kg weight loss, and a deficit of 1000 kcal/d should cause a loss of ~1 kg per week. Physical activity should be increased to a minimum of 150 min of moderate intensity physical activity per week.

Pharmacotherapy may be added to a lifestyle program for pts with a BMI ≥30 kg/m$^2$ or ≥27 kg/m$^2$ with concomitant obesity-related diseases. Orlistat (120 mg po tid), an inhibitor of intestinal lipase, causes modest weight loss (9–10% at 12 months with lifestyle measures) due to drug-induced fat malabsorption. Lorcaserin and phentermine/topiramate are anorexiants that were recently FDA-approved. Response to medications should be assessed after 3 months. Metformin, exenatide, and liraglutide tend to decrease body weight in pts with obesity and type 2 diabetes mellitus, but they are not indicated for pts without diabetes.

Bariatric surgery should be considered for pts with severe obesity (BMI ≥40 kg/m$^2$) or moderate obesity (BMI ≥35 kg/m$^2$) associated with a serious medical condition, with repeated failures of other therapeutic approaches, at eligible weight for >3 years, capable of tolerating surgery, and without addictions or major psychopathology. Weight-loss surgeries are either restrictive (limiting the amount of food the stomach can hold and slowing gastric emptying), such as laparoscopic adjustable silicone gastric banding, or restrictive-malabsorptive, such as Roux-en-Y gastric bypass (Fig. 172-1). These procedures generally produce a 30–35% weight loss that is maintained in about 40% of pts at 4 years. In many patients, there is significant improvement in co-morbid conditions including type 2 diabetes mellitus, hypertension, sleep apnea, hyperlipidemia, and cardiovascular

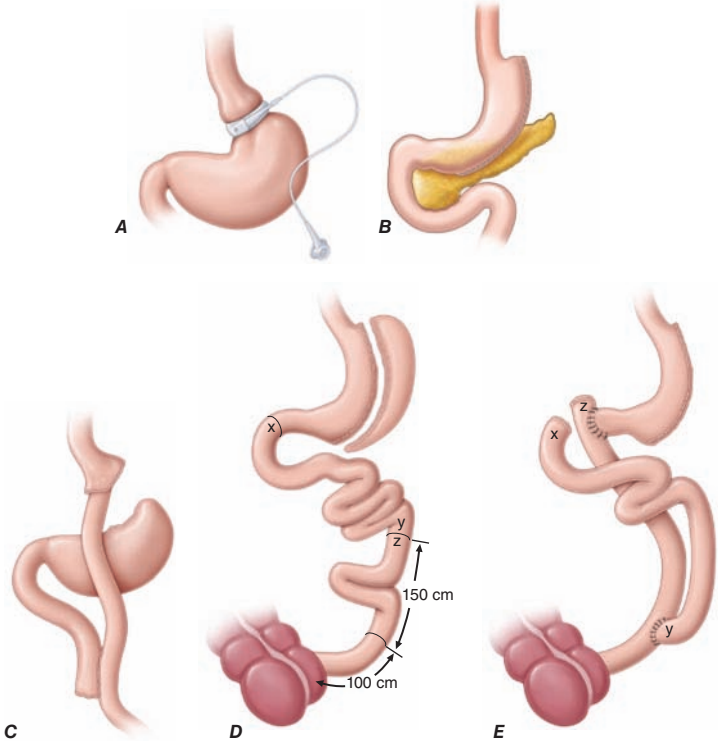



**FIGURE 172-1** Bariatric surgical procedures. Examples of operative interventions used for surgical manipulation of the gastrointestinal tract. ***A.*** Laparoscopic adjustable gastric banding. ***B.*** Laparoscopic sleeve gastrectomy. ***C.*** The Roux-en-Y gastric bypass. ***D.*** Biliopancreatic diversion with duodenal switch. ***E.*** Biliopancreatic diversion. *(From ML Kendrick, GF Dakin: Mayo Clin Proc 815:518, 2006; with permission.)*

events. The metabolic benefits appear to be the combined result of weight loss and physiologic responses of gut hormones and adipose tissue metabolism. Complications include stomal stenosis, marginal ulcers, and dumping syndrome. Procedures with a malabsorptive component require lifelong supplementation of micronutrients (iron, folate, calcium, vitamins $B_{12}$ and D) and are associated with a risk of islet cell hyperplasia and hypoglycemia.

For a more detailed discussion, see Flier JS, Maratos-Flier E: Biology of Obesity, Chap. 415e, and Kushner RF: Evaluation and Management of Obesity, Chap. 416, p. 2392, in HPIM-19.

# 173 Diabetes Mellitus

## ETIOLOGY AND PREVALENCE

Diabetes mellitus (DM) comprises a group of metabolic disorders that share the common feature of hyperglycemia. DM is currently classified on the basis of the pathogenic process that leads to hyperglycemia. Type 1 DM is characterized by insulin deficiency and a tendency to develop ketosis, whereas type 2 DM is a heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion, and excessive hepatic glucose production. Other specific types include DM caused by genetic defects (maturity-onset diabetes of the young [MODY] and other rare monogenic disorders), diseases of the exocrine pancreas (chronic pancreatitis, cystic fibrosis, hemochromatosis), endocrinopathies (acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism), drugs (nicotinic acid, glucocorticoids, thiazides, protease inhibitors), and pregnancy (gestational DM). The phenotype of these monogenetic and secondary types of DM typically resembles type 2 DM; its severity depends on the degree of beta cell dysfunction and prevailing insulin resistance. Type 1 DM usually results from autoimmune destruction of pancreatic beta cells; it is also known as juvenile-onset diabetes because its peak incidence is in children and adolescents.

The prevalence of DM is increasing rapidly; type 2 DM frequency in particular is rising in parallel with the epidemic of obesity (Chap. 172). Between 1985 and 2013, the worldwide prevalence of DM has risen more than 10-fold, from 30 million to 382 million cases. In the United States, DM prevalence at greater than 8% of the population, increasing with age. A significant portion of persons with DM are undiagnosed.

DM is attended by serious morbidity and significant mortality; it is the fifth leading cause of death worldwide.

## DIAGNOSIS

Criteria for the diagnosis of DM include one of the following:

- Fasting plasma glucose ≥7.0 mmol/L (≥126 mg/dL)
- Symptoms of diabetes plus a random blood glucose concentration ≥11.1 mmol/L (≥200 mg/dL)
- 2-h plasma glucose ≥11.1 mmol/L (≥200 mg/dL) during a 75-g oral glucose tolerance test.
- Hemoglobin $A_{1c}$ >6.5%

These criteria should be confirmed by repeat testing on a different day, unless unequivocal hyperglycemia is present.

Two intermediate categories also have been designated:

- Impaired fasting glucose (IFG) for a fasting plasma glucose level of 5.6–6.9 mmol/L (100–125 mg/dL)
- Impaired glucose tolerance (IGT) for plasma glucose levels of 7.8–11.1 mmol/L (140–199 mg/dL) 2 h after a 75-g oral glucose load

Individuals with IFG or IGT do not have DM, but are at substantial risk for developing type 2 DM and cardiovascular disease in the future.

Screening with a fasting plasma glucose level is recommended every 3 years for individuals over the age of 45, as well as for younger individuals who are

**TABLE 173-1 CRITERIA FOR TESTING FOR PRE-DIABETES AND DIABETES IN ASYMPTOMATIC INDIVIDUALS[a]**

| Risk Factors |
|---|
| • First-degree relative with diabetes |
| • Physical inactivity |
| • Race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander) |
| • Previously identified IFG, IGT, or a hemoglobin $A_{1C}$ of 5.7–6.4% |
| • History of GDM or delivery of baby >4 kg (>9 lb) |
| • Hypertension (blood pressure ≥140/90 mmHg) |
| • HDL cholesterol level ≤0.90 mmol/L (35 mg/dL) and/or a triglyceride level ≥2.82 mmol/L (250 mg/dL) |
| • Polycystic ovary syndrome or acanthosis nigricans |
| • History of vascular disease |

[a]Testing should be considered in all adults at age 45 and adults <45 years with BMI ≥25 kg/m$^2$ and one or more of the following risk factors for diabetes.

***Abbreviations:*** BMI, body mass index; GDM, gestational diabetes mellitus; HDL, high-density lipoprotein; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

***Source:*** Adapted from American Diabetes Association: *Diabetes Care 37*(Suppl 1): S14, 2014.

overweight (body mass index ≥25 kg/m$^2$) and have one or more additional risk factors (Table 173-1).

The *metabolic syndrome* (also known as *insulin resistance syndrome* or *syndrome X)* is a term used to describe a commonly found constellation of metabolic derangements that includes insulin resistance (with or without diabetes), hypertension, dyslipidemia, central or visceral obesity, and endothelial dysfunction and is associated with accelerated cardiovascular disease (Chap. 118).

## CLINICAL FEATURES

Common presenting symptoms of DM include polyuria, polydipsia, weight loss, fatigue, weakness, blurred vision, frequent superficial infections, and poor wound healing. In early type 2 DM, symptoms may be more subtle and consist of fatigue, poor wound healing, and paresthesias. The lack of symptoms is the main reason for the delayed diagnosis of type 2 DM. Many pts are diagnosed based on screening or during blood tests taken for other reasons. A complete medical history should be obtained with special emphasis on weight, exercise, smoking, ethanol use, family history of DM, and risk factors for cardiovascular disease. In a pt with established DM, assessment of prior diabetes care, $HbA_{1c}$ levels, self-monitoring blood glucose results, frequency of hypoglycemia, and pt's knowledge about DM should be obtained. Special attention should be given on physical examination to retinal examination, bp, foot examination (including vibratory sensation and monofilament testing), peripheral pulses, and insulin injection sites. Acute complications of DM that may be seen on presentation include diabetic ketoacidosis (DKA) (type 1 DM) and hyperglycemic hyperosmolar state (type 2 DM) (Chap. 23).

The chronic complications of DM are listed below:

- *Ophthalmologic:* nonproliferative or proliferative diabetic retinopathy, macular edema, rubeosis of iris, glaucoma, cataracts

- *Renal:* proteinuria, end-stage renal disease (ESRD), type IV renal tubular acidosis
- *Neurologic:* distal symmetric polyneuropathy, polyradiculopathy, mononeuropathy, autonomic neuropathy
- *Gastrointestinal:* gastroparesis, diarrhea, constipation
- *Genitourinary:* cystopathy, erectile dysfunction, female sexual dysfunction, vaginal candidiasis
- *Cardiovascular:* coronary artery disease, congestive heart failure, peripheral vascular disease, stroke
- *Lower extremity:* foot deformity (hammer toe, claw toe, Charcot foot), ulceration, amputation
- *Dermatologic:* Infections (folliculitis, furunculosis, cellulitis), necrobiosis, poor healing, ulcers, gangrene
- *Dental:* Periodontal disease

## TREATMENT DIABETES MELLITUS

Optimal treatment of DM requires more than plasma glucose management. Comprehensive diabetes care should also detect and manage DM-specific complications and modify risk factors for DM-associated diseases. The pt with type 1 or type 2 DM should receive education about nutrition, exercise, care of diabetes during illness, and medications to lower the plasma glucose. In general, the target $HbA_{1c}$ level should be <7.0%, although individual considerations (age, ability to implement a complex treatment regimen, and presence of other medical conditions) should also be taken into account. Intensive therapy reduces long-term complications but is associated with more frequent and more severe hypoglycemic episodes. Goal preprandial capillary plasma glucose levels should be 3.9–7.2 mmol/L (70–130 mg/dL) and postprandial levels should be <10.0 mmol/L (<180 mg/dL) 1–2 h after a meal.

In general, pts with type 1 DM require 0.5–1.0 U/kg per day of insulin divided into multiple doses. Combinations of insulin preparations with different times of onset and duration of action should be used (**Table 173-2**). Preferred regimens include injection of glargine at bedtime with preprandial lispro, glulisine, or insulin aspart or continuous SC insulin using an infusion device. Pramlintide, an injectable amylin analogue, can be used as adjunct therapy to control postprandial glucose excursions.

Pts with type 2 DM may be managed with diet and exercise alone or in conjunction with oral glucose-lowering agents, insulin, or a combination of oral agents and insulin. The classes of oral glucose-lowering agents and dosing regimens are listed in **Table 173-3**. In addition, exenatide and liraglutide are injectable glucagon-like peptide 1 (GLP-1, an incretin) analogues that may be used in combination with metformin or sulfonylureas. A reasonable treatment algorithm for initial therapy proposes metformin as initial therapy because of its efficacy (1–2% decrease in $HbA_{1c}$), known side-effect profile, and relatively low cost (**Fig. 173-1**). Metformin has the advantage that it promotes mild weight loss, lowers insulin levels, improves the lipid profile slightly, lowers cancer risk, and does not cause hypoglycemia when used as monotherapy, although it is contraindicated in renal insufficiency, congestive heart failure, any form of acidosis, liver disease, or severe hypoxia, and should be temporarily discontinued in pts who are seriously ill or receiving radiographic contrast material. Metformin therapy can be followed by addition of a second oral agent (insulin secretagogue, DPP-IV inhibitor, thiazolidinedione, α-glucosidase inhibitor, or SLGT2 inhibitor). Combinations of two oral agents may be used with additive effects, with stepwise addition of bedtime insulin or a third oral agent if adequate control is not achieved. As endogenous insulin production falls, multiple injections of long-acting and short-acting insulin may be required, as in type

**TABLE 173-2 PROPERTIES OF INSULIN PREPARATIONS[a]**

| Preparation | Time of Action | | |
|---|---|---|---|
| | Onset, h | Peak, h | Effective Duration, h |
| Short-acting | | | |
| Aspart | <0.25 | 0.5–1.5 | 2–4 |
| Glulisine | <0.25 | 0.5–1.5 | 2–4 |
| Lispro | <0.25 | 0.5–1.5 | 2–4 |
| Regular | 0.5–1.0 | 2–3 | 3–6 |
| Long-acting | | | |
| Detemir | 1–4 | —[b] | 12-24[c] |
| Glargine | 2–4 | —[b] | 20–24 |
| NPH | 2–4 | 4–10 | 10–16 |
| Insulin combinations[d] | | | |
| 75/25–75% protamine lispro, 25% lispro | <0.25 | Dual[e] | 10–16 |
| 70/30–70% protamine aspart, 30% aspart | <0.25 | Dual[e] | 15–18 |
| 50/50–50% protamine lispro, 50% lispro | <0.25 | Dual[e] | 10–16 |
| 70/30–70% NPH, 30% regular | 0.5–1 | Dual[e] | 10–16 |

[a]Insulin preparations available in the United States; others are available in the United Kingdom and Europe.
[b]Glargine and detemir have minimal peak activity.
[c]Duration is dose-dependent (shorter at lower doses).
[d]Other insulin combinations are available
[e]Dual: two peaks—one at 2–3 h and the second one several hours later.
***Source:*** Adapted from FR Kaufman: *Medical Management of Type 1 Diabetes, 6th edition*. Alexandria, VA: American Diabetes Association, 2012.

1 DM. Individuals who require >1 U/kg per day of long-acting insulin should be considered for combination therapy with an insulin-sensitizing agent such as metformin or a thiazolidinedione. Insulin-requiring type 2 DM pts may also benefit from addition of pramlintide.

Bariatric surgery should be considered in selected pts (Chap. 172).

The morbidity and mortality of DM-related complications can be greatly reduced by timely and consistent surveillance procedures (Table 173-4). A routine urinalysis may be performed as an initial screen for diabetic nephropathy. If it is positive for protein, quantification of protein on a 24-h urine collection should be performed. If the urinalysis is negative for protein, a spot collection for microalbuminuria should be performed (present if 30–300 μg/mg creatinine on two of three tests within a 3- to 6-month period). A resting ECG should be performed in adults, with more extensive cardiac testing for high-risk pts. Therapeutic goals to prevent complications of DM include management of proteinuria with ACE inhibitor or angiotensin receptor blocker therapy, bp control (<130/80 mmHg if no proteinuria, <125/75 if proteinuria), and dyslipidemia management (LDL <2.6 mmol/L [<100 mg/dL], HDL >1.1 mmol/L [>40 mg/dL] in men and >1.38 mmol/L [50 mg/dL] in women, triglycerides <1.7 mmol/L [<150 mg/dL]). In addition, any diabetic pt >40 years should take a statin, regardless of the LDL cholesterol, and in those with existing cardiovascular disease, the LDL target should be <1.8 mmol/L (70 mg/dL).

**TABLE 173-3 AGENTS USED FOR TREATMENT OF TYPE 1 OR TYPE 2 DIABETES**

| | Mechanism of Action | Examples[a] | $HbA_{1c}$ Reduction (%)[b] | Agent-Specific Advantages | Agent-Specific Disadvantages | Contraindications |
|---|---|---|---|---|---|---|
| **Oral** | | | | | | |
| Biguanides[c*] | ↓ Hepatic glucose production | Metformin | 1–2 | Weight neutral, do not cause hypoglycemia, inexpensive, extensive experience, ↓ CV events | Diarrhea, nausea, lactic acidosis | Serum creatinine >1.5 mg/dL (men) >1.4 mg/dL (women) (see text), CHF, radiographic contrast studies, hospitalized patients, acidosis |
| α-Glucosidase inhibitors[c**] | ↓ GI glucose absorption | Acarbose, miglitol, voglibose | 0.5–0.8 | Reduce postprandial glycemia | GI flatulence, liver function tests | Renal/liver disease |
| Dipeptidyl peptidase IV inhibitors[c***] | Prolong endogenous GLP-1 action | Alogliptin, Anagliptin, Gemigliptin, linagliptin, saxagliptin, sitagliptin, teneligliptin, vildagliptin | 0.5–0.8 | Well tolerated, do not cause hypoglycemia | | Reduced dose with renal disease; one associated with increase heart failure risk; possible association with ACE inhibitor–induced angioedema |
| Insulin secretagogues: Sulfonylureas[c*] | ↑ Insulin secretion | Glibornuride, gliclazide, glimepiride, glipizide, gliquidone, glyburide, glyclopyramide | 1–2 | Short onset of action, lower postprandial glucose, inexpensive | Hypoglycemia, weight gain | Renal/liver disease |

| | | | | | | |
|---|---|---|---|---|---|---|
| Insulin secretagogues: Nonsulfonylureas[c***] | ↑ Insulin secretion | Nateglinide, repaglinide, mitiglinide | 0.5–1.0 | Short onset of action, lower postprandial glucose | Hypoglycemia | Renal/liver disease |
| Sodium-glucose co-transporter 2 inhibitors[***] | ↑ Urinary glucose excretion | Canagliflozin, dapagliflozin, empagliflozin | 0.5–1.0 | Insulin secretion and action independent | Urinary and vaginal infections, dehydration, exacerbate tendency to hyperkalemia | Limited clinical experience; moderate renal insufficiency |
| Thiazolidinediones[c***] | ↓ Insulin resistance, ↑ glucose utilization | Rosiglitazone, pioglitazone | 0.5–1.4 | Lower insulin requirements | Peripheral edema, CHF, weight gain, fractures, macular edema | CHF, liver disease |
| **Parenteral** | | | | | | |
| Amylin agonists[cd***] | Slow gastric emptying, ↓ glucagon | Pramlintide | 0.25–0.5 | Reduce postprandial glycemia, weight loss | Injection, nausea, ↑ risk of hypoglycemia with insulin | Agents that also slow GI motility |
| GLP-1 receptor agonists[c***] | ↑ Insulin, ↓ glucagon, slow gastric emptying, satiety | Exenatide, liraglutide, dulaglutide | 0.5–1.0 | Weight loss, do not cause hypoglycemia | Injection, nausea, ↑ risk of hypoglycemia with insulin secretagogues | Renal disease, agents that also slow GI motility; medullary carcinoma of thyroid |
| Insulin[cd****] | ↑ Glucose utilization, ↓ hepatic glucose production, and other anabolic actions | See text and Table 418-4 in HPIM-19 | Not limited | Known safety profile | Injection, weight gain, hypoglycemia | |

(*Continued*)

**TABLE 173-3 AGENTS USED FOR TREATMENT OF TYPE 1 OR TYPE 2 DIABETES (*CONTINUED*)**

| | Mechanism of Action | Examples[a] | $HbA_{1c}$ Reduction (%)[b] | Agent-Specific Advantages | Agent-Specific Disadvantages | Contraindications |
|---|---|---|---|---|---|---|
| Medical nutrition therapy and physical activity[c,*] | ↓ Insulin resistance, ↑ insulin secretion | Low-calorie, low-fat diet, exercise | 1–3 | Other health benefits | Compliance difficult, long-term success low | |

[a]Examples are approved for use in at least one country, but may not be available in the United States or all countries. Examples may not include all agents in the class.
[b]HbA*1c* reduction (absolute) depends partly on starting $HbA_{1c}$.
[c]Used for treatment of type 2 diabetes.
[d]Used in conjunction with insulin for treatment of type 1 diabetes. Cost of agent: *low, **moderate, ***high, ****variable.
***Note:*** Some agents used to treat type 2 DM are not included in table (see text).
***Abbreviations:*** CV, cardiovascular; $HbA_{1c}$, hemoglobin $A_{1c}$.

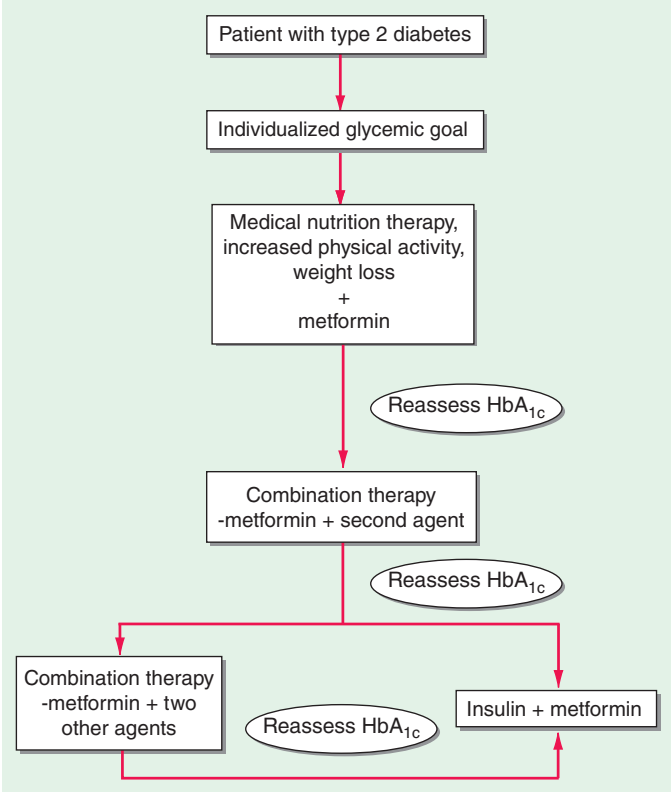



**FIGURE 173-1** Glycemic management of type 2 diabetes. Agents that can be combined with metformin include insulin secretagogues, thiazolidinediones, α-glucosidase inhibitors, DPP-IV inhibitors, GLP-1 receptor agonists, SLGT2 inhibitors, and insulin. $HbA_{1c}$, hemoglobin $HbA_{1c}$.

## MANAGEMENT OF THE HOSPITALIZED PATIENT

The goals of diabetes management during hospitalization are near-normal glycemic control, avoidance of hypoglycemia, and transition back to the outpatient diabetes treatment regimen. Pts with type 1 DM undergoing general anesthesia and surgery, or with serious illness, should receive continuous insulin, either through an IV insulin infusion or by SC administration of a reduced dose of long-acting insulin. Short-acting insulin alone is insufficient to prevent the onset of diabetic ketoacidosis. Oral hypoglycemic agents should be discontinued in pts with type 2 DM at the time of hospitalization. Either regular insulin infusion (0.05–0.15 U/kg per hour) or a reduced dose (by 30–50%) of long-acting insulin and short-acting insulin (held, or reduced by 30–50%), with infusion of a solution of 5% dextrose, should be administered when pts are NPO for a procedure. A regimen of long- and short-acting SC insulin should be used in type 2 pts who are eating. The glycemic goal for hospitalized pts with DM should be a preprandial glucose of <7.8 mmol/L (<140 mg/dL) and <10 mmol/L (<180 mg/dL) at post-meal times. For critically ill pts,

**TABLE 173-4 GUIDELINES FOR ONGOING, COMPREHENSIVE MEDICAL CARE FOR PATIENTS WITH DIABETES**

- Optimal and individualized glycemic control
- Self-monitoring of blood glucose (individualized frequency)
- $HbA_{1c}$ testing (2–4 times/year)
- Patient education in diabetes management (annual); diabetes-self management education and support
- Medical nutrition therapy and education (annual)
- Eye examination (annual or biannual)
- Foot examination (1–2 times/year by physician; daily by patient)
- Screening for diabetic nephropathy (annual)
- Blood pressure measurement (quarterly)
- Lipid profile and serum creatinine (estimate GFR) (annual)
- Influenza/pneumococcal/hepatitis B immunizations
- Consider antiplatelet therapy

***Abbreviations:*** $HbA_{1c}$, hemoglobin $A_{1c}$.

glucose levels of 7.8–10.0 mmol/L (140–180 mg/dL) are recommended. Those with DM undergoing radiographic procedures with contrast dye should be well hydrated before and after dye exposure, and the serum creatinine should be monitored after the procedure.

For a more detailed discussion, see Powers AC: Diabetes Mellitus: Diagnosis, Classification, and Pathophysiology Chap. 417, p. 2399; Powers AC: Diabetes Mellitus: Management and Therapies, Chap. 418, p. 2407; and Powers AC: Diabetes Mellitus: Complications Chap. 419, p. 2422, in HPIM-19.

# 174 Disorders of the Male Reproductive System

The testes produce sperm and testosterone. Inadequate production of sperm can occur in isolation or in the presence of androgen deficiency, which impairs spermatogenesis secondarily.

## ANDROGEN DEFICIENCY

### Etiology

Androgen deficiency can be due to either testicular failure (*primary hypogonadism*) or hypothalamic-pituitary defects (*secondary hypogonadism*).

Primary hypogonadism is diagnosed when testosterone levels are low and gonadotropin levels (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]) are high. Klinefelter's syndrome is the most common cause (~1 in 1000 male births) and is due to the presence of one or more extra X chromosomes, usually a 47,XXY karyotype. Other genetic causes of testicular development, androgen biosynthesis, or androgen action are uncommon. Acquired primary testicular failure usually results from viral orchitis but may be due to trauma, testicular torsion, cryptorchidism, radiation damage, or systemic diseases such as amyloidosis, Hodgkin's disease, sickle cell disease, or granulomatous diseases. Testicular failure can occur as a part of polyglandular autoimmune failure syndrome. Malnutrition, AIDS, renal failure, liver cirrhosis, myotonic dystrophy, paraplegia, and toxins such as alcohol, marijuana, heroin, methadone, lead, and antineoplastic and chemotherapeutic agents also can cause testicular failure. Testosterone synthesis may be blocked by ketoconazole, and testosterone action may be blocked at the androgen receptor level by spironolactone or cimetidine.

Secondary hypogonadism is diagnosed when levels of both testosterone and gonadotropins are low (*hypogonadotropic hypogonadism*). Kallmann syndrome is due to maldevelopment of neurons producing gonadotropin-releasing hormone (GnRH) and is characterized by GnRH deficiency, low levels of LH and FSH, and anosmia. Several other types of GnRH deficiency or gonadotropin deficiency present without anosmia. Acquired causes of isolated hypogonadotropic hypogonadism include critical illness, excessive stress, obesity, Cushing's syndrome, opioid and marijuana use, hemochromatosis, and hyperprolactinemia (due to pituitary adenomas or drugs such as phenothiazines). Destruction of the pituitary gland by tumors, infection, trauma, or metastatic disease causes hypogonadism in conjunction with deficiency of other pituitary hormones (see Chap. 168). Normal aging is associated with a progressive decline of testosterone production, which is due to downregulation of the entire hypothalamo-pituitary-testicular axis.

## Clinical Features

The history should focus on developmental stages such as puberty and growth spurts, as well as androgen-dependent events such as early morning erections, frequency and intensity of sexual thoughts, and frequency of masturbation or intercourse. The physical examination should focus on secondary sex characteristics such as hair growth on the face, axilla, chest, and pubic regions; gynecomastia; testicular volume; prostate; and height and body proportions. Eunuchoidal proportions are defined as an arm span >2 cm greater than height and suggest that androgen deficiency occurred prior to epiphyseal fusion. Normal testicular size ranges from 3.5 to 5.5 cm in length, which corresponds to a volume of 12–25 mL. The presence of varicocele should be sought by palpation of the testicular veins with the pt standing. Pts with Klinefelter's syndrome have small (1–2 mL), firm testes.

A morning total testosterone level <10.4 nmol/L (<300 ng/dL), in association with symptoms, suggests testosterone deficiency. A level of >12.1 nmol/L (>350 ng/dL) makes the diagnosis of androgen deficiency unlikely. In men with testosterone levels between 6.9 and 12.1 nmol/L (200 and 350 ng/dL), the total testosterone level should be repeated and a free testosterone level should be measured by a reliable method. In older men and in pts with other clinical states that are associated with alterations in sex hormone–binding globulin levels, a direct measurement of free testosterone by equilibrium dialysis can be useful to confirm testosterone deficiency. When androgen deficiency has been found, LH should be measured to classify the pt as having primary (high LH) or secondary (low or inappropriately normal LH) hypogonadism. In men with primary hypogonadism of unknown cause, a karyotype should be performed to exclude Klinefelter's syndrome. Measurement of a prolactin level and MRI of the hypothalamic-pituitary region should be considered in men with secondary hypogonadism. Gynecomastia in the absence of androgen deficiency should be further evaluated (Fig. 174-1).

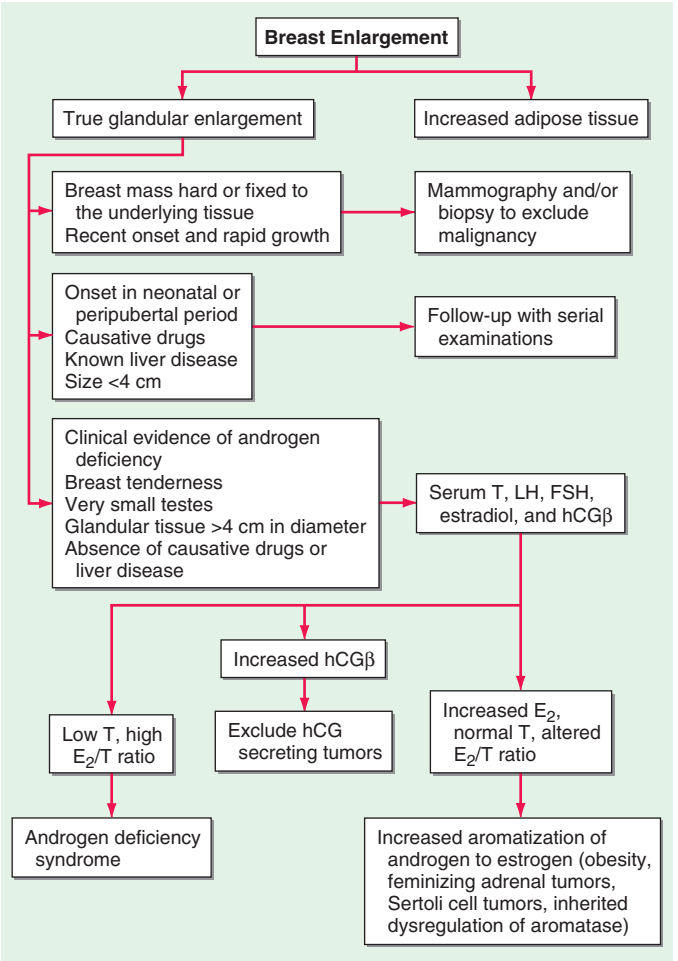



**FIGURE 174-1** Evaluation of gynecomastia. E2, 17β-estradiol; FSH, follicle-stimulating hormone; hCGβ, human chorionic gonadotropin β; LH, luteinizing hormone; T, testosterone.

## TREATMENT ANDROGEN DEFICIENCY

Treatment of hypogonadal men with androgens restores normal male secondary sexual characteristics (beard, body hair, external genitalia), male sexual drive, and masculine somatic development (hemoglobin, muscle mass), but not fertility. Administration of gradually increasing doses of testosterone is recommended for disorders in which hypogonadism occurred prior to puberty. Testosterone levels in the normal range may be achieved through daily application of transdermal testosterone patches (5–10 mg/d) or gel (50–100 mg/d), parenteral administration of a long-acting testosterone ester (e.g., 100–200 mg testosterone enanthate at 1- to 3-week intervals) or buccal testosterone tablets (30 mg/d). Hct should

be monitored initially during testosterone therapy and the dose lowered if Hct is >54%. Prostate cancer, severe symptoms of lower urinary tract obstruction, baseline Hct >50%, severe sleep apnea, and class IV congestive heart failure are contraindications for androgen replacement. Gonadotropin therapy for secondary hypogonadism should be reserved for fertility induction.

## MALE INFERTILITY

### Etiology

Male infertility plays a role in 25% of infertile couples (couples who fail to conceive after 1 year of unprotected intercourse). Known causes of male infertility include primary hypogonadism (30–40%), disorders of sperm transport (10–20%), and secondary hypogonadism (2%), with an unknown etiology in up to half of men with suspected male factor infertility. Impaired spermatogenesis occurs with testosterone deficiency but may also be present without testosterone deficiency. Y chromosome microdeletions and substitutions, viral orchitis, tuberculosis, STDs, radiation, chemotherapeutic agents, and environmental toxins have all been associated with isolated impaired spermatogenesis. Prolonged elevations of testicular temperature, as in varicocele, in cryptorchidism, or after an acute febrile illness, may impair spermatogenesis. Ejaculatory obstruction can be a congenital (cystic fibrosis, in utero diethylstilbestrol exposure, or idiopathic) or acquired (vasectomy, accidental ligation of the vas deferens, or obstruction of the epididymis). Androgen abuse by male athletes can lead to testicular atrophy and a low sperm count.

### Clinical Features

Evidence of hypogonadism may or may not be present. Testicular size and consistency may be abnormal, and a varicocele may be apparent on palpation. When the seminiferous tubules are damaged prior to puberty, the testes are small (usually <12 mL) and firm, whereas postpubertal damage causes the testes to be soft (the capsule, once enlarged, does not contract to its previous size). The key diagnostic test is a *semen analysis*. Sperm counts of <13 million/mL, motility of <32%, and <9% normal morphology are associated with subfertility. Testosterone levels should be measured if the sperm count is low on repeated exam or if there is clinical evidence of hypogonadism.

**TREATMENT** MALE INFERTILITY

Men with primary hypogonadism occasionally respond to androgen therapy if there is minimal damage to the seminiferous tubules, whereas those with secondary hypogonadism require gonadotropin therapy to achieve fertility. Fertility occurs in about half of men with varicocele who undergo surgical repair. In vitro fertilization is an option for men with mild to moderate defects in sperm quality; intracytoplasmic sperm injection (ICSI) has been a major advance for men with severe defects in sperm quality.

## ERECTILE DYSFUNCTION

### Etiology

Erectile dysfunction (ED) is the failure to achieve erection, ejaculation, or both. It affects 10–25% of middle-aged and elderly men. ED may result from three basic mechanisms: (1) failure to initiate (psychogenic, endocrinologic, or neurogenic); (2) failure to fill (arteriogenic); or (3) failure to store adequate blood volume within the lacunar network (venoocclusive dysfunction). Diabetic, atherosclerotic, and drug-related causes account for >80% of cases of ED in older men. The most

common organic cause of ED is vasculogenic; 35–75% of men with diabetes have ED due to a combination of vascular and neurologic complications. Psychogenic causes of ED include performance anxiety, depression, relationship conflict, sexual inhibition, history of sexual abuse in childhood, and fear of pregnancy or sexually transmitted disease. Among the antihypertensive agents, the thiazide diuretics and beta blockers have been implicated most frequently. Estrogens, GnRH agonists and antagonists, $H_2$ antagonists, and spironolactone suppress gonadotropin production or block androgen action. Antidepressant and antipsychotic agents—particularly neuroleptics, tricyclics, and selective serotonin reuptake inhibitors—are associated with erectile, ejaculatory, orgasmic, and sexual desire difficulties. Recreational drugs, including ethanol, cocaine, and marijuana, also may cause ED. Any disorder that affects the sacral spinal cord or the sensory nerves or autonomic fibers innervating the penis may lead to ED.

## Clinical Features

Men with sexual dysfunction may complain of loss of libido, inability to initiate or maintain an erection, ejaculatory failure, premature ejaculation, or inability to achieve orgasm, but frequently are embarrassed to bring up the subject unless specifically asked by the physician. Initial questions should focus on the onset of symptoms, the presence and duration of partial erections, the progression of ED, and ejaculation. Psychosocial history, libido, relationship issues, sexual orientation and sexual practices should be part of the clinical assessment. A history of nocturnal or early morning erections is useful for distinguishing physiologic from psychogenic ED. Relevant risk factors should be identified, such as diabetes mellitus, coronary artery disease, lipid disorders, hypertension, peripheral vascular disease, smoking, alcoholism, and endocrine or neurologic disorders. The pt's surgical history should be explored, with an emphasis on bowel, bladder, prostate, or vascular procedures. Evaluation includes a detailed general as well as genital physical examination. Penile abnormalities (Peyronie's disease), testicular size, and gynecomastia should be noted. Peripheral pulses should be palpated, and bruits should be sought. Neurologic examination should assess anal sphincter tone, perineal sensation, and bulbocavernosus reflex. Serum testosterone and prolactin should be measured. Penile arteriography, electromyography, or penile Doppler ultrasound is occasionally performed.

## TREATMENT ERECTILE DYSFUNCTION

Correction of the underlying disorders or discontinuation of responsible medications should be attempted as an initial step. Oral inhibitors of phosphodiesterase-5 (sildenafil, tadalafil, and vardenafil) enhance erections after sexual stimulation, with an onset of approximately 60–120 min. They are contraindicated in men receiving any form of nitrate therapy and should be avoided in those with congestive heart failure. Vacuum constriction devices or injection of alprostadil into the urethra or corpora cavernosa may also be effective. The insertion of a penile prosthesis is reserved for pts with refractory ED.

For a more detailed discussion, see Bhasin S, Jameson JL: Disorders of the Testes and Male Reproductive System, Chap. 411, p. 2357; Hall JE: The Female Reproductive System, Infertility, and Contraception, Chap. 412, p. 2375; and McVary KT: Sexual Dysfunction, Chap. 67, p. 324, in HPIM-19.

# 175 Disorders of the Female Reproductive System

The pituitary hormones, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), stimulate ovarian follicular development and result in ovulation at about day 14 of the 28-day menstrual cycle.

## AMENORRHEA

### Etiology

*Amenorrhea* refers to the absence of menstrual periods. It is classified as *primary*, if menstrual bleeding has never occurred by age 15 in the absence of hormonal treatment, or *secondary*, if menstrual periods are absent for >3 months in a woman with previous periodic menses. Pregnancy should be excluded in women of childbearing age with amenorrhea, even when history and physical examination are not suggestive. *Oligomenorrhea* is defined as a cycle length of >35 days or <10 menses per year. Both the frequency and amount of bleeding are irregular in oligomenorrhea. Frequent or heavy irregular bleeding is termed *dysfunctional uterine bleeding* if anatomic uterine lesions or a bleeding diathesis has been excluded.

The causes of primary and secondary amenorrhea overlap, and it is generally more useful to classify disorders of menstrual function into disorders of the uterus and outflow tract and disorders of ovulation (Fig. 175-1).

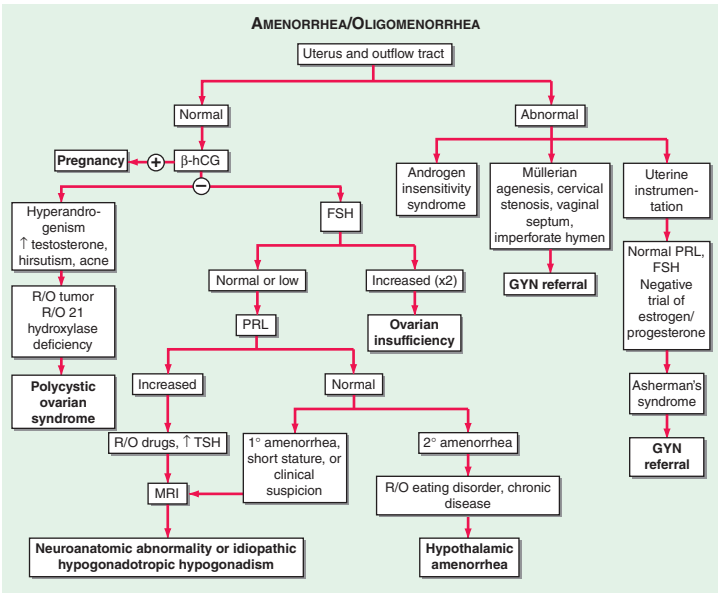



**FIGURE 175-1** Algorithm for evaluation of amenorrhea. β-hCG, beta-human chorionic gonadotropin; FSH, follicle-stimulating hormone; GYN, gynecologist; PRL, prolactin; R/O, rule out; TSH, thyroid-stimulating hormone.

Anatomic defects of the outflow tract that prevent vaginal bleeding include absence of vagina or uterus, imperforate hymen, transverse vaginal septae, and cervical stenosis.

Women with amenorrhea and low FSH and LH levels have hypogonadotropic hypogonadism due to disease of either the hypothalamus or the pituitary. Hypothalamic causes include congenital idiopathic hypogonadotropic hypogonadism, hypothalamic lesions (craniopharyngiomas and other tumors, tuberculosis, sarcoidosis, metastatic tumors), hypothalamic trauma or irradiation, vigorous exercise, eating disorders, stress, and chronic debilitating diseases (end-stage renal disease, malignancy, malabsorption). The most common form of hypothalamic amenorrhea is functional, reversible gonadotropin-releasing hormone (GnRH) deficiency due to psychological or physical stress, including excess exercise and anorexia nervosa. Disorders of the pituitary include rare developmental defects, pituitary adenomas, granulomas, postradiation hypopituitarism, and Sheehan's syndrome. They can lead to amenorrhea by two mechanisms: direct interference with gonadotropin production, or inhibition of GnRH secretion via excess prolactin production (Chap. 168).

Women with amenorrhea and high FSH levels have ovarian failure, which may be due to Turner's syndrome, pure gonadal dysgenesis, premature ovarian failure, the resistant-ovary syndrome, and chemotherapy or radiation therapy for malignancy. The diagnosis of premature ovarian failure is applied to women who cease menstruating before age 40.

*Polycystic ovarian syndrome* (PCOS) is characterized by the presence of clinical or biochemical hyperandrogenism (hirsutism, acne, male pattern baldness) in association with amenorrhea or oligomenorrhea. The metabolic syndrome and infertility are often present; these features are worsened with coexistent obesity. Additional disorders with a similar presentation include excess androgen production from adrenal or ovarian tumors and adult-onset congenital adrenal hyperplasia. Hyperthyroidism may be associated with oligo- or amenorrhea; hypothyroidism more typically with metrorrhagia.

## Diagnosis

The initial evaluation involves careful physical examination including assessment of hyperandrogenism, serum or urine human chorionic gonadotropin (hCG), and serum FSH levels (Fig. 175-1). Anatomic defects are usually diagnosed by physical examination, though hysterosalpingography or direct visual examination by hysteroscopy may be required. A karyotype should be performed when gonadal dysgenesis is suspected. The diagnosis of PCOS is based on the coexistence of chronic anovulation and androgen excess, after ruling out other etiologies for these features. The evaluation of pituitary function and hyperprolactinemia is described in Chap. 168. In the absence of a known etiology for hypogonadotropic hypogonadism, MRI of the pituitary-hypothalamic region should be performed when gonadotropins are low or inappropriately normal.

## TREATMENT AMENORRHEA

Disorders of the outflow tract are managed surgically. Decreased estrogen production, whether from ovarian failure or hypothalamic/pituitary disease, should be treated with cyclic estrogens, either in the form of oral contraceptives or conjugated estrogens (0.625–1.25 mg/d PO) and medroxyprogesterone acetate (2.5 mg/d PO or 5–10 mg during the last 5 days of the month). PCOS may be treated with medications to induce periodic withdrawal menses (medroxyprogesterone acetate 5–10 mg or progesterone 200 mg daily for 10–14 days of each month, or oral contraceptive agents) and weight reduction, along with treatment of hirsutism and, if desired, ovulation induction (see below). Individuals with PCOS may benefit from insulin-sensitizing drugs, such as metformin, and should be screened for diabetes mellitus.

## PELVIC PAIN

### Etiology

Pelvic pain may be associated with normal or abnormal menstrual cycles and may originate in the pelvis or be referred from another region of the body. A high index of suspicion must be entertained for extrapelvic disorders that refer to the pelvis, such as appendicitis, diverticulitis, cholecystitis, intestinal obstruction, and urinary tract infections. A thorough history including the type, location, radiation, and status with respect to increasing or decreasing severity can help to identify the cause of acute pelvic pain. Associations with vaginal bleeding, sexual activity, defecation, urination, movement, or eating should be sought. Determination of whether the pain is acute versus chronic, constant versus spasmodic, and cyclic versus noncyclic will direct further investigation (Table 175-1).

### Acute Pelvic Pain

Pelvic inflammatory disease most commonly presents with bilateral lower abdominal pain. Unilateral pain suggests adnexal pathology from rupture, bleeding, or torsion of ovarian cysts, or, less commonly, neoplasms of the ovary, fallopian tubes, or paraovarian areas. Ectopic pregnancy is associated with right- or left-sided lower abdominal pain, vaginal bleeding, and menstrual cycle abnormalities, with clinical signs appearing 6–8 weeks after the last normal menstrual period. Orthostatic signs and fever may be present. Uterine pathology includes endometritis and degenerating leiomyomas.

### Chronic Pelvic Pain

Many women experience lower abdominal discomfort with ovulation (*mittelschmerz*), characterized as a dull, aching pain at midcycle that lasts minutes to hours. In addition, ovulatory women may experience somatic symptoms during the few days prior to menses, including edema, breast engorgement, and abdominal bloating or discomfort. A symptom complex of cyclic irritability, depression, and lethargy is known as *premenstrual syndrome* (PMS). Severe or incapacitating cramping with ovulatory menses in the absence of demonstrable disorders of the pelvis is termed *primary dysmenorrhea*. *Secondary dysmenorrhea* is caused by underlying pelvic pathology such as endometriosis, adenomyosis, or cervical stenosis.

### Diagnosis

Evaluation includes a history, pelvic examination, hCG measurement, tests for chlamydial and gonococcal infections, and pelvic ultrasound. Laparoscopy or laparotomy is indicated in some cases of pelvic pain of undetermined cause.

**TABLE 175-1 CAUSES OF PELVIC PAIN**

| | Acute | Chronic |
|---|---|---|
| Cyclic pelvic pain | | Premenstrual symptoms<br>Mittelschmerz<br>Dysmenorrhea<br>Endometriosis |
| Noncyclic pelvic pain | Pelvic inflammatory disease<br>Ruptured or hemorrhagic ovarian cyst or ovarian torsion<br>Ectopic pregnancy<br>Endometritis<br>Acute growth or degeneration of uterine myoma | Pelvic congestion syndrome<br>Adhesions and retroversion of the uterus<br>Pelvic malignancy<br>Vulvodynia<br>Chronic pelvic inflammatory disease<br>History of sexual abuse |

## TREATMENT PELVIC PAIN

Primary dysmenorrhea is best treated with NSAIDs or oral contraceptive agents. Secondary dysmenorrhea not responding to NSAIDs suggests pelvic pathology, such as endometriosis. Infections should be treated with the appropriate antibiotics. Symptoms from PMS may improve with selective serotonin reuptake inhibitor (SSRI) therapy. The majority of unruptured ectopic pregnancies are treated with methotrexate, which has 85–95% success rate. Surgery may be required for structural abnormalities.

# HIRSUTISM

## Etiology

*Hirsutism*, defined as excessive male-pattern hair growth, affects ~10% of women. It may be familial or caused by PCOS, ovarian or adrenal neoplasms, congenital adrenal hyperplasia, Cushing's syndrome, pregnancy, and drugs (androgens, oral contraceptives containing androgenic progestins). Other drugs, such as minoxidil, phenytoin, diazoxide, and cyclosporine, can cause excessive growth of non-androgen-dependent vellus hair, leading to hypertrichosis.

## Clinical Features

An objective clinical assessment of hair distribution and quantity is central to the evaluation. A commonly used method to grade hair growth is the Ferriman-Gallwey score (see Fig. 68-1, p. 333, in HPIM-19). Associated manifestations of androgen excess include acne and male-pattern balding (androgenic alopecia). *Virilization*, on the other hand, refers to the state in which androgen levels are sufficiently high to cause deepening of the voice, breast atrophy, increased muscle bulk, clitoromegaly, and increased libido. Historic elements include menstrual history and the age of onset, rate of progression, and distribution of hair growth. Sudden development of hirsutism, rapid progression, and virilization suggests an ovarian or adrenal neoplasm.

## Diagnosis

An approach to testing for androgen excess is depicted in Fig. 175-2. PCOS is a relatively common cause of hirsutism. The dexamethasone androgen-suppression test (0.5 mg PO every 6 h × 4 days, with free testosterone levels obtained before and after administration of dexamethasone) may distinguish ovarian from adrenal overproduction. Incomplete suppression suggests ovarian androgen excess. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency can be excluded by a 17-hydroxyprogesterone level that is <6 nmol/L (<2 μg/L) either in the morning during the follicular phase or 1 h after administration of 250 μg of cosyntropin. CT may localize an adrenal mass, and ultrasound may identify an ovarian mass, if evaluation suggests these possibilities.

## TREATMENT HIRSUTISM

Treatment of a remediable underlying cause (e.g., Cushing's syndrome, adrenal or ovarian tumor) also improves hirsutism. In idiopathic hirsutism or PCOS, symptomatic physical or pharmacologic treatment is indicated. Nonpharmacologic treatments include (1) bleaching; (2) depilatory such as shaving and chemical treatments; and (3) epilatory such as plucking, waxing, electrolysis, and laser therapy. Pharmacologic therapy includes oral contraceptives with a low androgenic progestin and spironolactone (100–200 mg/d PO), often in combination. Flutamide is also effective as an antiandrogen, but its use is

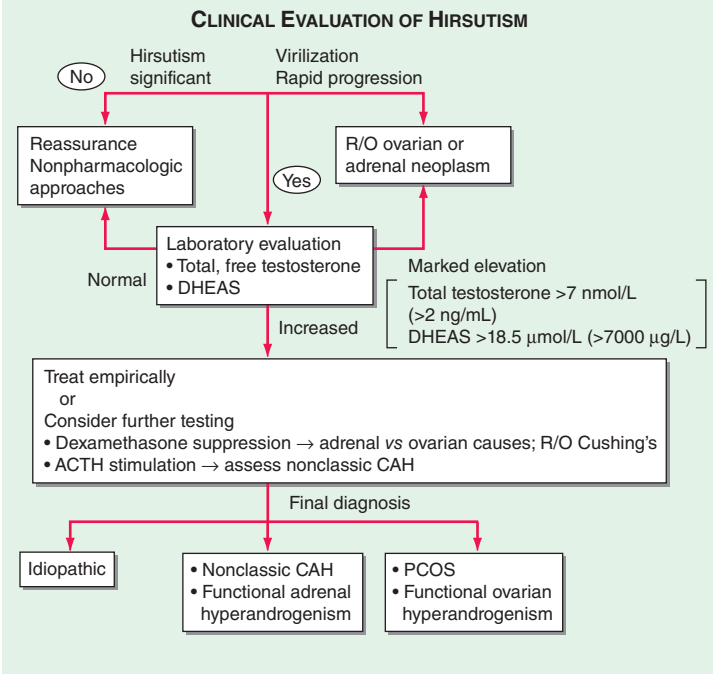



**FIGURE 175-2** Algorithm for the evaluation and differential diagnosis of hirsutism. ACTH, adrenocorticotropic hormone; CAH, congenital adrenal hyperplasia; DHEAS, sulfated form of dehydroepiandrosterone; PCOS, polycystic ovarian syndrome; R/O, rule out.

limited by hepatotoxicity. Glucocorticoids (dexamethasone, 0.25–0.5 mg at bedtime, or prednisone, 5–10 mg at bedtime) are the mainstay of treatment in pts with congenital adrenal hyperplasia. Attenuation of hair growth with pharmacologic therapy is typically not evident until 6 months after initiation of medical treatment and therefore should be used in conjunction with nonpharmacologic treatments.

## MENOPAUSE

### Etiology

*Menopause* is defined as the final episode of menstrual bleeding and occurs at a median age of 51 years. It is the consequence of depletion of ovarian follicles or of oophorectomy. The onset of *perimenopause*, when fertility wanes and menstrual irregularity increases, precedes the final menses by 2–8 years.

### Clinical Features

The most common menopausal symptoms are vasomotor instability (hot flashes and night sweats), mood changes (nervousness, anxiety, irritability, and depression), insomnia, and atrophy of the urogenital epithelium and skin. FSH levels are elevated to ≥40 IU/L with estradiol levels that are <30 pg/mL.

## TREATMENT MENOPAUSE

During perimenopause, low-dose combined oral contraceptives may be of benefit. The rational use of postmenopausal hormone therapy requires balancing the potential benefits and risks. Concerns include increased risks of endometrial cancer, breast cancer, thromboembolic disease, and gallbladder disease, as well as probably increased risks of stroke, cardiovascular events, and ovarian cancer. Benefits include a delay in postmenopausal bone loss and probably decreased risks of colorectal cancer and diabetes mellitus. Short-term therapy (<5 years) may be beneficial in controlling intolerable symptoms of menopause, as long as no contraindications exist. These include unexplained vaginal bleeding, active liver disease, venous thromboembolism, history of endometrial cancer (except stage I without deep invasion), breast cancer, preexisting cardiovascular disease, and diabetes. Hypertriglyceridemia (>400 mg/dL) and active gallbladder disease are relative contraindications. Alternative therapies for symptoms include venlafaxine, fluoxetine, paroxetine, gabapentin, clonidine, vitamin E, or soy-based products. Vaginal estradiol tablets may be used for genitourinary symptoms. Long-term therapy (≥5 years) should be undertaken only after careful consideration, particularly in light of alternative therapies for osteoporosis (bisphosphonates, raloxifene) and of the risks of venous thromboembolism and breast cancer. Estrogens should be given in the minimal effective doses (conjugated estrogen, 0.625 mg/d PO; micronized estradiol, 1.0 mg/d PO; or transdermal estradiol, 0.05–1.0 mg once or twice a week). Women with an intact uterus should be given estrogen in combination with a progestin (medroxyprogesterone either cyclically, 5–10 mg/d PO for days 15–25 each month, or continuously, 2.5 mg/d PO) to avoid the increased risk of endometrial carcinoma seen with unopposed estrogen use.

## CONTRACEPTION

The most widely used methods for fertility control include (1) barrier methods, (2) oral contraceptives, (3) intrauterine devices, (4) long-acting progestins, (5) sterilization, and (6) abortion.

Oral contraceptive agents are widely used for both prevention of pregnancy and control of dysmenorrhea and anovulatory bleeding. Combination oral contraceptive agents contain synthetic estrogen (ethinyl estradiol or mestranol) and synthetic progestins. Some progestins possess an inherent androgenic action. Low-dose norgestimate and third-generation progestins (desogestrel, gestodene, drospirenone) have a less androgenic profile; levonorgestrel appears to be the most androgenic of the progestins and should be avoided in pts with hyperandrogenic symptoms. The three major formulation types include fixed-dose estrogen-progestin, phasic estrogen-progestin, and progestin only.

Despite overall safety, oral contraceptive users are at risk for venous thromboembolism, hypertension, and cholelithiasis. Risks for myocardial infarction and stroke are increased with smoking and aging. Side effects, including breakthrough bleeding, amenorrhea, breast tenderness, and weight gain, are often responsive to a change in formulation.

Absolute contraindications to the use of oral contraceptives include previous thromboembolic disorders, cerebrovascular or coronary artery disease, carcinoma of the breasts or other estrogen-dependent neoplasia, liver disease, hypertriglyceridemia, heavy smoking with age over 35, undiagnosed uterine bleeding, or known or suspected pregnancy. Relative contraindications include hypertension and anticonvulsant drug therapy.

New methods include a weekly contraceptive patch, a monthly contraceptive injection, and a monthly vaginal ring. Long-term progestins may be administered in the form of Depo-Provera or a subdermal progestin implant.

Emergency contraceptive pills, containing progestin only, can be used within 72 h of unprotected intercourse for prevention of pregnancy. Plan B is an emergency contraceptive kit specifically designed for postcoital contraception. Mifepristone (RU486) also may be used but is not available in most countries.

## INFERTILITY

### Etiology

*Infertility* is defined as the inability to conceive after 12 months of unprotected sexual intercourse. The causes of infertility are outlined in Fig. 175-3. Male infertility is discussed in Chap. 174.

### Clinical Features

The initial evaluation includes discussion of the appropriate timing of intercourse, semen analysis in the male, confirmation of ovulation in the female, and, in the majority of situations, documentation of tubal patency in the female. Abnormalities in menstrual function constitute the most common cause of female infertility (Fig. 175-1). A history of regular, cyclic, predictable, spontaneous menses usually indicates ovulatory cycles, which may be confirmed by urinary ovulation predictor kits, basal body temperature graphs, or plasma progesterone measurements during the luteal phase of the cycle. An FSH level <10 IU/mL on day 3 of the cycle predicts adequate ovarian oocyte reserve. Tubal disease can be evaluated by obtaining a hysterosalpingogram or by diagnostic laparoscopy. Endometriosis may be suggested by history and examination, but is often clinically silent and can only be excluded definitively by laparoscopy.

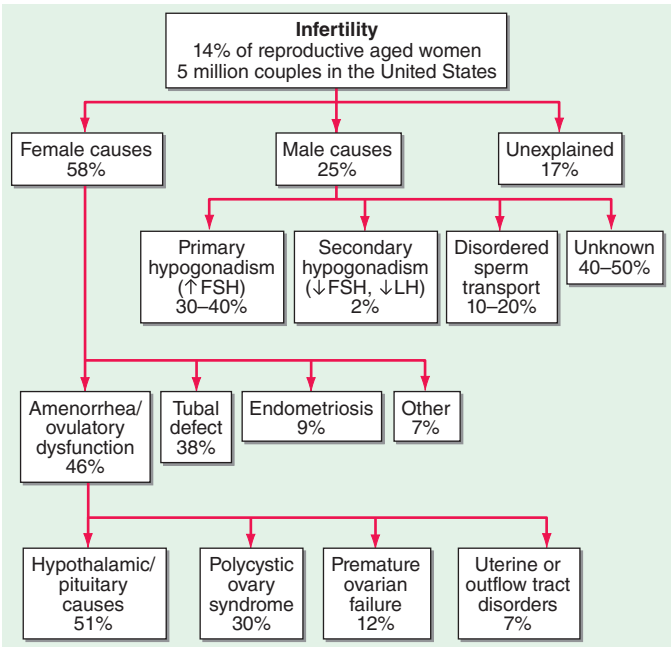



**FIGURE 175-3** Causes of infertility. FSH, follicle-stimulating hormone; LH, luteinizing hormone.

**TREATMENT INFERTILITY**

The treatment of infertility should be tailored to the problems unique to each couple. Treatment options include expectant management, clomiphene citrate with or without intrauterine insemination (IUI), gonadotropins with or without IUI, and in vitro fertilization (IVF). In specific situations, surgery, gonadotropin therapy, intracytoplasmic sperm injection (ICSI), or assisted reproductive technologies with donor egg or sperm may be required.

For a more detailed discussion, see Ehrmann DA: Hirsutism, Chap. 68, p. 331; Hall JE: Menstrual Disorders and Pelvic Pain, Chap. 69, p. 335; Hall JE: Disorders of the Female Reproductive System, Chap. 412, p. 2375; Manson JE, Bassuk SS: Menopause and Postmenopausal Hormone Therapy, Chap. 413, p. 2381, in HPIM-19; Hall JE: Infertility and Contraception, Chap. 414, p. 2387.

# 176 Hypercalcemia and Hypocalcemia

## HYPERCALCEMIA

Hypercalcemia from any cause can result in fatigue, depression, mental confusion, anorexia, nausea, constipation, renal tubular defects, polyuria, a short QT interval, and arrhythmias. CNS and GI symptoms can occur at levels of serum calcium >2.9 mmol/L (>11.5 mg/dL), and nephrocalcinosis and impairment of renal function occur when serum calcium is >3.2 mmol/L (>13 mg/dL). Severe hypercalcemia, usually defined as >3.7 mmol/L (>15 mg/dL), can be a medical emergency, leading to coma and cardiac arrest.

### Etiology

The regulation of the calcium homeostasis is depicted in **Fig. 176-1**. The causes of hypercalcemia are listed in **Table 176-1**. Hyperparathyroidism and malignancy account for >90% of cases.

Primary hyperparathyroidism is a generalized disorder of bone metabolism due to increased secretion of parathyroid hormone (PTH) by an adenoma (80%) or rarely a carcinoma in a single gland, or by parathyroid hyperplasia (15%). Familial hyperparathyroidism may be part of multiple endocrine neoplasia type 1 (MEN 1), which also includes pituitary and pancreatic islet tumors, or of MEN 2A, in which hyperparathyroidism occurs with pheochromocytoma and medullary carcinoma of the thyroid.

Hypercalcemia associated with malignancy is often severe and difficult to manage. Mechanisms for this include excess production and release of PTH-related protein

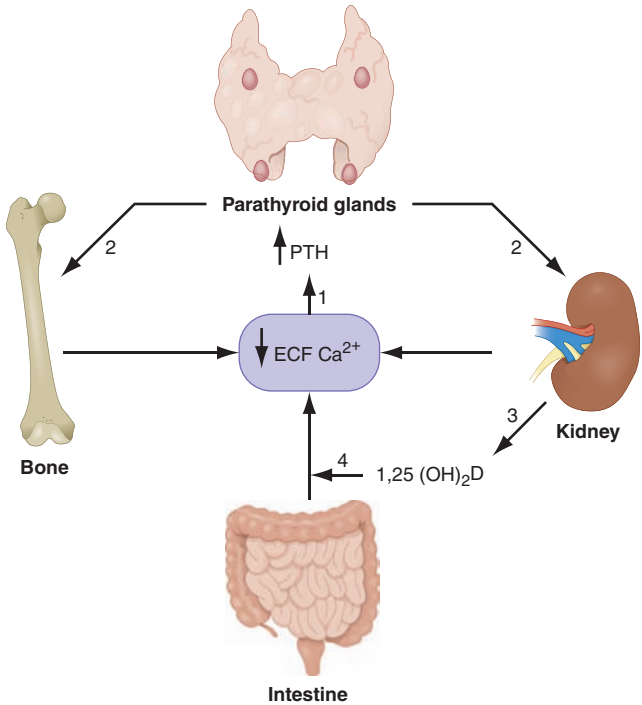



**FIGURE 176-1** Feedback mechanisms maintaining extracellular calcium concentrations within a narrow, physiologic range (8.9–10.1 mg/dL [2.2–2.5 m*M*]). A decrease in extracellular fluid (ECF) calcium ($Ca^{2+}$) triggers an increase in parathyroid hormone (PTH) secretion (1) via the calcium sensor receptor on parathyroid cells. PTH, in turn, results in increased tubular reabsorption of calcium by the kidney (2) and resorption of calcium from bone (2) and also stimulates renal $1,25(OH)_2D$ production (3). $1,25(OH)_2D$, in turn, acts principally on the intestine to increase calcium absorption (4). Collectively, these homeostatic mechanisms serve to restore serum calcium levels to normal.

(PTHrP) in lung, kidney, and squamous cell carcinoma (humoral hypercalcemia of malignancy); local bone destruction in myeloma and breast carcinoma; activation of lymphocytes leading to release of cytokines in myeloma and lymphoma; or an increased synthesis of $1,25(OH)_2D$ in lymphoma.

Several other conditions have been associated with hypercalcemia. These include sarcoidosis and other granulomatous diseases, which lead to increased synthesis of $1,25(OH)_2D$; vitamin D intoxication from chronic ingestion of large vitamin doses (50–100 × physiologic requirements); lithium therapy, which results in hyperfunctioning of the parathyroid glands; and familial hypocalciuric hypercalcemia (FHH) due autosomal dominant inheritance of an inactivating mutation in the calcium-sensing receptor, which results in inappropriately normal or even high secretion of PTH, despite hypercalcemia and enhanced renal calcium resorption. Severe secondary hyperparathyroidism associated with end-stage renal disease may progress to tertiary hyperthyroidism, in which PTH hypersecretion becomes autonomous, causes hypercalcemia, and is no longer responsive to medical therapy.

**TABLE 176-1 CLASSIFICATION OF CAUSES OF HYPERCALCEMIA**

I. Parathyroid-related
   A. Primary hyperparathyroidism
      1. Solitary adenomas or rarely carcinoma
      2. Multiple endocrine neoplasia
   B. Lithium therapy
   C. Familial hypocalciuric hypercalcemia
II. Malignancy-related
   A. Solid tumor with humoral mediation of hypercalcemia (lung, kidney, squamous cell carcinoma)
   B. Solid tumor with metastases (breast)
   C. Hematologic malignancies (multiple myeloma, lymphoma, leukemia)
III. Vitamin D–related
   A. Vitamin D intoxication
   B. ↑ $1,25(OH)_2D$; sarcoidosis and other granulomatous diseases
   C. ↑ $1,25(OH)_2D$; impaired $1,25(OH)_2D$ metabolism due to 24-hydroxylase deficiency
IV. Associated with high bone turnover
   A. Hyperthyroidism
   B. Immobilization
   C. Thiazides
   D. Vitamin A intoxication
   E. Fat necrosis
V. Associated with renal failure
   A. Severe secondary or tertiary hyperparathyroidism
   B. Aluminum intoxication
   C. Milk-alkali syndrome

## Clinical Features

Most pts with mild to moderate hyperparathyroidism are asymptomatic, even when the disease involves the kidneys and the skeletal system. Pts frequently have hypercalciuria and polyuria, and calcium can be deposited in the renal parenchyma (nephrocalcinosis) or form calcium oxalate stones. The characteristic skeletal lesion is osteopenia or osteoporosis; rarely, the more severe disorder osteitis fibrosa cystica occurs as a manifestation of long-standing, more severe hyperparathyroidism. Increased bone resorption primarily involves cortical rather than trabecular bone. Hypercalcemia may be intermittent or sustained, and serum phosphate is usually low but may be normal.

## Diagnosis

Primary hyperparathyroidism is confirmed by demonstration of an inappropriately high PTH level for the degree of hypercalcemia. Hypercalciuria helps to distinguish this disorder from FHH, in which PTH levels are usually in the normal range and the urine calcium level is low. Differentiation between primary hyperparathyroidism and FHH is important because the latter does not respond to parathyroid surgery. Levels of PTH are low in hypercalcemia of malignancy (**Table 176-2**).

Total serum calcium should be corrected when serum albumin is abnormal (addition of 0.2 m*M* [0.8 mg/dL] to calcium value for every 1.0-g/dL decrement in

**TABLE 176-2 DIFFERENTIAL DIAGNOSIS OF HYPERCALCEMIA: LABORATORY CRITERIA**

| | Blood[a] | | | |
|---|---|---|---|---|
| | Ca | $P_i$ | $1,25(OH)_2D$ | iPTH |
| Primary hyperparathyroidism | ↑ | ↓ | ↑↔ | ↑(↔) |
| Malignancy-associated hypercalcemia: | | | | |
| Humoral hypercalcemia | ↑↑ | ↓ | ↓↔ | ↓ |
| Local destruction (osteolytic metastases) | ↑ | ↔ | ↓↔ | ↓ |

[a]Symbols in parentheses refer to values rarely seen in the particular disease.
***Abbreviations:*** $P_i$, inorganic phosphate; iPTH, immunoreactive parathyroid hormone.
***Source:*** JT Potts Jr: HPIM-12, p. 1911.

albumin below 4.1 g/dL, or the converse for an increase in albumin). Alternatively, ionized calcium can be measured. Third-generation PTH assays should be used for PTH measurement, especially in pts with renal impairment.

## TREATMENT HYPERCALCEMIA

The type of treatment is based on the severity of the hypercalcemia and the nature of the associated symptoms. Table 176-3 shows general recommendations

**TABLE 176-3 THERAPIES FOR SEVERE HYPERCALCEMIA**

| Treatment | Onset of Action | Duration of Action | Advantages | Disadvantages |
|---|---|---|---|---|
| Hydration with saline (≤6 L/d) | Hours | During infusion | Rehydrates; rapid action | Volume overload; electrolyte disturbance |
| Forced diuresis (furosemide along with aggressive hydration) | Hours | During treatment | Rapid action | Monitoring required to avoid dehydration |
| Pamidronate 30–90 mg IV over 4 h | 1–2 days | 10–14 days | High potency; intermediate onset of action | Fever in 20%, ↓ Ca, ↓ phosphate, ↓ Mg, rarely jaw necrosis |
| Zoledronate 4–8 mg IV over 15 min | 1–2 days | >3 weeks | High potency; prolonged action; rapid infusion | Minor: Fever; rare ↓ Ca, ↓ phosphate, jaw necrosis |
| Calcitonin (2–8 U/kg SC q6-12h) | Hours | 1–2 days | Rapid onset | Limited effect; rapid tachyphylaxis |
| Glucocorticoids (prednisone 10–25 mg PO qid) | Days | Days-weeks | Useful in myeloma, lymphoma, breast CA, sarcoid, vitamin D intox | Effects limited to certain disorders; glucocorticoid side effects |
| Dialysis | Hours | During use–2 days | Useful in renal failure; immediate effect | Complex procedure |

that apply to therapy of severe hypercalcemia (levels of >3.2 mmol/L [>13 mg/dL]) from any cause.

In pts with severe primary hyperparathyroidism, surgical parathyroidectomy should be performed promptly. Asymptomatic disease may not require surgery; usual surgical indications include age <50, nephrolithiasis, creatinine clearance <60 mL/min, reduction in bone mass (T score <–2.5), or serum calcium >0.25 mmol/L (>1 mg/dL) above the normal range. A minimally invasive approach may be used if preoperative localization via sestamibi scans with single-photon emission computed tomography (SPECT) or neck ultrasound demonstrates a solitary adenoma and intraoperative PTH assays are available. Otherwise, neck exploration is required. Surgery in a center experienced in parathyroid interventions is recommended. Postoperative management requires close monitoring of calcium and phosphorus, as transient hypocalcemia is common. Calcium supplementation is given for symptomatic hypocalcemia.

Hypercalcemia of malignancy is managed by treating the underlying tumor. Adequate hydration and parenteral bisphosphonates can be used to reduce calcium levels. Long-term control of hypercalcemia is difficult unless the underlying cause can be eliminated.

No therapy is recommended for FHH. Secondary hyperparathyroidism should be treated with phosphate restriction, the use of nonabsorbable antacids or sevelamer, and calcitriol. Tertiary hyperparathyroidism requires parathyroidectomy.

## HYPOCALCEMIA

Chronic hypocalcemia is less common than hypercalcemia, but is usually symptomatic and requires treatment. Symptoms include peripheral and perioral paresthesia, muscle spasms, carpopedal spasm, tetany, laryngeal spasm, seizure, and respiratory arrest. Increased intracranial pressure and papilledema may occur with long-standing hypocalcemia, and other manifestations may include irritability, depression, psychosis, intestinal cramps, and chronic malabsorption. Chvostek's and Trousseau's signs are frequently positive, and the QT interval is prolonged. Both hypomagnesemia and alkalosis lower the threshold for tetany.

### Etiology

Transient hypocalcemia often occurs in critically ill pts with burns, sepsis, and acute renal failure; following transfusion with citrated blood; or with medications such as protamine and heparin. Hypoalbuminemia can reduce serum calcium below normal, although ionized calcium levels remain normal. The above-mentioned correction (see "Hypercalcemia") can be used to assess whether the serum calcium concentration is abnormal when serum proteins are low. Alkalosis increases calcium binding to proteins, and in this setting direct measurements of ionized calcium should be used.

The causes of hypocalcemia can be divided into those in which PTH is absent (hereditary or acquired hypoparathyroidism, hypomagnesemia), PTH is ineffective (chronic renal failure, vitamin D deficiency, anticonvulsant therapy, intestinal malabsorption, pseudohypoparathyroidism), or PTH is overwhelmed (severe, acute hyperphosphatemia in tumor lysis, acute renal failure, or rhabdomyolysis; hungry bone syndrome following parathyroidectomy). The most common forms of chronic severe hypocalcemia are autoimmune hypoparathyroidism and postoperative hypoparathyroidism following neck surgery. Chronic renal insufficiency is associated with mild hypocalcemia compensated for by secondary hyperparathyroidism. The cause of hypocalcemia associated with acute pancreatitis is unclear.

## TREATMENT HYPOCALCEMIA

Symptomatic hypocalcemia may be treated with IV calcium gluconate (bolus of 1–2 g IV over 10–20 min followed by infusion of 10 ampoules of 10% calcium gluconate diluted in 1 L $D_5W$ infused at 30–100 mL/h). Management of chronic hypocalcemia requires a high oral calcium intake, usually with vitamin D supplementation. Hypoparathyroidism requires administration of calcium (1–3 g/d) and calcitriol (0.25–1 μg/d), adjusted according to serum calcium levels and urinary excretion. Restoration of magnesium stores may be required to reverse hypocalcemia in the setting of severe hypomagnesemia.

## HYPOPHOSPHATEMIA

Mild hypophosphatemia is not usually associated with clinical symptoms. In severe hypophosphatemia, pts may have muscle weakness, numbness, paresthesia, and confusion. Rhabdomyolysis may develop during rapidly progressive hypophosphatemia. Respiratory insufficiency can result from diaphragm muscle weakness.

### Etiology

The causes of hypophosphatemia include decreased intestinal absorption (vitamin D deficiency, phosphorus-binding antacids, malabsorption); urinary losses (hyperparathyroidism, hyperglycemic states, X-linked hypophosphatemic rickets, oncogenic osteomalacia, alcoholism, or certain toxins); and shifts of phosphorus from extracellular to intracellular compartments (administration of insulin in diabetic ketoacidosis or by hyperalimentation or refeeding in a malnourished pt). In syndromes of severe primary renal phosphate wasting (X-linked hypophosphatemic rickets, autosomal dominant hypophosphatemic rickets, oncogenic osteomalacia), the phosphatonin hormone FGF23 (fibroblast growth factor 23) plays a key pathogenetic role.

## TREATMENT HYPOPHOSPHATEMIA

Mild hypophosphatemia can be replaced orally with milk, carbonated beverages, or Neutra-Phos or K-Phos (up to 2 g/d in divided doses). For severe hypophosphatemia (0.75 mmol/L; [<2.0 mg/dL]), IV phosphate may be administered at initial doses of 0.2–0.8 mmol/kg of elemental phosphorus over 6 h. The total body phosphate depletion cannot be predicted from the serum phosphate level; careful monitoring of therapy is therefore required. Hypocalcemia should be corrected first, and the dose reduced 50% in hypercalcemia. Serum calcium and phosphate levels should be measured every 6–12 h; a serum calcium × phosphate product of >50 must be avoided.

## HYPERPHOSPHATEMIA

In adults, hyperphosphatemia is defined as a level >1.8 mmol/L (>5.5 mg/dL). The most common causes are acute and chronic renal failure, but it may also be seen in hypoparathyroidism, vitamin D intoxication, acromegaly, acidosis, rhabdomyolysis, and hemolysis. The clinical consequences of severe hyperphosphatemia are hypocalcemia and calcium phosphate deposition in tissues. Depending on the location of tissue calcifications, serious chronic or acute complications may ensue (e.g., nephrocalcinosis, cardiac arrhythmias). Therapy consists of treating the underlying disorder and limiting dietary phosphorus intake and absorption. Oral aluminum phosphate binders or sevelamer may be used, and hemodialysis should be considered in severe cases.

## HYPOMAGNESEMIA

Hypomagnesemia usually indicates significant whole body magnesium depletion. Muscle weakness, prolonged PR and QT intervals, and cardiac arrhythmias are the most common manifestations of hypomagnesemia. Magnesium is important for effective PTH secretion as well as the renal and skeletal responsiveness to PTH. Therefore, hypomagnesemia is often associated with hypocalcemia.

### Etiology

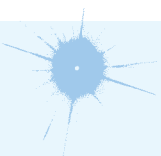
Hypomagnesemia generally results from a derangement in renal or intestinal handling of magnesium and is classified as primary (hereditary) or secondary (acquired). Hereditary causes include both disorders of absorption (rare) and those of renal loss (e.g., Bartter's and Gitelman syndromes). Secondary causes are much more common, with renal losses being due to volume expansion, hypercalcemia, osmotic diuresis, loop diuretics, alcohol, aminoglycosides, cisplatin, cyclosporine, and amphotericin B, and gastrointestinal losses most commonly resulting from vomiting and diarrhea.

### TREATMENT HYPOMAGNESEMIA

For mild deficiency, oral replacement in divided doses totaling 20–30 mmol/d (40–60 meq/d) is effective, although diarrhea may result. Parenteral magnesium administration is usually needed for serum levels <0.5 mmol/L (<1.2 mg/dL), with a continuous infusion of magnesium chloride IV to deliver 50 mmol/d over a 24-h period (dose reduced by 50–75% in renal failure). Therapy may be required for several days in order to replete tissue magnesium stores; serum Mg should be monitored every 12–24 h during treatment. Other electrolyte disturbances should be treated simultaneously. Pts with associated seizures or acute arrhythmias can be given 1–2 g of magnesium sulfate IV over 5–10 min.

## HYPERMAGNESEMIA

Hypermagnesemia is rare but can be seen in renal failure when pts are taking magnesium-containing antacids, laxatives, enemas, or infusions, or in acute rhabdomyolysis. The most readily detectable clinical sign of hypermagnesemia is the disappearance of deep tendon reflexes, but hypocalcemia, hypotension, paralysis of respiratory muscles, complete heart block, and cardiac arrest can occur. Treatment includes stopping the preparation, clearing the intestines of residual offending laxatives or antacids with magnesium-free enemas or cathartics, dialysis against a low magnesium bath, or, if associated with life-threatening complications, 100–200 mg of elemental calcium IV over 1–2 h.



For a more detailed discussion, see Bringhurst FR, Demay MB, Krane SM, Kronenberg HM: Bone and Mineral Metabolism in Health and Disease, Chap. 423, p. 2454; Khosla S: Hypercalcemia and Hypocalcemia, Chap. 65, p. 313; Potts JT Jr, Jüppner H: Disorders of the Parathyroid Gland and Calcium Homeostasis, Chap. 424, p. 2466, in HPIM-19.

# 177 Osteoporosis and Osteomalacia

## OSTEOPOROSIS

*Osteoporosis* is defined as a reduction in the strength of bone that leads to increased risk of fractures. It is defined operationally as a bone density that falls 2.5 SD below the mean for a young normal individual (a T-score of <–2.5). Those with a T-score of <1.0 (osteopenia) have low bone density and are at increased risk for osteoporosis. The most common sites for osteoporosis-related fractures are the vertebrae, hip, and distal radius.

Osteoporosis is a common condition in the elderly; women are at particularly high risk. In the United States, 8 million women and 2 million men have osteoporosis; an additional 18 million have osteopenia. The annual incidence of osteoporosis-related fractures is at least 2 million; almost half of them are vertebral crush fractures, followed in frequency by hip and wrist fractures. Hip fractures are associated with significant morbidity (thromboembolism) and a 5–20% mortality within a year.

### Etiology

Low bone density may result from low peak bone mass or increased bone loss. Risk factors for an osteoporotic fracture are listed in Table 177-1, and conditions associated with osteoporosis are listed in Table 177-2. Certain drugs, primarily glucocorticoids, cyclosporine, cytotoxic drugs, thiazolidinediones, anticonvulsants, aluminum, heparin, excessive levothyroxine, GnRH agonists, and aromatase inhibitors also have detrimental effects on the skeleton.

### Clinical Features

Pts with multiple vertebral crush fractures may have loss of height, kyphosis, and secondary pain from altered biomechanics of the back. Thoracic fractures can be associated with restrictive lung disease, whereas lumbar fractures are sometimes associated with abdominal symptoms or nerve compression leading to sciatica.

**TABLE 177-1 RISK FACTORS FOR OSTEOPOROSIS FRACTURE**

| | |
|---|---|
| Nonmodifiable | Estrogen deficiency |
| Personal history of fracture as an adult | Early menopause (<45 years) or bilateral ovariectomy |
| History of fracture in first-degree relative | Prolonged premenopausal amenorrhea (>1 year) |
| Female sex | Low calcium intake |
| Advanced age | Alcoholism |
| White race | Impaired eyesight despite adequate correction |
| Dementia | |
| Potentially modifiable | Recurrent falls |
| Current cigarette smoking | Inadequate physical activity |
| Low body weight (<58 kg [127 lb]) | Poor health/frailty |

**TABLE 177-2 CONDITIONS, DISEASES, AND MEDICATIONS THAT CONTRIBUTE TO OSTEOPOROSIS AND FRACTURES**

| | | |
|---|---|---|
| **Lifestyle factors** | | |
| Alcohol abuse | High salt intake | Falling |
| Low calcium intake | Inadequate physical activity | Excessive thinness |
| Vitamin D insufficiency | Immobilization | Prior fractures |
| Excess vitamin A | Smoking (active or passive) | |
| **Genetic factors** | | |
| Cystic fibrosis | Homocystinuria | Osteogenesis imperfecta |
| Ehlers-Danlos syndrome | Hypophosphatasia | Parental history of hip fracture |
| Gaucher's disease | Idiopathic hypercalciuria | Porphyria |
| Glycogen storage diseases | Marfan's syndrome | Riley-Day syndrome |
| Hemochromatosis | Menkes' steely hair syndrome | |
| **Hypogonadal states** | | |
| Androgen insensitivity | Hyperprolactinemia | Athletic amenorrhea |
| | | Panhypopituitarism |
| Anorexia nervosa and bulimia | Premature menopause | |
| | Premature ovarian failure | |
| Turner's & Klinefelter's syndromes | | |
| **Endocrine disorders** | | |
| Adrenal insufficiency | Cushing's syndrome | Central adiposity |
| Diabetes mellitus (types 1 and 2) | Hyperparathyroidism | Thyrotoxicosis |
| **Gastrointestinal disorders** | | |
| Celiac disease | Inflammatory bowel disease | Primary biliary cirrhosis |
| Gastric bypass | Malabsorption | |
| Gastrointestinal surgery | Pancreatic disease | |
| **Hematologic disorders** | | |
| Multiple myeloma | Monoclonal gammopathies | Sickle cell disease |
| Hemophilia | Leukemia and lymphomas | Systemic mastocytosis |
| Thalassemia | | |
| **Rheumatologic and autoimmune diseases** | | |
| Ankylosing spondylitis | Lupus | Rheumatoid arthritis |
| Other rheumatic and autoimmune diseases | | |

(*Continued*)

**TABLE 177-2 CONDITIONS, DISEASES, AND MEDICATIONS THAT CONTRIBUTE TO OSTEOPOROSIS AND FRACTURES (*CONTINUED*)**

| | | |
|---|---|---|
| **Central nervous system disorders** | | |
| Epilepsy | Parkinson's disease | Stroke |
| Multiple sclerosis | Spinal cord injury | |
| **Miscellaneous conditions and diseases** | | |
| AIDS/HIV | Congestive heart failure | Posttransplant bone disease |
| Alcoholism | Depression | Sarcoidosis |
| Amyloidosis | End-stage renal disease | Weight loss |
| Chronic metabolic acidosis | Hypercalciuria | |
| Chronic obstructive lung disease | Idiopathic scoliosis | |
| | Muscular dystrophy | |
| **Medications** | | |
| Aluminum (in antacids) | Glucocorticoids (≥5 mg/d prednisone or equivalent for ≥3 months) | Tamoxifen (premenopausal use) |
| Anticoagulants (heparin) | Gonadotropin-releasing hormone antagonists and agonists | Thiazolidinediones (such as pioglitazone and rosiglitazone) |
| Anticonvulsants | Lithium | Thyroid hormones (in excess) |
| Aromatase inhibitors | Methotrexate | Parenteral nutrition |
| Barbiturates | Proton pump inhibitors | |
| Cancer chemotherapeutic drugs | Selective serotonin reuptake inhibitors | |
| Cyclosporine A and tacrolimus | | |
| Depo-medroxyprogesterone (premenopausal contraception) | | |

***Source:*** From the 2014 National Osteoporosis Foundation Clinician's Guide to the Prevention and Treatment of Osteoporosis. © National Osteoporosis Foundation.

Dual-energy x-ray absorptiometry (DEXA) has become the standard for measuring bone density. Women age 65 and older should be screened routinely for osteoporosis, and screening should begin at age 60 for women with increased risk. Indications for bone mass measurement are summarized in Table 177-3. A general laboratory evaluation includes complete blood count, serum and 24-h urine calcium, 25(OH) D level, and renal and hepatic function tests. Further testing is based on clinical suspicion and may include thyroid-stimulating hormone (TSH), urinary free cortisol, parathyroid hormone (PTH), serum and urine electrophoresis, and testosterone levels (in men). Tissue transglutaminase Ab testing may identify asymptomatic celiac disease. Markers of bone resorption (e.g., urine cross-linked *N*-telopeptide) may be helpful in detecting an early response to antiresorptive therapy if measured prior to and 4–6 months after initiating therapy.

## TREATMENT OSTEOPOROSIS

Treatment involves the management of acute fractures, modifying risk factors, and treating any underlying disorders that lead to reduced bone mass. Treatment decisions are based on an individual's risk factors, but active treatment

**TABLE 177-3 INDICATIONS FOR BONE DENSITY TESTING**

**Consider BMD testing in the following individuals:**

- Women age 65 and older and men age 70 and older, regardless of clinical risk factors
- Younger postmenopausal women, women in the menopausal transition, and men aged 50–69 with clinical risk factors for fracture
- Adults who have a fracture after age 50
- Adults with a condition (e.g., rheumatoid arthritis) or taking a medication (e.g., glucocorticoids in a daily dose ≥5-mg prednisone or equivalent for ≥3 months) associated with low bone mass or bone loss

***Abbreviation:*** BMD, bone mineral density.
***Source:*** From the 2014 National Osteoporosis Foundation Clinician's Guide to the Prevention and Treatment of Osteoporosis. © National Osteoporosis Foundation.

is generally recommended if the T-score is ≤2.5. Risk factor reduction is a key part of management; smoking cessation and reduced alcohol intake should be encouraged; offending drugs should be discontinued or doses minimized (e.g., glucocorticoids), an exercise program should be instituted, and fall prevention strategies should be put in place. Oral calcium (1–1.2 g/d of elemental calcium in divided doses) and vitamin D (400–800 IU/d) should be initiated in all pts with osteoporosis. Adequate vitamin D status should be verified by measuring serum 25(OH)D, the value of which should be at least 75 nmol/L (30 ng/mL). Some pts may require higher vitamin D supplements than those recommended above. Moderate sun exposure also generates vitamin D, although recommending outdoor exposure is controversial because of concerns about skin cancer. Bisphosphonates (alendronate, 70 mg PO weekly; risedronate, 35 mg PO weekly; ibandronate, 150 mg PO monthly or 3 mg IV every 3 mo; zoledronic acid, 5 mg IV annually) inhibit bone resorption, augment bone density, and decrease fracture rates. Oral bisphosphonates are poorly absorbed and should be taken in the morning on an empty stomach with 0.25 L (8 oz) of tap water. Long-term bisphosphonate treatment may be associated with atypical femur fractures; a tentative recommendation is to limit therapy to 5 years. Osteonecrosis of the jaw is a rare complication of bisphosphonate treatment mainly seen with high-dose IV zoledronic acid or pamidronate administered in cancer pts. Estrogen decreases the rate of bone reabsorption, but therapy should be carefully weighed in the context of increased risks of cardiovascular disease and breast cancer. Raloxifene (60 mg/d PO), a selective estrogen receptor modulator (SERM), is an alternative antiresorptive agent that can be used in lieu of estrogen. It increases bone density and decreases total and LDL cholesterol without stimulating endometrial hyperplasia, although it may precipitate hot flashes. A new antiresorptive agent is denosumab, a monoclonal antibody against receptor activator of nuclear factor kappa-B ligand (RANKL), an osteoclast differentiation factor. It is approved for pts at high risk for fracture and is given as an injection twice a year (60 mg SC every 6 months). Clinical experience with denosumab is still limited.

The only available drug that induces bone *formation* is teriparatide [PTH(1-34)] 20 μg SC qd. It is indicated for treatment of severe osteoporosis for a maximum of 2 years. Teriparatide therapy must be followed by antiresorptive agent therapy to prevent rapid loss of the newly formed bone.

## OSTEOMALACIA

### Etiology

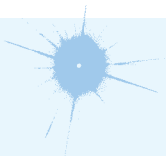
Defective mineralization of the organic matrix of bone results in *osteomalacia*. The childhood form of osteomalacia is called rickets. Osteomalacia is caused by inadequate intake or malabsorption of vitamin D (chronic pancreatic insufficiency, gastrectomy, malabsorption) and disorders of vitamin D metabolism (anticonvulsant therapy, chronic renal failure, genetic disorders of vitamin D activation or action). Osteomalacia can also be caused by long-standing hypophosphatemia, which can be due to renal phosphate wasting (e.g., X-linked hypophosphatemic rickets or oncogenic osteomalacia) or excessive use of phosphate binders.

### Clinical Features

Skeletal deformities may be overlooked until fractures occur after minimal trauma. Symptoms include diffuse skeletal pain and bony tenderness and may be subtle. Proximal muscle weakness is a feature of vitamin D deficiency and may mimic primary muscle disorders. A decrease in bone density is usually associated with loss of trabeculae and thinning of the cortices. Characteristic x-ray findings are radiolucent bands (looser's zones or pseudofractures) ranging from a few millimeters to several centimeters in length, usually perpendicular to the surface of the femur, pelvis, and scapula. Changes in serum calcium, phosphorus, 25(OH)D, and $1,25(OH)_2D$ levels vary depending on the cause. The most specific test for vitamin D deficiency in an otherwise healthy individual is a low serum 25(OH)D level. Even modest vitamin D deficiency leads to compensatory secondary hyperparathyroidism characterized by increased levels of PTH and alkaline phosphatase, hyperphosphaturia, and low serum phosphate. With advancing osteomalacia, hypocalcemia may develop due to impaired calcium mobilization from undermineralized bone. 1,25-Dihydroxyvitamin D levels may be preserved, reflecting upregulation of 1α-hydroxylase activity.

### TREATMENT OSTEOMALACIA

In osteomalacia due to vitamin D deficiency (serum 25(OH)D <50 nmol/L [<20 ng/mL]), vitamin $D_2$ (ergocalciferol) is given orally in doses of 50,000 IU weekly for 8 weeks, followed by maintenance therapy with 800 IU daily. Osteomalacia due to malabsorption requires larger doses of vitamin D (up to 50,000 IU/d orally or 250,000 IU IM biannually). In pts taking anticonvulsants or those with disorders of abnormal vitamin D activation, vitamin D should be administered in doses that maintain the serum calcium and 25(OH)D levels in the normal range. Calcitriol (0.25–0.5 μg/d PO) is effective in treating hypocalcemia or osteodystrophy caused by chronic renal failure. Vitamin D deficiency should always be repleted in conjunction with calcium supplementation (1.5–2.0 g of elemental calcium daily). Serum and urinary calcium measurements are efficacious for monitoring resolution of vitamin D deficiency, with a goal 24-h urinary calcium excretion of 100–250 mg/24 h.



For a more detailed discussion, see Bringhurst FR, Demay MB, Krane SM, Kronenberg HM: Bone and Mineral Metabolism in Health and Disease, Chap. 423, p. 2454; Lindsay R, Cosman F: Osteoporosis, Chap. 425, p. 2488, in HPIM-19.

# 178 Hypercholesterolemia and Hypertriglyceridemia

Hyperlipoproteinemia may be characterized by hypercholesterolemia, isolated hypertriglyceridemia, or both. Genetic causes of hyperlipoproteinemia are summarized in Table 178-1. Diabetes mellitus, obesity, ethanol consumption, oral contraceptives, glucocorticoids, renal disease, hepatic disease, and hypothyroidism can cause secondary hyperlipoproteinemias or worsen underlying hyperlipoproteinemic states.

Standard lipoprotein analysis assesses total cholesterol, HDL cholesterol, and triglycerides with a calculation of LDL cholesterol levels using the following equation: LDL cholesterol = total cholesterol – HDL cholesterol – (triglycerides/5). The LDL cholesterol concentration can be estimated using this method only if triglycerides are <4.0 mmol/L (<350 mg/dL). Both LDL and HDL cholesterol levels are temporarily decreased for several weeks after myocardial infarction or acute inflammatory states, but can be accurately measured if blood is obtained within 8 h of the event.

## ISOLATED HYPERCHOLESTEROLEMIA

Elevated levels of fasting plasma total cholesterol (>5.2 mmol/L [>200 mg/dL]) in the presence of normal levels of triglycerides are almost always associated with increased concentrations of plasma LDL cholesterol. Elevations of LDL cholesterol can result from single-gene defects, from polygenic disorders, or from the secondary effects of other disease states.

### FAMILIAL HYPERCHOLESTEROLEMIA (FH)

FH is a codominant genetic disorder due to mutations in the gene for the LDL receptor. Plasma LDL levels are elevated at birth and remain so throughout life. In untreated heterozygous adults, total cholesterol levels range from 7.1 to 12.9 mmol/L (275–500 mg/dL). Plasma triglyceride levels are typically normal, and HDL cholesterol levels are normal or reduced. Heterozygotes, especially men, are prone to accelerated atherosclerosis and premature coronary artery disease (CAD). *Tendon xanthomas* (most commonly of the Achilles tendons and the extensor tendons of the knuckles), *tuberous xanthomas* (softer, painless nodules on the ankles and buttocks), and *xanthelasmas* (deposits on the eyelids) are common. In its homozygous form, FH leads to severe atherosclerosis during childhood.

### FAMILIAL DEFECTIVE APO B-100

This autosomal dominant disorder impairs the synthesis and/or function of apo B-100, thereby reducing the affinity for the LDL receptor, slowing LDL catabolism, and causing a phenocopy of FH.

### POLYGENIC HYPERCHOLESTEROLEMIA

Most moderate hypercholesterolemia (<9.1 mmol/L [<350 mg/dL]) arises from an interaction of multiple genetic defects and environmental factors such as diet, age, and exercise. Plasma HDL and triglyceride levels are normal, and xanthomas are not present.

## TREATMENT ISOLATED HYPERCHOLESTEROLEMIA

Therapy for all of these disorders includes restriction of dietary cholesterol and HMG-CoA reductase inhibitors (statins). Cholesterol absorption inhibitors and bile acid sequestrants or nicotinic acid may also be required (Table 178-2).

**TABLE 178-1 PRIMARY HYPERLIPOPROTEINEMIAS CAUSED BY KNOWN SINGLE-GENE MUTATIONS**

| Genetic Disorder | Protein (Gene) Defect | Lipoproteins Elevated | Clinical Findings | Genetic Transmission | Estimated Incidence |
|---|---|---|---|---|---|
| **Hypertriglyceridemia** | | | | | |
| Lipoprotein lipase deficiency | LPL (*LPL*) | Chylomicrons, VLDL | Eruptive xanthomas, hepato-splenomegaly, pancreatitis | AR | ~1/1,000,000 |
| Familial apo CII deficiency | Apo CII (*APOC2*) | Chylomicrons, VLDL | Eruptive xanthomas, hepato-splenomegaly, pancreatitis | AR | <1/1,000,000 |
| Apo A-V deficiency | Apo A-V (*APOA5*) | Chylomicrons, VLDL | Eruptive xanthomas, hepato-splenomegaly, pancreatitis | AR | <1/1,000,000 |
| GPIHBP1 deficiency | *GPIHBP1* | Chylomicrons | Eruptive xanthomas, pancreatitis | AR | <1/1,000,000 |
| **Combined Hyperlipidemia** | | | | | |
| Familial hepatic lipase deficiency | Hepatic lipase (*LIPC*) | VLDL remnants, HDL | Pancreatitis, CHD | AR | <1/1,000,000 |
| Familial dysbetalipoproteinemia | ApoE (*APOE*) | Chylomicron remnants, VLDL remnants | Palmar and tuberoeruptive xanthomas, CHD, PVD | AR | ~1/10,000 |
| **Hypercholesterolemia** | | | | | |
| Familial hypercholesterolemia | LDL receptor (*LDLR*) | LDL | Tendon xanthomas, CHD | AD | ~1/250 to 1/500 |
| Familial defective apoB-100 | ApoB-100 (*APOB*) | LDL | Tendon xanthomas, CHD | AD | <~1/1500 |
| Autosomal dominant hypercholes-terolemia, type 3 | PCSK9 (*PCSK9*) | LDL | Tendon xanthomas, CHD | AD | <1/1,000,000 |
| Autosomal recessive hypercholesterolemia | ARH (*LDLRAP*) | LDL | Tendon xanthomas, CHD | AR | <1/1,000,000 |
| Sitosterolemia | *ABCG5* or *ABCG8* | LDL | Tendon xanthomas, CHD | AR | <1/1,000,000 |

***Abbreviations:*** AD, autosomal dominant; apo, apolipoprotein; AR, autosomal recessive; ARH, autosomal recessive hypercholesterolemia; CHD, coronary heart disease; LDL, low-density lipoprotein; LPL, lipoprotein lipase; PVD, peripheral vascular disease; VLDL, very-low density lipoprotein.

**TABLE 178-2 SUMMARY OF THE MAJOR APPROVED DRUGS USED FOR THE TREATMENT OF DYSLIPIDEMIA**

| Drug | Major Indications | Starting Dose | Maximal Dose | Mechanism | Common Side Effects |
|---|---|---|---|---|---|
| HMG-CoA reductase inhibitors (statins) | Elevated LDL-C; increased CV risk | | | ↓ Cholesterol synthesis, ↑ Hepatic LDL receptors, ↓ VLDL production | Myalgias, arthralgias, elevated transaminases, dyspepsia |
| Lovastatin | | 20–40 mg daily | 80 mg daily | | |
| Pravastatin | | 40–80 mg daily | 80 mg daily | | |
| Simvastatin | | 20–40 mg daily | 80 mg daily | | |
| Fluvastatin | | 20–40 mg daily | 80 mg daily | | |
| Atorvastatin | | 20–40 mg daily | 80 mg daily | | |
| Rosuvastatin | | 5–20 mg daily | 40 mg daily | | |
| Pitavastatin | | 1–2 mg daily | 4 mg daily | | |
| Cholesterol absorption inhibitor | Elevated LDL-C | | | ↓ Cholesterol absorption, ↑ LDL receptors | Elevated transaminases |
| Ezetimibe | | 10 mg daily | 10 mg daily | | |
| Bile acid sequestrants | Elevated LDL-C | | | ↑ Bile acid excretion and ↑ LDL receptors | Bloating, constipation, elevated triglycerides |
| Cholestyramine | | 4 g daily | 32 g daily | | |

| | | | | | |
|---|---|---|---|---|---|
| Colestipol | | 5 g daily | 40 g daily | | |
| Colesevelam | | 3750 mg daily | 4375 mg daily | | |
| MTP inhibitor<br>Lomitapide | HoFH | 5 mg daily | 60 mg daily | ↓ VLDL production | Nausea, diarrhea, increased hepatic fat |
| apoB inhibitor<br>Mipomersen | HoFH | 200 mg SC weekly | 200 mg SC weekly | ↓ VLDL production | Injection site reactions, flu-like symptoms, increased hepatic fat |
| Nicotinic acid | Elevated LDL-C, elevated TG | | | ↓ VLDL production | Cutaneous flushing, GI upset, elevated glucose, uric acid, and elevated liver function tests |
| Immediate-release | | 100 mg tid | 1 g tid | | |
| Sustained-release | | 250 mg bid | 1.5 g bid | | |
| Extended-release | | 500 mg qhs | 2 g qhs | | |
| Fibric acid derivatives | Elevated TG | | | ↑ LPL, ↓ VLDL synthesis | Dyspepsia, myalgia, gallstones, elevated transaminases |
| Gemfibrozil | | 600 mg bid | 600 mg bid | | |
| Fenofibrate | | 145 mg qd | 145 mg qd | | |
| Omega-3 fatty acids<br>Omega-3 acid ethyl esters | Elevated TG | 4 g daily | 4 g daily | ↑ TG catabolism | Dyspepsia, fishy odor to breath |
| Icosapent ethyl | | 4 g daily | 4 g daily | | |

***Abbreviations:*** CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; HoFH, homozygous familial hypercholesterolemia; LDL-C, LDL-cholesterol; LPL, lipoprotein lipase; MTP, microsomal triglyceride transfer protein; TG, triglyceride; VLDL, very-low-density lipoprotein.

## ISOLATED HYPERTRIGLYCERIDEMIA

The diagnosis of hypertriglyceridemia is made by measuring plasma lipid levels after an overnight fast (≥12 h). Hypertriglyceridemia in adults is defined as a triglyceride level >2.3 mmol/L (>200 mg/dL). An isolated increase in plasma triglycerides indicates that chylomicrons and/or very low-density lipoprotein (VLDL) are increased. Plasma is usually clear when triglyceride levels are <4.5 mmol/L (<400 mg/dL) and cloudy when levels are higher due to VLDL (and/or chylomicron) particles becoming large enough to scatter light. When chylomicrons are present, a creamy layer floats to the top of plasma after refrigeration for several hours. Tendon xanthomas and xanthelasmas do not occur with isolated hypertriglyceridemia, but *eruptive xanthomas* (small orange-red papules) can appear on the trunk and extremities and *lipemia retinalis* (orange-yellow retinal vessels) may be seen when the triglyceride levels are >11.3 mmol/L (>1000 mg/dL). Pancreatitis is associated with these high concentrations.

### FAMILIAL HYPERTRIGLYCERIDEMIA

In this relatively common (~1 in 500), likely polygenic disorder, increased plasma VLDL causes elevated plasma triglyceride concentrations. Obesity, hyperglycemia, and hyperinsulinemia are characteristic, and diabetes mellitus, ethanol consumption, oral contraceptives, and hypothyroidism may exacerbate the condition. The diagnosis is suggested by the triad of elevated plasma triglycerides (2.8–11.3 mmol/L [250–1000 mg/dL]), normal or only mildly increased cholesterol levels (<6.5 mmol/L [<250 mg/dL]), and reduced plasma HDL. Secondary forms of hypertriglyceridemia due to the conditions listed above should be ruled out before making the diagnosis of familial hypertriglyceridemia. The identification of other first-degree relatives with hypertriglyceridemia is useful in making the diagnosis. Familial dysbetalipoproteinemia and familial combined hyperlipidemia (FCHL) should be ruled out, as these two conditions are associated with accelerated atherosclerosis.

### LIPOPROTEIN LIPASE DEFICIENCY

This rare autosomal recessive disorder results from the absence or deficiency of lipoprotein lipase, which in turn impairs the metabolism of chylomicrons. Accumulation of chylomicrons in plasma causes recurrent bouts of pancreatitis, usually beginning in childhood, and hepatosplenomegaly is present. Accelerated atherosclerosis is not a feature.

### APO CII DEFICIENCY

This rare autosomal recessive disorder is due to the absence of apo CII, an essential cofactor for lipoprotein lipase. As a result, chylomicrons and triglycerides accumulate and cause manifestations similar to those in lipoprotein lipase deficiency.

### TREATMENT ISOLATED HYPERTRIGLYCERIDEMIA

Pts with severe hypertriglyceridemia should be placed on a fat-free diet with fat-soluble vitamin supplementation. Pts with moderate hypertriglyceridemia should restrict fat, carbohydrate, and alcohol intake. In those with familial hypertriglyceridemia, fibric acid derivatives, omega-3 fatty acids, or niacin can be administered if dietary measures fail (Table 178-2).

## HYPERCHOLESTEROLEMIA AND HYPERTRIGLYCERIDEMIA

Elevations of both triglycerides and cholesterol are caused by elevations in both VLDL and LDL or in VLDL remnant particles.

### FAMILIAL COMBINED HYPERLIPIDEMIA (FCHL)

This inherited disorder, present in 1/200 persons, can cause different lipoprotein abnormalities in affected individuals, including hypercholesterolemia (elevated LDL), hypertriglyceridemia (elevated triglycerides and VLDL), or both. Atherosclerosis is accelerated. A mixed dyslipidemia (plasma triglycerides 2.3–9.0 mmol/L [200–800 mg/dL], cholesterol levels 5.2–10.3 mmol/L [200–400 mg/dL], and HDL levels <10.3 mmol/L [<40 mg/dL] in men and <12.9 mmol/L [<50 mg/dL] in women) and a family history of hyperlipidemia and/or premature cardiovascular disease suggest the diagnosis of FCHL. Many of these pts also have the metabolic syndrome (Chap. 118), and it may be difficult to differentiate familial from secondary causes of hyperlipidemia. All pts should restrict dietary cholesterol and fat and avoid alcohol and oral contraceptives; pts with diabetes should be treated aggressively. An HMG-CoA reductase inhibitor is usually required, and many pts will require a second drug (cholesterol absorption inhibitor, niacin, or fibrate) for optimal control.

### DYSBETALIPOPROTEINEMIA

This rare genetic disorder is associated with homozygosity for an apoprotein variant (apoE2) that has reduced affinity for the LDL receptor. Development of disease requires additional environmental and/or genetic factors. Plasma cholesterol (6.5–13.0 mmol/L [250–500 mg/dL]) and triglycerides (2.8–5.6 mmol/L [250–500 mg/dL]) are increased due to accumulation of VLDL and chylomicron remnant particles. Pts usually present in adulthood with xanthomas and premature coronary and peripheral vascular disease. Cutaneous xanthomas are distinctive, in the form of *palmar* and *tuberoeruptive xanthomas*. Triglycerides and cholesterol are both elevated. Diagnosis is established by lipoprotein electrophoresis (showing a broad beta band) or a ratio of VLDL (by ultracentrifugation) to total plasma triglycerides of >0.3. The disorder is associated with accelerated atherosclerosis. Dietary modifications should be instituted, and HMG-CoA reductase inhibitors, fibrates, and/or niacin may be necessary. Comorbidities, such as diabetes mellitus, obesity, or hypothyroidism, should be optimally managed.

## PREVENTION OF THE COMPLICATIONS OF ATHEROSCLEROSIS

Abundant and compelling data demonstrate that interventions to reduce LDL-C substantially reduces the risk of cardiovascular disease, including MI and stroke, as well as total mortality. Thus, is it imperative that patients with hypercholesterolemia be assessed for cardiovascular risk and for the need for intervention. Patients at high risk for cardiovascular disease who have plasma LDL-C levels in the "normal" range also benefit from intervention to reduce LDL-C levels.

**Lifestyle** The first approach to a patient with hypercholesterolemia and high cardiovascular risk is to make any necessary lifestyle changes. In obese patients, efforts should be made to reduce body weight to the ideal level. Dietary counseling to reduce the content of saturated fats, trans fats, and cholesterol in the diet. Regular aerobic exercise has relatively little impact on reducing plasma LDL-C levels, though has cardiovascular benefits independent of LDL lowering.

**Pharmacologic therapy for hypercholesterolemia** The decision to use LDL-lowering drug therapy—with a statin being first-line therapy—depends on the level of LDL-C as well as the level of cardiovascular risk. In general, patients with a Mendelian disorder of elevated LDL-C such as FH must be treated to reduce the very high lifetime risk of cardiovascular disease, and treatment should be initiated as early as possible in adulthood, and in some cases during childhood. Otherwise, the decision to initiate LDL-lowering drug therapy is generally determined by the level of cardiovascular risk. In patients with established CVD, statin therapy is well supported by clinical trial data and should be used regardless of the LDL-C

level. For patients >40 years old without clinical CVD, the AHA/ACC risk calculator (http://professional.heart.org/professional/GuidelinesStatements/Prevention-Guidelines/UCM_457698_Prevention-Guidelines.jsp) can be used to determine the 10-year absolute risk for CVD, and current guidelines suggest that a 10-year risk >7.5% merits consideration of statin therapy regardless of plasma LDL-C level. For younger patients, the assessment of lifetime risk of CVD may help inform the decision to start a statin.

For a more detailed discussion, see Rader DJ, Hobbs HH: Disorders of Lipoprotein Metabolism, Chap. 421, p. 2435; in HPIM-19.

# 179 Hemochromatosis, Porphyrias, and Wilson's Disease

## HEMOCHROMATOSIS

Hemochromatosis is a disorder of iron storage that results in increased intestinal iron absorption with Fe deposition and damage to many tissues. The classic clinical constellation of hemochromatosis is a pt presenting with bronze skin, liver disease, diabetes, arthropathy, cardiac conduction abnormalities, and hypogonadism. Two major causes of hemochromatosis exist: hereditary (due to inheritance of mutant *HFE* genes) and secondary iron overload (usually the result of ineffective erythropoiesis, such as thalassemia or sideroblastic anemia). *HFE* encodes a protein that is involved in cellular iron sensing and in regulating intestinal iron absorption. *HFE* mutations are very common in populations of Northern European origin (1 in 10 is a carrier). Heterozygotes are asymptomatic; homozygotes show a disease penetrance of ~30%. There is progressive iron overload, with clinical manifestations appearing after age 30–40, typically earlier in men than in women. Alcoholic liver disease and chronic excessive Fe ingestion may also be associated with a moderate increase in hepatic Fe and elevated body Fe stores.

### Clinical Features

Early symptoms include weakness, lassitude, weight loss, a bronze pigmentation or darkening of skin, abdominal pain, and loss of libido. Hepatomegaly occurs in 95% of pts, sometimes in the presence of normal LFTs. If untreated, liver disease progresses to cirrhosis, and further to hepatocellular carcinoma in ~30% of pts with cirrhosis. Other manifestations include skin pigmentation (bronzing), diabetes mellitus (65% of pts), arthropathy (25–59%), cardiac arrhythmias and CHF (15%), and hypogonadotropic hypogonadism. Diabetes mellitus is more common in pts with a family history of diabetes, and hypogonadism may be an isolated early manifestation. Typical signs of portal hypertension and decompensated hepatic cirrhosis may appear late in the clinical course. Adrenal insufficiency, hypothyroidism, and hypoparathyroidism rarely occur.

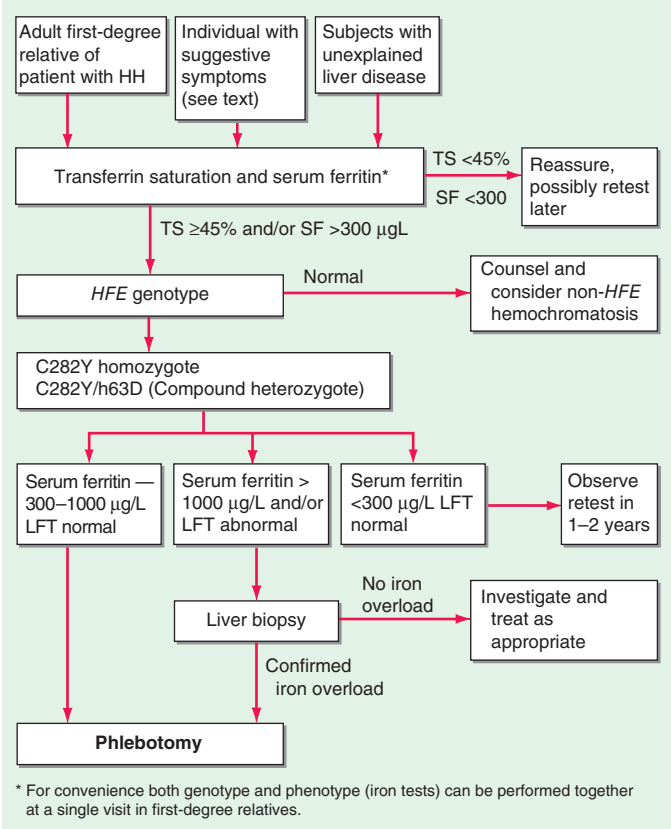



**FIGURE 179-1** Algorithm for screening for *HFE*-associated hemochromatosis. HH, hereditary hemochromatosis, homozygous subject (C282Y +/+); LFT, liver function tests; SF, serum ferritin concentration; TS, transferrin saturation. *(From EJ Eijkelkamp et al: Can J Gastroenterol 14:2, 2000; with permission.)*

## Diagnosis

Serum Fe, percent transferrin saturation, and serum ferritin levels are increased. In an otherwise-healthy person, a fasting serum transferrin saturation >50% is abnormal and suggests homozygosity for hemochromatosis. In most untreated pts with hemochromatosis, the serum ferritin level is also greatly increased. If either the percent transferrin saturation or the serum ferritin level is abnormal, genetic testing for hemochromatosis should be performed. All first-degree relatives of pts with hemochromatosis should be tested for the C282Y and H63D mutations in *HFE*. Liver biopsy may be required in affected individuals to evaluate possible cirrhosis and to quantify tissue iron. An algorithm for evaluating pts with possible hemochromatosis is shown in Fig. 179-1. Death in untreated pts results from cardiac failure (30%), cirrhosis (25%), and hepatocellular carcinoma (30%); the latter may develop despite adequate Fe removal.

### TREATMENT HEMOCHROMATOSIS

Therapy involves removal of excess body Fe, usually by intermittent phlebotomy, and supportive treatment of damaged organs. Since one unit of blood contains ~250 mg Fe, and since up to 25 g of Fe must be removed, phlebotomy is performed weekly for 1–2 years. Less frequent phlebotomy is then used to maintain serum Fe at 9–18 μmol/L (50–100 μg/dL). Chelating agents such as deferoxamine (infused subcutaneously using a portable pump) remove 10–20 mg iron per day, a fraction of that mobilized by weekly phlebotomy. Chelation therapy is indicated, however, when phlebotomy is inappropriate, such as with anemia or hypoproteinemia. Alcohol consumption should be eliminated. End-stage liver disease may require liver transplantation.

## PORPHYRIAS

The porphyrias are inherited disturbances in heme biosynthesis. Each of the nine disorders causes a unique pattern of overproduction, accumulation, and excretion of intermediates of heme synthesis. These disorders are classified as either hepatic or erythropoietic, depending on the primary site of overproduction and accumulation of the porphyrin precursor or porphyrin. The major manifestations of the hepatic porphyrias are neurologic (neuropathic abdominal pain, neuropathy, and mental disturbances), whereas the erythropoietic porphyrias characteristically cause cutaneous photosensitivity. Laboratory testing is required to confirm or exclude the various types of porphyria. However, a definite diagnosis requires demonstration of the specific enzyme deficiency or gene defect. Only the three most common porphyrias are discussed here.

### ACUTE INTERMITTENT PORPHYRIA

This is an autosomal dominant disorder with variable expressivity caused by partial (50%) deficiency in hydroxymethylbilane synthase. It has a prevalence of 1–3 in 100,000 but is much more common in certain parts of the world (Northern Sweden, Great Britain). Manifestations include colicky abdominal pain, vomiting, constipation, port wine–colored urine, and neurologic and psychiatric disturbances. Acute attacks rarely occur before puberty and may last from days to months. Photosensitivity does not occur. Clinical and biochemical manifestations may be precipitated by barbiturates, anticonvulsants, estrogens, oral contraceptives, the luteal phase of the menstrual cycle, alcohol, or low-calorie diets. Diagnosis is established by demonstrating elevation of urinary porphobilinogen (PBG) and γ-aminolevulinic acid (ALA) during an acute attack. Genetic testing, if available, should be used to confirm the diagnosis.

### TREATMENT ACUTE INTERMITTENT PORPHYRIA

As soon as possible after the onset of an attack, 3–4 mg of heme, in the form of heme arginate, heme albumin, or hematin, should be infused daily for 4 days. Heme acts by inhibiting ALA synthase, thereby restraining ALA and PBG production. Administration of IV glucose at rates up to 20 g/h or parenteral nutrition, if oral feeding is not possible for long periods, can be effective in acute attacks. Narcotic analgesics may be required during acute attacks for abdominal pain, and phenothiazines are useful for nausea, vomiting, anxiety, and restlessness. Treatment between attacks involves adequate nutritional intake, avoidance of drugs known to exacerbate the disease, and prompt treatment of other intercurrent diseases or infections. Liver transplantation has been effective in selected patient and gene replacement trials are underway.

### PORPHYRIA CUTANEA TARDA

This is the most common porphyria (2–4 in 100,000) and is characterized by cutaneous photosensitivity and, usually, hepatic disease. It is due to partial deficiency (familial, sporadic, or acquired) of hepatic uroporphyrinogen decarboxylase. Photosensitivity causes facial pigmentation, increased fragility of skin, erythema, and vesicular and ulcerative lesions, typically involving face, forehead, and forearms. Neurologic manifestations are not observed. Contributing factors include excess alcohol, iron, and estrogens. Pts with liver disease are at risk for cirrhosis and hepatocellular carcinoma. Plasma and urine uroporphyrin and 7-carboxylate porphyrin are increased.

#### TREATMENT PORPHYRIA CUTANEA TARDA

Avoidance of precipitating factors, including abstinence from alcohol, estrogens, iron supplements, and other exacerbating drugs, is the first line of therapy. A complete response can almost always be achieved by repeated phlebotomy (every 1–2 weeks) until hepatic iron is reduced. Chloroquine or hydroxychloroquine may be used in low doses (e.g., 125-mg chloroquine phosphate twice weekly) to promote porphyrin excretion in pts unable to undergo or unresponsive to phlebotomy.

### ERYTHROPOIETIC PROTOPORPHYRIA

Erythropoietic protoporphyria is an autosomal dominant disorder due to partial deficiency of ferrochelatase, the last enzyme in the heme biosynthetic pathway. Its prevalence is 1 in 100,000. Porphyrins (primarily protoporphyrin IX) from bone marrow erythrocytes and plasma are deposited in the skin and lead to cutaneous photosensitivity. Skin photosensitivity usually begins in childhood. The skin manifestations differ from those of other porphyrias, in that vesicular lesions are uncommon. Redness, swelling, burning, and itching can develop within minutes of sun exposure and resemble angioedema. Symptoms may seem out of proportion to the visible skin lesions. Chronic skin changes may include lichenification, leathery pseudovesicles, labial grooving, and nail changes. Liver function is usually normal, but liver disease and gallstones may occur. Protoporphyrin levels are increased in bone marrow, circulating erythrocytes, plasma, bile, and feces; protoporphyrin in erythrocytes is free rather than zinc complexed as it is in other types of porphyria or hematologic disorders. Urinary porphyrin levels are normal. Diagnosis is confirmed by identifying a mutation in the ferrochelatase gene.

#### TREATMENT ERYTHROPOIETIC PROTOPORPHYRIA

Avoidance of sun exposure is essential. Oral β-carotene (120–180 mg/d) improves tolerance to sunlight in many pts. The dosage may be adjusted to maintain serum carotene levels between 10 and 15 μmol/L (600–800 μg/dL). Cholestyramine or activated charcoal may promote fecal excretion of protoporphyrin. Plasmapheresis or IV heme therapy may be beneficial.

## WILSON'S DISEASE

Wilson's disease is a rare inherited disorder of copper metabolism, resulting in the toxic accumulation of copper in the liver, brain, and other organs. Individuals with Wilson's disease have mutations in the *ATP7B* gene, which encodes a membrane-bound copper-transporting adenosine triphosphatase (ATPase). Deficiency of this protein impairs copper excretion into the bile and copper incorporation into ceruloplasmin, leading to its rapid degradation.

## Clinical Features

Clinical manifestations typically appear in the mid- to late-teen years but may occur later. Hepatic disease may present as hepatitis, cirrhosis, or hepatic decompensation. In other pts, neurologic or psychiatric disturbances are the first clinical sign and are always accompanied by Kayser-Fleischer rings (corneal deposits of copper). Dystonia, incoordination, or tremor may be present, and dysarthria and dysphagia are common. Autonomic disturbances also may be present. Microscopic hematuria is common. In about 5% of pts, the first manifestation may be primary or secondary amenorrhea or repeated spontaneous abortions.

## Diagnosis

Serum ceruloplasmin levels are often low but may be normal in up to 10% of pts. Urine copper levels are elevated. The "gold standard" for diagnosis is an elevated copper level on liver biopsy. Genetic testing can be confirmatory but the disorder can be caused by a large number of different mutations.

### TREATMENT WILSON'S DISEASE

Hepatitis or cirrhosis without decompensation should be treated with zinc acetate (50-mg elemental Zn PO three times a day). Zinc is effective by blocking intestinal copper absorption and inducing metallothionein, which sequesters copper in a nontoxic complex. For pts with hepatic decompensation, the chelator trientene (500 mg PO twice a day) plus zinc (separated by at least 1 h to avoid zinc chelation in the intestinal lumen) is recommended, although liver transplantation should be considered for severe hepatic decompensation. For initial neurologic therapy, trientine and zinc are recommended for 8 weeks, followed by therapy with zinc alone. Tetrathiomolybdate is an alternative therapeutic option available in the future. Penicillamine is no longer first-line therapy. Zinc treatment does not require monitoring for toxicity, and 24-h urine copper can be followed for a therapeutic response. Trientine may induce bone marrow suppression and proteinuria. With chelation therapy, measuring free serum copper levels (adjusting total serum copper for ceruloplasmin copper) rather than urine copper is used to monitor therapeutic response. Anticopper therapy must be lifelong.

For a more detailed discussion, see Powell LW: Hemochromatosis, Chap. 428, p. 2514; Desnick RJ, Balwani M: The Porphyrias, Chap. 430, p. 2521; Brewer GJ: Wilson's Disease, Chap. 429, p. 2519, in HPIM-19.

# 180 The Neurologic Examination

## MENTAL STATUS EXAMINATION

- *The bare minimum: During the interview, look for difficulties with communication and determine whether the pt has recall and insight into recent and past events.*

The mental status examination is underway as soon as the physician begins observing and talking with the pt. The goal is to evaluate attention, orientation, memory, insight, judgment, and grasp of general information. Attention: ask pt to respond every time a specific item recurs in a list. Orientation: ask about the day, date, and location. Memory: ask pt to immediately recall a sequence of numbers and test recall of a series of objects after defined times (e.g., 5 and 15 min). Remote memory is also evaluated by assessing pt's ability to provide a cogent chronologic history of the illness or personal life events. Recall of historic events or dates of current events can be used to assess knowledge. Evaluation of language function should include assessment of spontaneous speech, naming, repetition, reading, writing, and comprehension. Additional tests such as ability to draw and copy, perform calculations, interpret proverbs or logic problems, identify right versus left, name and identify body parts, etc., are also important.

A useful screening examination of cognitive function is the mini-mental status examination (MMSE), a 30-point test of cognitive function, with each correct answer being scored as 1 point. It includes tests in the areas of: orientation (e.g., identify season/date/month/year/floor/hospital/town/state/country); registration (e.g., name and restate 3 objects); recall (e.g., remember the same three objects 5 minutes later); and language (e.g., name pencil and watch; repeat "no if's and's or but's"; follow a three-step command; obey a written command; and write a sentence and copy a design).

## CRANIAL NERVE (CN) EXAMINATION

- *The bare minimum: Check the fundi, visual fields (VFs), pupil size and reactivity, extraocular movements, and facial movements.*

### CN I

Occlude each nostril sequentially and ask pt to gently sniff and identify a mild test stimulus, such as toothpaste or coffee.

### CN II

Check visual acuity with eyeglasses or contact lens correction using a Snellen chart or similar tool. Map VFs by confrontation testing in each quadrant of VF for each eye individually. The best method is to sit facing pt (2–3 ft apart) and then have pt cover one eye gently and fix uncovered eye on examiner's nose. A small white object (e.g., a cotton-tipped applicator) is then moved slowly from periphery of field toward center until seen. Pt's VF should be mapped against examiner's for comparison. Formal perimetry and tangent screen examination are essential to identify small defects. Optic fundi should be examined with an ophthalmoscope, and the color, size, and degree of swelling or elevation of the optic disc recorded. The retinal vessels should be checked for size, regularity, arteriovenous (AV) nicking at crossing points,

hemorrhage, exudates, and aneurysms. The retina, including the macula, should be examined for abnormal pigmentation and other lesions.

### CN III, IV, VI

Describe size, regularity, and shape of pupils; reaction (direct and consensual) to light; and convergence (pt follows an object as it moves closer). Check for lid drooping, lag, or retraction. Ask pt to follow your finger (and report any double vision) as you move it horizontally to left and right and vertically with each eye first fully adducted then fully abducted. Check for failure to move fully in particular directions and for presence of regular, rhythmic, involuntary oscillations of eyes (nystagmus). Test quick voluntary eye movements (saccades) as well as pursuit (e.g., follow the finger).

### CN V

Feel the masseter and temporalis muscles as pt bites down and test jaw opening, protrusion, and lateral motion against resistance. Examine sensation over entire face. Testing of the corneal reflex is indicated when suggested by the history.

### CN VII

Look for asymmetry of face at rest and with spontaneous movements. Test eyebrow elevation, forehead wrinkling, eye closure, smiling, frowning; check puff, whistle, lip pursing, and chin muscle contraction. Observe for differences in strength of lower and upper facial muscles. Taste on the anterior two-thirds of tongue can be affected by lesions of the seventh CN proximal to the chorda tympani.

### CN VIII

Check ability to hear tuning fork, finger rub, watch tick, and whispered voice at specified distances with each ear. Check for air versus mastoid bone conduction (Rinne) and lateralization of a tuning fork placed on center of forehead (Weber). Accurate, quantitative testing of hearing requires formal audiometry. Remember to examine tympanic membranes.

### CN IX, X

Check for symmetric elevation of palate-uvula with phonation ("ahh"), as well as position of uvula and palatal arch at rest. Sensation in region of tonsils, posterior pharynx, and tongue may also require testing. Pharyngeal ("gag") reflex is evaluated by stimulating posterior pharyngeal wall on each side with a blunt object (e.g., tongue blade). Direct examination of vocal cords by laryngoscopy is necessary in some situations.

### CN XI

Check shoulder shrug (trapezius muscle) and head rotation to each side (sternocleidomastoid muscle) against resistance.

### CN XII

Examine bulk and power of tongue. Look for atrophy, deviation from midline with protrusion, tremor, and small flickering or twitching movements (fasciculations).

## MOTOR EXAMINATION

- *The bare minimum: Look for muscle atrophy and check extremity tone. Assess upper limb strength by checking for pronator drift and strength of wrist or finger extensors. Test for lower limb strength by asking pt to walk normally and on heels and toes and testing power of the toe extensors.*

Power should be systematically tested for major movements at each joint (**Table 180-1**). Strength should be recorded using a reproducible scale (e.g., 0 = no movement,

**TABLE 180-1 MUSCLES THAT MOVE JOINTS**

| | Muscle | Nerve | Segmental Innervation | Function |
|---|---|---|---|---|
| Shoulder | Supraspinatus | Suprascapular n. | C5,6 | Abduction of upper arm |
| | Deltoid | Axillary n. | C5,6 | Abduction of upper arm |
| Forearm | Biceps | Musculocutaneous n. | C5,6 | Flexion of the supinated forearm |
| | Brachioradialis | Radial n. | C5,6 | Forearm flexion with arm between pronation and supination |
| | Triceps | Radial n. | C6,7,8 | Extension of forearm |
| | Ext. carpi radialis | Radial n. | C5,6 | Extension and abduction of hand at the wrist |
| | Ext. carpi ulnaris | P. interosseous n. | C7,8 | Extension and adduction of hand at the wrist |
| | Ext. digitorum | P. interosseous n. | C7,8 | Extension of fingers at the MCP joints |
| | Supinator | P. interosseous n. | C6,7 | Supination of the extended forearm |
| | Flex. carpi radialis | Median n. | C6,7 | Flexion and abduction of hand at the wrist |
| | Flex. carpi ulnaris | Ulnar n. | C7,8,T1 | Flexion and adduction of hand at the wrist |
| | Pronator teres | Median n. | C6,7 | Pronation of the forearm |
| Wrist | Ext. carpi ulnaris | Ulnar n. | C7,8,T1 | Extension/adduction at the wrist |
| | Flex. carpi radialis | Median n. | C6,7 | Flexion/abduction at the wrist |
| Hand | Lumbricals | Median + ulnar n. | C8,T1 | Extension of fingers at PIP joint with the MCP joint extended and fixed |
| | Interossei | Ulnar n. | C8,T1 | Abduction/adduction of the fingers |
| | Flex. digitorum | Median + A. interosseous n. | C7,C8,T1 | Flexion of the fingers |

(*Continued*)

**TABLE 180-1 MUSCLES THAT MOVE JOINTS (*CONTINUED*)**

| | Muscle | Nerve | Segmental Innervation | Function |
|---|---|---|---|---|
| Thumb | Opponens pollicis | Median n. | C8,T1 | Touching the base of the 5th finger with thumb |
| | Ext. pollicis | P. interosseous n. | C7,8 | Extension of the thumb |
| | Add. pollicis | Ulnar n. | C8,T1 | Adduction of the thumb |
| | Abd. pollicis | Median n. | C8,T1 | Abduction of the thumb |
| | Flex. pollicis br. | Ulnar n. | C8,T1 | Flexion of the thumb |
| Thigh | Iliopsoas | Femoral n. | L1,2,3 | Flexion of the thigh |
| | Glutei | Sup. + inf. gluteal n. | L4,L5,S1,S2 | Abduction, extension, and internal rotation of the leg |
| | Quadriceps | Femoral n. | L2,3,4 | Extension of the leg at the knee |
| | Adductors | Obturator n. | L2,3,4 | Adduction of the leg |
| | Hamstrings | Sciatic n. | L5,S1,S2 | Flexion of the leg at the knee |
| Foot | Gastrocnemius | Tibial n. | S1,S2 | Plantar flexion of the foot |
| | Tibialis ant. | Deep peroneal n. | L4,5 | Dorsiflexion of the foot |
| | Peronei | Deep peroneal n. | L5,S1 | Eversion of the foot |
| | Tibialis post. | Tibial n. | L4,5 | Inversion of the foot |
| Toes | Ext. hallucis l. | Deep peroneal n. | L5,S1 | Dorsiflexion of the great toe |

***Abbreviation:*** MCP, metacarpophalangeal; PIP, proximal interphalangeal.

1 = flicker or trace of contraction with no associated movement at a joint, 2 = movement present but cannot be sustained against gravity, 3 = movement against gravity but not against applied resistance, 4 = movement against some degree of resistance, and 5 = full power; 4 values can be supplemented with + and – signs to provide additional gradations). Speed of movement, ability to relax contractions promptly, and fatigue with repetition should all be noted. Loss in bulk and size of muscle (atrophy) should be noted, as well as the presence of irregular involuntary contraction (twitching) of groups of muscle fibers (fasciculations). Any involuntary movements should be noted at rest, during maintained posture, and with voluntary action.

## REFLEXES

- *The bare minimum: Tap the biceps, patellar, and Achilles reflexes.*

Important muscle-stretch reflexes to test routinely and the spinal cord segments involved in their reflex arcs include biceps (C5, 6); brachioradialis (C5, 6); triceps (C7, 8); patellar (L3, 4); and Achilles (S1, 2). A common grading scale is 0 = absent, 1 = present but diminished, 2 = normal, 3 = hyperactive, and 4 = hyperactive with clonus (repetitive rhythmic contractions with maintained stretch). The plantar reflex should be tested by using a blunt-ended object such as the point of a key to stroke the outer border of the sole of the foot from the heel toward the base of the great toe. An abnormal response (Babinski sign) is extension (dorsiflexion) of the great toe at the metatarsophalangeal joint. In some cases, this may be associated with abduction (fanning) of other toes and variable degrees of flexion at ankle, knee, and hip. Normal response is plantar flexion of the toes. Superficial abdominal and anal reflexes are important in certain situations; unlike muscle stretch reflexes, these cutaneous reflexes disappear with CNS lesions.

## SENSORY EXAMINATION

- *The bare minimum: Ask whether the pt can feel light touch and the temperature of a cool object in each distal extremity. Check double simultaneous stimulation using light touch on the hands.*

For most purposes it is sufficient to test sensation to pinprick, touch, position, and vibration in each of the four extremities (**Figs. 180-1** and **180-2**). The Romberg maneuver, primarily a test of proprioception, is tested as follows: pt is asked to stand with feet together while eyes are open, and eyes are then closed; loss of balance with the eyes closed is an abnormal response. Specific problems often require more thorough evaluation. Pts with cerebral lesions may have abnormalities in "discriminative sensation" such as the ability to perceive double simultaneous stimuli, to localize stimuli accurately, to identify closely approximated stimuli as separate (two-point discrimination), to identify objects by touch alone (stereognosis), or to judge weights, evaluate texture, or identify letters or numbers written on the skin surface (graphesthesia).

## COORDINATION AND GAIT

- *The bare minimum: Test rapid alternating movements of the hands and feet, and the finger-to-nose maneuver. Observe the pt while he or she is walking along a straight line.*

The ability to move the index finger accurately from the nose to the examiner's outstretched finger and the ability to slide the heel of each foot from the knee down the shin are tests of coordination. Additional tests (drawing objects in the air, following a moving finger, tapping with index finger against thumb or alternately against each

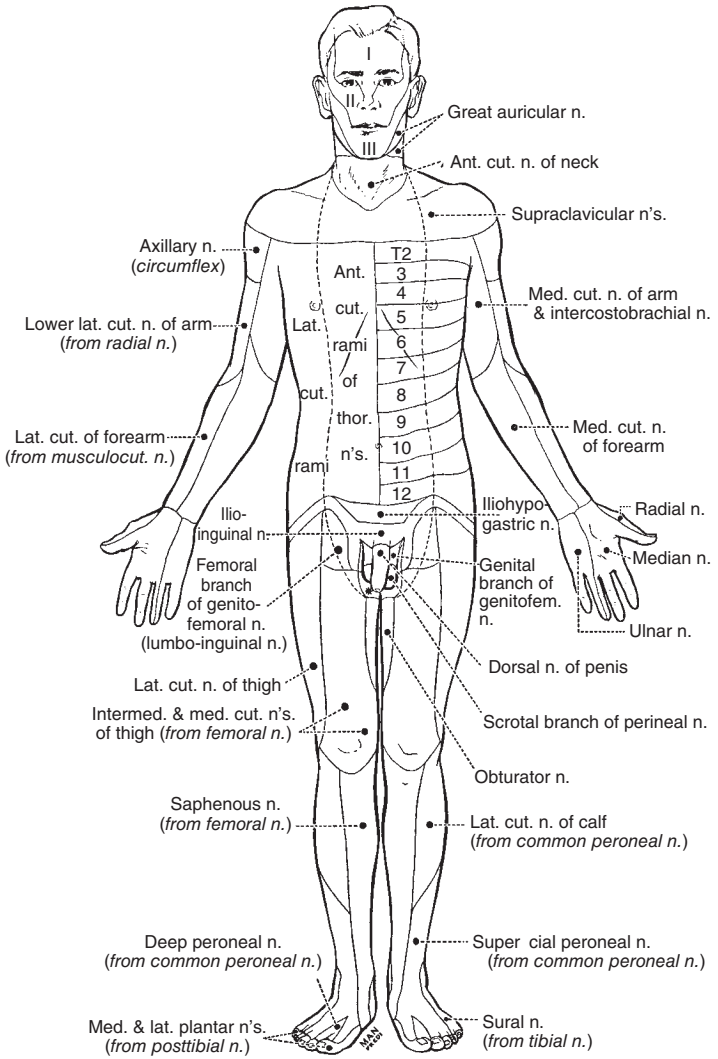



**FIGURE 180-1** The cutaneous fields of peripheral nerves. *(Reproduced by permission from W Haymaker, B Woodhall: Peripheral Nerve Injuries, 2nd ed. Philadelphia, Saunders, 1953.)*

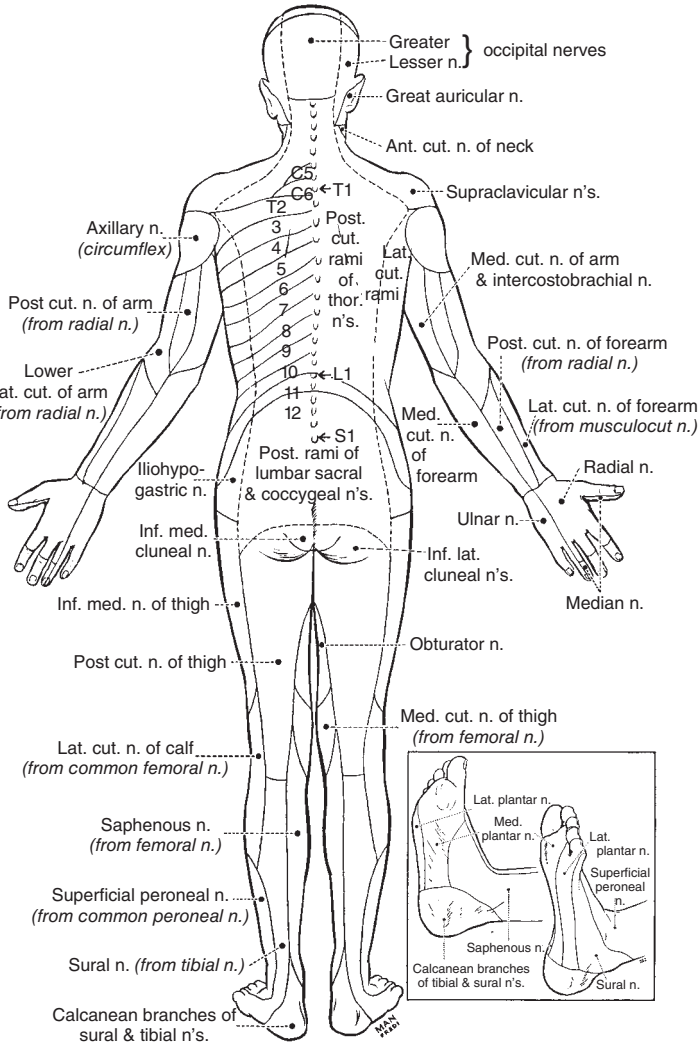



**FIGURE 180-1** (*Continued*)

individual finger) may also be useful. The ability to walk normally, on a straight line (tandem walk), and to turn should all be observed.

## THE NEUROLOGIC METHOD AND LOCALIZATION

The clinical data obtained from the neurologic examination coupled with a careful history are interpreted to arrive at an anatomic localization that best explains the clinical findings (Table 180-2), to narrow the list of diagnostic possibilities, and to select the diagnostic tests most likely to be informative.

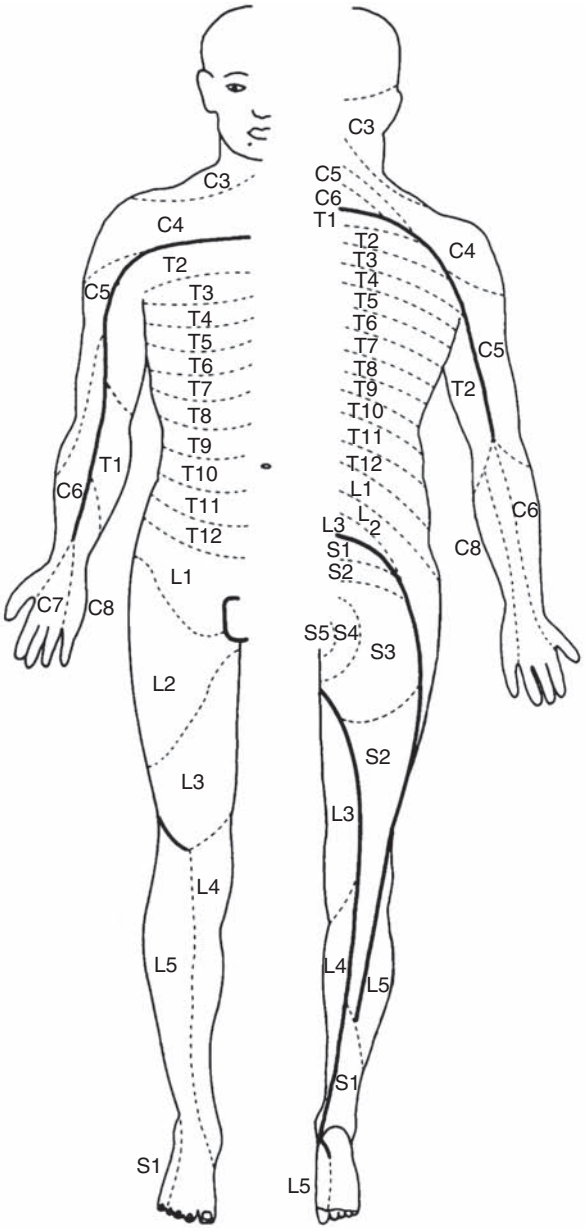
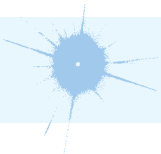



**FIGURE 180-2** Distribution of the sensory spinal roots on the surface of the body (dermatomes). *(From D Sinclair: Mechanisms of Cutaneous Sensation. Oxford, UK, Oxford University Press, 1981; with permission from Dr. David Sinclair.)*

**TABLE 180-2 FINDINGS HELPFUL FOR LOCALIZATIONS WITHIN THE NERVOUS SYSTEM**

| | Signs |
|---|---|
| Cerebrum | Abnormal mental status or cognitive impairment |
| | Seizures |
| | Unilateral weakness[a] and sensory abnormalities including head and limbs |
| | Visual field abnormalities |
| | Movement abnormalities (e.g., diffuse incoordination, tremor, chorea) |
| Brainstem | Isolated cranial nerve abnormalities (single or multiple) |
| | "Crossed" weakness[a] and sensory abnormalities of head and limbs, e.g., weakness of right face and left arm and leg |
| Spinal cord | Back pain or tenderness |
| | Weakness[a] and sensory abnormalities sparing the head |
| | Mixed upper and lower motor neuron findings |
| | Sensory level |
| | Sphincter dysfunction |
| Spinal roots | Radiating limb pain |
| | Weakness[b] or sensory abnormalities following root distribution (see Figs. 180-1 and 180-2) |
| | Loss of reflexes |
| Peripheral nerve | Mid or distal limb pain |
| | Weakness[b] or sensory abnormalities following nerve distribution (see Figs. 180-1 and 180-2) |
| | "Stocking or glove" distribution of sensory loss |
| | Loss of reflexes |
| Neuromuscular junction | Bilateral weakness including face (ptosis, diplopia, dysphagia) and proximal limbs |
| | Increasing weakness with exertion |
| | Sparing of sensation |
| Muscle | Bilateral proximal or distal weakness |
| | Sparing of sensation |

[a]Weakness along with other abnormalities having an "upper motor neuron" pattern, i.e., spasticity, weakness of extensors > flexors in the upper extremity and flexors > extensors in the lower extremity, and hyperreflexia.
[b]Weakness along with other abnormalities having a "lower motor neuron" pattern, i.e., flaccidity and hyporeflexia.



For a more detailed discussion, see Lowenstein DH, Martin JB, Hauser SL: Approach to the Patient with Neurologic Disease, Chap. 437, p. 2535, in HPIM-19.

# 181 Seizures and Epilepsy

A *seizure* is a paroxysmal event due to abnormal excessive or synchronous neuronal activity in the brain. *Epilepsy* is diagnosed when there are recurrent seizures due to a chronic, underlying process.

## APPROACH TO THE PATIENT: Seizure

*Seizure classification*: Essential for diagnosis, therapy, and prognosis (Table 181-1). Seizures are focal or generalized: *focal seizures* originate in networks limited to one cerebral hemisphere, and *generalized seizures* rapidly engage networks distributed across both hemispheres. *Focal seizures* are further divided based on presence or absence of cognitive impairment.

*Generalized seizures* may occur as a primary disorder or result from secondary generalization of a focal seizure. *Tonic-clonic seizures* (grand mal) cause sudden loss of consciousness, loss of postural control, and tonic muscular contraction producing teeth-clenching and rigidity in extension (tonic phase), followed by rhythmic muscular jerking (clonic phase). Tongue-biting and incontinence may occur during the seizure. Recovery of consciousness is typically gradual over many minutes to hours. Headache and confusion are common postictal phenomena. In *absence seizures* (petit mal) there is sudden, brief impairment of consciousness without loss of postural control. Events rarely last longer than 5–10 s but can recur many times per day. Minor motor symptoms are common, while complex automatisms and clonic activity are not. Other types of generalized seizures include tonic, atonic, and myoclonic seizures.

*Etiology*: Seizure type and age of pt provide important clues to etiology (Table 181-2).

**TABLE 181-1 CLASSIFICATION OF SEIZURES**

1. **Focal seizures**
   (Can be further described as having motor, sensory, autonomic, cognitive, or other features)
2. **Generalized seizures**
   a. Absence
      Typical
      Atypical
   b. Tonic clonic
   c. Clonic
   d. Tonic
   e. Atonic
   f. Myoclonic
3. **May be focal, generalized, or unclear**
   Epileptic spasms

**TABLE 181-2 CAUSES OF SEIZURES**

| | |
|---|---|
| Neonates (<1 month) | Perinatal hypoxia and ischemia<br>Intracranial hemorrhage and trauma<br>CNS infection<br>Metabolic disturbances (hypoglycemia, hypocalcemia, hypomagnesemia, pyridoxine deficiency)<br>Drug withdrawal<br>Developmental disorders<br>Genetic disorders |
| Infants and children (>1 month and <12 years) | Febrile<br>Genetic disorders (metabolic, degenerative, primary epilepsy syndromes)<br>CNS infection<br>Developmental disorders<br>Trauma |
| Adolescents (12–18 years) | Trauma<br>Genetic disorders<br>Infection<br>Illicit drug use<br>Brain tumor |
| Young adults (18–35 years) | Trauma<br>Alcohol withdrawal<br>Illicit drug use<br>Brain tumor<br>Autoantibodies |
| Older adults (>35 years) | Cerebrovascular disease<br>Brain tumor<br>Alcohol withdrawal<br>Metabolic disorders (uremia, hepatic failure, electrolyte abnormalities, hypoglycemia, hyperglycemia)<br>Alzheimer's disease and other degenerative CNS diseases<br>Autoantibodies |

## CLINICAL EVALUATION

Careful history is essential since diagnosis of seizures and epilepsy is often based solely on clinical grounds. Differential diagnosis (Table 181-3) includes syncope or psychogenic seizures ("pseudoseizures"). General examination includes search for infection, trauma, toxins, systemic illness, neurocutaneous abnormalities, and vascular disease. A number of drugs lower the seizure threshold (Table 181-4).

**TABLE 181-3 DIFFERENTIAL DIAGNOSIS OF SEIZURES**

| | |
|---|---|
| **Syncope** | **Transient ischemic attack (TIA)** |
| Vasovagal syncope | Basilar artery TIA |
| Cardiac arrhythmia | **Sleep disorders** |
| Valvular heart disease | Narcolepsy/cataplexy |
| Cardiac failure | Benign sleep myoclonus |
| Orthostatic hypotension | **Movement disorders** |
| **Psychological disorders** | Tics |
| Psychogenic seizure | Nonepileptic myoclonus |
| Hyperventilation | Paroxysmal choreoathetosis |
| Panic attack | **Special considerations in children** |
| **Metabolic disturbances** | Breath-holding spells |
| **Alcoholic blackouts** | Migraine with recurrent abdominal pain and cyclic vomiting |
| Delirium tremens | Benign paroxysmal vertigo |
| Hypoglycemia | Apnea |
| Hypoxia | Night terrors |
| **Psychoactive drugs** (e.g., hallucinogens) | Sleepwalking |
| **Migraine** | |
| Confusional migraine | |
| Basilar migraine | |

Asymmetries in neurologic exam suggest brain tumor, stroke, trauma, or other focal lesions. An algorithmic approach is shown in Fig. 181-1.

## LABORATORY EVALUATION

Routine blood studies are indicated to identify the more common metabolic causes of seizures such as abnormalities in electrolytes, glucose, calcium, or magnesium, and hepatic or renal disease. A screen for toxins in blood and urine should be obtained especially when no clear precipitating factor has been identified. A lumbar puncture is indicated if there is any suspicion of CNS infection such as meningitis or encephalitis; it is mandatory in HIV-infected pts even in the absence of symptoms or signs suggesting infection. Testing for autoantibodies in the serum and CSF should be considered in pts presenting with an aggressive form of epilepsy associated with cognitive disturbances.

### Electroencephalography

All pts should be evaluated as soon as possible with an EEG, which measures electrical activity of the brain by recording from electrodes placed on the scalp. The presence of *electrographic seizure activity* during the clinically evident event (i.e., abnormal, repetitive, rhythmic activity having an abrupt onset and termination) clearly establishes the diagnosis. The absence of electrographic seizure activity does not exclude a seizure disorder, however. The EEG is always abnormal during generalized tonic-clonic seizures. Continuous monitoring for prolonged periods may be required to capture the EEG abnormalities. The EEG can show abnormal discharges during the interictal period that support the diagnosis of epilepsy and is useful for classifying seizure disorders, selecting anticonvulsant medications, and determining prognosis.

**TABLE 181-4 DRUGS AND OTHER SUBSTANCES THAT CAN CAUSE SEIZURES**

| |
|---|
| **Alkylating agents** (e.g., busulfan, chlorambucil) |
| **Antimalarials** (chloroquine, mefloquine) |
| **Antimicrobials/antivirals** |
| β-lactam and related compounds |
| Quinolones |
| Acyclovir |
| Isoniazid |
| Ganciclovir |
| **Anesthetics and analgesics** |
| Meperidine |
| Fentanyl |
| Tramadol |
| Local anesthetics |
| **Dietary supplements** |
| Ephedra (ma huang) |
| Gingko |
| **Immunomodulatory drugs** |
| Cyclosporine |
| OKT3 (monoclonal antibodies to T cells) |
| Tacrolimus |
| Interferons |
| **Psychotropics** |
| Antidepressants (e.g., bupropion) |
| Antipsychotics (e.g., clozapine) |
| Lithium |
| **Radiographic contrast agents** |
| **Drug withdrawal** |
| Alcohol |
| Baclofen |
| Barbiturates (short-acting) |
| Benzodiazepines (short-acting) |
| Zolpidem |
| **Drugs of abuse** |
| Amphetamine |
| Cocaine |
| Phencyclidine |
| Methylphenidate |
| **Flumazenil**[a] |

[a]In benzodiazepine-dependent patients.

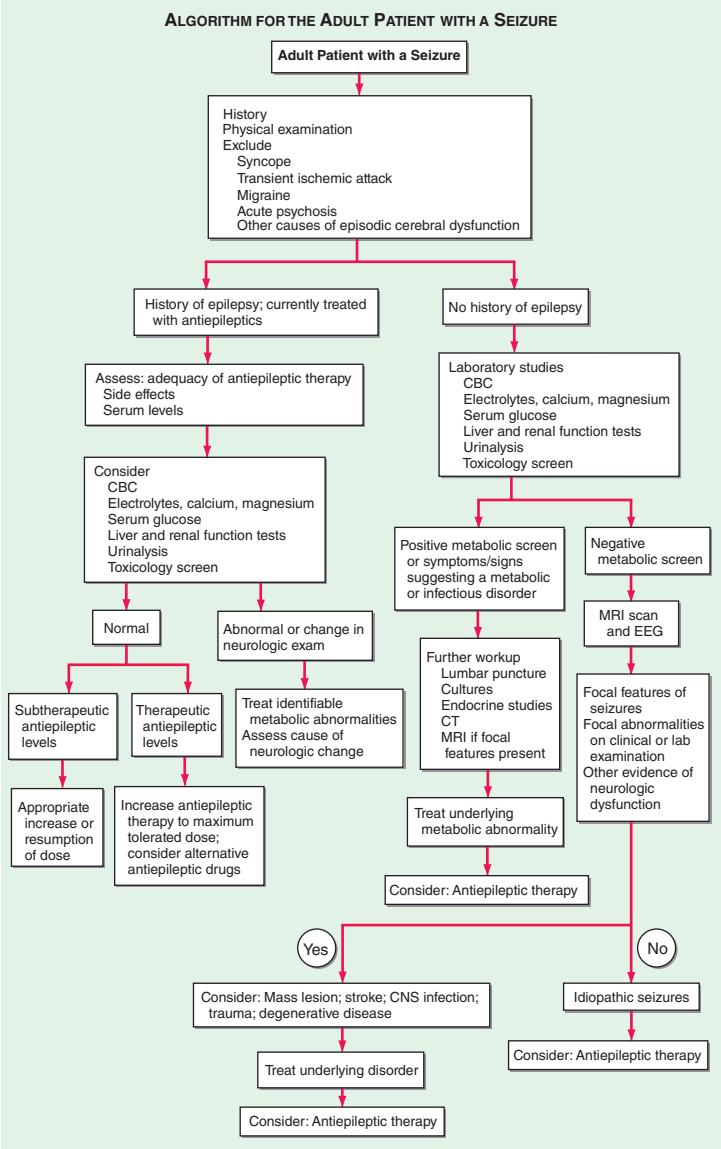



**FIGURE 181-1** Evaluation of the adult pt with a seizure.

## Brain Imaging

All pts with unexplained new-onset seizures should have a brain imaging study (MRI or CT) to search for an underlying structural abnormality; the only exception may be children who have an unambiguous history and examination suggestive of a

**TABLE 181-5 DOSAGE AND ADVERSE EFFECTS OF COMMONLY USED ANTIEPILEPTIC DRUGS**

| Generic Name | Trade Name | Principal Uses | Typical Dose; Dose Interval | Half-Life | Therapeutic Range | Adverse Effects | | Drug Interactions[a] |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Neurologic | Systemic | |
| Carbamazepine | Tegretol[c] | Tonic-clonic<br>Focal-onset | 600–1800 mg/d (15–35 mg/kg, child); bid (capsules or tablets), tid-qid (oral suspension) | 10–17 h (variable due to auto-induction: complete 3–5 wk after initiation) | 4–12 μg/mL | Ataxia<br>Dizziness<br>Diplopia<br>Vertigo | Aplastic anemia<br>Leukopenia<br>Gastrointestinal irritation<br>Hepatotoxicity<br>Hyponatremia | Level decreased by enzyme-inducing drugs[b]<br>Level increased by erythromycin, propoxyphene, isoniazid, cimetidine, fluoxetine |
| Clobazam | Onfi | Lennox-Gastaut syndrome | 10–40 mg/d (5–20 mg/d for patients <30 kg body weight); bid | 36–42 h (71–82 h for less active metabolite) | Not established | Fatigue<br>Sedation<br>Ataxia<br>Aggression<br>Insomnia | Constipation<br>Anorexia<br>Skin rash | Level increased by CYP2C19 inhibitors |
| Clonazepam | Klonopin | Absence<br>Atypical absence<br>Myoclonic | 1–12 mg/d; qd-tid | 24–48 h | 10–70 ng/mL | Ataxia<br>Sedation<br>Lethargy | Anorexia | Level decreased by enzyme-inducing drugs[b] |

(*Continued*)

**TABLE 181-5 DOSAGE AND ADVERSE EFFECTS OF COMMONLY USED ANTIEPILEPTIC DRUGS (*CONTINUED*)**

| Generic Name | Trade Name | Principal Uses | Typical Dose; Dose Interval | Half-Life | Therapeutic Range | Adverse Effects | | Drug Interactions[a] |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Neurologic | Systemic | |
| Ethosuximide | Zarontin | Absence | 750–1250 mg/d (20-40 mg/kg); qd-bid | 60 h, adult<br>30 h, child | 40–100 µg/mL | Ataxia<br>Lethargy<br>Headache | Gastrointestinal irritation<br>Skin rash<br>Bone marrow suppression | Level decreased by enzyme-inducing drugs[b]<br>Level increased by valproic acid |
| Ezogabine | Potiga | Focal-onset | 800–1200 mg/d; tid | 7–11 h | Not established | Dizziness<br>Fatigue<br>Sedation<br>Confusion<br>Vertigo<br>Tremor | Retinal abnormalities<br>Skin discoloration<br>Cardiac conduction (QT interval prolongation)<br>Urinary retention | Level decreased by enzyme-inducing drugs[b] |
| Felbamate | Felbatol | Focal-onset<br>Lennox-Gastaut syndrome<br>Tonic-clonic | 2400–3600 mg/d, tid-qid | 16–22 h | 30–60 µg/mL | Insomnia<br>Dizziness<br>Sedation<br>Headache | Aplastic anemia<br>Hepatic failure<br>Weight loss<br>Gastrointestinal irritation | Increases phenytoin, valproic acid, active carbamazepine metabolite |
| Gabapentin | Neurontin | Focal-onset | 900–2400 mg/d; tid-qid | 5–9 h | 2–20 µg/mL | Sedation<br>Dizziness<br>Ataxia<br>Fatigue | Gastrointestinal irritation<br>Weight gain<br>Edema | No known significant interactions |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Lacosamide | Vimpat | Focal-onset | 200–400 mg/d; bid | 13 h | Not established | Dizziness<br>Ataxia<br>Diplopia<br>Vertigo | Gastrointestinal irritation<br>Cardiac conduction (PR interval prolongation) | Level decreased by enzyme-inducing drugs[b] |
| Lamotrigine | Lamictal[c] | Focal-onset<br>Tonic-clonic<br>Atypical absence<br>Myoclonic<br>Lennox-Gastaut syndrome | 150–500 mg/d; bid (immediate release), daily (extended release) (lower daily dose for regimens with valproic acid; higher daily dose for regimens with an enzyme inducer) | 25 h<br>14 h (with enzyme-inducers), 59 h (with valproic acid) | 2.5–20 µg/mL | Dizziness<br>Diplopia<br>Sedation<br>Ataxia<br>Headache | Skin rash<br>Stevens-Johnson syndrome | Level decreased by enzyme-inducing drugs[b] and oral contraceptives<br>Level increased by valproic acid |
| Levetiracetam | Keppra[c] | Focal-onset | 1000–3000 mg/d; bid (immediate release), daily (extended release) | 6–8 h | 5–45 µg/mL | Sedation<br>Fatigue<br>Incoordination<br>Mood changes | Anemia<br>Leukopenia | No known significant interactions |

(*Continued*)

**TABLE 181-5 DOSAGE AND ADVERSE EFFECTS OF COMMONLY USED ANTIEPILEPTIC DRUGS (*CONTINUED*)**

| Generic Name | Trade Name | Principal Uses | Typical Dose; Dose Interval | Half-Life | Therapeutic Range | Adverse Effects | | Drug Interactions[a] |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Neurologic | Systemic | |
| Oxcarbazepine[c] | Trileptal | Focal-onset<br>Tonic-clonic | 900–2400 mg/d (30–45 mg/kg, child); bid | 10–17 h (for active metabolite) | 10–35 μg/mL | Fatigue<br>Ataxia<br>Dizziness<br>Diplopia<br>Vertigo<br>Headache | See carbamazepine | Level decreased by enzyme-inducing drugs[b]<br>May increase phenytoin |
| Phenobarbital | Luminal | Tonic-clonic<br>Focal-onset | 60–180 mg/d; qd-tid | 90 h | 10–40 μg/mL | Sedation<br>Ataxia<br>Confusion<br>Dizziness<br>Decreased libido<br>Depression | Skin rash | Level increased by valproic acid, phenytoin |
| Phenytoin (diphenylhydantoin) | Dilantin | Tonic-clonic<br>Focal-onset | 300–400 mg/d (3–6 mg/kg, adult; 4–8 mg/kg, child); qd-tid | 24 h (wide variation, dose-dependent) | 10–20 μg/mL | Dizziness<br>Diplopia<br>Ataxia<br>Incoordination<br>Confusion | Gingival hyperplasia<br>Lymphadenopathy<br>Hirsutism<br>Osteomalacia<br>Facial coarsening<br>Skin rash | Level increased by isoniazid, sulfonamides, fluoxetine<br>Level decreased by enzyme-inducing drugs[b]<br>Altered folate metabolism |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Primidone | Mysoline | Tonic-clonic<br>Focal-onset | 750–1000 mg/d; bid-tid | Primidone, 8–15 h<br>Phenobarbital, 90 h | Primidone, 4–12 μg/mL<br>Phenobarbital, 10–40 μg/mL | Same as phenobarbital | | Level increased by valproic acid<br>Level decreased by phenytoin (increased conversion to phenobarbital) |
| Rufinamide | Banzel | Lennox-Gastaut syndrome | 3200 mg/d (45 mg/kg, child); bid | 6–10 h | Not established | Sedation<br>Fatigue<br>Dizziness<br>Ataxia<br>Headache<br>Diplopia | Gastrointestinal irritation<br>Leukopenia<br>Cardiac conduction (QT interval shortening) | Level decreased by enzyme-inducing drugs[b]<br>Level increased by valproic acid<br>May increase phenytoin |
| Tiagabine | Gabitril | Focal-onset | 32–56 mg/d; bid-qid (as adjunct to enzyme-inducing antiepileptic drug regimen) | 2–5 h (with enzyme inducer), 7–9 h (without enzyme inducer) | Not established | Confusion<br>Sedation<br>Depression<br>Dizziness<br>Speech or language problems<br>Paresthesias<br>Psychosis | Gastrointestinal irritation | Level decreased by enzyme-inducing drugs[b] |

(*Continued*)

**TABLE 181-5 DOSAGE AND ADVERSE EFFECTS OF COMMONLY USED ANTIEPILEPTIC DRUGS (*CONTINUED*)**

| Generic Name | Trade Name | Principal Uses | Typical Dose; Dose Interval | Half-Life | Therapeutic Range | Adverse Effects | | Drug Interactions[a] |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Neurologic | Systemic | |
| Topiramate | Topamax | Focal-onset<br>Tonic-clonic<br>Lennox-Gastaut syndrome | 200–400 mg/d; bid (immediate release), daily (extended release) | 20 h (immediate release), 30 h (extended release) | 2–20 μg/mL | Psychomotor slowing<br>Sedation<br>Speech or language problems<br>Fatigue<br>Paresthesias | Renal stones (avoid use with other carbonic anhydrase inhibitors)<br>Glaucoma<br>Weight loss<br>Hypohidrosis | Level decreased by enzyme-inducing drugs[b] |
| Valproic acid (valproate sodium, divalproex sodium) | Depakene<br>Depakote[c] | Tonic-clonic<br>Absence<br>Atypical absence<br>Myoclonic<br>Focal-onset<br>Atonic | 750–2000 mg/d (20–60 mg/kg); bid-qid (immediate and delayed release), daily (extended release) | 15 h | 50–125 μg/mL | Ataxia<br>Sedation<br>Tremor | Hepatotoxicity<br>Thrombocytopenia<br>Gastrointestinal irritation<br>Weight gain<br>Transient alopecia<br>Hyperammonemia | Level decreased by enzyme-inducing drugs[b] |
| Zonisamide | Zonegran | Focal-onset<br>Tonic-clonic | 200–400 mg/d; qd-bid | 50–68 h | 10–40 μg/mL | Sedation<br>Dizziness<br>Confusion<br>Headache<br>Psychosis | Anorexia<br>Renal stones<br>Hypohidrosis | Level decreased by enzyme-inducing drugs[b] |

[a]Examples only; please refer to other sources for comprehensive listings of all potential drug-drug interactions.
[b]Phenytoin, carbamazepine, phenobarbital. [c]Extended-release product available.

**TABLE 181-6 SELECTION OF ANTIEPILEPTIC DRUGS**

| Generalized-Onset Tonic-Clonic | Focal | Typical Absence | Atypical Absence, Myoclonic, Atonic |
|---|---|---|---|
| **First-Line** | | | |
| Lamotrigine | Lamotrigine | Valproic acid | Valproic acid |
| Valproic acid | Carbamazepine | Ethosuximide | Lamotrigine |
| | Oxcarbazepine | Lamotrigine | Topiramate |
| | Phenytoin | | |
| | Levetiracetam | | |
| **Alternatives** | | | |
| Zonisamide[a] | Topiramate | Lamotrigine | Clonazepam |
| Phenytoin | Zonisamide[a] | Clonazepam | Felbamate |
| Carbamazepine | Valproic acid | | Clobazam |
| Oxcarbazepine | Tiagabine[a] | | Rufinamide |
| Topiramate | Gabapentin[a] | | |
| Phenobarbital | Lacosamide[a] | | |
| Primidone | Exogabine[a] | | |
| Felbamate | Phenobarbital | | |
| | Primidone | | |
| | Felbamate | | |

[a]As adjunctive therapy.

benign, generalized seizure disorder such as absence epilepsy. Newer MRI methods have increased the sensitivity for detection of abnormalities of cortical architecture, including hippocampal atrophy associated with mesial temporal sclerosis, as well as abnormalities of cortical neuronal migration.

## TREATMENT SEIZURES AND EPILEPSY

- Acute management of seizures
  - Pt should be placed in semiprone position with head to the side to avoid aspiration.
  - Tongue blades or other objects should not be forced between clenched teeth.
  - Oxygen should be given via face mask.
  - Reversible metabolic disorders (e.g., hypoglycemia, hyponatremia, hypocalcemia, drug or alcohol withdrawal) should be promptly corrected.
  - Treatment of status epilepticus is discussed in Chap. 22.
- Longer-term therapy includes treatment of underlying conditions, avoidance of precipitating factors, prophylactic therapy with antiepileptic medications or surgery, and addressing various psychological and social issues.
- Choice of antiepileptic drug therapy depends on a variety of factors including seizure type, dosing schedule, and potential side effects (**Tables 181-5** and **181-6**).
- Therapeutic goal is complete cessation of seizures without side effects using a single drug (monotherapy) and a dosing schedule that is easy for the pt to follow.
  - If ineffective, medication should be increased to maximal tolerated dose based primarily on clinical response rather than serum levels.

– If still unsuccessful, a second drug should be added, and when control is obtained, the first drug can be slowly tapered. Some pts will require polytherapy with two or more drugs, although monotherapy should be the goal.
– Pts with certain epilepsy syndromes (e.g., temporal lobe epilepsy) are often refractory to medical therapy and benefit from surgical excision of the seizure focus.

For a more detailed discussion, see Lowenstein DH: Seizures and Epilepsy, Chap. 445, p. 2542, in HPIM-19.

# 182 Dementia

## Dementia

Dementia is an acquired deterioration in cognitive ability that impairs the successful performance of activities of daily living. Memory is the most common cognitive ability lost with dementia; 10% of persons over age 70 and 20–40% of individuals over age 85 have clinically identifiable memory loss. Other mental faculties are also affected in dementia, such as language, visuospatial ability, calculation, judgment, and problem solving. Neuropsychiatric and social deficits develop in many dementia syndromes, resulting in depression, withdrawal, hallucinations, delusions, agitation, insomnia, and disinhibition. Dementia is usually chronic and progressive.

## Diagnosis

Brief screening tools such as the Mini-Mental State Examination (MMSE), the Montreal Cognitive Assessment (MOCA), and the Cognistat are useful screening tests and can follow progression. A functional assessment should also be performed to help determine the day-to-day impact of the disorder.

### APPROACH TO THE PATIENT: Dementia

*Differential Diagnosis*: Dementia has many causes (Table 182-1). It is essential to exclude treatable etiologies; the most common potentially reversible diagnoses are depression, hydrocephalus, and alcohol dependence. The major degenerative dementias can usually be distinguished by distinctive symptoms, signs, and neuroimaging features (Table 182-2).

*History*: A subacute onset of confusion may represent delirium and should trigger the search for intoxication, infection, or metabolic derangement (Chap. 16). An elderly person with slowly progressive memory loss over several years is likely to have Alzheimer's disease (AD). A change in personality, disinhibition, gain of weight, or compulsive eating suggests frontotemporal dementia (FTD), not AD;

**TABLE 182-1 DIFFERENTIAL DIAGNOSIS OF DEMENTIA**

| **Most Common Causes of Dementia** | |
|---|---|
| Alzheimer's disease | Alcoholism[a] |
| Vascular dementia | PDD/LBD spectrum |
| Multi-infarct | Drug/medication intoxication[a] |
| Diffuse white matter disease (Binswanger's) | |
| **Less Common Causes of Dementia** | |
| Vitamin deficiencies | Toxic disorders |
| Thiamine ($B_1$): Wernicke's encephalopathy[a] | Drug, medication, and narcotic poisoning[a] |
| $B_{12}$ (subacute combined degeneration)[a] | Heavy metal intoxication[a] |
| Nicotinic acid (pellagra)[a] | Organic toxins |
| Endocrine and other organ failure | Psychiatric |
| Hypothyroidism[a] | Depression (pseudodementia)[a] |
| Adrenal insufficiency and Cushing's syndrome[a] | Schizophrenia[a] |
| Hypo- and hyperparathyroidism[a] | Conversion disorder[a] |
| Renal failure[a] | Degenerative disorders |
| Liver failure[a] | Huntington's disease |
| Pulmonary failure[a] | Multisystem atrophy |
| Chronic infections | Hereditary ataxias (some forms) |
| HIV | Frontotemporal lobar degeneration spectrum |
| Neurosyphilis[a] | Multiple sclerosis |
| Papovavirus (JC virus) (progressive multifocal leukoencephalopathy) | Adult Down's syndrome with Alzheimer's disease |
| Tuberculosis, fungal, and protozoal[a] | ALS-parkinsonism-dementia complex of Guam |
| Whipple's disease[a] | Prion (Creutzfeldt-Jakob and Gerstmann-Sträussler-Scheinker diseases) |
| Head trauma and diffuse brain damage | Miscellaneous |
| Chronic traumatic encephalopathy | Sarcoidosis[a] |
| Chronic subdural hematoma[a] | Vasculitis[a] |
| Postanoxia | CADASIL, etc. |
| Postencephalitis | Acute intermittent porphyria[a] |
| Normal-pressure hydrocephalus[a] | Recurrent nonconvulsive seizures[a] |
| Intracranial hypotension | Additional conditions in children or adolescents |
| Neoplastic | Pantothenate kinase–associated neurodegeneration |
| Primary brain tumor[a] | Subacute sclerosing panencephalitis |
| Metastatic brain tumor[a] | Metabolic disorders (e.g., Wilson's and Leigh's diseases, leukodystrophies, lipid storage diseases, mitochondrial mutations) |
| Paraneoplastic/autoimmune limbic encephalitis[a] | |

[a]Potentially reversible dementia.

***Abbreviations:*** CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; LBD, Lewy body disease; PDD, Parkinson's disease dementia.

**TABLE 182-2 CLINICAL DIFFERENTIATION OF THE MAJOR DEMENTIAS**

| Disease | First Symptom | Mental Status | Neuropsychiatry | Neurology | Imaging |
|---|---|---|---|---|---|
| AD | Memory loss | Episodic memory loss | Irritability, anxiety, depression | Initially normal | Entorhinal cortex and hippocampal atrophy |
| FTD | Apathy; poor judgment/insight, speech/language; hyperorality | Frontal/executive and/or language; spares drawing | Apathy, disinhibition, overeating, compulsivity | May have vertical gaze palsy, axial rigidity, dystonia, alien hand, or MND | Frontal, insular, and/or temporal atrophy; usually spares posterior parietal lobe |
| DLB | Visual hallucinations, REM sleep behavior disorder, delirium, Capgras syndrome, parkinsonism | Drawing and frontal/executive; spares memory; delirium-prone | Visual hallucinations, depression, sleep disorder, delusions | Parkinsonism | Posterior parietal atrophy; hippocampi larger than in AD |
| CJD | Dementia, mood, anxiety, movement disorders | Variable, frontal/executive, focal cortical, memory | Depression, anxiety, psychosis in some | Myoclonus, rigidity, parkinsonism | Cortical ribboning and basal ganglia or thalamus hyperintensity on diffusion/FLAIR MRI |
| Vascular | Often but not always sudden; variable; apathy, falls, focal weakness | Frontal/executive, cognitive slowing; can spare memory | Apathy, delusions, anxiety | Usually motor slowing, spasticity; can be normal | Cortical and/or subcortical infarctions, confluent white matter disease |

***Abbreviations:*** AD, Alzheimer's disease; CBD, cortical basal degeneration; CJD, Creutzfeldt-Jakob disease; DLB, dementia with Lewy bodies; FLAIR, fluid-attenuated inversion recovery; FTD, frontotemporal dementia; MND, motor neuron disease; MRI, magnetic resonance imaging; PSP, progressive supranuclear palsy; REM, rapid eye movement.

apathy, loss of executive function, progressive abnormalities in speech, or relative sparing of memory or visuospatial abilities also suggests FTD. Dementia with Lewy bodies (DLB) is suggested by the early presence of visual hallucinations, parkinsonism, tendency to delirium, sensitivity to psychoactive medications, or a REM behavior disorder (RBD, the loss of skeletal muscle paralysis during dreaming).

A history of stroke suggests vascular dementia, which may also occur with hypertension, atrial fibrillation, peripheral vascular disease, and diabetes. Rapid progression of dementia with myoclonus suggests a prion disease such as Creutzfeldt-Jakob disease (CJD). A rapidly progressive dementia with psychiatric symptoms and seizures suggests paraneoplastic *encephalitis associated with NMDA receptor antibodies*; affected pts are often young women with ovarian teratoma. Gait disturbance is prominent with vascular dementia, Parkinson's disease, DLB, or normal-pressure hydrocephalus. Multiple sex partners or IV drug use should trigger search for an infection, especially HIV or syphilis. A history of head trauma could indicate chronic subdural hematoma, chronic traumatic encephalopathy, or normal-pressure hydrocephalus. Alcoholism may suggest malnutrition and thiamine deficiency. A history of gastric surgery may result in loss of intrinsic factor and vitamin $B_{12}$ deficiency. A careful review of medications, especially of sedatives and tranquilizers, may raise the issue of drug intoxication. A family history of dementia is found in Huntington's disease and in familial forms of AD, FTD, DLB, or prion disorders. Insomnia or weight loss is often seen with depression-related cognitive impairments, which can also be caused by the recent death of a loved one.

*Examination*: It is essential to document the dementia, look for other signs of nervous system involvement, and search for clues of a systemic disease that might be responsible for the cognitive disorder. Typical AD does not affect motor systems until late in the course. In contrast, FTD pts often develop axial rigidity, supranuclear gaze palsy, or features of amyotrophic lateral sclerosis. In DLB, initial symptoms may be the new onset of a parkinsonian syndrome (resting tremor, cogwheel rigidity, bradykinesia, and festinating gait). Unexplained falls, axial rigidity, dysphagia, and gaze deficits suggest progressive supranuclear palsy (PSP).

Focal neurologic deficits may occur in vascular dementia or brain tumor. Dementia with a myelopathy and peripheral neuropathy suggests vitamin $B_{12}$ deficiency. A peripheral neuropathy could also indicate an underlying vitamin deficiency or heavy metal intoxication. Dry cool skin, hair loss, and bradycardia suggest hypothyroidism. Confusion associated with repetitive stereotyped movements may indicate ongoing seizure activity. Hearing impairment or visual loss may produce confusion and disorientation misinterpreted as dementia. Such sensory deficits are common in the elderly.

*Choice of Diagnostic Studies*: A reversible or treatable cause must not be missed, yet no single etiology is common; thus a screen must employ multiple tests, each of which has a low yield. **Table 182-3** lists most screening tests for dementia. Guidelines recommend the routine measurement of a complete blood count, electrolytes, renal and thyroid function, a vitamin $B_{12}$ level, and a neuroimaging study (CT or MRI). Lumbar puncture need not be done routinely but is indicated if infection or inflammation is a consideration; CSF levels of tau protein and amyloid $\beta_{42}$ show differing patterns with the various dementias although their sensitivity and specificity are not yet sufficiently high to warrant routine use. An EEG is rarely helpful except to suggest a prion disease or an underlying nonconvulsive seizure disorder. The role of functional-metabolic imaging in the diagnosis of dementia is still under study; amyloid imaging has recently shown promise for the diagnosis of AD; currently the main clinical value is to exclude AD as the likely cause of dementia in pts who have negative scans. Brain biopsy may be indicated to diagnose vasculitis, potentially treatable neoplasms, or unusual infections.

**TABLE 182-3 EVALUATION OF THE PATIENT WITH DEMENTIA**

| Routine Evaluation | Optional Focused Tests | Occasionally Helpful Tests |
|---|---|---|
| History | Psychometric testing | EEG |
| Physical examination | Chest x-ray | Parathyroid function |
| Laboratory tests | Lumbar puncture | Adrenal function |
| Thyroid function (TSH) | Liver function | Urine heavy metals |
| Vitamin $B_{12}$ | Renal function | RBC sedimentation rate |
| Complete blood count | Urine toxin screen | Angiogram |
| Electrolytes | HIV | Brain biopsy |
| CT/MRI | Apolipoprotein E | SPECT |
| | RPR or VDRL | PET |
| | | Lab screen for autoantibodies |

**Diagnostic Categories**

| Reversible Causes | Irreversible/Degenerative Dementias | Psychiatric Disorders |
|---|---|---|
| Examples | Examples | Depression |
| Hypothyroidism | Alzheimer's | Schizophrenia |
| Thiamine deficiency | Frontotemporal dementia | Conversion reaction |
| Vitamin $B_{12}$ deficiency | Huntington's | |
| Normal-pressure hydrocephalus | Dementia with Lewy bodies | |
| Subdural hematoma | Vascular | |
| Chronic infection | Leukoencephalopathies | |
| Brain tumor | Parkinson's | |
| Drug intoxication | | |
| Autoimmune encephalopathy | | |

**Associated Treatable Conditions**

| | |
|---|---|
| Depression | Agitation |
| Seizures | Caregiver "burnout" |
| Insomnia | Drug side effects |

***Abbreviations:*** PET, positron emission tomography; RPR, rapid plasma reagin (test); SPECT, single-photon emission computed tomography; TSH, thyroid-stimulating hormone; VDRL, Venereal Disease Research Laboratory (test for syphilis).

## ALZHEIMER'S DISEASE

Most common cause of dementia; 10% of all persons over age 70 have significant memory loss, and in more than half the cause is AD. Cost is >$50,000 annually for a single pt with advanced AD.

### Clinical Manifestations

Cognitive changes follow a characteristic pattern beginning with memory impairment and spreading to language and visuospatial deficits, although 20% present with non-memory complaints such as word-finding, organizational, or navigational difficulty. Memory loss is often not recognized initially, in part due to preservation of social

graces until later phases; impaired activities of daily living (keeping track of finances, appointments) draw attention of friends/family. Once the memory loss becomes noticeable to the pt and spouse and falls 1.5 standard deviations below normal on standardized memory tests, the term *mild cognitive impairment* (MCI) is applied; roughly 50% will progress to AD over 4 years. Disorientation, poor judgment, poor concentration, aphasia, and apraxia are increasingly evident as the disease progresses. Pts may be frustrated or unaware of deficit. In end-stage AD, pts become rigid, mute, incontinent, and bedridden. Help may be needed with the simplest tasks, such as eating, dressing, and toilet function. Often, death results from malnutrition, secondary infections, pulmonary emboli, heart disease, or, most commonly, aspiration. Typical duration is 8–10 years, but the course can range from 1 to 25 years.

## Pathogenesis

Risk factors for AD: old age, positive family history, and a history of head trauma with concussion. Pathology: neuritic plaques composed in part of Aβ amyloid, derived from amyloid precursor protein (APP); neurofibrillary tangles composed of abnormally phosphorylated tau protein. The apolipoprotein E (apoE) ε4 allele accelerates age of onset of AD and is associated with sporadic and late-onset familial cases. ApoE testing is not indicated as a predictive test. Rare genetic causes of AD are Down syndrome and mutations in APP, presenilin-1, and presenilin-2 genes; all increase production of Aβ amyloid. Genetic testing available for presenilin mutations; likely to be revealing only in early-age-of-onset familial AD.

## TREATMENT ALZHEIMER'S DISEASE

- AD cannot be cured, and no highly effective drug exists. The focus is on judicious use of cholinesterase inhibitor drugs; symptomatic management of behavioral problems; and building rapport with the pt, family members, and other caregivers.
- Donepezil, rivastigmine, galantamine, and memantine are approved by the FDA for treatment of AD. Due to hepatotoxicity, tacrine is no longer used. With the exception of memantine, their action is inhibition of cholinesterase, with a resulting increase in cerebral levels of acetylcholine. Memantine appears to act by blocking overexcited *N*-methyl-D-aspartate (NMDA) channels.
  - These compounds are only modestly effective and offer little or no benefit in the late stages of AD; they are associated with improved caregiver ratings of pts' functioning and with an apparent decreased rate of decline in cognitive test scores over periods of up to 3 years.
  - Donepezil (Aricept), target dose 10 mg/d PO, has the advantages of few side effects and single daily dosage.
- There is no role for hormone replacement therapy in prevention of AD in women, and no benefit has been found in the treatment of established AD with estrogen.
- Randomized trials of *Ginkgo biloba* have found it to be ineffective. Retrospective studies suggest that NSAIDs and statin medications may have a protective effect on dementia if used prior to the onset of the disease but do not benefit established AD.
- Other experimental approaches target amyloid either through diminishing its production or promoting clearance by passive immunization with monoclonal antibodies. New trials have targeted cognitively normal elderly who are amyloid positive with PET.
- Depression, common in early stages of AD, may respond to antidepressants or cholinesterase inhibitors. Selective serotonin reuptake inhibitors (SSRIs)

are often used due to their low anticholinergic side effects. Management of behavioral problems in conjunction with family and caregivers is essential. Mild sedation may help insomnia.

- Control of agitation usually involves low doses of atypical antipsychotic medications, but recent trials have shown mild efficacy with significant side effects related to sleep and gait; in addition, all of the antipsychotics carry a black box warning in the elderly, increasing the risk of cardiovascular complications and death, and therefore should be used with caution.
- Notebooks and posted daily reminders can function as memory aids in early stages. Kitchens, bathrooms, and bedrooms need evaluation for safety. Pts must eventually stop driving. Caregiver burnout is common; nursing home placement may be necessary. Local and national support groups (Alzheimer's Disease and Related Disorders Association) are valuable resources.

## OTHER CAUSES OF DEMENTIA

### Frontotemporal Dementia

Often begins in the fifth to seventh decades; in this age group it is nearly as prevalent as AD. Unlike AD, behavioral symptoms may predominate in the early stages of FTD. Extremely heterogeneous; presents with combinations of disinhibition, dementia, apraxia, parkinsonism, and motor neuron disease. May be sporadic or inherited. Treatment is symptomatic; no therapies known to slow progression or improve cognitive symptoms. Many of the behaviors that accompany FTD such as depression, hyperorality, compulsions, and irritability may be helped with SSRIs.

### Dementia with Lewy Bodies

Characterized by visual hallucinations, parkinsonism, fluctuating alertness, falls, and often RBD. Dementia can precede or follow the appearance of parkinsonism; when it occurs after an established diagnosis of Parkinson's disease, many use the term Parkinson's disease dementia (PDD). Lewy bodies are intraneuronal cytoplasmic inclusions. Anticholinesterase compounds often provide significant benefit due to a severe cholinergic deficit in DLB. Exercise programs to maximize motor function and protect against fall-related injury, and antidepressants to treat depressive syndromes may be helpful. Antipsychotics in low doses to alleviate psychosis may be considered, although DLB pts are extremely sensitive to these agents and may experience worsening of extrapyramidal symptoms.

### Vascular Dementia

Typically follows a pattern of either multiple strokelike episodes (multi-infarct dementia) or diffuse white matter disease (leukoaraiosis, subcortical arteriosclerotic encephalopathy, Binswanger's disease) (Fig. 182-1). Unlike AD, focal neurologic signs (e.g., hemiparesis) may be apparent at presentation. Treatment focuses on underlying causes of atherosclerosis.

### Normal-Pressure Hydrocephalus (NPH)

Uncommon; presents as a gait disorder (ataxic or apractic), dementia, and urinary incontinence. Gait improves in some pts following ventricular shunting; dementia and incontinence do not improve. The diagnosis is difficult to make, and the clinical picture may overlap with several other causes of dementia including AD; historically many individuals treated for NPH have suffered from other dementias.

### Huntington's Disease

Chorea, behavioral disturbance, and a frontal/executive disorder (Chap. 54). Typical onset fourth to fifth decade but can present at almost any age. Autosomal dominant

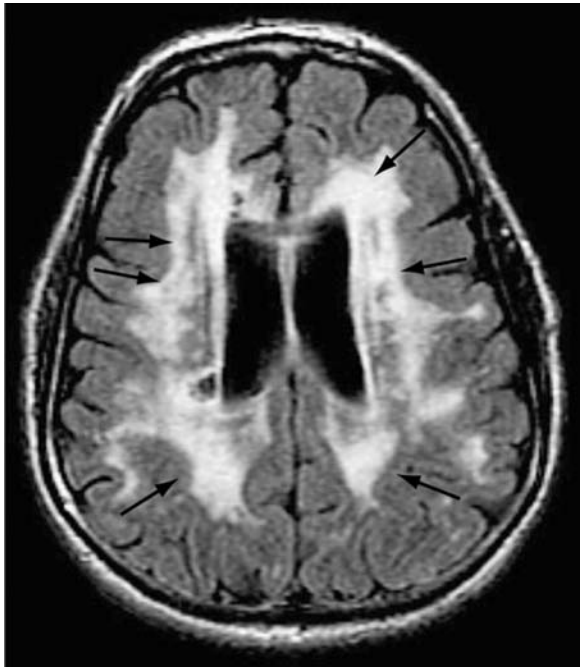


**FIGURE 182-1** Diffuse white matter disease. Axial fluid-attenuated inversion recovery (FLAIR) magnetic resonance image through the lateral ventricles reveals multiple areas of hyperintensity (*arrows*) involving the periventricular white matter as well as the corona radiata and striatum. Although seen in some individuals with normal cognition, this appearance is more pronounced in pts with dementia of a vascular etiology.

inheritance due to expanded trinucleotide repeat in gene encoding the protein huntingtin. Diagnosis confirmed with genetic testing coupled with genetic counseling. Symptomatic treatment of movements and behaviors; SSRIs may help depression.

## Creutzfeldt-Jakob Disease

Prion disorders such as CJD are rare (~1 per million). CJD is a rapidly progressive disorder with dementia, focal cortical signs, rigidity, and myoclonus; death in <1 year from first symptom. The markedly abnormal periodic discharges on EEG and cortical ribboning and basal ganglia hyperintensities on diffusion-weighted and fluid-attenuated inversion recovery MRI are diagnostic features. No proven treatments exist.

For a more detailed discussion, see Seeley WW, Miller BL: Dementia, Chap. 35, p. 170, in HPIM-19; Seeley WW, Miller BL: Alzheimer's Disease and Other Dementias, Chap. 448, p. 2598, in HPIM-19.

# 183 Parkinson's Disease

## CLINICAL FEATURES

*Parkinsonism* is a general term used to define a syndrome manifest as bradykinesia (slowness of voluntary movements) with rigidity and/or tremor; it has a wide differential diagnosis (Table 183-1). *Parkinson's disease* (PD) is idiopathic parkinsonism without evidence of more widespread neurologic involvement. PD afflicts >1 million individuals in the United States. Mean age of onset is about 60 years; course progressive over 10–25 years. Tremor ("pill rolling" of hands) at rest (4–6 Hz). Presentation with tremor confined to one limb or one side of body is common. Other findings: rigidity ("cogwheeling"—increased ratchet-like resistance to passive limb movements), bradykinesia, fixed expressionless face (facial masking) with reduced frequency of blinking, hypophonic voice, drooling, impaired rapid alternating movements, micrographia (small handwriting), reduced arm swing, and flexed "stooped" posture with walking, shuffling gait, difficulty initiating or stopping walking, en-bloc turning (multiple small steps required to turn), retropulsion (tendency to fall backwards). Nonmotor aspects of PD include depression and anxiety, cognitive impairment, sleep disturbances, sensation of inner restlessness, loss of smell (*anosmia*), and disturbances of autonomic function. Normal muscular strength, deep tendon reflexes, and sensory examination. Diagnosis based on history and examination; neuroimaging, EEG, and CSF studies usually normal for age.

**TABLE 183-1 DIFFERENTIAL DIAGNOSIS OF PARKINSONISM**

| Parkinson's Disease | Atypical Parkinsonism | Secondary Parkinsonism | Other Neurodegenerative Disorders |
|---|---|---|---|
| Genetic | Multiple-system atrophy (MSA) | Drug-induced | Wilson's disease |
| Sporadic | Cerebellar type (MSA-c) | Tumor | Huntington's disease |
| Dementia with Lewy bodies | Parkinson type (MSA-p) | Infection | Neurodegeneration with brain iron accumulation |
| | Progressive supranuclear palsy | Vascular | |
| | Corticobasal ganglionic degeneration | Normal-pressure hydrocephalus | SCA 3 (spinocerebellar ataxia) |
| | Frontotemporal dementia | Trauma<br>Liver failure | Fragile X–associated ataxia-tremor-parkinsonism |
| | | Toxins (e.g., carbon monoxide, manganese, MPTP, cyanide, hexane, methanol, carbon disulfide) | Prion disease |
| | | | Dystonia-parkinsonism (DYT3) |
| | | | Alzheimer's disease with parkinsonism |

***Abbreviations:*** MPTP, 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine.

## PATHOPHYSIOLOGY

Most PD cases occur sporadically and are of unknown cause. Degeneration of pigmented pars compacta neurons of the substantia nigra in the midbrain resulting in lack of dopaminergic input to striatum; accumulation of cytoplasmic intraneural inclusion granules (Lewy bodies). Cause of cell death is unknown, but it may result from generation of free radicals and oxidative stress, inflammation, or mitochondrial dysfunction; no environmental factor has yet been conclusively determined to cause typical PD. Rare genetic forms of parkinsonism exist (~5% of cases); most common are mutations in glucocerebrosidase, *LRRK2*, α-synuclein or parkin genes. Early age of onset suggests a possible genetic cause of PD, although *LLRK2* mutations cause PD in the same age range as sporadic.

## DIFFERENTIAL DIAGNOSIS

*Atypical parkinsonism* refers to a group of neurodegenerative conditions usually associated with more widespread neurodegeneration than is found in PD including multiple-system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal ganglionic degeneration (CBGD), and frontotemporal dementia (FTD). Secondary parkinsonism can be associated with drugs (neuroleptics as well as GI medications such as metoclopramide, all of which block dopamine), infection, or exposure to toxins such as carbon monoxide or manganese. Some features to suggest that parkinsonism might be due to a condition other than PD are shown in Table 183-2.

**TABLE 183-2 FEATURES SUGGESTING AN ATYPICAL OR SECONDARY CAUSE OF PARKINSONISM**

| Symptoms/Signs | Alternative Diagnosis to Consider |
|---|---|
| **History** | |
| Early speech and gait impairment (Lack of tremor, lack of motor asymmetry) | Atypical parkinsonism |
| Exposure to neuroleptics | Drug-induced parkinsonism |
| Onset prior to age 40 | Genetic form of PD |
| Liver disease | Wilson's disease, non-Wilsonian hepatolenticular degeneration |
| Early hallucinations and dementia with later development of PD features | Dementia with Lewy bodies |
| Diplopia, impaired down gaze | PSP |
| Poor or no response to an adequate trial of levodopa | Atypical or secondary parkinsonism |
| **Physical Examination** | |
| Dementia as first or early feature | Dementia with Lewy bodies |
| Prominent orthostatic hypotension | MSA-p |
| Prominent cerebellar signs | MSA-c |
| Slow saccades with impaired down gaze | PSP |
| High-frequency (6–10 Hz) symmetric postural tremor with a prominent kinetic component | Essential tremor |

***Abbreviations:*** MSA-c, multiple-system atrophy–cerebellar type; MSA-p, multiple-system atrophy–Parkinson's type; PD, Parkinson's disease; PSP, progressive supranuclear palsy.

## TREATMENT PARKINSON'S DISEASE (SEE FIG. 183-1, TABLE 183-3)

Goals are to maintain function and avoid drug-induced complications; start therapy when symptoms interfere with quality of life. Bradykinesia, tremor, rigidity, and abnormal posture respond early in illness; cognitive symptoms, hypophonia, autonomic dysfunction, and balance difficulties respond poorly.

### LEVODOPA

- Routinely administered in combination with a decarboxylase inhibitor to prevent its peripheral metabolism to dopamine and the development of nausea and vomiting. In the United States, levodopa is combined with carbidopa (Sinemet).
- Levodopa is also available in controlled-release formulations and in with a catechol-O-methyl transferase (COMT) inhibitor (see below).
- Levodopa remains the most effective symptomatic treatment for PD, and lack of response to the medication despite an adequate trial should cause the diagnosis to be questioned.
- Side effects include nausea, vomiting, and orthostatic hypotension that can be avoided by gradual titration.
- Levodopa-induced motor complications consist of fluctuations in motor response and involuntary movements known as dyskinesias.
- When pts initially take the drug, the benefits are long-lasting; with continued treatment, the duration of benefit following an individual dose becomes progressively shorter ("wearing-off effect").

### DOPAMINE AGONISTS

- A diverse group of drugs that act directly on dopamine receptors. Second-generation non-ergot dopamine agonists are commonly used (e.g., pramipexole, ropinirole, rotigotine).
- Compared with levodopa, dopamine agonists are longer acting and thus provide a more uniform stimulation of dopamine receptors; less prone to induce dyskinesias compared with levodopa.
- They are effective as monotherapeutic agents and as adjuncts to carbidopa/levodopa therapy.
- Side effects include nausea, vomiting, and postural hypotension. Hallucinations and cognitive impairment are more common than with levodopa, so caution is urged in those older than 70.
- Sedation with sudden episodes of falling asleep while driving have been reported.
- Associated with impulse-control disorders including pathologic gambling, hypersexuality, and compulsive eating and shopping.

### MAO-B INHIBITORS

- Block central dopamine metabolism and increase synaptic concentrations of the neurotransmitter; generally safe and well tolerated.
- Provide modest antiparkinson benefits when used as monotherapy in early disease.
- Recent work has examined whether these drugs could have a disease-modifying effect; however, long-term significance is uncertain.

### COMT INHIBITORS

- When levodopa is administered with a decarboxylase inhibitor, it is primarily metabolized by COMT; inhibitors of COMT increase the elimination half-life of levodopa and enhance its brain availability.
- Combining levodopa with a COMT inhibitor reduces wearing-off time.

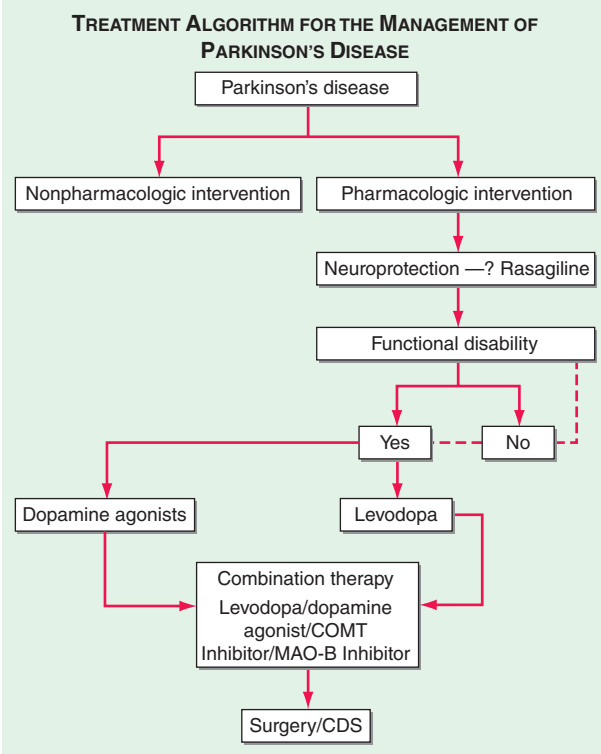



**FIGURE 183-1** Treatment options for the management of Parkinson's disease (PD). Decision points include: (1) Introduction of a neuroprotective therapy: No drug has been established to have or is currently approved for neuroprotection or disease modification, but there are several agents that have this potential based on laboratory and preliminary clinical studies (e.g., rasagiline 1 mg/d, coenzyme Q10 1200 mg/d, the dopamine agonists ropinirole, and pramipexole). (2) When to initiate symptomatic therapy: There is a trend toward initiating therapy at the time of diagnosis or early in the course of the disease because pts may have some disability even at an early stage, and there is the possibility that early treatment may preserve beneficial compensatory mechanisms; however, some experts recommend waiting until there is functional disability before initiating therapy. (3) What therapy to initiate: Many experts favor starting with a monoamine oxidase type B (MAO-B) inhibitor in mildly affected pts because of the good safety profile of the drug and the potential for a disease-modifying effect; dopamine agonists for younger pts with functionally significant disability to reduce the risk of motor complications; and levodopa for pts with more advanced disease, the elderly, or those with cognitive impairment. Recent studies suggest the early employment of polypharmacy using low doses of multiple drugs to avoid side effects associated with high doses of any one agent. (4) Management of motor complications: Motor complications are typically approached with combination therapy to try and reduce dyskinesia and enhance the "on" time. When medical therapies cannot provide satisfactory control, surgical therapies such as DBS or continuous infusion of levodopa/carbidopa intestinal gel can be considered. (5) Nonpharmacologic approaches: Interventions such as exercise, education, and support should be considered throughout the course of the disease. CDS, continuous dopaminergic stimulation; COMT, catechol-O-methyltransferase. (*Adapted from C Olanow et al: Neurology 72:S1, 2009.*)

**TABLE 183-3 DRUGS COMMONLY USED FOR TREATMENT OF PARKINSON'S DISEASE[a]**

| Agent | Available Dosages | Typical Dosing |
|---|---|---|
| Levodopa[a] | | |
| Carbidopa/levodopa | 10/100, 25/100, 25/250 mg | 200–1000 mg levodopa/d 2–4 times/d |
| Benserazide/levodopa | 25/100, 50/200 mg | |
| Carbidopa/levodopa CR | 25/100, 50/200 mg | |
| Benserazide/levodopa MDS | 25/200, 25/250 mg | |
| Parcopa | 10/100, 25/100, 25/250 | |
| Carbidopa/levodopa/ entacapone | 12.5/50/200, 18.75/75/200, 25/100/200, 31.25/125/200, 37.5/150/200, 50/200/200 mg | |
| Dopamine agonists | | |
| Pramipexole | 0.125, 0.25, 0.5, 1.0, 1.5 mg | 0.25–1.0 mg tid |
| Pramipexole ER | 0.375, 0.75, 1.5. 3.0, 4.5 mg | 1–3 mg/d |
| Ropinirole | 0.25, 0.5, 1.0, 3.0 mg | 6–24 mg/d |
| Ropinirole XL | 2, 4, 6, 8 mg | 6–24 mg/d |
| Rotigotine patch | 2-, 4-, 6-, 8-mg patches | 4–24 mg/d |
| Apomorphine SC | | 2–8 mg |
| COMT inhibitors | | |
| Entacapone | 200 mg | 200 mg with each levodopa dose |
| Tolcapone | 100, 200 mg | 100–200 mg tid |
| MAO-B inhibitors | | |
| Selegiline | 5 mg | 5 mg bid |
| Rasagiline | 0.5, 1.0 mg | 1.0 mg QAM |

[a]Treatment should be individualized. Generally, drugs should be started in low doses and titrated to optimal dose.

***Note:*** Drugs should not be withdrawn abruptly but should be gradually lowered or removed as appropriate.

***Abbreviations:*** COMT, catechol-*O*-methyltransferase; MAO-B, monoamine oxidase type B; QAM, every morning.

## OTHER MEDICAL THERAPIES

- Anticholinergics (trihexyphenidyl, benztropine) have their major clinical effect on tremor. Use in the elderly is limited due to propensity for inducing urinary dysfunction, glaucoma, and particularly cognitive impairment.
- The mechanism of action of amantadine is unknown; it has N-methyl-D-aspartate (NMDA) antagonist properties; it is most commonly used as an anti-dyskinesia agent in pts with advanced PD. Side effects include livedo reticularis, weight gain, and impaired cognitive function; discontinue slowly as pts can experience withdrawal symptoms.

## SURGICAL TREATMENTS

- In refractory cases, surgical treatment of PD should be considered.

- Deep-brain stimulation (DBS) of the subthalamic nucleus (STN) or globus pallidus interna (GPi) has largely replaced ablation surgery (e.g., pallidotomy or thalamotomy).
- DBS is primarily indicated for pts who suffer disability resulting from severe tremor or levodopa-induced motor complications; the procedure is profoundly beneficial to many pts.
- Contraindications to surgery include atypical PD, advanced cognitive impairment, major psychiatric illness, substantial medical comorbidities, and advanced age (a relative factor).
- Experimental surgical procedures including cell-based therapies, gene therapies, and trophic factors are under investigation.

For a more detailed discussion, see Olanow CW, Schapira AHV, Obeso JA: Parkinson's Disease and Other Movement Disorders, Chap. 449, p. 2609, in HPIM-19.

# 184 Ataxic Disorders

## CLINICAL PRESENTATION

Symptoms and signs may include gait impairment, visual blurring due to nystagmus, unclear ("scanning") speech, hand incoordination, and tremor with movement. *Differential diagnosis*: Unsteady gait associated with vertigo from vestibular nerve or labyrinthine disease can resemble gait instability of cerebellar disease but produces a perception of movement, dizziness, or light-headedness. Sensory disturbances also can simulate cerebellar disease; with sensory ataxia, imbalance dramatically worsens when visual input is removed (Romberg sign). Bilateral proximal leg weakness also can rarely mimic cerebellar ataxia.

## APPROACH TO THE PATIENT: **Ataxia**

Causes are best grouped by determining whether ataxia is symmetric or focal and by the time course (Table 184-1). Also important to distinguish whether ataxia is present in isolation or is part of a multisystem neurologic disorder. Acute symmetric ataxia is usually due to medications, toxins including alcohol, viral infection, or a postinfectious syndrome (especially varicella). Subacute or chronic symmetric ataxia can result from hypothyroidism, vitamin deficiencies, infections (Lyme disease, tabes dorsalis, prions), alcohol, other toxins, or an inherited condition (see below). An immune-mediated progressive ataxia is associated with antigliadin antibodies; biopsy of the small intestine may reveal villous atrophy of gluten enteropathy. Elevated serum anti–glutamic acid decarboxylase (GAD) antibodies have been associated with a progressive ataxic syndrome affecting speech and gait. Progressive nonfamilial cerebellar ataxia after age 45 suggests a paraneoplastic syndrome, either subacute cortical cerebellar

**TABLE 184-1 ETIOLOGY OF CEREBELLAR ATAXIA**

| Symmetric and Progressive Signs | | | Focal and Ipsilateral Cerebellar Signs | | |
|---|---|---|---|---|---|
| **Acute (Hours to Days)** | **Subacute (Days to Weeks)** | **Chronic (Months to Years)** | **Acute (Hours to Days)** | **Subacute (Days to Weeks)** | **Chronic (Months to Years)** |
| Intoxication: alcohol, lithium, phenytoin, barbiturates (positive history and toxicology screen)<br>Acute viral cerebellitis (CSF supportive of acute viral infection)<br>Postinfection syndrome | Intoxication: mercury, solvents, gasoline, glue; cytotoxic chemotherapeutic, hemotherapeutic drugs<br>Alcoholic-nutritional (vitamin $B_1$ and $B_{12}$ deficiency)<br>Lyme disease | Paraneoplasticsyndrome<br>Antigliadin antibody syndrome<br>Hypothyroidism<br>Inherited diseases<br>Tabes dorsalis (tertiary syphilis)<br>Phenytoin toxicity<br>Amiodarone | Vascular: cerebellar infarction, hemorrhage, or subdural hematoma<br>Infectious: cerebellar abscess (mass lesion on MRI/CT, history in support of lesion) | Neoplastic: cerebellar glioma or metastatic tumor (positive for neoplasm on MRI/CT)<br>Demyelinating: multiple sclerosis (history, CSF, and MRI are consistent)<br>AIDS-related multifocal leukoencephalopathy (positive HIV test and CD4+ cell count for AIDS) | Stable gliosis secondary to vascular lesion or demyelinating plaque (stable lesion on MRI/CT older than several months)<br>Congenital lesion: Chiari or Dandy-Walker malformations (malformation noted on MRI/CT) |

degeneration (ovarian, breast, lung, Hodgkin's) or opsoclonus-myoclonus (neuroblastoma, breast, lung).

Unilateral ataxia suggests a focal lesion in the ipsilateral cerebellar hemisphere or its connections. An important cause of acute unilateral ataxia is stroke. Mass effect from cerebellar hemorrhage or swelling from cerebellar infarction can compress brainstem structures, producing altered consciousness and ipsilateral pontine signs (small pupils, sixth or seventh nerve palsies); limb ataxia may not be prominent. Other diseases producing asymmetric or unilateral ataxia include tumors, multiple sclerosis, progressive multifocal leukoencephalopathy (immunodeficiency states), and congenital malformations.

## INHERITED ATAXIAS

May be autosomal dominant, autosomal recessive, or mitochondrial (maternal inheritance); more than 30 disorders recognized (see Chap. 451e in HPIM-19). Friedreich's ataxia is most common; autosomal recessive, onset before age 25; ataxia with areflexia, upgoing toes, vibration and position sense deficits, cardiomyopathy, hammer toes, scoliosis; linked to expanded trinucleotide repeat in the intron of gene encoding frataxin; a second form is associated with genetically determined vitamin E deficiency syndrome. Common dominantly inherited ataxias are spinocerebellar ataxia (SCA)1 (olivopontocerebellar atrophy; "ataxin-1" gene) (Fig. 184-1), SCA2 (ataxin-2; pts from Cuba and India) and SCA3 (Machado-Joseph disease); all may

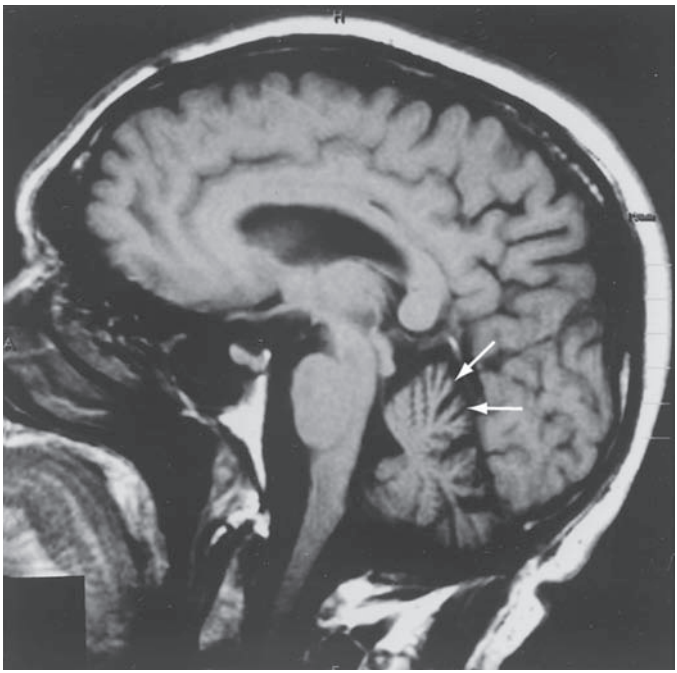


**FIGURE 184-1** Sagittal MRI of the brain of a 60-year-old man with gait ataxia and dysarthria due to SCA1, illustrating cerebellar atrophy (*arrows*). SCA1, spinocerebellar ataxia type 1.

manifest as ataxia with brainstem and/or extrapyramidal signs; SCA3 may also have dystonia and amyotrophy; genes for each disorder contain unstable trinucleotide repeats in coding region.

### EVALUATION

Diagnostic approach is determined by the nature of the ataxia (Table 184-1). For symmetric ataxias, drug and toxicology screens; vitamin $B_1$, $B_{12}$, and E levels; thyroid function tests; antibody tests for syphilis and Lyme infection; antigliadin and anti-GAD antibodies; paraneoplastic antibodies (Chap. 77); and CSF studies often indicated. Genetic testing is available for many inherited ataxias. For unilateral or asymmetric ataxias, brain MRI or CT scan is the initial test of choice; CT is insensitive for nonhemorrhagic lesions of the cerebellum.

### TREATMENT ATAXIA

- The most important goal is to identify treatable entities including hypothyroidism, vitamin deficiency, and infectious causes.
- Ataxia with antigliadin antibodies and gluten enteropathy may improve with a gluten-free diet.
- Paraneoplastic disorders are often refractory to therapy, but some pts improve following removal of the tumor or immunotherapy (Chap. 77).
- Vitamins $B_1$, $B_{12}$, and E should be administered to pts with deficient levels.
- The deleterious effects of phenytoin and alcohol on the cerebellum are well known, and these exposures should be avoided in pts with ataxia of any cause.
- There is no proven therapy for any of the autosomal dominant ataxias; family and genetic counseling are important.
- There is preliminary evidence that idebenone, a free-radical scavenger, can improve myocardial hypertrophy in Friedreich's ataxia; there is no evidence that it improves neurologic function.
- Cerebellar hemorrhage and other mass lesions of the posterior fossa may require emergent surgical treatment to prevent fatal brainstem compression.

For a more detailed discussion, see Rosenberg RN: Ataxic Disorders, Chap. 450, p. 2626, in HPIM-19.

# 185 ALS and Other Motor Neuron Diseases

Amyotrophic lateral sclerosis (ALS) is the most common form of progressive motor neuron disease (Table 185-1). ALS is caused by degeneration of motor neurons at all levels of the CNS, including anterior horns of the spinal cord, brainstem motor nuclei, and motor cortex. Familial ALS (FALS) represents 5–10% of the total and is inherited usually as an autosomal dominant disorder.

**TABLE 185-1 SPORADIC MOTOR NEURON DISEASES**

| Chronic | Entity |
|---|---|
| Upper and lower motor neuron | Amyotrophic lateral sclerosis |
| Predominantly upper motor neuron | Primary lateral sclerosis |
| Predominantly lower motor neuron | Multifocal motor neuropathy with conduction block |
| | Motor neuropathy with paraproteinemia or cancer |
| | Motor predominant peripheral neuropathies |
| **Other** | |
| Associated with other neurodegenerative disorders | |
| Secondary motor neuron disorders (see Table 185-2) | |
| **Acute** | |
| Poliomyelitis | |
| Herpes zoster | |
| Coxsackie virus | |
| West Nile virus | |

## CLINICAL FEATURES

Onset is usually midlife, with most cases progressing to death in 3–5 years. In most societies there is an incidence of 1–3 per 100,000 and a prevalence of 3–5 per 100,000. Presentation is variable depending on whether upper motor or lower motor neurons are more prominently involved initially.

Common initial symptoms are weakness, muscle wasting, stiffness and cramping, and twitching in muscles of hands and arms, often first in the intrinsic hand muscles. Legs are less severely involved than arms, with complaints of leg stiffness, cramping, and weakness common. Symptoms of brainstem involvement include dysphagia, which may lead to aspiration pneumonia and compromised energy intake; there may be prominent wasting of the tongue leading to difficulty in articulation (dysarthria), phonation, and deglutition. Weakness of ventilatory muscles leads to respiratory insufficiency. Additional features that characterize ALS are lack of sensory abnormalities, pseudobulbar palsy (e.g., involuntary laughter, crying), and absence of bowel or bladder dysfunction. Dementia is not a component of sporadic ALS; in some families ALS is co-inherited with frontotemporal dementia characterized by behavioral abnormalities due to frontal lobe dysfunction (Chap. 182).

## PATHOPHYSIOLOGY

Pathologic hallmark is death of lower motor neurons (consisting of anterior horn cells in the spinal cord and their brainstem homologues innervating bulbar muscles) and upper, or corticospinal, motor neurons (originating in layer five of the motor cortex and descending via the pyramidal tract to synapse with lower motor neurons). Although at onset ALS may involve selective loss of only upper or lower motor neurons, it ultimately causes progressive loss of both; the absence of clear involvement of both motor neuron types should call into question the diagnosis of ALS.

## LABORATORY EVALUATION

EMG provides objective evidence of extensive muscle denervation not confined to the territory of individual peripheral nerves and nerve roots. CSF is usually normal. Muscle enzymes (e.g., CK) may be elevated.

Several types of secondary motor neuron disorders that resemble ALS are treatable (Table 185-2); therefore all pts should have a careful search for these disorders.

**TABLE 185-2 ETIOLOGY OF MOTOR NEURON DISORDERS**

| Diagnostic Category | Investigation |
|---|---|
| Structural lesions<br>Parasagittal or foramen magnum tumors<br>Cervical spondylosis<br>Chiari malformation of syrinx<br>Spinal cord arteriovenous malformation | MRI scan of head (including foramen magnum and cervical spine) |
| Infections<br>Bacterial—tetanus, Lyme<br>Viral—poliomyelitis, herpes zoster<br>Retroviral—myelopathy | CSF examination, culture<br>Lyme titer<br>Anti-viral antibody<br>HTLV-1 titers |
| Intoxications, physical agents<br>Toxins—lead, aluminum, others<br>Drugs—strychnine, phenytoin<br>Electric short, x-irradiation | 24-h urine for heavy metals<br>Serum lead level |
| Immunologic mechanisms<br>Plasma cell dyscrasias<br>Autoimmune polyradiculopathy<br>Motor neuropathy with conduction block<br>Paraneoplastic<br>Paracarcinomatous | Complete blood count[a]<br>Sedimentation rate[a]<br>Total protein[a]<br>Anti-GM1 antibodies[a]<br>Anti-Hu antibody<br>MRI scan, bone marrow biopsy |
| Metabolic<br>Hypoglycemia<br>Hyperparathyroidism<br>Hyperthyroidism<br>Deficiency of folate, vitamin $B_{12}$, vitamin E<br>Malabsorption<br>Deficiency of copper, zinc<br>Mitochondrial dysfunction | Fasting blood sugar[a]<br>Routine chemistries including calcium[a]<br>PTH<br>Thyroid function[a]<br>Vitamin $B_{12}$, vitamin E, folate[a]<br>Serum zinc, copper[a]<br>24-h stool fat, carotene, prothrombin time<br>Fasting lactate, pyruvate, ammonia<br>Consider mtDNA |

(*Continued*)

**TABLE 185-2 ETIOLOGY OF MOTOR NEURON DISORDERS (*CONTINUED*)**

| Diagnostic Category | Investigation |
|---|---|
| Hyperlipidemia | Lipid electrophoresis |
| Hyperglycinuria | Urine and serum amino acids |
| | CSF amino acids |
| Hereditary disorders | WBC DNA for mutational analysis |
| Superoxide dismutase | |
| TDP43 | |
| FUS/TLS | |
| Androgen receptor defect (Kennedy's disease) | |
| Hexosaminidase deficiency | |
| Infantile a-glucosidase deficiency (Pompe's disease) | |

[a]Should be obtained in all cases.
***Abbreviations:*** FUS/TLS, fused in sarcoma/translocated in liposarcoma; HTLV-1, human T-cell lymphotropic virus; PTH, parathyroid.

MRI or CT myelography is often required to exclude compressive lesions of the foramen magnum or cervical spine. When involvement is restricted to lower motor neurons only, another important entity is multifocal motor neuropathy with conduction block (MMN). A diffuse, lower motor axonal neuropathy mimicking ALS sometimes evolves in association with hematopoietic disorders such as lymphoma or multiple myeloma; an M-component in serum should prompt consideration of a bone marrow biopsy. Lyme disease may also cause an axonal, lower motor neuropathy, typically with intense proximal limb pain and a CSF pleocytosis. Other treatable disorders that occasionally mimic ALS are chronic lead poisoning and thyrotoxicosis.

Pulmonary function studies may aid in management of ventilation. Swallowing evaluation identifies those at risk for aspiration. Genetic testing is available for superoxide dismutase 1 (SOD1) (20% of FALS) and for rare mutations in other genes.

## TREATMENT AMYOTROPHIC LATERAL SCLEROSIS

- There is no treatment that arrests the underlying pathologic process in ALS.
- The drug riluzole produces modest lengthening of survival; in one trial the survival rate at 18 months with riluzole (100 mg/d) was similar to placebo at 15 months. It may act by diminishing glutamate release and thereby decreasing excitotoxic neuronal cell death. Side effects of riluzole include nausea, dizziness, weight loss, and elevation of liver enzymes.
- Multiple therapies are presently in clinical trials for ALS including small molecules, mesenchymal stem cells, and immunosuppression; interventions such as antisense oligonucleotides that diminish expression of mutant SOD1 protein are nearing trial for SOD1-mediated ALS.
- A variety of rehabilitative aids may substantially assist ALS pts. Foot-drop splints facilitate ambulation, and finger extension splints can potentiate grip.
- Respiratory support may be life-sustaining. For pts who decide against long-term ventilation by tracheostomy, positive-pressure ventilation by mouth or nose provides transient (several weeks) relief from hypercarbia and hypoxia.

Also beneficial are respiratory devices that produce an artificial cough; these help to clear airways and prevent aspiration pneumonia.

- When bulbar disease prevents normal chewing and swallowing, gastrostomy is helpful in restoring normal nutrition and hydration.
- Speech synthesizers can augment speech when there is advanced bulbar palsy.
- Web-based information on ALS is offered by the Amyotrophic Lateral Sclerosis Association (*www.alsa.org*).

For a more detailed discussion, see Brown RH Jr: Amyotrophic Lateral Sclerosis and Other Motor Neuron Diseases, Chap. 452, p. 2631, in HPIM-19.

# 186 Autonomic Nervous System Disorders

The autonomic nervous system (ANS) (Fig. 186-1) innervates the entire neuraxis and permeates all organ systems. It regulates bp, heart rate, sleep, and bladder and bowel function. It operates automatically, so that its full importance becomes recognized only when ANS function is compromised, resulting in dysautonomia.

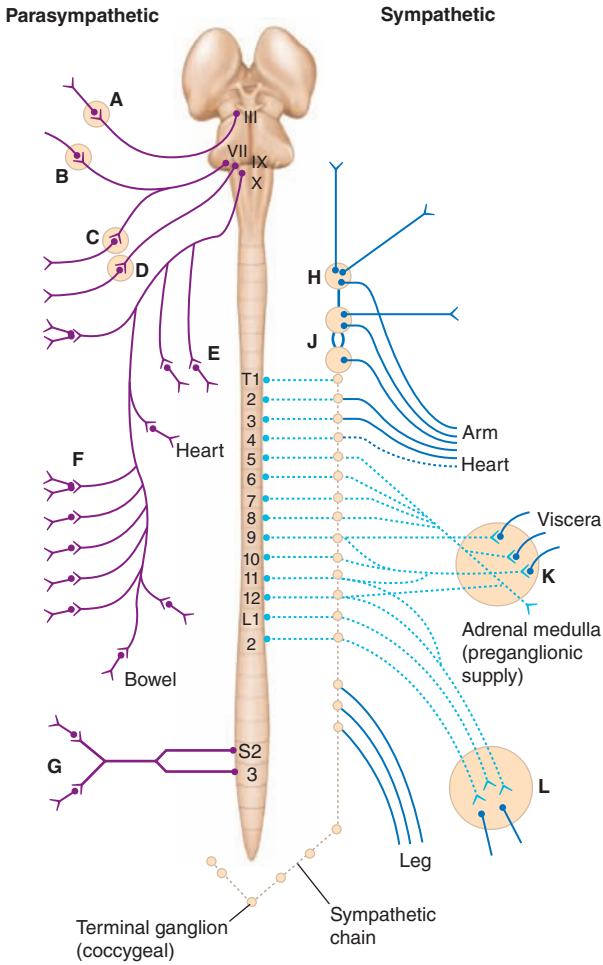
Key features of the ANS are summarized in Table 186-1. Responses to sympathetic or parasympathetic activation often have opposite effects; partial activation of both systems allows for simultaneous integration of multiple body functions.

Consider disorders of autonomic function in the differential diagnosis of pts with unexplained orthostatic hypotension (OH), sleep dysfunction, impotence, bladder dysfunction (urinary frequency, hesitancy, or incontinence), diarrhea, constipation, upper gastrointestinal symptoms (bloating, nausea, vomiting of old food), impaired lacrimation, or altered sweating (hyperhidrosis or hypohidrosis).

OH is often the most disabling feature of autonomic dysfunction. Syncope results when the drop in bp impairs cerebral perfusion (Chap. 50). Other manifestations of impaired baroreflexes are supine hypertension, a fixed heart rate regardless of posture, postprandial hypotension, and a high nocturnal bp. Many pts with OH have a preceding diagnosis of hypertension. Most causes of OH are not neurologic in origin; these must be distinguished from neurogenic causes.

## APPROACH TO THE PATIENT: Autonomic Nervous System Disorders

The first step in the evaluation of OH is to exclude treatable causes. History should include a review of medications that may cause OH (e.g., diuretics, antihypertensives, antidepressants, ethanol, narcotics, insulin, dopamine agonists, barbiturates, and calcium channel-blocking agents); precipitation of OH by medications may also be the first sign of an underlying autonomic disorder. History may reveal an underlying cause for symptoms (e.g., diabetes, Parkinson's




**Parasympathetic system**
from cranial nerves III, VII, IX, X and from sacral nerves 2 and 3

**Sympathetic system**
from T1 to L2
Preganglionic fibers
Postganglionic fibers

- **A** Ciliary ganglion
- **B** Sphenopalatine (pterygopalatine) ganglion
- **C** Submandibular ganglion
- **D** Otic ganglion
- **E** Vagal ganglion cells in the heart wall
- **F** Vagal ganglion cells in bowel wall
- **G** Pelvic ganglia
- **H** Superior cervical ganglion
- **J** Middle cervical ganglion and inferior cervical (stellate) ganglion including T1 ganglion
- **K** Coeliac and other abdominal ganglia
- **L** Lower abdominal sympathetic ganglia

**FIGURE 186-1** Schematic representation of the autonomic nervous system. *(From M. Moskowitz: Clin Endocrinol Metab 6:745, 1977.)*

**TABLE 186-1 FUNCTIONAL CONSEQUENCES OF NORMAL ANS ACTIVATION**

| | Sympathetic | Parasympathetic |
|---|---|---|
| Heart rate | Increased | Decreased |
| Blood pressure | Increased | Mildly decreased |
| Bladder | Increased sphincter tone | Voiding (decreased tone) |
| Bowel motility | Decreased motility | Increased |
| Lung | Bronchodilation | Bronchoconstriction |
| Sweat glands | Sweating | — |
| Pupils | Dilation | Constriction |
| Adrenal glands | Catecholamine release | — |
| Sexual function | Ejaculation, orgasm | Erection |
| Lacrimal glands | — | Tearing |
| Parotid glands | — | Salivation |

***Abbreviation:*** ANS, autonomic nervous system.

disease) or identify causative mechanisms (e.g., cardiac pump failure, reduced intravascular volume). Any relationship of symptoms to meals (splanchnic pooling), standing on awakening in the morning (intravascular volume depletion), ambient warming (vasodilatation), or exercise (muscle arteriolar vasodilatation) should be sought.

Physical examination includes measurement of supine and standing pulse and bp. OH is defined as a sustained drop in systolic (≥20 mmHg) or diastolic (≥10 mmHg) bp within 2–3 min of standing. In nonneurogenic causes of OH (such as hypovolemia), the bp drop is accompanied by a compensatory increase in heart rate of >15 beats/min. A clue to neurogenic OH is aggravation or precipitation of OH by autonomic stressors (such as a meal, hot tub/hot bath, and exercise). Neurologic evaluation should include a mental status examination (to exclude neurodegenerative disorders), cranial nerve examination (impaired downgaze in progressive supranuclear palsy), pupils (Horner's or Adie's pupils), motor tone (Parkinson's), and sensory examination (polyneuropathies). In pts without a clear initial diagnosis, follow-up evaluations every few months or whenever symptoms worsen may reveal the underlying cause.

*Autonomic testing :* Autonomic function tests are helpful when history and physical examination findings are inconclusive, to detect subclinical involvement, or to follow the course of an autonomic disorder. Heart rate variation with deep breathing is a measure of vagal function. The Valsalva maneuver measures changes in heart rate and bp while a constant expiratory pressure of 40 mmHg is maintained for 15 s. The Valsalva ratio is the maximum heart rate during the maneuver divided by the minimum heart rate following the maneuver; the ratio reflects cardiovagal function. Tilt-table beat-to-beat bp measurements in the supine, 70° tilt, and tilt-back positions can be used to evaluate orthostatic failure in bp control in pts with unexplained syncope. Most pts with syncope do not have autonomic failure; the tilt-table test can be used to diagnose vasovagal syncope with high sensitivity, specificity, and reproducibility.

Other tests of autonomic function include the quantitative sudomotor axon reflex test (QSART) and the thermoregulatory sweat test (TST). The QSART provides quantitative measure of regional autonomic function mediated by

acetylcholine (ACh)-induced sweating. The TST provides a qualitative measure of sweating in response to a standardized elevation of body temperature. For a more complete discussion of autonomic function tests, see Chap. 454, HPIM-19.

## DISORDERS OF THE AUTONOMIC NERVOUS SYSTEM

Autonomic disorders may occur with many disorders of the central and/or peripheral nervous systems (Table 186-2). Diseases of the CNS may cause ANS dysfunction at many levels, including hypothalamus, brainstem, or spinal cord.

*Multiple system atrophy* (MSA) is a progressive neurodegenerative disorder comprising autonomic failure (OH and/or a neurogenic bladder) combined with either parkinsonism (MSA-p) or cerebellar signs (MSA-c), often with progressive cognitive dysfunction. Dysautonomia is also common in advanced Parkinson's disease and in dementia with Lewy bodies.

*Spinal cord injury* may produce autonomic hyperreflexia affecting bowel, bladder, sexual, temperature-regulation, or cardiovascular functions. With spinal cord lesions above T6, increased autonomic discharges (autonomic dysreflexia) can be elicited by stimulation of bladder, skin, or muscles. Bladder distention from palpation, catheter insertion, catheter obstruction, or urinary infection is a common and correctable trigger of autonomic dysreflexia. Dangerous increases or decreases in body temperature can result from an inability to experience the sensory accompaniments of heat or cold exposure below the level of injury.

*Peripheral neuropathies* affecting small myelinated and unmyelinated fibers of the sympathetic and parasympathetic nerves are the most common cause of chronic autonomic insufficiency (Chap. 193). Autonomic involvement in *diabetes mellitus* typically begins ~10 years after onset of diabetes and slowly progresses. Diabetic enteric neuropathy produces gastroparesis, nausea and vomiting, malnutrition, achlorhydria, and bowel incontinence. Impotence, urinary incontinence, pupillary abnormalities, and OH may occur as well. Prolongation of the QT interval increases risk of sudden death. Autonomic neuropathy occurs in sporadic and familial forms of *amyloidosis*. Pts typically present with distal, painful polyneuropathy. *Alcoholic polyneuropathy* produces symptoms of autonomic failure when the neuropathy is severe, and autonomic involvement contributes to the high mortality rates associated with alcoholism. Attacks of *acute intermittent porphyria* (AIP) are associated with tachycardia, sweating, urinary retention, and hypertension; other prominent symptoms include anxiety, abdominal pain, nausea, and vomiting. BP fluctuation and cardiac arrhythmias can be severe in *Guillain-Barré syndrome*. *Autoimmune autonomic ganglionopathy* presents as the subacute development of autonomic failure with OH, enteric neuropathy (gastroparesis, ileus, constipation/diarrhea), flaccid bladder, loss of sweating, sicca complex, and a tonic pupil. Onset may follow a viral infection; serum antibodies to the ganglionic ACh receptor ($A_3$ AChR) are diagnostic, and some pts appear to respond to immunotherapy. Rare pts develop *dysautonomia* as a paraneoplastic disorder (Chap. 77). There are five known hereditary sensory and autonomic neuropathies (*HSAN I–V*).

*Botulism* is associated with blurred vision, dry mouth, nausea, unreactive or sluggishly reactive pupils, urinary retention, and constipation. *Postural orthostatic tachycardia syndrome* (POTS) presents with symptoms of orthostatic intolerance (not OH), including shortness of breath, light-headedness, and exercise intolerance accompanied by an increase in heart rate but no drop in bp. *Primary hyperhidrosis* affects 0.6–1.0% of the population; the usual symptoms are excessive sweating of the palms and soles. Onset is in adolescence, and symptoms tend to improve with age. Although not dangerous, this condition is socially embarrassing; treatment with sympathectomy or local injection of botulinum toxin is often effective.

**TABLE 186-2 CLASSIFICATION OF CLINICAL AUTONOMIC DISORDERS**

I. Autonomic disorders with brain involvement
   A. Associated with multisystem degeneration
      1. Multisystem degeneration: autonomic failure clinically prominent
         a. Multiple system atrophy
         b. Parkinson's disease with autonomic failure
         c. Diffuse Lewy body disease (some cases)
      2. Multisystem degeneration: autonomic failure clinically not usually prominent
         a. Parkinson's disease
         b. Other extrapyramidal disorders (inherited spinocerebellar atrophies, progressive supranuclear palsy, corticobasal degeneration, Machado-Joseph disease, FXTAS)
   B. Unassociated with multisystem degeneration (focal CNS disorders)
      1. Disorders mainly due to cerebral cortex involvement
         a. Frontal cortex lesions causing urinary/bowel incontinence
         b. Focal seizures (temporal lobe or anterior cingulate)
         c. Cerebral infarction of the insula
      2. Disorders of the limbic and paralimbic circuits
         a. Shapiro's syndrome (agenesis of corpus callosum, hyperhidrosis, hypothermia)
         b. Autonomic seizures
         c. Limbic encephalitis
      3. Disorders of the hypothalamus
         a. Thiamine deficiency (Wernicke-Korsakoff syndrome)
         b. Diencephalic syndrome
         c. Neuroleptic malignant syndrome
         d. Serotonin syndrome
         e. Fatal familial insomnia
         f. ADH syndromes (diabetes insipidus, inappropriate ADH secretion)
         g. Disturbances of temperature regulation (hyperthermia, hypothermia)
         h. Disturbances of sexual function
         i. Disturbances of appetite
         j. Disturbances of bp/HR and gastric function
         k. Horner's syndrome
      4. Disorders of the brainstem and cerebellum
         a. Posterior fossa tumors
         b. Syringobulbia and Arnold-Chiari malformation
         c. Disorders of bp control (hypertension, hypotension)
         d. Cardiac arrhythmias
         e. Central sleep apnea

(*Continued*)

**TABLE 186-2 CLASSIFICATION OF CLINICAL AUTONOMIC DISORDERS (*CONTINUED*)**

- f. Baroreflex failure
- g. Horner's syndrome
- h. Vertebrobasilar and lateral medullary (Wallenberg's) syndromes
- i. Brainstem encephalitis

II. Autonomic disorders with spinal cord involvement
- A. Traumatic quadriplegia
- B. Syringomyelia
- C. Subacute combined degeneration
- D. Multiple sclerosis and neuromyelitis optica
- E. Amyotrophic lateral sclerosis
- F. Tetanus
- G. Stiff-person syndrome
- H. Spinal cord tumors

III. Autonomic neuropathies
- A. Acute/subacute autonomic neuropathies
  - 1. Subacute AAG
    - a. Subacute paraneoplastic autonomic neuropathy
    - b. Guillain-Barré syndrome
    - c. Botulism
    - d. Porphyria
    - e. Drug-induced autonomic neuropathies-stimulants, drug withdrawal, vasoconstrictor, vasodilators, beta-receptor antagonists, beta-agonists
    - f. Toxin-induced autonomic neuropathies
    - g. Subacute cholinergic neuropathy
- B. Chronic peripheral autonomic neuropathies
  - 1. Distal small fiber neuropathy
  - 2. Combined sympathetic and parasympathetic failure
    - a. Amyloid
    - b. Diabetic autonomic neuropathy
    - c. Autoimmune autonomic ganglionopathy (paraneoplastic and idiopathic)
    - d. Sensory neuronopathy with autonomic failure
    - e. Familial dysautonomia (Riley-Day syndrome)
    - f. Diabetic, uremic, or nutritional deficiency
    - g. Dysautonomia of old age
  - 3. Disorders of reduced orthostatic intolerance: reflex syncope, POTS, associated with prolonged bed rest, associated with space flight, chronic fatigue

***Abbreviations:*** AAG, autoimmune autonomic ganglionopathy; ADH, antidiuretic hormone; FXTAS, fragile X–associated tremor/ataxia syndrome; HR, heart rate; POTS, postural orthostatic tachycardia syndrome.

## COMPLEX REGIONAL PAIN SYNDROME (REFLEX SYMPATHETIC DYSTROPHY AND CAUSALGIA)

Complex regional pain syndrome (CRPS) type I is a regional pain syndrome that usually develops after tissue trauma. *Allodynia* (the perception of a nonpainful stimulus as painful), *hyperpathia* (an exaggerated pain response to a painful stimulus), and spontaneous pain occur. Symptoms are unrelated to the severity of the initial trauma and are not confined to the distribution of a single peripheral nerve. CRPS type II is a regional pain syndrome that develops after injury to a peripheral nerve, usually a major nerve trunk. Spontaneous pain initially develops within the territory of the affected nerve but eventually may spread outside the nerve distribution.

- Early mobilization with physical therapy or a brief course of glucocorticoids may be helpful for CRPS type I.
- Other treatments include the use of adrenergic blockers, NSAIDs, calcium channel blockers, phenytoin, opioids, and calcitonin.
- Stellate ganglion blockade is a commonly used invasive therapeutic technique that often provides temporary pain relief, but the efficacy of repetitive blocks is uncertain.

## TREATMENT AUTONOMIC NERVOUS SYSTEM DISORDERS

- Of particular importance is the removal of drugs or amelioration of underlying conditions that cause or aggravate symptoms. For example, OH can be related to angiotensin-converting enzyme inhibitors, calcium channel blocking agents, tricyclic antidepressants, levodopa, alcohol, or insulin.
- Nonpharmacologic approaches are summarized in **Table 186-3**. Adequate intake of salt and fluids to produce a voiding volume between 1.5 and 2.5 L of urine (containing >170 meq of $Na^+$) each 24 h is essential. Sleeping with the head of the bed elevated will minimize the effects of supine nocturnal hypertension.
- Prolonged recumbency should be avoided. Pts are advised to sit with legs dangling over the edge of the bed for several minutes before attempting to stand in the morning. Compressive garments such as compression stockings and abdominal binders may be helpful if they can be tolerated. Anemia should be corrected, if necessary, with erythropoietin; the increased intravascular volume that accompanies the rise in hematocrit can exacerbate supine hypertension. Postprandial OH may respond to frequent, small, low-carbohydrate meals.
- If these measures are not sufficient, drug treatment might be necessary.
- Midodrine is a directly acting $\alpha_1$-agonist that does not cross the blood-brain barrier. The dose is 5–10 mg orally three times a day, but some pts respond best

**TABLE 186-3 INITIAL TREATMENT OF ORTHOSTATIC HYPOTENSION (OH)**

| |
|---|
| Pt education: mechanisms and stressors of OH |
| High salt diet (10–20 g/d) |
| High fluid intake (2 L/d) |
| Elevate head of bed 10 cm (4 in.) to minimize supine hypertension |
| Maintain postural stimuli |
| Learn physical counter-maneuvers |
| Compression garments |
| Correct anemia |

to a decremental dose (e.g., 15 mg on awakening, 10 mg at noon, and 5 mg in the afternoon). Midodrine should not be taken after 6 P.M. Side effects include pruritus, uncomfortable piloerection, and supine hypertension.

- Droxidopa was recently approved for treatment of neurogenic OH associated with autonomic failure, Parkinson's disease, or MSA; the oral form is converted to norepinephrine and has been shown to be effective in short-term clinical trials.
- Pyridostigmine appears to improve OH without aggravating supine hypertension by enhancing ganglionic transmission (maximal when orthostatic, minimal supine).
- Fludrocortisone (0.1–0.3 mg PO twice daily) will reduce OH, but it aggravates supine hypertension. Susceptible pts may develop fluid overload, congestive heart failure, supine hypertension, or hypokalemia.

For a more detailed discussion, see Low PA, Engstrom JW: Disorders of the Autonomic Nervous System, Chap. 454, p. 2637, in HPIM-19.

# 187 Trigeminal Neuralgia, Bell's Palsy, and Other Cranial Nerve Disorders

Disorders of vision and ocular movement are discussed in Chap. 52 and dizziness and vertigo in Chap. 51.

## FACIAL PAIN OR NUMBNESS (TRIGEMINAL NERVE [V])

(See Fig. 187-1)

### Trigeminal Neuralgia (Tic Douloureux)

Frequent, excruciating paroxysms of pain in lips, gums, cheek, or chin (rarely in ophthalmic division of fifth nerve) lasting seconds to minutes. Typically presents in middle or old age. Pain is often stimulated at trigger points. Sensory deficit cannot be demonstrated. Must be distinguished from other forms of facial pain arising from diseases of jaw, teeth, or sinuses. Rare causes are herpes zoster or a tumor. An onset in young adulthood or if bilateral raises the possibility of multiple sclerosis (Chap. 190).

**TREATMENT** TRIGEMINAL NEURALGIA

- Carbamazepine is effective in 50–75% of cases. Begin at 100-mg single daily dose taken with food and advance by 100 mg every 1–2 days until substantial (>50%) pain relief occurs. Most pts require 200 mg four times a day; doses >1200 mg daily usually provide no additional benefit.
- Oxcarbazepine (300–1200 mg bid) is an alternative with less bone marrow toxicity and probably similar efficacy.
- For nonresponders, lamotrigine (400 mg daily), phenytoin (300–400 mg/d), or baclofen (initially 5–10 mg three times a day) can be tried.

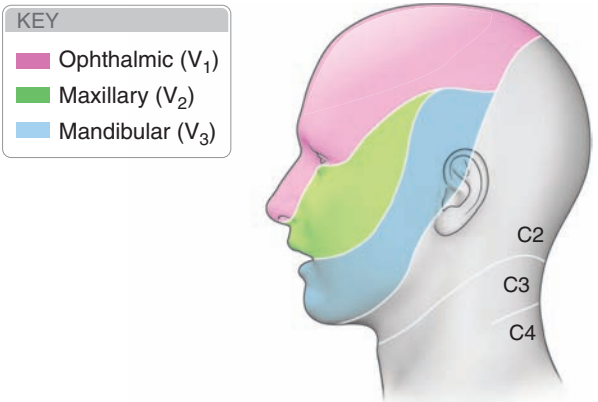



**FIGURE 187-1** The three major sensory divisions of the trigeminal nerve consist of the ophthalmic, maxillary, and mandibular nerves. *(Adapted from Waxman SG: Clinical Neuroanatomy, 26th ed. http://www.accessmedicine.com. Copyright The McGraw-Hill Companies, Inc. All rights reserved.)*

- When medications fail, surgical microvascular decompression to relieve pressure on the trigeminal nerve can be offered.
- Other options include gamma knife radiosurgery and radiofrequency thermal rhizotomy.

## Trigeminal Neuropathy

Usually presents as facial sensory loss or weakness of jaw muscles. Causes are varied (Table 187-1), including tumors of middle cranial fossa or trigeminal nerve, metastases to base of skull, or lesions in cavernous sinus (affecting first and second divisions of fifth nerve) or superior orbital fissure (affecting first division of fifth nerve).

### FACIAL WEAKNESS (FACIAL NERVE [VII]) (SEE FIG. 187-2)

Look for hemifacial weakness that includes muscles of forehead and orbicularis oculi. If lesion is in middle ear portion, taste is lost over the anterior two-thirds of tongue and there may be hyperacusis; if lesion is at internal auditory meatus, there may be involvement of auditory and vestibular nerves; pontine lesions usually affect abducens (sixth cranial) nerve and often corticospinal tract. Peripheral nerve lesions with incomplete recovery may produce continuous contractions of affected musculature (*facial myokymia*); contraction of all facial muscles on attempts to move one group selectively (*synkinesis*); hemifacial spasms; or anomalous tears when facial muscles activated as in eating (*crocodile tears*).

## Bell's Palsy

Most common form of idiopathic facial paralysis; affects 1 in 60 persons over a lifetime. Association with herpes simplex virus type 1. Risk factors include pregnancy and diabetes mellitus. Weakness evolves gradually with maximal weakness by 48 h, sometimes preceded by retroaural pain. Hyperacusis may be present. Full recovery within several weeks or months in 80%; incomplete paralysis in first week is the most favorable prognostic sign.

Diagnosis can be made clinically in pts with (1) a typical presentation, (2) no risk factors or preexisting symptoms for other causes of facial paralysis, (3) no lesions

**TABLE 187-1 TRIGEMINAL NERVE DISORDERS**

| | |
|---|---|
| **Nuclear (brainstem) lesions** | **Peripheral nerve lesions** |
| Multiple sclerosis | Nasopharyngeal carcinoma |
| Stroke | Trauma |
| Syringobulbia | Guillain-Barré syndrome |
| Glioma | Sjögren's syndrome |
| Lymphoma | Collagen-vascular diseases |
| **Preganglionic lesions** | Sarcoidosis |
| Acoustic neuroma | Leprosy |
| Meningioma | Drugs (stilbamidine, trichloroethylene) |
| Metastasis | Idiopathic trigeminal neuropathy |
| Chronic meningitis | |
| Cavernous carotid aneurysm | |
| **Gasserian ganglion lesions** | |
| Trigeminal neuroma | |
| Herpes zoster | |
| Infection (spread from otitis media or mastoiditis) | |

of herpes zoster in the external ear canal, and (4) a normal neurologic examination with the exception of the facial nerve. In uncertain cases, an ESR, testing for diabetes mellitus, a Lyme titer, angiotensin-converting enzyme level and chest imaging study for possible sarcoidosis, a lumbar puncture for possible Guillain-Barré syndrome, or MRI scanning may be indicated.

**TREATMENT BELL'S PALSY**

- Protect the eye with paper tape to depress the upper eyelid during sleep and prevent corneal drying.
- Massage of the weakened muscle may help symptomatically as well.
- Prednisone (60–80 mg/d over 5 days, tapered off over the next 5 days) modestly shortens the recovery period and improves functional outcome.
- Large randomized trials found no added benefit for valacyclovir or acyclovir compared with glucocorticoids alone.

## Other Facial Nerve Disorders

*Ramsay Hunt syndrome* is caused by herpes zoster infection of geniculate ganglion; distinguished from Bell's palsy by a vesicular eruption in pharynx and external auditory canal, and by frequent involvement of eighth cranial nerve. *Acoustic neuromas* often compress the seventh nerve. *Infarcts*, *demyelinating lesions of multiple sclerosis*, and *tumors* are common pontine causes. *Bilateral facial weakness* may occur in Guillain-Barré syndrome, sarcoidosis, Lyme disease, and leprosy. *Hemifacial spasm* may occur with Bell's palsy, compression and/or demyelination of the nerve by tumor, infection or multiple sclerosis (MS), or as an idiopathic disorder. *Blepharospasm* consists of involuntary recurrent spasms of both eyelids, usually occurring in the elderly and sometimes with associated facial spasm; may subside spontaneously.

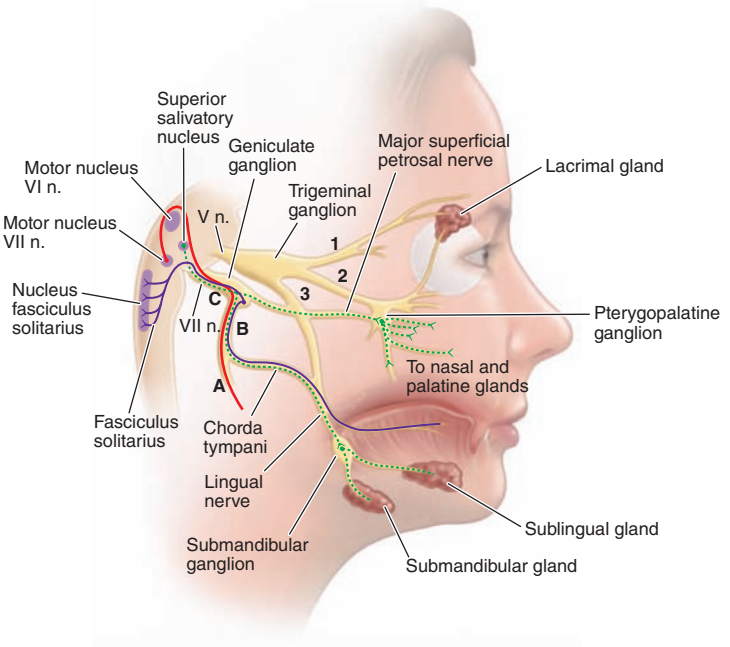



**FIGURE 187-2** The facial nerve. A, B, and C denote lesions of the facial nerve at the stylomastoid foramen, distal and proximal to the geniculate ganglion, respectively. Green lines indicate the parasympathetic fibers, red line indicates motor fibers, and purple lines indicate visceral afferent fibers (taste). *(Adapted from MB Carpenter: Core Text of Neuroanatomy, 2nd ed. Baltimore, Williams & Wilkins, 1978.)*

Hemifacial spasm or blepharospasm can be treated by injection of botulinum toxin into the orbicularis oculi.

## OTHER CRANIAL NERVE DISORDERS

### Disorders of the Sense of Smell

Olfactory nerve (I) disorders are due to interference with access of the odorant to the olfactory neuroepithelium (transport loss), injury to receptor region (sensory loss), or damage to central olfactory pathways (neural loss). The causes of olfactory disorders are summarized in Table 187-2); most common other than aging are severe upper respiratory infections, head trauma, and chronic rhinosinusitis. Although more than half of people between 65 and 80 years of age suffer from olfactory dysfunction that is idiopathic (*presbyosmia*), it is increasingly recognized that a number of neurodegenerative disorders are accompanied by olfactory impairment. Pts often present with a complaint of loss of the sense of taste even though their taste thresholds may be within normal limits.

**TREATMENT DISORDERS OF THE SENSE OF SMELL**

- Therapy for allergic rhinitis, bacterial rhinitis and sinusitis, polyps, neoplasms, and structural abnormalities of the nasal cavities is usually successful in restoring the sense of smell.

**TABLE 187-2 DISORDERS AND CONDITIONS ASSOCIATED WITH COMPROMISED OLFACTORY FUNCTION, AS MEASURED BY OLFACTORY TESTING**

| | |
|---|---|
| 22q11 deletion syndrome | Liver disease |
| AIDS/HIV infection | Lubag disease |
| Adenoid hypertrophy | Medications |
| Adrenal cortical insufficiency | Migraine |
| Age | Multiple sclerosis |
| Alcoholism | Multi-infarct dementia |
| Allergies | Myasthenia gravis |
| Alzheimer's disease | Narcolepsy with cataplexy |
| ALS | Neoplasms, cranial/nasal |
| Anorexia nervosa | Nutritional deficiencies |
| Asperger's syndrome | Obesity |
| Ataxias | Obsessive compulsive disorder |
| Attention deficit/hyperactivity disorder | Obstructive pulmonary disease |
| Bardet-Biedl syndrome | Orthostatic tremor |
| Chagas' disease | Panic disorder |
| Chemical exposure | PD |
| Chronic obstructive pulmonary disease | Pick's disease |
| Congenital | Posttraumatic stress disorder |
| Cushing's syndrome | Pregnancy |
| Cystic fibrosis | Pseudohypoparathyroidism |
| Degenerative ataxias | Psychopathy |
| Diabetes | Radiation (therapeutic, cranial) |
| Down's syndrome | Refsum's disease |
| Epilepsy | REM behavior disorder |
| Facial paralysis | Renal failure/end-stage kidney disease |
| Frontotemporal lobe degeneration | Restless leg syndrome |
| Gonadal dysgenesis (Turner's syndrome) | Rhinosinusitis/polyposis |
| Guamanian ALS/PD/dementia syndrome | Schizophrenia |
| Head trauma | Seasonal affective disorder |
| Herpes simplex encephalitis | Sjögren's syndrome |
| Hypothyroidism | Stroke |
| Huntington's disease | Tobacco smoking |
| Iatrogenesis | Toxic chemical exposure |
| Kallmann's syndrome | Upper respiratory infections |
| Korsakoff's psychosis | Usher syndrome |
| Leprosy | Vitamin $B_{12}$ deficiency |

***Abbreviations:*** ALS, amyotrophic lateral sclerosis; PD, Parkinson's disease; REM, rapid eye movement.

- There is no proven treatment for sensorineural olfactory losses; fortunately, spontaneous recovery can occur.
- Cases due to exposure to cigarette smoke and other airborne toxic chemicals can recover if the insult is discontinued.
- A nonblinded study reported that pts with hyposmia may benefit from smelling strong odors before going to bed and upon awakening over the course of several months.

## Glossopharyngeal Neuralgia

This neuralgia involves the ninth (glossopharyngeal) and sometimes portions of the tenth (vagus) cranial nerves. Presents with paroxysmal, intense pain in tonsillar fossa of throat that may be precipitated by swallowing. There is no objective sensory or motor deficit. Other diseases affecting this nerve include herpes zoster, MS, or compressive neuropathy due to tumor or aneurysm in region of jugular foramen (when associated with vagus and accessory nerve palsies).

### TREATMENT GLOSSOPHARYNGEAL NEURALGIA

- Medical therapy is similar to that for trigeminal neuralgia, and carbamazepine is generally the first choice.
- If drug therapy is unsuccessful, surgical procedures (including microvascular decompression if vascular compression is evident, or rhizotomy of glossopharyngeal and vagal fibers in the jugular bulb) are frequently successful.

## Dysphagia and Dysphonia

Lesions of the vagus nerve (X) may be responsible. Unilateral lesions produce drooping of soft palate, loss of gag reflex, and "curtain movement" of lateral wall of pharynx with hoarse, nasal voice. Etiologies include neoplastic and infectious processes of the meninges, tumors and vascular lesions in the medulla, motor neuron disease (e.g., ALS), or compression of the recurrent laryngeal nerve by intrathoracic processes. Aneurysm of the aortic arch, an enlarged left atrium, and tumors of the mediastinum and bronchi are much more frequent causes of an isolated vocal cord palsy than are intracranial disorders. A substantial number of cases of recurrent laryngeal palsy remain idiopathic.

With laryngeal palsy, first determine the site of the lesion. If intramedullary, there are usually other brainstem or cerebellar signs. If extramedullary, the glossopharyngeal (IX) and spinal accessory (XI) nerves are frequently involved (jugular foramen syndrome). If extracranial in the posterior laterocondylar or retroparotid space, there may be combinations of ninth, tenth, eleventh, and twelfth cranial nerve palsies and a Horner's syndrome. If there is no sensory loss over the palate and pharynx and no palatal weakness or dysphagia, lesion is below the origin of the pharyngeal branches, which leave the vagus nerve high in the cervical region; the usual site of disease is then the mediastinum.

## Neck Weakness

Isolated involvement of the accessory (XI) nerve can occur anywhere along its route, resulting in paralysis of the sternocleidomastoid and trapezius muscles. More commonly, involvement occurs in combination with deficits of the ninth and tenth cranial nerves in the jugular foramen or after exit from the skull. An idiopathic form of accessory neuropathy, similar to Bell's palsy, has been described; most pts recover but it may recur.

## Tongue Paralysis

The hypoglossal (XII) nerve supplies the ipsilateral muscles of the tongue. The nucleus of the nerve or its fibers of exit may be involved by intramedullary lesions such as tumor, poliomyelitis, or most often motor neuron disease. Lesions of the basal meninges and the occipital bones (platybasia, invagination of occipital condyles, Paget's disease) may compress the nerve in its extramedullary course or in the hypoglossal canal. Isolated lesions of unknown cause can occur. Atrophy and fasciculation of the tongue develop weeks to months after interruption of the nerve.

## MULTIPLE CRANIAL NERVE PALSIES

### APPROACH TO THE PATIENT: Multiple Cranial Nerve Palsies

First determine whether the process is within the brainstem or outside it. Lesions on the surface of the brainstem tend to involve adjacent cranial nerves in succession with only late and slight involvement of long sensory and motor pathways. The opposite is true of processes within the brainstem. Involvement of multiple cranial nerves outside the brainstem may be due to trauma, localized infections including varicella zoster virus, infectious and noninfectious (especially carcinomatous) causes of meningitis; granulomatous diseases such as granulomatosis with polyangiitis, Behçet's disease, vascular disorders including those associated with diabetes, enlarging aneurysms, or locally infiltrating tumors. A purely motor disorder without atrophy raises the question of myasthenia gravis. *Facial diplegia* is common in Guillain-Barré syndrome. *Ophthalmoplegia* may occur with Guillain-Barré syndrome (Fisher variant) or Wernicke's encephalopathy.

The *cavernous sinus syndrome* (**Fig. 187-3**) is frequently life threatening. It often presents as orbital or facial pain; orbital swelling and chemosis; fever;

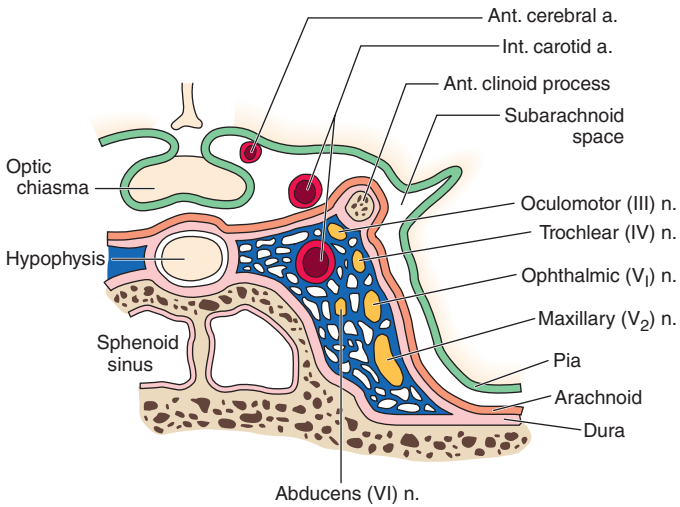



**FIGURE 187-3** Anatomy of the cavernous sinus in coronal section, illustrating the location of the cranial nerves in relation to the vascular sinus, internal carotid artery (which loops anteriorly to the section), and surrounding structures.

oculomotor neuropathy; and trigeminal neuropathy affecting the ophthalmic ($V_1$) and occasionally maxillary ($V_2$) divisions. Cavernous sinus thrombosis, often secondary to infection from orbital cellulitis, a cutaneous source on the face, or sinusitis, is the most frequent cause; other etiologies include aneurysm of the carotid artery, a carotid-cavernous fistula (orbital bruit may be present), meningioma, nasopharyngeal carcinoma, other tumors, or an idiopathic granulomatous disorder (Tolosa-Hunt syndrome). In infectious cases, prompt administration of broad-spectrum antibiotics, drainage of any abscess cavities, and identification of the offending organism are essential. Anticoagulant therapy may benefit cases of primary thrombosis. Repair or occlusion of the carotid artery may be required for treatment of fistulas or aneurysms. Tolosa-Hunt syndrome generally responds to glucocorticoids.

For a more detailed discussion, see Beal MF, Hauser SL: Trigeminal Neuralgia, Bell's Palsy, and Other Cranial Nerve Disorders, Chap. 455, p. 2645; Doty RL, Bromley SM: Disorders of Smell and Taste, Chap. 42, p. 211, in HPIM-19.

# 188 Spinal Cord Diseases

Spinal cord disorders can be devastating, but many are treatable if recognized early (Table 188-1). Knowledge of relevant spinal cord anatomy is often the key to correct diagnosis (Fig. 188-1).

## SYMPTOMS AND SIGNS

Sensory symptoms often include paresthesias; may begin in one or both feet and ascend. Sensory level to pin sensation or vibration often correlates well with location of transverse lesions. May have isolated pain/temperature sensation loss over the shoulders ("cape" or "syringomyelic" pattern) or loss of sensation to vibration/position sense on one side of the body and pain/temperature loss on the other (Brown-Séquard hemicord syndrome).

Motor symptoms are caused by disruption of corticospinal tracts that leads to quadriplegia or paraplegia with increased muscle tone, hyperactive deep tendon reflexes, and extensor plantar responses. With acute severe lesions, there may be initial flaccidity and areflexia (spinal shock).

Autonomic dysfunction includes primarily urinary retention; should raise suspicion of spinal cord disease when associated with back or neck pain, weakness, and/or a sensory level.

Interscapular pain may be first sign of midthoracic cord compression; radicular pain may mark site of more laterally placed spinal lesion; pain from lower cord (conus medullaris) lesion may be referred to low back.

## SPECIFIC SIGNS BY SPINAL CORD LEVEL

Approximate indicators of level of lesion include the location of a sensory level, a band of hyperalgesia/hyperpathia at the upper end of the sensory disturbance,

**TABLE 188-1 TREATABLE SPINAL CORD DISORDERS**

| |
|---|
| **Compressive** |
| Epidural, intradural, or intramedullary neoplasm |
| Epidural abscess |
| Epidural hemorrhage |
| Cervical spondylosis |
| Herniated disk |
| Posttraumatic compression by fractured or displaced vertebra or hemorrhage |
| **Vascular** |
| Arteriovenous malformation and dural fistula |
| Antiphospholipid syndrome and other hypercoagulable states |
| **Inflammatory** |
| Multiple sclerosis |
| Neuromyelitis optica |
| Transverse myelitis |
| Sarcoidosis |
| Sjögren-related myelopathy |
| Systemic lupus erythematosus-related myelopathy |
| Vasculitis |
| **Infectious** |
| Viral: VZV, HSV-1 and 2, CMV, HIV, HTLV-1, others |
| Bacterial and mycobacterial: *Borrelia*, *Listeria*, syphilis, others |
| *Mycoplasma pneumoniae* |
| Parasitic: schistosomiasis, toxoplasmosis |
| **Developmental** |
| Syringomyelia |
| Meningomyelocele |
| Tethered cord syndrome |
| **Metabolic** |
| Vitamin $B_{12}$ deficiency (subacute combined degeneration) |
| Copper deficiency |

***Abbreviation:*** HTLV, human T-cell lymphotropic virus.

isolated atrophy or fasciculations, or lost tendon reflex at a specific spinal cord segment.

## Lesions Near the Foramen Magnum

Weakness of the ipsilateral shoulder and arm, followed by weakness of ipsilateral leg, then contralateral leg, then contralateral arm, often with respiratory paralysis. There is often suboccipital pain spreading to the neck and shoulders.

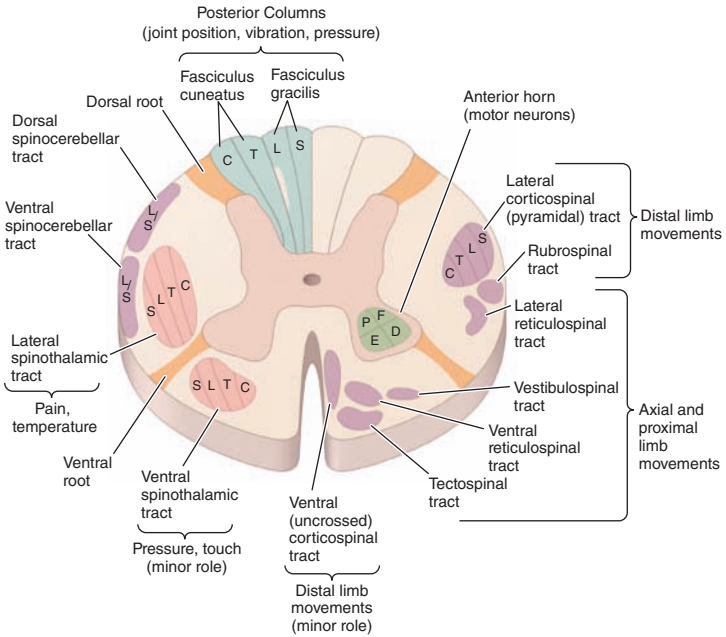



**FIGURE 188-1** Transverse section through the spinal cord, composite representation, illustrating the principal ascending *(left)* and descending *(right)* pathways. The lateral and ventral spinothalamic tracts ascend contralateral to the side of the body that is innervated. C, cervical; D, distal; E, extensors; F, flexors; L, lumbar; P, proximal; S, sacral; T, thoracic.

## Cervical Cord

Best localized by noting pattern of motor weakness and areflexia; shoulder (C5), biceps (C5–6), brachioradialis (C6), triceps/finger and wrist extensors (C7), finger and wrist flexors (C8).

## Thoracic Cord

Localized by identification of a sensory level on the trunk. Useful markers are the nipples (T4) and umbilicus (T10).

## Lumbar Cord

Upper lumbar cord lesions paralyze hip flexion and knee extension and abolish the patella reflex, whereas lower lumbar lesions affect foot and ankle movements, knee flexion, and thigh extension, while abolishing the ankle jerks.

## Sacral Cord (Conus Medullaris)

Saddle anesthesia, early bladder/bowel dysfunction, impotence; muscle strength is largely preserved.

## Cauda Equina (Cluster of Nerve Roots Derived from Lower Cord)

Lesions below spinal cord termination at the L1 vertebral level produce a flaccid, areflexic, asymmetric paraparesis with possible bladder/bowel dysfunction and sensory loss below L1; pain is common and projected to perineum or thighs.

## INTRAMEDULLARY AND EXTRAMEDULLARY SYNDROMES

Spinal cord disorders may be intramedullary (arising from within the substance of the cord) or extramedullary (compressing the cord or its blood supply). Extramedullary lesions often produce radicular pain, early corticospinal signs, and sacral sensory loss. Intramedullary lesions produce poorly localized burning pain, less prominent corticospinal signs, and often spare perineal/sacral sensation.

## ACUTE AND SUBACUTE SPINAL CORD DISEASES (SEE CHAP. 20)

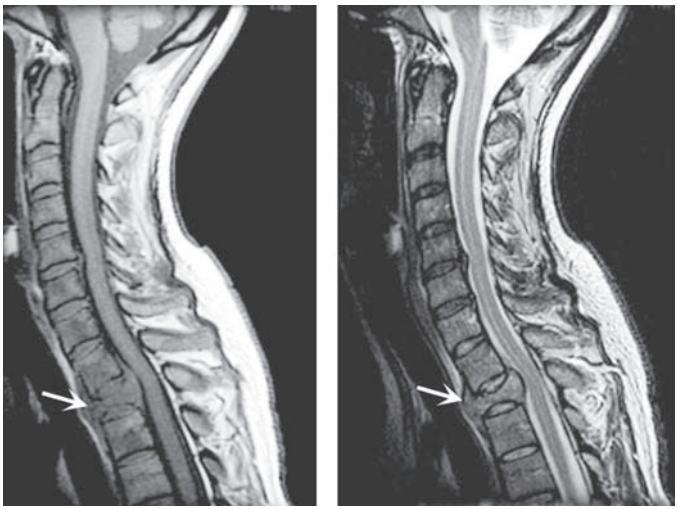
*Neoplastic spinal cord compression* (Chap. 20): Most are epidural in origin, resulting from metastases to the adjacent spinal bones (Fig. 188-2). Almost any tumor can be responsible: breast, lung, prostate, kidney, lymphoma, and myeloma most frequent. Thoracic cord most commonly involved. Initial symptom is usually back pain, worse when recumbent, with local tenderness preceding other symptoms by many weeks. Spinal cord compression due to metastases is a medical emergency; in general, therapy will not reverse paralysis of >48 h duration.

*Spinal epidural abscess:* Triad of fever, localized midline dorsal spine or neck pain, and progressive limb weakness; once neurologic signs appear, cord compression rapidly progresses.

*Spinal epidural hematoma:* Presents as acute focal or radicular pain followed by variable signs of a spinal cord or conus medullaris disorder.

*Acute disk herniation:* Cervical and thoracic disk herniations are less common than lumbar.

*Spinal cord infarction:* Anterior spinal artery infarction produces paraplegia or quadriplegia, sensory loss affecting pain/temperature but sparing vibration/position sensation (supplied by posterior spinal arteries), and loss of sphincter control. Onset sudden or progressive, evolving over minutes or a few hours. Associated conditions:



A B

**FIGURE 188-2** Epidural spinal cord compression due to breast carcinoma. Sagittal T1-weighted **(A)** and T2-weighted **(B)** MRI scans through the cervicothoracic junction reveal an infiltrated and collapsed second thoracic vertebral body with posterior displacement and compression of the upper thoracic spinal cord. The low-intensity bone marrow signal in **A.** signifies replacement by tumor.

aortic atherosclerosis, dissecting aortic aneurysm, vertebral artery occlusion or dissection in the neck, aortic surgery, or profound hypotension. Therapy is directed at the predisposing condition. Lumbar drainage of spinal fluid is sometimes used prophylactically during aortic surgery but has not been studied systematically.

*Immune-mediated myelopathies:* Acute transverse myelopathy (ATM) occurs in 1% of pts with SLE; associated with antiphospholipid antibodies. Sjögren's and Behçet's syndromes, mixed connective tissue disease, and p-ANCA vasculitis are other causes. Sarcoid can produce ATM with large edematous swelling of the spinal cord. Demyelinating diseases, either neuromyelitis optica (NMO) or multiple sclerosis (MS), also can present as ATM; glucocorticoids, consisting of IV methylprednisolone followed by oral prednisone, are indicated for moderate to severe symptoms and refractory cases may respond to plasma exchange (**Chap. 190**). Treatment with azathioprine, mycophenolate mofetil, or rituximab may protect against relapses in NMO. Other cases of ATM are idiopathic.

*Infectious myelopathies:* Herpes zoster is the most common viral agent, but herpes simplex virus types 1 and 2, EBV, CMV, and rabies virus are also well described; in cases of suspected viral myelitis, antivirals may be appropriately started pending laboratory confirmation. A number of enteroviruses and flaviviruses (e.g., West Nile virus) can cause a polio-like syndrome. Bacterial and mycobacterial causes are less common. Schistosomiasis is an important cause worldwide.

## CHRONIC MYELOPATHIES

*Spondylitic myelopathies:* One of the most common causes of gait difficulty in the elderly. Presents as neck and shoulder pain with stiffness, radicular arm pain, and progressive spastic paraparesis with paresthesias and loss of vibration sense; in advanced cases, urinary incontinence may occur. A tendon reflex in the arms is often diminished at some level. Diagnosis is best made by MRI. Treatment is surgical (**Chap. 48**).

*Vascular malformations:* An important treatable cause of progressive or episodic myelopathy. May occur at any level; diagnosis is often suggested by contrast-enhanced MRI (**Fig. 188-3**), but is confirmed by selective spinal angiography. Treatment is embolization or surgery with occlusion of the major feeding vessels.

*Retrovirus-associated myelopathies:* Infection with human T-cell lymphotropic virus I (HTLV-I) may produce a slowly progressive spastic paraparesis with variable pain, sensory loss, and bladder disturbance; diagnosis is made by demonstration of specific serum antibody. Treatment is symptomatic. A progressive vacuolar myelopathy may also result from HIV infection.

*Syringomyelia:* Cavitary expansion of the spinal cord resulting in progressive myelopathy; may be an isolated finding or associated with protrusion of cerebellar tonsils into cervical spinal canal (Chiari type 1). Classic presentation is loss of pain/temperature sensation in the neck, shoulders, forearms, or hands with areflexic weakness in the upper limbs and progressive spastic paraparesis; cough headache, facial numbness, or thoracic kyphoscoliosis may occur. Diagnosis is by MRI; treatment is surgical and often unsatisfactory.

*Multiple sclerosis:* Spinal cord involvement is common and is a major cause of disability especially in progressive forms of MS (**Chap. 190**).

*Subacute combined degeneration (vitamin $B_{12}$ deficiency):* Paresthesias in hands and feet, early loss of vibration/position sense, progressive spastic/ataxic weakness, and areflexia due to associated peripheral neuropathy; mental changes and optic atrophy may be present along with a serum macrocytic anemia. Diagnosis is confirmed by a low serum $B_{12}$ level, elevated levels of homocysteine and methylmalonic acid. Treatment is vitamin replacement beginning with 1 mg of IM vitamin $B_{12}$ repeated at regular intervals or by subsequent oral treatment.

*Hypocupric myelopathy:* Clinically nearly identical to subacute combined degeneration (above) except there is no neuropathy. Low levels of serum copper and usually ceruloplasmin make the diagnosis. Some cases are idiopathic and others follow GI

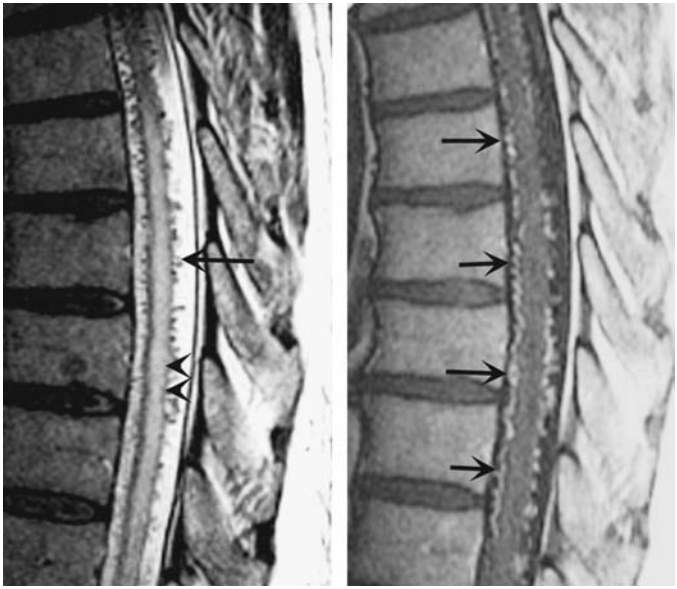


**FIGURE 188-3** Arteriovenous malformation. Sagittal MR scans of the thoracic spinal cord: T2 fast spin-echo technique (*left*) and T1 postcontrast image (*right*). On the T2-weighted image (*left*), abnormally high signal intensity is noted in the central aspect of the spinal cord (*arrowheads*). Numerous punctate flow voids indent the dorsal and ventral spinal cord (*arrow*). These represent the abnormally dilated venous plexus supplied by the dural arteriovenous fistula. After contrast administration (*right*), multiple, serpentine, enhancing veins (*arrows*) on the ventral and dorsal aspect of the thoracic spinal cord are visualized, diagnostic of arteriovenous malformation. This pt was a 54-year-old man with a 4-year history of progressive paraparesis.

procedures that hinder absorption; excess zinc ingestion is another cause. Treatment is oral copper supplementation.

*Tabes dorsalis (tertiary syphilis):* May present as lancinating pains, gait ataxia, bladder disturbances, and visceral crises. Cardinal signs are areflexia in the legs, impaired vibration/position sense, Romberg sign, and Argyll Robertson pupils which fail to constrict to light but accommodate.

*Familial spastic paraplegia:* Progressive spasticity and weakness in the legs occurring on a familial basis; may be autosomal dominant, recessive, or X-linked. More than 30 different loci identified.

*Adrenomyeloneuropathy:* X-linked disorder that is a variant of adrenoleukodystrophy. Usually, affected males have a history of adrenal insufficiency and then develop a progressive spastic paraparesis. Female heterozygotes may develop a slower progressive myelopathy without adrenal insufficiency. Diagnosis made by elevated very long chain fatty acids in plasma and in cultured fibroblasts. No therapy is clearly effective although bone marrow transplantation and nutritional supplements have been tried.

## COMPLICATIONS

Bladder dysfunction with risk of urinary tract infection; bowel dysmotility; pressure sores; in high cervical cord lesions, mechanical respiratory failure; paroxysmal

hypertension or hypotension with volume changes; severe hypertension and bradycardia in response to noxious stimuli or bladder or bowel distention; venous thrombosis and pulmonary embolism.

For a more detailed discussion, see Hauser SL, Ropper AH: Diseases of the Spinal Cord, Chap. 456, p. 2650, in HPIM-19.

# 189 Tumors of the Nervous System

## APPROACH TO THE PATIENT: Tumors of the Nervous System

*Clinical Presentation:* Brain tumors of any type can present with general and/or focal symptoms and signs. General nonspecific symptoms include headache with or without nausea and vomiting, cognitive difficulties, personality change, and gait disorder. The classic headache associated with a brain tumor is most evident in the morning and improves during the day, but this pattern is actually seen in only a minority of pts. Papilledema may suggest elevated intracranial pressure. Focal symptoms and signs include hemiparesis, aphasia, or visual field deficit; these are typically subacute and progressive. Seizures are a common presentation, occurring in about 25% of pts with brain metastases or malignant glioma.

*Evaluation:* Primary brain tumors, unlike metastases, have no serologic features of malignancy such as an elevated ESR or tumor-specific antigens. Cranial MRI with contrast is the preferred diagnostic test for any pt suspected of having a brain tumor; CT should be reserved for pts unable to undergo MRI. Malignant brain tumors typically enhance with contrast and may have central areas of necrosis; they are characteristically surrounded by edema of the neighboring white matter. Low-grade gliomas typically do not enhance. Additional testing such as cerebral angiogram, EEG, or lumbar puncture is rarely indicated or helpful.

## TREATMENT TUMORS OF THE NERVOUS SYSTEM

### SYMPTOMATIC TREATMENT

- Glucocorticoids (dexamethasone 12–16 mg/d in divided doses PO or IV) to temporarily reduce edema
- Anticonvulsants (levetiracetam, topiramate, lamotrigine, valproic acid, or lacosamide) for pts who present with seizures; there is no role for prophylactic anticonvulsant drugs
- Low-dose SC heparin for immobile pts

### DEFINITIVE TREATMENT

- Based on the specific tumor types and includes surgery, radiotherapy (RT), and chemotherapy

## PRIMARY INTRACRANIAL TUMORS

### Astrocytomas

Infiltrative tumors with a presumptive glial cell of origin. Most common primary intracranial neoplasm. Only known risk factors are ionizing radiation and uncommon hereditary syndromes (neurofibromatosis, tuberous sclerosis). Infiltration along white matter pathways often prevents total resection. Imaging studies (Fig. 189-1) fail to indicate full tumor extent. Grade I tumors (pilocytic astrocytomas) are the most common tumor of childhood, typically in the cerebellum; can be cured if completely resected. Grade II astrocytomas usually present with seizures in young adults; if feasible should be surgically resected. RT is helpful and chemotherapeutic agents such as temozolomide are increasingly used. Grade III (anaplastic astrocytoma) and grade IV (glioblastoma) astrocytomas are treated similarly with maximal safe surgical resection followed by RT with concomitant temozolomide, followed by 6–12 months of adjuvant temozolomide. Median survival in glioblastoma is 12–15 months. Glioblastomas invariably recur, and treatment options include reoperation, carmustine wafer implantation, and chemotherapeutic regimens including bevacizumab. The most important adverse prognostic factors in high-grade astrocytomas are older age, histologic features of glioblastoma, poor performance status, and unresectable tumor.

### Oligodendrogliomas

Generally more responsive to therapy and have a better prognosis than pure astrocytic tumors. Usually nonenhancing; often partially calcified. Treated with surgery and, if necessary, RT and chemotherapy. Median survival in excess of 10 years. Chemotherapy response improved when deletions of chromosomes 1p and 19q present.

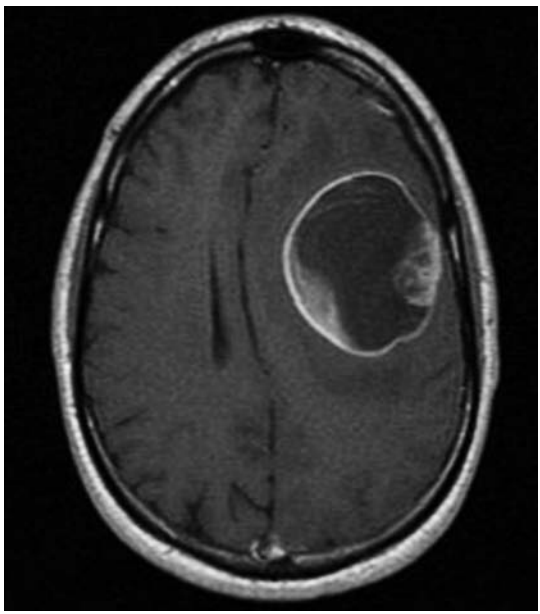


**FIGURE 189-1** Postgadolinium T1 MRI of a large cystic left frontal glioblastoma.

## Ependymomas

Derived from ependymal cells; highly cellular. Location—spinal canal more than intracranial in adults. If total excision possible, may be curable. Partially resected tumors will recur and require irradiation.

## Primary CNS Lymphomas

B-cell malignancy; most occur in immunosuppressed pts (organ transplantation, HIV). May present as a single mass lesion or as multiple mass lesions or meningeal disease. Dramatic, transient responses occur with glucocorticoids; therefore, whenever possible, steroids should be withheld until after biopsy has been obtained. Pts should be tested for HIV and the extent of disease assessed by performing positron emission tomography (PET) or CT of the body, MRI of the spine, CSF analysis, and slit-lamp examination of the eye. In immunocompetent pts, high-dose methotrexate produces median survival up to 50 months, which may be increased with concurrent whole-brain RT and combinations of other chemotherapeutic agents such as cytarabine or rituximab. In immunocompromised pts, prognosis is worse and treatment is with high-dose methotrexate, whole-brain RT, and, in HIV, antiretroviral therapy.

## Medulloblastomas

Most common malignant brain tumor of childhood. Half in posterior fossa; highly cellular; derived from neural precursor cells. Treatment with surgery, RT, and chemotherapy. Approximately 70% of pts have long-term survival, but usually at the cost of significant neurocognitive impairment.

## Meningiomas

The most common primary brain tumor. Extra-axial mass attached to dura; dense and uniform contrast enhancement is diagnostic (Fig. 189-2). Total surgical resection of large, symptomatic benign meningiomas is curative. With subtotal resection, local RT reduces recurrence. Small, asymptomatic meningiomas may be followed radiologically without surgery. Treat rare aggressive meningiomas with excision and RT.

## Schwannomas

Vestibular schwannomas present as progressive, unexplained unilateral hearing loss. MRI reveals dense, uniformly enhancing tumor at the cerebellopontine angle. Surgical excision may preserve hearing.

# TUMORS METASTATIC TO THE NERVOUS SYSTEM

Hematogenous spread most common. Skull metastases rarely invade CNS; may compress adjacent brain or cranial nerves or obstruct intracranial venous sinuses. Primary tumors that commonly metastasize to the nervous system are listed in Table 189-1. Brain metastases are well demarcated by MRI and enhance with gadolinium. Ring enhancement is nonspecific; differential diagnosis includes brain abscess, radiation necrosis, toxoplasmosis, granulomas, tuberculosis, sarcoidosis, demyelinating lesions, primary brain tumors, CNS lymphoma, stroke, hemorrhage, and trauma. Screen for occult cancer: examine skin and thyroid gland; blood carcinoembryonic antigen (CEA) and liver function tests; CT of chest, abdomen, and pelvis. In approximately 10% of pts, a systemic cancer may present with brain metastases; biopsy of primary tumor or accessible brain metastasis is needed to plan treatment. Treatment with glucocorticoids, anticonvulsants, RT, or surgery. Whole-brain RT is often given because multiple microscopic tumor deposits are likely throughout the brain; stereotaxic radiosurgery is of benefit in pts with three or fewer metastases demonstrated by MRI. If a single metastasis is found, it may be surgically excised followed by whole-brain RT. Systemic chemotherapy may produce dramatic responses in rare cases of a highly chemosensitive tumor type such

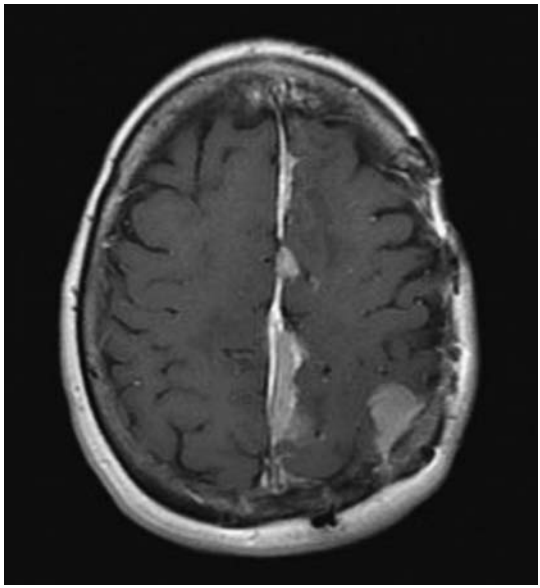


**FIGURE 189-2** Postgadolinium T1 MRI demonstrating multiple meningiomas along the falx and left parietal cortex.

as germ cell tumors or small-cell lung cancer harboring specific epidermal growth factor receptor (EGFR) mutations that sensitize them to EGFR inhibitors.

## Leptomeningeal Metastases

Presents as headache, encephalopathy, cranial nerve, or polyradicular symptoms. Diagnosis by CSF cytology, MRI (nodular meningeal tumor deposits or diffuse meningeal enhancement), or meningeal biopsy. Associated with hydrocephalus due to CSF pathway obstruction. Treatment is palliative, often with RT or chemotherapy (systemic or intrathecal).

**TABLE 189-1 FREQUENCY OF NERVOUS SYSTEM METASTASES BY COMMON PRIMARY TUMORS**

| | Brain % | LM % | ESCC % |
|---|---|---|---|
| Lung | 41 | 17 | 15 |
| Breast | 19 | 57 | 22 |
| Melanoma | 10 | 12 | 4 |
| Prostate | 1 | 1 | 10 |
| GIT | 7 | — | 5 |
| Renal | 3 | 2 | 7 |
| Lymphoma | <1 | 10 | 10 |
| Sarcoma | 7 | 1 | 9 |
| Other | 11 | — | 18 |

***Abbreviations:*** ESCC, epidural spinal cord compression; GIT, gastrointestinal tract; LM, leptomeningeal metastases.

## Spinal Cord Compression from Metastases

(See Chap. 20) Expansion of vertebral body metastasis posteriorly into epidural space compresses cord. Most common primary tumors are breast, lung, prostate, kidney, lymphoma, and myeloma. Back pain (>90%) precedes development of weakness, sensory level, or incontinence. Medical emergency; early recognition of impending spinal cord compression essential to avoid devastating sequelae. Diagnosis is by spine MRI.

### COMPLICATIONS OF RADIATION THERAPY

Three patterns of radiation injury after CNS RT:

1. Acute: headache, sleepiness, worse neurologic deficits during or immediately after RT. Rarely seen with current protocols. Can be both prevented and treated with glucocorticoids.
2. Early delayed: somnolence (children), Lhermitte's sign; within weeks to months of RT. Increased T2 signal and sometimes enhancement on MRI that can mimic tumor recurrence ("pseudoprogression"). Self-limited and improves with glucocorticoids; if very symptomatic may require resection.
3. Late delayed: dementia or other progressive neurologic deficits; typically months to years after RT. White matter abnormalities on MRI (leukoencephalopathy) or ring-enhancing mass (radiation necrosis). PET can distinguish delayed necrosis from tumor recurrence as can MR perfusion sequences. Progressive radiation necrosis is best treated palliatively with surgical resection unless it can be managed with glucocorticoids. Radiation injury of large arteries accelerates the development of atherosclerosis, increasing the risk of stroke years after RT. Endocrine dysfunction due to hypothalamus or pituitary gland injury can be due to delayed effects of RT. Development of a second neoplasm after RT also is a risk year after exposure.

For a more detailed discussion, see DeAngelis LM, Wen PY: Primary and Metastatic Tumors of the Nervous System, Chap. 118, p. 598, in HPIM-19.

# 190 Multiple Sclerosis

Characterized by chronic inflammation and selective destruction of CNS myelin; peripheral nervous system is spared. Pathologically, the multifocal scarred lesions of multiple sclerosis (MS) are termed *plaques*. Etiology is autoimmune, with susceptibility determined by genetic and environmental factors. MS affects >350,000 in the United States and 2.5 million worldwide; onset is often in early to middle adulthood, and women are affected three times as often as men.

### CLINICAL FEATURES

Onset may be abrupt or insidious. Some pts have symptoms that are so trivial that they may not seek medical attention for months or years. Recurrent attacks of focal neurologic dysfunction lasting weeks or months and followed by variable

recovery, are typical; some pts initially present with slowly progressive neurologic deterioration. Symptoms often transiently worsen with fatigue, stress, exercise, or heat. Manifestations include weakness and/or sensory symptoms, visual difficulties, abnormalities of gait and coordination, urinary urgency or frequency, and abnormal fatigue. Motor involvement can present as a heavy, stiff, weak, or clumsy limb. Localized tingling, "pins and needles," and "dead" sensations are common. Optic neuritis produces monocular blurring of vision, especially in the central visual field, often with associated retro-orbital pain accentuated by eye movement. Involvement of the brainstem may result in diplopia, nystagmus, vertigo, or facial pain, numbness, weakness, hemispasm, or myokymia (rippling muscular contractions). Ataxia, tremor, and dysarthria may reflect disease of cerebellar pathways. Lhermitte's symptom, a momentary electric shock–like sensation evoked by neck flexion, indicates disease in the cervical spinal cord. Diagnostic criteria are listed in Table 190-1; MS mimics are summarized in Table 190-2.

## PHYSICAL EXAMINATION

Abnormal signs usually more widespread than expected from the history. Check for abnormalities in visual fields, loss of visual acuity, disturbed color perception, optic pallor or papillitis, afferent pupillary defect (paradoxical dilation to direct light following constriction to consensual light), nystagmus, internuclear ophthalmoplegia (slowness or loss of adduction in one eye with nystagmus in the abducting eye on lateral gaze), facial numbness or weakness, dysarthria, weakness and spasticity, hyperreflexia, ankle clonus, upgoing toes, ataxia, sensory abnormalities.

## DISEASE COURSE

Three major subtypes:

- *Relapsing-remitting MS* (RRMS) is characterized by recurrent attacks of neurologic dysfunction over days to weeks with or without recovery; between attacks, no progression of neurologic impairment is noted. Accounts for 85% of new-onset MS cases.
- *Secondary progressive MS* (SPMS) always initially presents as RRMS but evolves in many pts into SPMS (~1–2% each year).

**TABLE 190-1 DIAGNOSTIC CRITERIA FOR MULTIPLE SCLEROSIS (MS)**

| Clinical Presentation | Additional Data Needed for MS Diagnosis |
|---|---|
| 2 or more attacks; objective clinical evidence of 2 or more lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack | None |
| 2 or more attacks; objective clinical evidence of 1 lesion | Dissemination in space, demonstrated by<br>• ≥1 T2 lesion on MRI in at least 2 out of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)<br>*or*<br>• Await a further clinical attack implicating a different CNS site |

(*Continued*)

**TABLE 190-1 DIAGNOSTIC CRITERIA FOR MULTIPLE SCLEROSIS (MS) (*CONTINUED*)**

| Clinical Presentation | Additional Data Needed for MS Diagnosis |
|---|---|
| 1 attack; objective clinical evidence of 2 or more lesions | Dissemination in time, demonstrated by<br>• Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time<br>*or*<br>• A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan<br>*or*<br>• Await a second clinical attack |
| 1 attack; objective clinical evidence of 1 lesion (clinically isolated syndrome) | Dissemination in space and time, demonstrated by:<br>For dissemination in space<br>• ≥1 T2 lesion in at least 2 out of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)<br>*or*<br>• Await a second clinical attack implicating a different CNS site<br>*and*<br>For dissemination in time<br>• Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time<br>*or*<br>• A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan<br>*or*<br>• Await a second clinical attack |
| Insidious neurologic progression suggestive of MS (PPMS) | 1 year of disease progression (retrospectively or prospectively determined)<br>*plus*<br>2 out of the 3 following criteria<br>Evidence for dissemination in space in the brain based on ≥1 T2+ lesions in the MS-characteristic periventricular, juxtacortical, or infratentorial regions<br>Evidence for dissemination in space in the spinal cord based on ≥2 T2+ lesions in the cord<br>Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index) |

***Abbreviations:*** MS, multiple sclerosis; PPMS, primary progressive multiple sclerosis.
***Source:*** From CH Polman et al: Diagnostic Criteria for Multiple Sclerosis: 2010 Revisions to the "McDonald Criteria." *Ann Neurol* 69:292, 2011.

**TABLE 190-2 DISORDERS THAT CAN MIMIC MULTIPLE SCLEROSIS (MS)**

| |
|---|
| Acute disseminated encephalomyelitis (ADEM) |
| Antiphospholipid antibody syndrome |
| Behçet's disease |
| CADASIL |
| Congenital leukodystrophies (e.g., adrenoleukodystrophy, metachromatic leukodystrophy) |
| HIV infection |
| Ischemic optic neuropathy (arteritic and nonarteritic) |
| Lyme disease |
| MELAS |
| Neoplasms (e.g., lymphoma, glioma, meningioma) |
| Sarcoid |
| Sjögren's syndrome |
| Stroke and ischemic cerebrovascular disease |
| Syphilis |
| Systemic lupus erythematosus and related collagen vascular disorders |
| Tropical spastic paraparesis (HTLV-1/2 infection) |
| Vascular malformations (especially spinal dural AV fistulas) |
| Vasculitis (primary CNS or other) |
| Vitamin $B_{12}$ deficiency |

***Abbreviations:*** AV, arteriovenous; CADASIL, cerebral autosomal dominant arteriopathy, subcortical infarcts, and leukoencephalopathy; HTLV, human T-cell lymphotropic virus; MELAS, mitochondrial encephalopathy with lactic acidosis and stroke.

- *Primary progressive MS* (PPMS) is characterized by gradual progression of disability from onset without discrete attacks; 15% of new-onset MS cases.

Historically, 15 years after diagnosis only 20% of pts have no functional limitation and one-third to one-half have progressed to SPMS and require assistance with ambulation. With the introduction of disease modifying therapies for MS, the long-term course of the disease may have become less disabling.

## LABORATORY EVALUATION

MRI reveals multifocal bright areas on T2-weighted sequences in >95% of pts, often in periventricular location; gadolinium enhancement indicates acute lesions with disruption of blood-brain barrier (Fig. 190-1). MRI also useful to exclude MS mimics, although findings in MS are not completely specific for the disorder. CSF findings include mild lymphocytic pleocytosis (5–75 cells in 25%), oligoclonal bands (>75% have two or more), elevated IgG (80%), and normal total protein level. Visual, auditory, and somatosensory evoked response tests can identify lesions that are clinically silent; one or more evoked response tests are prolonged in 80–90% of pts. Urodynamic studies aid in management of bladder symptoms.

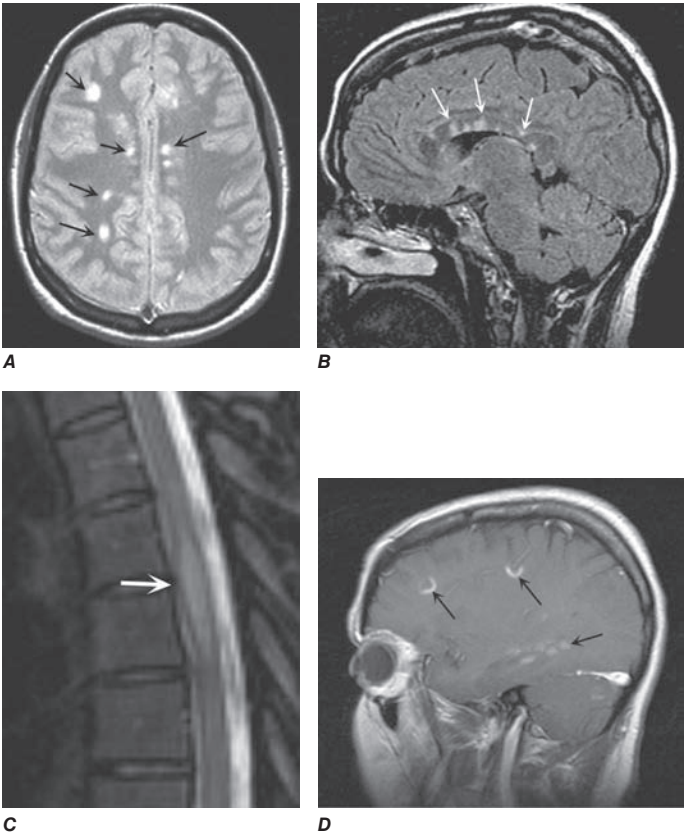
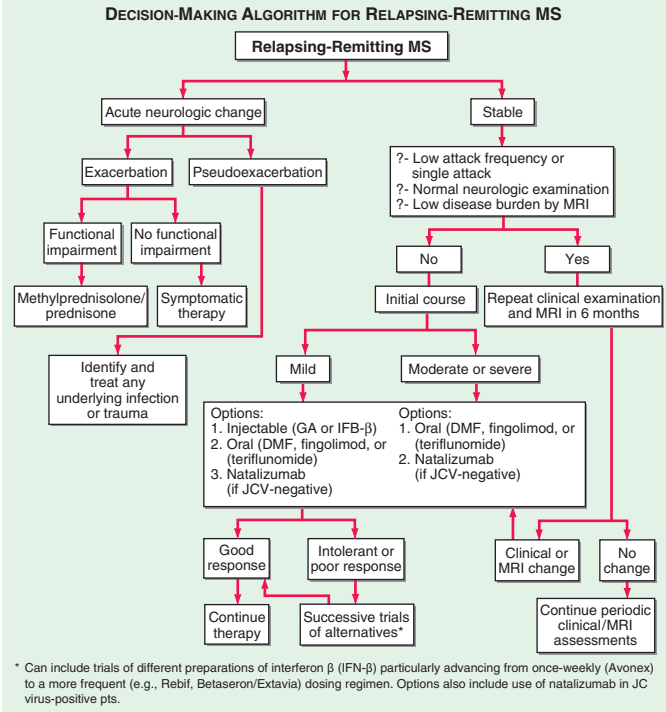



**FIGURE 190-1** MRI findings in MS. **A.** Axial first-echo image from T2-weighted sequence demonstrates multiple bright signal abnormalities in white matter, typical for MS. **B.** Sagittal T2-weighted fluid-attenuated inversion recovery image (FLAIR) in which the high signal of CSF has been suppressed. CSF appears dark, while areas of brain edema or demyelination appear high in signal as shown here in the corpus callosum (*arrows*). Lesions in the anterior corpus callosum are frequent in MS and rare in vascular disease. **C.** Sagittal T2-weighted fast spin-echo image of the thoracic spine demonstrates a fusiform high-signal-intensity lesion in the midthoracic spinal cord. **D.** Sagittal T1-weighted image obtained after the IV administration of gadolinium reveals focal areas of blood-brain barrier disruption, identified as high-signal-intensity regions (*arrows*).

## TREATMENT MULTIPLE SCLEROSIS (SEE FIG. 190-2)

### DISEASE-MODIFYING THERAPIES FOR RELAPSING FORMS OF MS (RRMS, SPMS WITH EXACERBATIONS)

- Ten treatments are available in the United States: interferon (IFN)-β1a (Avonex; 30 μg IM once a week), IFN-β1a (Rebif; 44 μg SC thrice weekly), IFN-β1b (Betaseron; 250 μg SC every other day or Extavia; 0.25 mg SC every other day), glatiramer acetate (Copaxone; 12 mg/d SC), natalizumab (Tysabri; 300 mg IV every 4 weeks), fingolimod (Gilenya; 0.5 mg PO daily), dimethyl fumarate

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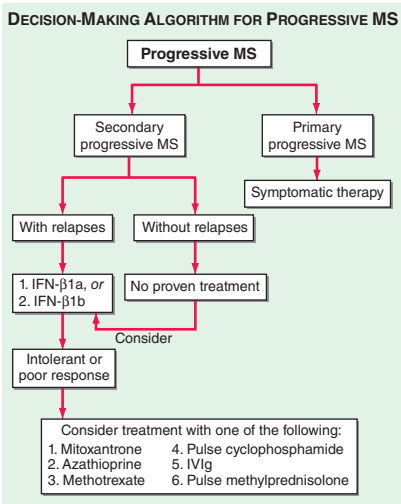


*B*

**FIGURE 190-2** Therapeutic decision-making for MS.

(Tecfidera; 240 mg PO twice daily after initial lower starting dose), teriflunomide (Aubagio; 7–14 mg PO daily), mitoxantrone (Novantrone; 12 mg/m$^2$ IV every 3 months), and alemtuzumab (Lemtrada; 12 mg IV daily for 5 days followed 12 months later with 12 mg IV daily for 5 days).

- IFN preparations that are given multiple times weekly (e.g., Rebif or Betaseron/Extavia) appear to have slightly greater efficacy compared with once-weekly agents (e.g., Avonex).
- Side effects of IFN include flulike symptoms, injection-site reactions (with SC dosing), and mild abnormalities on laboratory evaluation (e.g., elevated liver function tests or lymphopenia). Rarely, severe hepatotoxicity may occur. Side effects of IFN often subside with time. Injection-site reactions also occur with glatiramer acetate but are less severe than with IFN. Approximately 15% of pts receiving glatiramer acetate experience one or more episodes of flushing, chest tightness, dyspnea, palpitations, and anxiety.
- Fingolimod is generally well tolerated, and oral dosing is convenient for pts. First-degree heart block and bradycardia can occur, necessitating the prolonged (6-h) observation of pts receiving their first dose.
- Dimethyl fumarate has a twice-daily oral dosing schedule that makes it somewhat less convenient for pts. GI side effects are common as treatment is initiated, but usually subside with continued administration.
- Teriflunomide is well-tolerated and convenient for pts given its once daily oral dosing. However, there is less evidence of its superiority to the injectable medications than for the other oral agents A major limitation in women of childbearing age is its possible teratogenicity.
- Natalizumab is the most effective MS agent available; however, because of the development of progressive multifocal leukoencephalopathy (PML) in 0.3% of pts, it is generally used only for pts who have failed other therapies or who have particularly aggressive presentations. A blood test to detect antibodies against the PML (JC) virus can identify individuals who are at highest risk for this complication.
- Most pts with relapsing MS and a mild initial course receive an injectable (IFN-β or glatiramer acetate) or oral (dimethyl fumarate, fingolimod, or teriflunomide) agent as first-line therapy.
- For pts presenting with a moderate or severe initial course, either an oral agent (dimethyl fumarate or fingolimod) or, if the pt is JC virus antibody seronegative, infusion therapy with natalizumab is recommended.
- Regardless of which agent is chosen first, treatment should probably be altered in pts who continue to have frequent attacks (Fig. 190-2).
- Several studies suggest that these agents can improve the long-term outcome of MS. Thus, early treatment with a disease-modifying drug is appropriate for most pts. It may be reasonable to delay initiating treatment in pts with (1) a normal neurologic examination, (2) a single attack or a low attack frequency, and (3) a low burden of disease as assessed by brain MRI.
- Untreated pts need to be followed closely; the need for therapy is reassessed if there is evidence of ongoing disease.
- Vitamin D deficiency should be corrected in all pts with MS, usually by oral supplementation with vitamin $D_3$, 4000–5000 IU daily.

## ACUTE RELAPSES

- Acute relapses that produce functional impairment may be treated with a short course of IV methylprednisolone (500–1000 mg IV q A.M. × 3–5 days) followed often by oral prednisone (60 mg q A.M. × 4, 40 mg q A.M. × 4, 20 mg q A.M. × 3). This regimen modestly reduces the severity and shortens the duration of attacks.

- Plasma exchange (seven exchanges: 40–60 mL/kg, every other day for 14 days) may benefit pts with fulminant attacks of demyelination (not only MS) that are unresponsive to glucocorticoids; cost is high and conclusive evidence of efficacy is lacking.

## PROGRESSIVE SYMPTOMS

- For pts with SPMS who continue to experience relapses, treatment with one of the IFNs is reasonable; however, the IFNs are ineffective against purely progressive MS symptoms.
- Mitoxantrone is approved in the United States for treatment of SPMS; however, this is not the population studied in the pivotal trial, evidence for efficacy is relatively weak, and leukemia risk as well as dose-related cardiac toxicity are important concerns.
- Methotrexate (7.5–20 mg PO once each week) or azathioprine (2–3 mg/kg per day PO) is sometimes tried.
- Pulse therapy with cyclophosphamide is employed in some centers for young adults with aggressive forms of MS.
- Other smaller studies have examined monthly pulses of IV immunoglobulin (IVIg) or IV methylprednisolone.
- For pts with PPMS, symptomatic therapy only is recommended, although a preplanned secondary analysis of a negative rituximab trial was promising and a follow-up trial with a related agent (ocrelizumab) is ongoing.

## SYMPTOMATIC THERAPY

- Spasticity may respond to physical therapy, baclofen (20–120 mg/d), diazepam (2–40 mg/d), tizanidine (8–32 mg/d), dantrolene (25–400 mg/d), and cyclobenzaprine hydrochloride (10–60 mg/d).
- Dysesthesia may respond to carbamazepine (100–1000 mg/d in divided doses), phenytoin (300–600 mg/d), gabapentin (300–3600 mg/d), pregabalin (50–300 mg/d), or amitriptyline (25–150 mg/d).
- Treatment of bladder symptoms is based on the underlying pathophysiology investigated with urodynamic testing: bladder hyperreflexia is treated with evening fluid restriction and frequent voiding; if this fails, anticholinergics such as oxybutynin (5–15 mg/d) may be tried; hyporeflexia is treated with the cholinergic drug bethanechol (30–150 mg a day), and dyssynergia due to loss of coordination between bladder wall and sphincter muscles is treated with anticholinergics and intermittent catheterization.
- Depression should be treated aggressively.

## CLINICAL VARIANTS OF MS

*Neuromyelitis optica* (NMO) consists of separate attacks of acute optic neuritis (bilateral or unilateral) and myelitis. In contrast to MS, the brain MRI is typically, but not always, normal. A focal enhancing region of swelling and cavitation, extending over three or more spinal cord segments, is typically seen on spinal MRI. A highly specific autoantibody directed against the water channel aquaporin-4 is present in the sera of two-thirds of pts with a clinical diagnosis of NMO. Acute attacks are usually treated with high-dose glucocorticoids as for MS exacerbations. Plasma exchange has also been used empirically for acute episodes that fail to respond to glucocorticoids. Prophylaxis against relapses can be achieved with mycophenolate mofetil, rituximab, or a combination of glucocorticoids plus azathioprine.

*Acute MS* (Marburg's variant) is a fulminant demyelinating process that progresses to death within 1–2 years. No controlled trials of therapy exist; high-dose glucocorticoids, plasma exchange, and cyclophosphamide have been tried, with uncertain benefit.

### ACUTE DISSEMINATED ENCEPHALOMYELITIS (ADEM)

A fulminant, often devastating, demyelinating disease that has a monophasic course and may be associated with antecedent immunization or infection. Signs of disseminated neurologic disease are consistently present (e.g., hemiparesis or quadriparesis, extensor plantar responses, lost or hyperactive tendon reflexes, sensory loss, and brainstem involvement). Fever, headache, meningismus, lethargy progressing to coma, and seizures may occur. CSF pleocytosis, generally 200 cells/μL, is common. MRI may reveal extensive gadolinium enhancement of white matter in brain and spinal cord. Initial treatment is with high-dose glucocorticoids. Pts who fail to respond may benefit from a course of plasma exchange or IVIg.

For a more detailed discussion, see Hauser SL, Goodin DS: Multiple Sclerosis and Other Demyelinating Diseases, Chap. 458, p. 2661, in HPIM-19.

# 191 Acute Meningitis and Encephalitis

Acute infections of the nervous system include bacterial meningitis, viral meningitis, encephalitis, focal infections such as brain abscess and subdural empyema, and infectious thrombophlebitis. Key goals: emergently distinguish between these conditions, identify the pathogen, and initiate appropriate antimicrobial therapy.

## APPROACH TO THE PATIENT: Acute Infection of the Nervous System

(Fig. 191-1) First identify whether infection predominantly involves the subarachnoid space (*meningitis*) or brain tissue (termed *encephalitis* when viral, *cerebritis* or *abscess* if bacterial, fungal, or parasitic). Nuchal rigidity is the pathognomonic sign of meningeal irritation and is present when the neck resists passive flexion.

Principles of management:

- Initiate empirical therapy whenever bacterial meningitis is considered.
- All pts with head trauma, immunocompromised states, known malignancies, or focal neurologic findings (including papilledema or stupor/coma) should undergo a neuroimaging study of the brain prior to LP. If bacterial meningitis is suspected, begin empirical antibiotic therapy prior to neuroimaging and LP.
- Stupor/coma, seizures, or focal neurologic deficits do not occur in viral meningitis; pts with these symptoms should be hospitalized and treated empirically for bacterial and viral meningoencephalitis.
- Immunocompetent pts with a normal level of consciousness, no prior antimicrobial treatment, and a CSF profile consistent with viral meningitis (lymphocytic pleocytosis and a normal glucose concentration) can often be treated as outpatients. Failure of a pt with suspected viral meningitis to improve within 48 h should prompt reevaluation including follow-up examination, repeat imaging, and laboratory studies, often including a second LP.

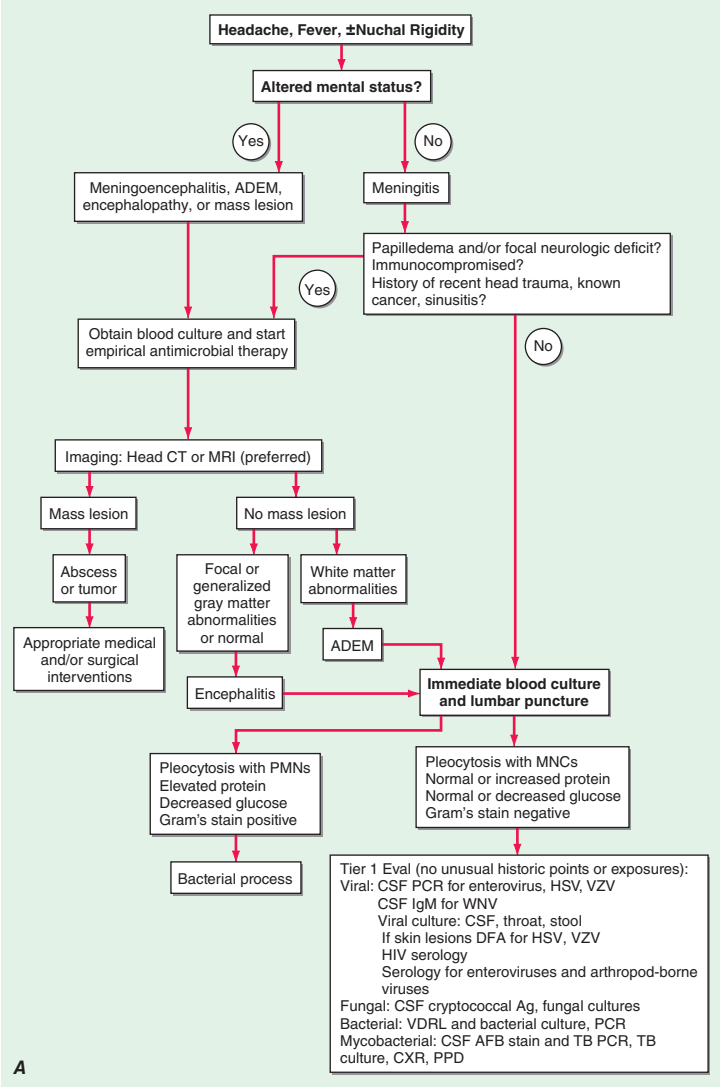


**FIGURE 191-1** The management of pts with suspected CNS infection. ADEM, acute disseminated encephalomyelitis; AFB, acid-fast bacillus; Ag, antigen; CTFV, Colorado tick fever virus; DFA, direct fluorescent antibody; HHV, human herpesvirus; LCMV, lymphocytic choriomeningitis virus; MNCs, mononuclear cells; TB, tuberculosis; WNV, West Nile virus.

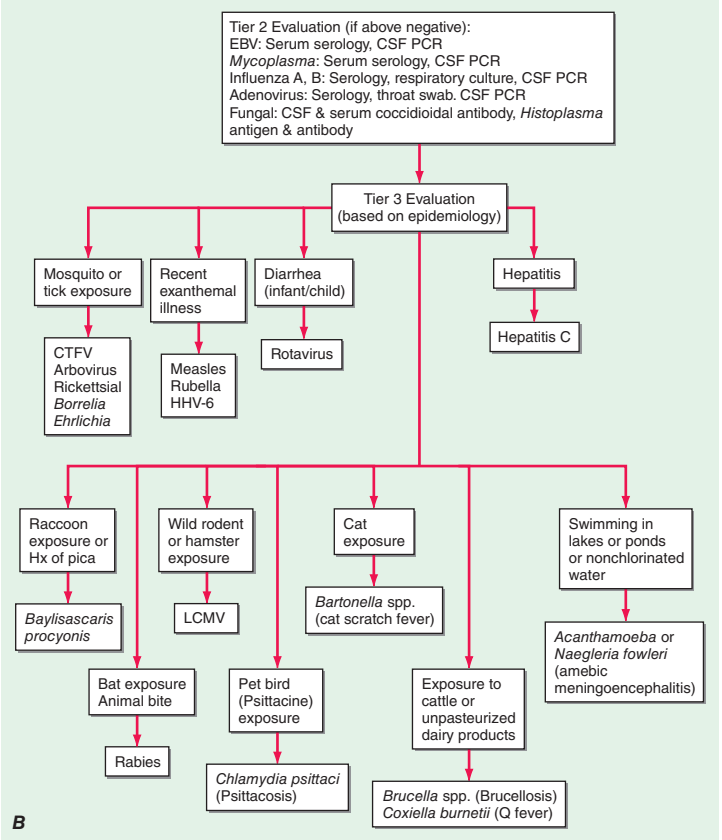


**FIGURE 191-1** *(Continued)*

## ACUTE BACTERIAL MENINGITIS

Pathogens most frequently involved in immunocompetent adults are *Streptococcus pneumoniae* ("pneumococcus," ~50%) and *Neisseria meningitidis* ("meningococcus," ~25%). Predisposing factors for pneumococcal meningitis include infection (pneumonia, otitis, sinusitis), asplenia, hypogammaglobulinemia, complement deficiency, alcoholism, diabetes, and head trauma with CSF leak. *Listeria monocytogenes* is a consideration in pregnant women, individuals >60 years, alcoholics, and immunocompromised individuals of all ages. Enteric gram-negative bacilli and group B streptococcus are increasingly common causes of meningitis in individuals with chronic medical conditions. *Staphylococcus aureus* and coagulase-negative staphylococci are causes following neurosurgical procedures, especially shunting procedures for hydrocephalus.

### Clinical Features

Presents as an acute fulminant illness that progresses rapidly in a few hours or as a subacute infection that progressively worsens over several days. The classic clinical triad of meningitis is fever, headache, and nuchal rigidity ("stiff neck"). Mental status

**TABLE 191-1 CEREBROSPINAL FLUID ABNORMALITIES IN BACTERIAL MENINGITIS**

| | |
|---|---|
| Opening pressure | >180 $mmH_2O$ |
| White blood cells | 10/μL to 10,000/μL; neutrophils predominate |
| Red blood cells | Absent in nontraumatic tap |
| Glucose | <2.2 mmol/L (<40 mg/dL) |
| CSF/serum glucose | <0.4 |
| Protein | >0.45 g/L (>45 mg/dL) |
| Gram's stain | Positive in >60% |
| Culture | Positive in >80% |
| Latex agglutination | May be positive in patients with meningitis due to *Streptococcus pneumoniae, Neisseria meningitidis, Haemophilus influenzae* type b, *Escherichia coli*, group B streptococci |
| Limulus lysate | Positive in cases of gram-negative meningitis |
| PCR | Detects bacterial DNA |

changes occur in >75% of pts and vary from lethargy to coma. Nausea, vomiting, and photophobia are also common. Seizures occur in 20–40% of pts. Raised intracranial pressure (ICP) is the major cause of obtundation and coma. The rash of meningococcemia begins as a diffuse maculopapular rash resembling a viral exanthem but rapidly becomes petechial on trunk and lower extremities, mucous membranes and conjunctiva, and occasionally palms and soles.

## Laboratory Evaluation

The CSF profile is shown in Table 191-1. CSF bacterial cultures are positive in >80% of pts, and CSF Gram's stain demonstrates organisms in >60%. A 16S rRNA conserved sequence broad-based bacterial PCR can detect small numbers of viable and nonviable organisms in the CSF and is useful for diagnosis in pts pretreated with antibiotics and when Gram's stain and CSF cultures are negative. When positive, more specific PCR tests for individual organisms can be obtained. The latex agglutination (LA) test for detection of bacterial antigens of *S. pneumoniae*, *N. meningitidis*, *Haemophilus influenzae* type b, group B streptococcus, and *Escherichia coli* K1 strains in the CSF is being replaced by the CSF bacterial PCR assay. The Limulus amebocyte lysate assay rapidly detects gram-negative endotoxin in CSF and thus is useful in diagnosis of gram-negative bacterial meningitis; false-positives may occur but sensitivity approaches 100%. Petechial skin lesions, if present, should be biopsied. Blood cultures should always be obtained.

## Differential Diagnosis

Includes viral meningoencephalitis, especially herpes simplex virus (HSV) encephalitis (see below); rickettsial diseases such as Rocky Mountain spotted fever (immunofluorescent staining of skin lesions); focal suppurative CNS infections including subdural and epidural empyema and brain abscess (see below); subarachnoid hemorrhage (Chap. 18); and the demyelinating disease acute disseminated encephalomyelitis (ADEM, Chap. 190).

**TABLE 191-2 ANTIBIOTICS USED IN EMPIRICAL THERAPY OF BACTERIAL MENINGITIS AND FOCAL CENTRAL NERVOUS SYSTEM INFECTIONS[a]**

| Indication | Antibiotic |
|---|---|
| Preterm infants to infants <1 month | Ampicillin + cefotaxime |
| Infants 1–3 months | Ampicillin + cefotaxime or ceftriaxone |
| Immunocompetent children >3 months and adults <55 | Cefotaxime, ceftriaxone, or cefepime + vancomycin |
| Adults >55 and adults of any age with alcoholism or other debilitating illnesses | Ampicillin + cefotaxime, ceftriaxone or cefepime + vancomycin |
| Hospital-acquired meningitis, posttraumatic or postneurosurgery meningitis, neutropenic patients, or patients with impaired cell-mediated immunity | Ampicillin + ceftazidime or meropenem + vancomycin |

| | Total Daily Dose and Dosing Interval | |
|---|---|---|
| **Antimicrobial Agent** | **Child (>1 month)** | **Adult** |
| Ampicillin | 300 (mg/kg)/d, q6h | 12 g/d, q4h |
| Cefepime | 150 (mg/kg)/d, q8h | 6 g/d, q8h |
| Cefotaxime | 225–300 (mg/kg)/d, q6h | 12 g/d, q4h |
| Ceftriaxone | 100 (mg/kg)/d, q12h | 4 g/d, q12h |
| Ceftazidime | 150 (mg/kg)/d, q8h | 6 g/d, q8h |
| Gentamicin | 7.5 (mg/kg)/d, q8h[b] | 7.5 (mg/kg)/d, q8h |
| Meropenem | 120 (mg/kg)/d, q8h | 6 g/d, q8h |
| Metronidazole | 30 (mg/kg)/d, q6h | 1500–2000 mg/d, q6h |
| Nafcillin | 100–200 (mg/kg)/d, q6h | 9–12 g/d, q4h |
| Penicillin G | 400,000 (U/kg)/d, q4h | 20–24 million U/d, q4h |
| Vancomycin | 45–60 (mg/kg)/d, q6h | 45–60 (mg/kg)/d, q6–12h[b] |

[a]All antibiotics are administered intravenously; doses indicated assume normal renal and hepatic function.
[b]Doses should be adjusted based on serum peak and trough levels: gentamicin therapeutic level: peak: 5–8 μg/mL; trough: <2 μg/mL; vancomycin therapeutic level: peak: 25–40 μg/mL; trough: 5–15 μg/mL.

## TREATMENT ACUTE BACTERIAL MENINGITIS

- Recommendations for empirical therapy are summarized in **Table 191-2**. Therapy is then modified based on results of CSF culture (**Table 191-3**).
- In general, the treatment course is 7 days for meningococcus, 14 days for pneumococcus, 21 days for gram-negative meningitis, and at least 21 days for *L. monocytogenes*.
- Adjunctive therapy with dexamethasone (10 mg IV), administered 15–20 min before the first dose of an antimicrobial agent and repeated every 6 h for 4 days,

**TABLE 191-3 ANTIMICROBIAL THERAPY OF CENTRAL NERVOUS SYSTEM BACTERIAL INFECTIONS BASED ON PATHOGEN[a]**

| Organism | Antibiotic |
|---|---|
| *Neisseria meningitides* | |
| Penicillin-sensitive | Penicillin G or ampicillin |
| Penicillin-resistant | Ceftriaxone or cefotaxime |
| *Streptococcus pneumonia* | |
| Penicillin-sensitive | Penicillin G |
| Penicillin-intermediate | Ceftriaxone or cefotaxime or cefepime |
| Penicillin-resistant | Ceftriaxone (or cefotaxime or cefepime) + vancomycin |
| Gram-negative bacilli (except *Pseudomonas* spp.) | Ceftriaxone or cefotaxime |
| *Pseudomonas aeruginosa* | Ceftazidime or cefepime or meropenem |
| *Staphylococci* spp. | |
| Methicillin-sensitive | Nafcillin |
| Methicillin-resistant | Vancomycin |
| *Listeria monocytogenes* | Ampicillin + gentamicin |
| *Haemophilus influenzae* | Ceftriaxone or cefotaxime or cefepime |
| *Streptococcus agalactiae* | Penicillin G or ampicillin |
| *Bacteroides fragilis* | Metronidazole |
| *Fusobacterium* spp. | Metronidazole |

[a]Doses are as indicated in Table 191-2.

improves outcome from bacterial meningitis; benefits most striking in pneumococcal meningitis. Dexamethasone may decrease the penetration of vancomycin into CSF, and thus higher vancomycin doses may be needed.

- In meningococcal meningitis, all close contacts should receive prophylaxis with rifampin [600 mg in adults (10 mg/kg in children >1 year)] every 12 h for 2 days; rifampin is not recommended in pregnant women. Alternatively, adults can be treated with one dose of azithromycin (500 mg), or one IM dose of ceftriaxone (250 mg).

## Prognosis

Moderate or severe sequelae occur in ~25% of survivors; outcome varies with the infecting organism and can include decreased intellectual function, memory impairment, seizures, hearing loss and dizziness, and gait disturbances.

## VIRAL MENINGITIS

Presents as fever, headache, and meningeal irritation associated with a CSF lymphocytic pleocytosis. Fever may be accompanied by malaise, myalgia, anorexia, nausea and vomiting, abdominal pain, and/or diarrhea. A mild degree of lethargy or drowsiness may occur; however, a more profound alteration in consciousness should prompt consideration of alternative diagnoses, including encephalitis.

**TABLE 191-4 VIRUSES CAUSING ACUTE MENINGITIS AND ENCEPHALITIS IN NORTH AMERICA**

| ***Acute Meningitis*** | |
|---|---|
| **Common** | **Less Common** |
| Enteroviruses (coxsackieviruses, echoviruses, and human enteroviruses 68–71) | Herpes simplex virus 1 |
| Varicella-zoster virus | Human herpesvirus 6 |
| Herpes simplex virus 2 | Cytomegalovirus |
| Epstein-Barr virus | Lymphocytic choriomeningitis virus |
| Arthropod-borne viruses | Mumps |
| HIV | |
| ***Acute Encephalitis*** | |
| **Common** | **Less Common** |
| Herpesviruses | Rabies |
| Cytomegalovirus[a] | Eastern equine encephalitis virus |
| Herpes simplex virus 1[b] | Powassan virus |
| Herpes simplex virus 2 | Cytomegalovirus[a] |
| Human herpesvirus 6 | Colorado tick fever virus |
| Varicella-zoster virus | Mumps |
| Epstein-Barr virus | |
| Arthropod-borne viruses | |
| La Crosse virus | |
| West Nile virus[c] | |
| St. Louis encephalitis virus | |
| Enteroviruses | |

[a]Immunocompromised host.
[b]The most common cause of sporadic encephalitis.
[c]The most common cause of epidemic encephalitis.

## Etiology

Using a variety of diagnostic techniques, including CSF PCR, culture, and serology, a specific viral cause can be found in 60–90% of cases. The most important agents are enteroviruses, VZV, HSV type 2, HIV, and arboviruses (Table 191-4). The incidence of enteroviral and arboviral infections is greatly increased during the summer.

## Diagnosis

Most important test is examination of the CSF. The typical profile is a lymphocytic pleocytosis (25–500 cells/μL), a normal or slightly elevated protein concentration [0.2–0.8 g/L (20–80 mg/dL)], a normal glucose concentration, and a normal or mildly elevated opening pressure (100–350 mm$H_2O$). Organisms are *not* seen on Gram or acid-fast stained smears or india ink preparations of CSF. Rarely, polymorphonuclear leukocytes (PMN) predominate in the first 48 h of illness, especially with echovirus 9, West Nile virus (WNV), eastern equine encephalitis virus, or mumps. The total CSF cell count in viral meningitis is typically 25–500/μL. As a general rule,

a lymphocytic pleocytosis with a low glucose concentration should suggest fungal, listerial, or tuberculous meningitis or noninfectious disorders (e.g., sarcoid, neoplastic meningitis).

CSF PCR testing is the procedure of choice for rapid, sensitive, and specific identification of enteroviruses, HSV, EBV, varicella zoster virus (VZV), human herpes virus 6 (HHV-6), and CMV. Attempts should also be made to culture virus from CSF and other sites and body fluids including blood, throat swabs, stool, and urine, although sensitivity of cultures is generally poor. Serologic studies, including those utilizing paired CSF and serum specimens, may be helpful for retrospective diagnosis; they are particularly important for diagnosis of WNV and other arbovirus etiologies.

### Differential Diagnosis

Consider bacterial, fungal, tuberculous, spirochetal, and other infectious causes of meningitis; parameningeal infections; partially treated bacterial meningitis; neoplastic meningitis; noninfectious inflammatory diseases including sarcoid and Behçet's disease.

**TREATMENT VIRAL MENINGITIS**

- Supportive or symptomatic therapy is usually sufficient, and hospitalization is not required.
- The elderly and immunocompromised pts should be hospitalized, as should individuals in whom the diagnosis is uncertain or those with significant alterations in consciousness, seizures, or focal neurologic signs or symptoms.
- Severe cases of meningitis due to HSV, EBV, and VZV can be treated with IV acyclovir (5–10 mg/kg every 8 h), followed by an oral drug (acyclovir (800 mg, five times daily; famciclovir 500 mg tid; or valacyclovir 1000 mg tid) for a total course of 7–14 days; for mildly affected patients, an oral course of antivirals alone may be appropriate.
- Additional supportive therapy can include analgesics and antipyretics.
- Prognosis for full recovery is excellent.
- Vaccination is an effective method of preventing meningitis and other neurologic complications associated with poliovirus, mumps, rubella, measles, and VZV infection.

## VIRAL ENCEPHALITIS

An infection of the brain parenchyma commonly associated with meningitis ("meningoencephalitis"). Clinical features are those of viral meningitis plus evidence of brain tissue involvement, commonly including altered consciousness such as behavioral changes and hallucinations; seizures; and focal neurologic findings such as aphasia, hemiparesis, involuntary movements, and cranial nerve deficits.

### Etiology

The same organisms responsible for viral meningitis are also responsible for encephalitis, although relative frequencies differ. The most common causes of sporadic encephalitis in immunocompetent adults are herpesviruses (HSV, VZV, EBV) (Table 191-4). HSV encephalitis should be considered when focal findings are present and when involvement of the inferomedial frontotemporal regions of the brain is likely (olfactory hallucinations, anosmia, bizarre behavior, or memory disturbance). Epidemics of encephalitis are usually caused by arboviruses. WNV has been responsible for the majority of arbovirus meningitis and encephalitis cases in the United States since 2002. Prominent motor manifestations, including acute poliomyelitis-like paralysis, may occur with WNV.

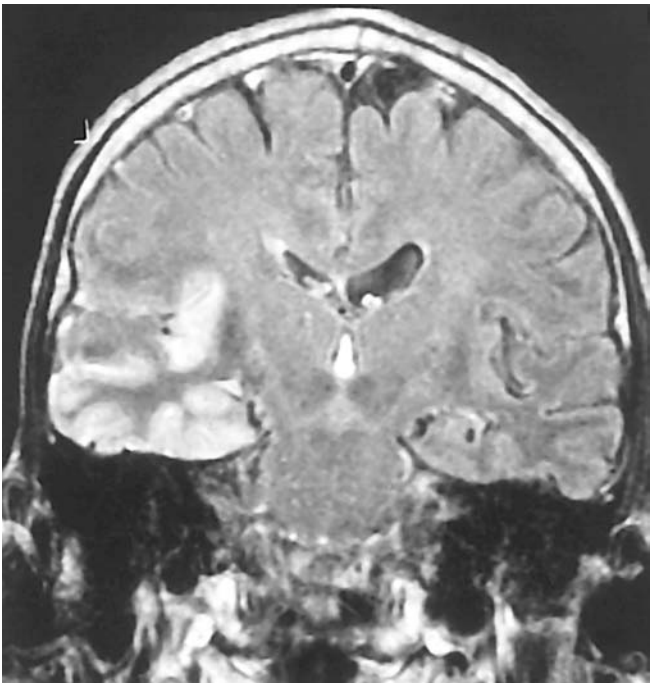

**FIGURE 191-2** Coronal FLAIR magnetic resonance image from a pt with herpes simplex encephalitis. Note the area of increased signal in the right temporal lobe (left side of image) confined predominantly to the gray matter. This pt had predominantly unilateral disease; bilateral lesions are more common, but may be quite asymmetric in their intensity.

## Diagnosis

CSF studies are essential; typical CSF profile is similar to viral meningitis. CSF PCR tests allow for rapid and reliable diagnosis of HSV, EBV, VZV, CMV, HHV-6, and enteroviruses. CSF virus cultures are generally negative. Serologic studies also have a role for some viruses. Demonstration of WNV IgM antibodies in the CSF is diagnostic of WNV encephalitis.

MRI is the neuroimaging procedure of choice and demonstrates areas of increased T2 signal. Bitemporal and orbitofrontal areas of increased signal are seen in HSV encephalitis, but are not diagnostic (Fig. 191-2). The EEG may suggest seizures or show temporally predominant periodic spikes on a slow, low-amplitude background suggestive of HSV encephalitis.

Brain biopsy is now used only when CSF PCR studies fail to identify the cause, focal abnormalities on MRI are present, and progressive clinical deterioration occurs despite treatment with acyclovir and supportive therapy.

## Differential Diagnosis

Includes both infectious and noninfectious causes of encephalitis, including vascular diseases; abscess and empyema; fungal (*Cryptococcus* and *Mucor*), spirochetal (*Leptospira*), rickettsial, bacterial (*Listeria*), tuberculous, and mycoplasmal infections; tumors; toxic encephalopathy; SLE; autoimmune or paraneoplastic encephalidities, and acute disseminated encephalomyelitis.

**TREATMENT VIRAL ENCEPHALITIS**

- All pts with suspected HSV encephalitis should be treated with IV acyclovir (10 mg/kg every 8 h) while awaiting diagnostic studies.
- Pts with a PCR-confirmed diagnosis of HSV encephalitis should receive a 14- to 21-day course of therapy. Consider repeat CSF PCR after completion of acyclovir therapy; pts with a persistently positive CSF PCR for HSV after completing a standard course of acyclovir therapy should receive additional treatment, followed by a repeat CSF PCR test.
- Acyclovir treatment may also be of benefit in severe encephalitis due to EBV and VZV. No therapy currently available for enteroviral, mumps, or measles encephalitis.
- IV ribavirin (15–25 mg/kg per day given in three divided doses) may benefit severe encephalitis due to California encephalitis (LaCrosse) virus.
- CMV encephalitis should be treated with ganciclovir (5 mg/kg every 12 h IV over 1 h, followed by maintenance therapy of 5 mg/kg every day), foscarnet (60 mg/kg every 8 h IV over 1 h, followed by maintenance therapy 60–120 mg/kg per day), or a combination of the two drugs; cidofovir (5 mg/kg IV once weekly for 2 weeks, then biweekly for two or more additional doses, depending on response; prehydrate with normal saline and pretreat with probenecid) may provide an alternative for nonresponders.
- No proven therapy is available for WNV encephalitis; small groups of pts have been treated with interferon, ribavirin, WNV-specific antisense oligonucleotides, IV immunoglobulin preparations of Israeli origin containing high-titer anti-WNV antibody, and humanized monoclonal antibodies directed against the viral envelope glycoprotein. There is optimism that a safe and effective human WNV vaccine can be developed.

### Prognosis

In HSV encephalitis treated with acyclovir, 81% survival in one series; neurologic sequelae were mild or absent in 46%, moderate in 12%, and severe in 42%.

## BRAIN ABSCESS

A focal, suppurative infection within the brain parenchyma, typically surrounded by a vascularized capsule. The term *cerebritis* is used to describe a nonencapsulated brain abscess. Predisposing conditions include otitis media and mastoiditis, paranasal sinusitis, pyogenic infections in the chest or other body sites, head trauma, neurosurgical procedures, and dental infections. Many brain abscesses occur in immunocompromised hosts and are caused less often by bacteria than by fungi and parasites including *Toxoplasma gondii*, *Aspergillus* spp., *Nocardia* spp., *Candida* spp., and *Cryptococcus* neoformans. In Latin America and in immigrants from Latin America, the most common cause of brain abscess is *Taenia solium* (neurocysticercosis). In India and the Far East, mycobacterial infection (tuberculoma) remains a major cause of focal CNS mass lesions.

### Clinical Features

Brain abscess typically presents as an expanding intracranial mass lesion, rather than as an infectious process. The classic triad of headache, fever, and a focal neurologic deficit is present in <50% of cases.

### Diagnosis

MRI is superior to CT for demonstrating abscesses in the early (cerebritis) stages and also for abscesses in the posterior fossa. A mature brain abscess appears on CT as a focal area of hypodensity surrounded by ring enhancement. The CT and MRI

appearance, particularly of the capsule, may be altered by treatment with glucocorticoids. The distinction between a brain abscess and other focal lesions such as tumors may be facilitated with diffusion-weighted imaging (DWI) sequences in which brain abscesses typically show increased signal due to restricted diffusion.

Microbiologic diagnosis best determined by Gram's stain and culture of abscess material obtained by stereotactic needle aspiration. Up to 10% of pts will also have positive blood cultures. CSF analysis contributes nothing to diagnosis or therapy, and LP increases the risk of herniation.

**TREATMENT BRAIN ABSCESS**

- Optimal therapy involves a combination of high-dose parenteral antibiotics and neurosurgical drainage.
- Empirical therapy of community-acquired brain abscess in an immunocompetent pt typically includes a third or fourth-generation cephalosporin (e.g., cefotaxime, ceftriaxone, or cefepime) and metronidazole (see Table 191-2 for antibiotic dosages).
- In pts with penetrating head trauma or recent neurosurgical procedures, treatment should include ceftazidime as the third-generation cephalosporin to enhance coverage of *Pseudomonas* spp. and vancomycin for coverage of resistant staphylococci. Meropenem plus vancomycin also provides good coverage in this setting.
- Aspiration and drainage essential in most cases. Empirical antibiotic coverage is modified based on the results of Gram's stain and culture of the abscess contents.
- Medical therapy alone is reserved for pts whose abscesses are neurosurgically inaccessible and for pts with small (<2–3 cm) or nonencapsulated abscesses (cerebritis).
- All pts should receive a minimum of 6–8 weeks of parenteral antibiotic therapy.
- Pts should receive prophylactic anticonvulsant therapy.
- Glucocorticoids should not be given routinely.
- Serial MRI or CT scans should be obtained on a monthly or twice-monthly basis to document resolution of the abscess.

### Prognosis

In modern series, the mortality is typically <15%. Significant sequelae including seizures, persisting weakness, aphasia, or mental impairment occur in ≥20% of survivors.

## PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

### Clinical Features

A progressive disorder due to infection with the JC virus, a human polyoma virus; characterized pathologically by multifocal areas of demyelination of varying size distributed throughout the CNS but sparing the spinal cord and optic nerves. In addition, there are characteristic cytologic alterations in both astrocytes and oligodendrocytes. Pts often present with visual deficits (45%), typically a homonymous hemianopia, and mental impairment (38%) (dementia, confusion, personality change), weakness, and ataxia. Seizures occur in ~20% of patients. Almost all pts have an underlying immune disorder or are receiving immunosuppressive therapy. More than 80% of currently diagnosed PML cases occur in pts with AIDS; it has been estimated that up to 5% of AIDS pts will develop PML. Immunosuppressant drugs such as natalizumab have also been associated with PML.

## Diagnostic Studies

MRI reveals multifocal asymmetric, coalescing white matter lesions located periventricularly, in the centrum semiovale, in the parietal-occipital region, and in the cerebellum. These lesions have increased T2 and decreased T1 signal, are generally nonenhancing (rarely they may show ring enhancement), and are not associated with edema or mass effect. CT scans, which are less sensitive than MRI for the diagnosis of PML, often show hypodense nonenhancing white matter lesions.

The CSF is typically normal, although mild elevation in protein and/or IgG may be found. Pleocytosis occurs in <25% of cases, is predominantly mononuclear, and rarely exceeds 25 cells/μL. PCR amplification of JC virus DNA from CSF has become an important diagnostic tool. A positive CSF PCR for JC virus DNA in association with typical MRI lesions in the appropriate clinical setting is diagnostic of PML. Pts with negative CSF PCR studies may require brain biopsy for definitive diagnosis as sensitivity of this test is variable; JC virus antigen and nucleic acid can be detected by immunocytochemistry, in situ hybridization, or PCR amplification on tissue. Detection of JC virus antigen or genomic material should be considered diagnostic of PML only if accompanied by characteristic pathologic changes, since both antigen and genomic material have been found in the brains of normal pts. Serologic studies are of no utility for diagnosis given high basal seroprevalence level, but are extremely useful for risk stratification in pts contemplating therapy with certain immunomodulatory drugs such as natalizumab.

### TREATMENT PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

- No effective therapy is available.
- Some pts with HIV-associated PML have shown dramatic clinical gains associated with improvement in immune status following institution of highly active antiretroviral therapy (HAART).

Ps suspected of having PML who are receiving immunomodulatory antibodies should have therapy halted and circulating antibodies cleared by plasma exchange; discontinuation of therapy may lead to transient clinical and radiologic worsening, termed immune reconstitution inflammatory syndrome (IRIS).

For a more detailed discussion, see Roos KL, Tyler KL: Meningitis, Encephalitis, Brain Abscess, and Empyema, Chap. 164, p. 883, in HPIM-19; and HPIM-19 chapters covering specific organisms or infections.

# 192 Chronic and Recurrent Meningitis

Chronic inflammation of the meninges (pia, arachnoid, and dura) can produce profound neurologic disability and may be fatal if not successfully treated. The causes are varied. Five categories of disease account for most cases of chronic meningitis:

- Meningeal infections
- Malignancy
- Noninfectious inflammatory disorders

**TABLE 192-1 SYMPTOMS AND SIGNS OF CHRONIC MENINGITIS**

| Symptom | Sign |
|---|---|
| Chronic headache | ±Papilledema |
| Neck or back pain/stiffness | Brudzinski's or Kernig's sign of meningeal irritation |
| Change in personality | Altered mental status—drowsiness, inattention, disorientation, memory loss, frontal release signs (grasp, suck, snout), perseveration |
| Facial weakness | Peripheral seventh CN paresis |
| Double vision | Paresis of CNs III, IV, VI |
| Diminished vision | Papilledema, optic atrophy |
| Hearing loss | Eighth CN paresis |
| Arm or leg weakness | Myelopathy or radiculopathy |
| Numbness in arms or legs | Myelopathy or radiculopathy |
| Urinary retention/incontinence | Myelopathy or radiculopathy<br>Frontal lobe dysfunction (hydrocephalus) |
| Clumsiness | Ataxia |

***Abbreviation:*** CN, cranial nerve.

- Chemical meningitis
- Parameningeal infections

## CLINICAL FEATURES

Neurologic manifestations consist of persistent headache with or without stiff neck and hydrocephalus; cranial neuropathies; radiculopathies; and/or cognitive or personality changes (Table 192-1). The diagnosis is usually made when clinical presentation leads the physician to examine CSF for signs of inflammation; on occasion the diagnosis is made when a neuroimaging study shows contrast enhancement of the meninges.

Two clinical forms of chronic meningitis exist. In the first, symptoms are chronic and persistent, whereas in the second there are recurrent, discrete episodes with complete resolution of meningeal inflammation between episodes without specific therapy. In the latter group, likely etiologies are herpes simplex virus type 2, chemical meningitis due to leakage from a tumor, a primary inflammatory condition, or drug hypersensitivity.

## APPROACH TO THE PATIENT: **Chronic Meningitis**

Once chronic meningitis is confirmed by CSF examination, effort is focused on identifying the cause (Tables 192-2 and 192-3) by (1) further analysis of the CSF, (2) diagnosis of an underlying systemic infection or noninfectious inflammatory condition, or (3) examination of meningeal biopsy tissue.

Proper analysis of the CSF is essential; if the possibility of raised intracranial pressure (ICP) exists, a brain imaging study should be performed before LP. In pts with communicating hydrocephalus caused by impaired resorption of CSF, LP is

**TABLE 192-2 INFECTIOUS CAUSES OF CHRONIC MENINGITIS**

| Causative Agent | CSF Formula | Helpful Diagnostic Tests | Risk Factors and Systemic Manifestations |
|---|---|---|---|
| **Common Bacterial Causes** | | | |
| Partially treated suppurative meningitis | Mononuclear or mixed mononuclear-polymorphonuclear cells | CSF culture and Gram's stain | History consistent with acute bacterial meningitis and incomplete treatment |
| Parameningeal infection | Mononuclear or mixed polymorphonuclear-mononuclear cells | Contrast-enhanced CT or MRI to detect parenchymal, subdural, epidural, or sinus infection | Otitis media, pleuropulmonary infection, right-to-left cardiopulmonary shunt for brain abscess; focal neurologic signs; neck, back, ear, or sinus tenderness |
| *Mycobacterium tuberculosis* | Mononuclear cells except polymorphonuclear cells in early infection (commonly <500 WBC/μL); low CSF glucose, high protein | Tuberculin skin test may be negative; AFB culture of CSF (sputum, urine, gastric contents if indicated); tuberculostearic acid detection in CSF; identify tubercle bacillus on acid-fast stain of CSF or protein pellicle; PCR | Exposure history; previous tuberculous illness; immunosuppressed, anti-TNF therapy or AIDS; young children; fever, meningismus, night sweats, miliary TB on x-ray or liver biopsy; stroke due to arteritis |
| Lyme disease (Bannwarth's syndrome) *Borrelia burgdorferi* | Mononuclear cells; elevated protein | Serum Lyme antibody titer; Western blot confirmation; (pts with syphilis may have false-positive Lyme titer) | History of tick bite or appropriate exposure history; erythema chronicum migrans skin rash; arthritis, radiculopathy, Bell's palsy, meningoencephalitis–multiple sclerosis-like syndrome |
| Syphilis (secondary, tertiary) *Treponema pallidum* | Mononuclear cells; elevated protein | CSF VDRL; serum VDRL (or RPR); fluorescent treponemal antibody-absorbed (FTA) or MHA-TP; serum VDRL may be negative in tertiary syphilis | Appropriate exposure history; HIV-seropositive individuals at increased risk of aggressive infection; "dementia"; cerebral infarction due to endarteritis |

(*Continued*)

**TABLE 192-2 INFECTIOUS CAUSES OF CHRONIC MENINGITIS (*CONTINUED*)**

| Causative Agent | CSF Formula | Helpful Diagnostic Tests | Risk Factors and Systemic Manifestations |
|---|---|---|---|
| **Uncommon Bacterial Causes** | | | |
| *Actinomyces* | Polymorphonuclear cells | Anaerobic culture | Parameningeal abscess or sinus tract (oral or dental focus); pneumonitis |
| *Nocardia* | Polymorphonuclear; occasionally mononuclear cells; often low glucose | Isolation may require weeks; weakly acid fast | Associated brain abscess may be present |
| *Brucella* | Mononuclear cells (rarely polymorphonuclear); elevated protein; often low glucose | CSF antibody detection; serum antibody detection | Intake of unpasteurized dairy products; exposure to goats, sheep, cows; fever, arthralgia, myalgia, vertebral osteomyelitis |
| Whipple's disease *Tropheryma whipplei* | Mononuclear cells | Biopsy of small bowel or lymph node; CSF PCR for *T. whipplei;* brain and meningeal biopsy (with PAS stain and EM examination) | Diarrhea, weight loss, arthralgias, fever; dementia, ataxia, paresis, ophthalmoplegia, oculomasticatory myoclonus |
| **Rare Bacterial Causes** | | | |
| Leptospirosis (occasionally if left untreated may last 3–4 weeks) | | | |
| **Fungal Causes** | | | |
| *Cryptococcus neoformans* | Mononuclear cells; count not elevated in some pts with AIDS | India ink or fungal wet mount of CSF (budding yeast); blood and urine cultures; antigen detection in CSF | AIDS and immune suppression; pigeon exposure; skin and other organ involvement due to disseminated infection |
| *Coccidioides immitis* | Mononuclear cells (sometimes 10–20% eosinophils); often low glucose | Antibody detection in CSF and serum | Exposure history—southwestern U.S.; increased virulence in dark-skinned races |

| | | | |
|---|---|---|---|
| *Candida* sp. | Polymorphonuclear or mononuclear | Fungal stain and culture of CSF | IV drug abuse; post surgery; prolonged IV therapy; disseminated candidiasis |
| *Histoplasma capsulatum* | Mononuclear cells; low glucose | Fungal stain and culture of large volumes of CSF; antigen detection in CSF, serum, and urine; antibody detection in serum, CSF | Exposure history—Ohio and central Mississippi River Valley; AIDS; mucosal lesions |
| *Blastomyces dermatitidis* | Mononuclear cells | Fungal stain and culture of CSF; biopsy and culture of skin, lung lesions; antibody detection in serum | Midwestern and southeastern U.S.; usually systemic infection; abscesses, draining sinus, ulcers |
| *Aspergillus* sp. | Mononuclear or polymorphonuclear | CSF culture | Sinusitis; granulocytopenia or immunosuppression |
| *Sporothrix schenckii* | Mononuclear cells | Antibody detection in CSF and serum; CSF culture | Traumatic inoculation; IV drug use; ulcerated skin lesion |
| **Rare Fungal Causes** | | | |
| *Xylohypha* (formerly *Cladosporium*) *trichoides* and other dark-walled (dematiaceous) fungi such as *Curvularia, Drechslera; Mucor*, and, after water aspiration, *Pseudallescheria boydii,* iatrogenic *Exserohilum rostratum* infection following spinal blocks | | | |
| **Protozoal Causes** | | | |
| *Toxoplasma gondii* | Mononuclear cells | Biopsy or response to empirical therapy in clinically appropriate context (including presence of antibody in serum) | Usually with intracerebral abscesses; common in HIV-seropositive pts |
| Trypanosomiasis *Trypanosoma gambiense*, *T. rhodesiense* | Mononuclear cells, elevated protein | Elevated CSF IgM; identification of trypanosomes in CSF and blood smear | Endemic in Africa; chancre, lymphadenopathy; prominent sleep disorder |



(*Continued*)

**TABLE 192-2 INFECTIOUS CAUSES OF CHRONIC MENINGITIS (*CONTINUED*)**

| Causative Agent | CSF Formula | Helpful Diagnostic Tests | Risk Factors and Systemic Manifestations |
|---|---|---|---|
| **Rare Protozoal Causes** | | | |
| *Acanthamoeba* sp. causing granulomatous amebic encephalitis and meningoencephalitis in immunocompromised and debilitated individuals. *Balamuthia mandrillaris* causing chronic meningoencephalitis in immunocompetent hosts. | | | |
| **Helminthic Causes** | | | |
| Cysticercosis (infection with cysts of *Taenia solium*) | Mononuclear cells; may have eosinophils; glucose level may be low | Indirect hemagglutination assay in CSF; ELISA immunoblotting in serum | Usually with multiple cysts in basal meninges and hydrocephalus; cerebral cysts, muscle calcification |
| *Gnathostoma spinigerum* | Eosinophils, mononuclear cells | Peripheral eosinophilia | History of eating raw fish; common in Thailand and Japan; subarachnoid hemorrhage; painful radiculopathy |
| *Angiostrongylus cantonensis* | Eosinophils, mononuclear cells | Recovery of worms from CSF | History of eating raw shellfish; common in tropical Pacific regions; often benign |
| *Baylisascaris procyonis* (raccoon ascarid) | Eosinophils, mononuclear cells | | Infection follows accidental ingestion of *B. procyonis* eggs from raccoon feces; fatal meningoencephalitis |

| **Rare Helminthic Causes** | | | |
|---|---|---|---|
| *Trichinella spiralis* (trichinosis); *Fasciola hepatica* (liver fluke), *Echinococcus* cysts; *Schistosoma* sp. The former may produce a lymphocytic pleocytosis whereas the latter two may produce an eosinophilic response in CSF associated with cerebral cysts (*Echinococcus*) or granulomatous lesions of brain or spinal cord | | | |
| **Viral Causes** | | | |
| Mumps | Mononuclear cells | Antibody in serum | No prior mumps or immunization; may produce meningoencephalitis; may persist for 3–4 weeks |
| Lymphocytic choriomeningitis | Mononuclear cells | Antibody in serum | Contact with rodents or their excreta; may persist for 3–4 weeks |
| Echovirus | Mononuclear cells; may have low glucose | Virus isolation from CSF | Congenital hypogammaglobulinemia; history of recurrent meningitis |
| HIV (acute retroviral syndrome) | Mononuclear cells | p24 antigen in serum and CSF; high level of HIV viremia. | HIV risk factors; rash, fever, lymphadenopathy; lymphopenia in peripheral blood; syndrome may persist long enough to be considered as "chronic meningitis"; or chronic meningitis may develop in later stages (AIDS) due to HIV |
| Herpes simplex (HSV) | Mononuclear cells | PCR for HSV, CMV DNA; CSF antibody for HSV, EBV | Recurrent meningitis due to HSV-2 (rarely HSV-1) often associated with genital recurrences; EBV associated with myeloradiculopathy, CMV with polyradiculopathy |

***Abbreviations:*** AFB, acid-fast bacillus; EM, electron microscopy; FTA, fluorescent treponemal antibody absorption test; HSV, herpes simplex virus; MHA-TP, microhemagglutination assay–*T. pallidum;* PAS, periodic acid–Schiff; RPR, rapid plasma reagin test; TB, tuberculosis; VDRL, Venereal Disease Research Laboratories test.

**TABLE 192-3 NONINFECTIOUS CAUSES OF CHRONIC MENINGITIS**

| Causative Agents | CSF Formula | Helpful Diagnostic Tests | Risk Factors and Systemic Manifestations |
|---|---|---|---|
| Malignancy | Mononuclear cells, elevated protein, low glucose | Repeated cytologic examination of large volumes of CSF; CSF exam by polarizing microscopy; clonal lymphocyte markers; deposits on nerve roots or meninges seen on myelogram or contrast-enhanced MRI; meningeal biopsy | Metastatic cancer of breast, lung, stomach, or pancreas; melanoma, lymphoma, leukemia; meningeal gliomatosis; meningeal sarcoma; cerebral dysgerminoma; meningeal melanoma or B cell lymphoma |
| Chemical compounds (may cause recurrent meningitis) | Mononuclear or PMNs, low glucose, elevated protein; xanthochromia from subarachnoid hemorrhage in week prior to presentation with "meningitis" | Contrast-enhanced CT scan or MRI; cerebral angiogram to detect aneurysm | History of recent injection into the subarachnoid space; history of sudden onset of headache; recent resection of acoustic neuroma or craniopharyngioma; epidermoid tumor of brain or spine, sometimes with dermoid sinus tract; pituitary apoplexy |
| **Primary inflammation** | | | |
| CNS sarcoidosis | Mononuclear cells; elevated protein; often low glucose | Serum and CSF angiotensin-converting enzyme levels; biopsy of extraneural affected tissues or brain lesion/meningeal biopsy | CN palsy, especially of CN VII; hypothalamic dysfunction, especially diabetes insipidus; abnormal chest radiograph; peripheral neuropathy or myopathy |
| Vogt-Koyanagi-Harada syndrome (recurrent meningitis) | Mononuclear cells | | Recurrent meningoencephalitis with uveitis, retinal detachment, alopecia, lightening of eyebrows and lashes, dysacousia, cataracts, glaucoma |
| Isolated granulomatous angiitis of the nervous system | Mononuclear cells, elevated protein | Angiography or meningeal biopsy | Subacute dementia; multiple cerebral infarctions; recent zoster ophthalmicus |

| | | | |
|---|---|---|---|
| Systemic lupus erythematosus | Mononuclear or PMNs | Anti-DNA antibody, antinuclear antibodies | Encephalopathy; seizures; stroke; transverse myelopathy; rash; arthritis |
| Behçet's syndrome (recurrent meningitis) | Mononuclear or PMNs, elevated protein | | Oral and genital aphthous ulcers; iridocyclitis; retinal hemorrhages; pathergic lesions at site of skin puncture |
| Chronic benign lymphocytic meningitis | Mononuclear cells | | Recovery in 2–6 months, diagnosis by exclusion |
| Mollaret's meningitis (recurrent meningitis) | Large endothelial cells and PMNs in first hours, followed by mononuclear cells | PCR for herpes; MRI/CT to rule out epidermoid tumor or dural cyst | Recurrent meningitis; exclude HSV-2; rare cases due to HSV-1; occasional case associated with dural cyst |
| Drug hypersensitivity | PMNs; occasionally mononuclear cells or eosinophils | Complete blood count (eosinophilia) | Exposure to nonsteroidal anti-inflammatory agents, sulfonamides, isoniazid, tolmetin, ciprofloxacin, penicillin, carbamazepine, lamotrigine, IV immunoglobulin, OKT3 antibodies, phenazopyridine; improvement after discontinuation of drug; recurrence with repeat exposure |
| Granulomatosis with polyangiitis (Wegener's) | Mononuclear cells | Chest and sinus radiographs; urinalysis; ANCA antibodies in serum | Associated sinus, pulmonary, or renal lesions; CN palsies; skin lesions; peripheral neuropathy |
| Other: multiple sclerosis, Sjögren's syndrome, monogenic autoinflammatory disorders, and rarer forms of vasculitis (e.g., Cogan's syndrome) | | | |

***Abbreviations:*** ANCA, antineutrophil cytoplasmic antibodies; CN, cranial nerve; PMNs, polymorphonuclear cells.

safe and may lead to temporary improvement. However, if ICP is elevated because of a mass lesion, brain swelling, or a block in ventricular CSF outflow (obstructive hydrocephalus), then LP carries the potential risk of brain herniation. Obstructive hydrocephalus usually requires direct ventricular drainage of CSF.

Contrast-enhanced MRI or CT studies of the brain and spinal cord can identify meningeal enhancement, parameningeal infections (including brain abscess), encasement of the spinal cord (malignancy or inflammation and infection), or nodular deposits on the meninges or nerve roots (malignancy or sarcoidosis). Imaging studies are also useful to localize areas of meningeal disease prior to meningeal biopsy. Cerebral angiography may identify arteritis.

A meningeal biopsy should be considered in pts who are disabled, who need chronic ventricular decompression, or whose illness is progressing rapidly. The diagnostic yield of meningeal biopsy can be increased by targeting regions that enhance with contrast on MRI or CT; in one series, biopsies most often identified sarcoid (31%) or metastatic adenocarcinoma (25%). Tuberculosis is the most common condition identified in many reports outside of the United States.

In approximately one-third of cases, the diagnosis is not established despite careful evaluation. A number of the organisms that cause chronic meningitis may take weeks to be identified by culture. It is reasonable to wait until cultures are finalized if symptoms are mild and not progressive. However, in many cases progressive neurologic deterioration occurs, and rapid treatment is required. Empirical therapy in the United States consists of antimycobacterial agents, amphotericin for fungal infection, or glucocorticoids for noninfectious inflammatory causes (most common). It is important to direct empirical therapy of lymphocytic meningitis at tuberculosis, particularly if the condition is associated with hypoglycorrhachia and sixth and other cranial nerve palsies, since untreated disease can be fatal within weeks. Carcinomatous or lymphomatous meningitis may be difficult to diagnose initially, but the diagnosis becomes evident with time. Important causes of chronic meningitis in HIV pts include infection with *Toxoplasma* (usually presents as intracranial abscesses), *Cryptococcus*, *Nocardia*, *Candida*, or other fungi; syphilis; and lymphoma.

For a more detailed discussion, see Koroshetz WJ, Nath A: Chronic and Recurrent Meningitis, Chap. 165, p. 906, in HPIM-19.

# 193 Peripheral Neuropathies, Including Guillain-Barré Syndrome

## APPROACH TO THE PATIENT: Peripheral Neuropathy

*Peripheral neuropathy* (PN) refers to a peripheral nerve disorder of any cause. Nerve involvement may be single (mononeuropathy) or multiple (polyneuropathy); pathology may be axonal or demyelinating. An approach to pts with suspected neuropathy appears in **Fig. 193-1**.

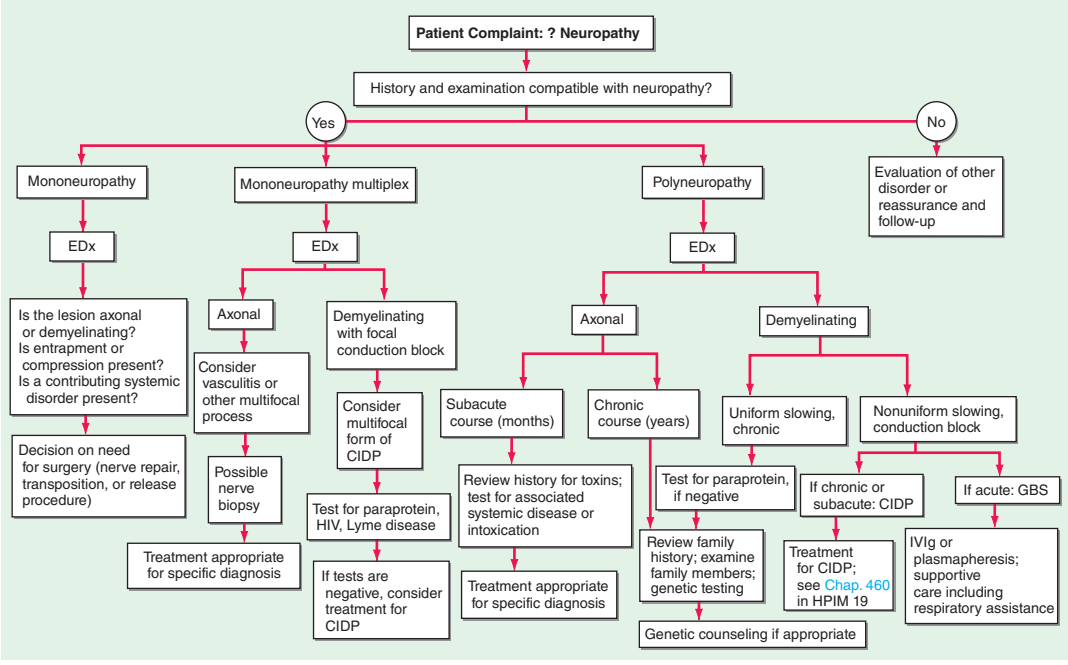


**FIGURE 193-1** Approach to evaluation of peripheral neuropathies. CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; EDx, electrodiagnostic studies; GBS, Guillain-Barré syndrome; IVIg, intravenous immunoglobulin.

Seven initial questions:

1. *What systems are involved?* Determine if symptoms and signs are predominantly motor, sensory, autonomic, or a combination of these. If only weakness is present without sensory or autonomic dysfunction, consider a motor neuropathy, neuromuscular junction disorder, or myopathy; myopathies usually have a proximal, symmetric pattern of weakness.
2. *What is the distribution of weakness?* Polyneuropathy involves widespread and often symmetric dysfunction of the peripheral nerves that is usually distal more than proximal; mononeuropathy involves a single nerve, usually due to trauma or compression; multiple mononeuropathies (mononeuropathy multiplex) can be a result of multiple entrapments, vasculitis, or infiltration.
3. *What is the nature of the sensory involvement?* Temperature loss or burning/stabbing pain suggests small fiber involvement. Vibratory or proprioceptive loss implicates large fibers.
4. *Is there evidence of upper motor neuron involvement?* The most common cause is combined system degeneration with $B_{12}$ deficiency, but should also consider copper deficiency, HIV infection, severe hepatic disease, and adrenomyeloneuropathy.
5. *What is the temporal evolution?* Most neuropathies are insidious and slowly progressive. Rapidly evolving neuropathies are often inflammatory, including acute inflammatory demyelinating polyneuropathy (AIDP) or *Guillain-Barré syndrome* (GBS); subacute evolution suggests an inflammatory, toxic, or nutritional cause; chronic neuropathies that are long-standing over years may be hereditary.
6. *Is there evidence for a hereditary neuropathy?* Consider in pts with a slowly progressive distal weakness over many years with few sensory symptoms but significant sensory deficits on clinical examination. Most common is Charcot-Marie-Tooth disease (CMT; look for foot abnormalities such as high or flat arches and hammer toes as well as scoliosis).
7. *Does the pt have other medical conditions?* Inquire about associated medical conditions (e.g., diabetes, systemic lupus erythematosus); preceding or concurrent infections (e.g., diarrheal illness preceding GBS); surgeries (e.g., gastric bypass and nutritional neuropathies); medications (toxic neuropathy); over-the-counter vitamin preparations ($B_6$); alcohol, dietary habits; and use of dentures (because fixatives contain zinc that can lead to copper deficiency).

Based on the answers to these seven key questions, neuropathic disorders can be classified into several patterns based on the pattern of sensory, motor, and autonomic involvement (**Table 193-1**).

## POLYNEUROPATHY

### Diagnostic Evaluation

Screening laboratory studies in a distal, symmetric polyneuropathy may include a complete blood count, basic chemistries including serum electrolytes and tests of renal and hepatic function, fasting blood glucose, $HbA_{1c}$, urinalysis, thyroid function tests, $B_{12}$, folate, ESR, rheumatoid factor, antinuclear antibodies (ANA), serum protein electrophoresis (SPEP) and immunoelectrophoresis or immunofixation, and urine for Bence Jones protein. An oral glucose tolerance test is indicated in pts with painful sensory neuropathies even if other screens for diabetes are negative.

Tests to further characterize the neuropathy include nerve conduction studies (NCS), electromyography (EMG), sural nerve biopsy, muscle biopsy, skin biopsies, and quantitative sensory testing. Diagnostic tests are more likely to be informative in pts with asymmetric, motor-predominant, rapid-onset, or demyelinating neuropathies.

**TABLE 193-1 PATTERNS OF NEUROPATHIC DISORDERS**

| |
|---|
| **Pattern 1: Symmetric proximal and distal weakness with sensory loss** |
| Consider: inflammatory demyelinating polyneuropathy (GBS and CIDP) |
| **Pattern 2: Symmetric distal sensory loss with or without distal weakness** |
| Consider: cryptogenic or idiopathic sensory polyneuropathy (CSPN), diabetes mellitus and other metabolic disorders, drugs, toxins, familial (HSAN), CMT, amyloidosis, and others |
| **Pattern 3: Asymmetric distal weakness with sensory loss** |
| With involvement of multiple nerves |
| Consider: multifocal CIDP, vasculitis, cryoglobulinemia, amyloidosis, sarcoid, infectious (leprosy, Lyme, hepatitis B, C, or E, HIV, CMV), HNPP, tumor infiltration |
| With involvement of single nerves/regions |
| Consider: may be any of the above but also could be compressive mononeuropathy, plexopathy, or radiculopathy |
| **Pattern 4: Asymmetric proximal and distal weakness with sensory loss** |
| Consider: polyradiculopathy or plexopathy due to diabetes mellitus, meningeal carcinomatosis or lymphomatosis, hereditary plexopathy (HNPP, HNA), idiopathic |
| **Pattern 5: Asymmetric distal weakness without sensory loss** |
| With upper motor neuron findings |
| Consider: motor neuron disease |
| Without upper motor neuron findings |
| Consider: progressive muscular atrophy, juvenile monomelic amyotrophy (Hirayama's disease), multifocal motor neuropathy, multifocal acquired motor axonopathy |
| **Pattern 6: Symmetric sensory loss and distal areflexia with upper motor neuron findings** |
| Consider: Vitamin $B_{12}$, vitamin E, and copper deficiency with combined system degeneration with peripheral neuropathy, hereditary leukodystrophies (e.g., adrenomyeloneuropathy) |
| **Pattern 7: Symmetric weakness without sensory loss** |
| With proximal and distal weakness |
| Consider: SMA |
| With distal weakness |
| Consider: hereditary motor neuropathy ("distal" SMA) or atypical CMT |
| **Pattern 8: Asymmetric proprioceptive sensory loss without weakness** |
| Consider causes of a sensory neuronopathy (ganglionopathy): |
| Cancer (paraneoplastic) |
| Sjögren's syndrome |
| Idiopathic sensory neuronopathy (possible GBS variant) |
| Cisplatin and other chemotherapeutic agents |
| Vitamin $B_6$ toxicity |
| HIV-related sensory neuronopathy |

(*Continued*)

**TABLE 193-1 PATTERNS OF NEUROPATHIC DISORDERS (*CONTINUED*)**

| Pattern 9: Autonomic symptoms and signs |
|---|
| Consider neuropathies associated with prominent autonomic dysfunction: |
| Hereditary sensory and autonomic neuropathy |
| Amyloidosis (familial and acquired) |
| Diabetes mellitus |
| Idiopathic pandysautonomia (may be a variant of Guillain-Barré syndrome) |
| Porphyria |
| HIV-related autonomic neuropathy |
| Vincristine and other chemotherapeutic agents |

***Abbreviations:*** CIDP, chronic inflammatory demyelinating polyneuropathy; CMT, Charcot-Marie-Tooth disease; GBS, Guillain-Barré syndrome; HNA, hereditary neuralgic amyotrophy; HNPP, hereditary neuropathy with liability to pressure palsies; HSAN, hereditary sensory and autonomic neuropathy; SMA, spinal muscular atrophy.

## Electrodiagnosis

NCS are carried out by stimulating motor or sensory nerves electrically. Demyelination is characterized by slowing of nerve conduction velocities (NCV), dispersion of evoked compound action potentials, conduction block (decreased amplitude of muscle compound action potentials on proximal, as compared to distal, stimulation of the nerve), and prolongation of distal latencies. In contrast, axonal neuropathies exhibit reduced amplitude of evoked compound action potentials with relative preservation of NCV. EMG records electrical potentials from a needle electrode in muscle, at rest and during voluntary contraction; it is most useful for distinguishing myopathic from neuropathic disorders. Myopathic disorders are marked by small, short-duration, polyphasic muscle action potentials; by contrast, neuropathic disorders are characterized by muscle denervation. Denervation decreases the number of motor units (e.g., an anterior horn cell, its axon, and the motor end plates and muscle fibers it innervates). In long-standing denervation, motor unit potentials become large and polyphasic due to collateral reinnervation of denervated muscle fibers by axonal sprouts from surviving motor axons. Other EMG features of denervation include fibrillations (random, unregulated firing of individual muscle fibers) and fasciculations (random, spontaneous firing of motor units).

## TREATMENT POLYNEUROPATHY

- Treatment of the underlying disorder, pain management, and supportive care to protect and rehabilitate damaged tissue all need to be considered.
- Examples of specific therapies include tight glycemic control in diabetic neuropathy, vitamin replacement for $B_{12}$ deficiency, IV immune globulin (IVIg) or plasmapheresis for GBS, and immunosuppression for vasculitis.
- Painful sensory neuropathies can be difficult to treat. Pain management usually begins with tricyclic antidepressants (TCAs), duloxetine hydrochloride, lidocaine patches, or anticonvulsants such as gabapentin or pregabalin (**Table 193-2**). Topical anesthetic agents including EMLA (lidocaine/prilocaine) and capsaicin cream can provide additional relief.

**TABLE 193-2 TREATMENT OF PAINFUL SENSORY NEUROPATHIES**

| Therapy | Route | Dose | Side Effects |
|---|---|---|---|
| **First-Line** | | | |
| Lidoderm 5% patch | Apply to painful area | Up to 3 patches qd | Skin irritation |
| Tricyclic antidepressants (e.g., amitriptyline, nortriptyline) | PO | 10–100 mg qhs | Cognitive changes, sedation, dry eyes and mouth, urinary retention, constipation |
| Gabapentin | PO | 300–1200 mg tid | Cognitive changes, sedation, peripheral edema |
| Pregabalin | PO | 50–100 mg tid | Cognitive changes, sedation, peripheral edema |
| Duloxetine | PO | 30–60 mg qd | Cognitive changes, sedation, dry eyes, diaphoresis, nausea, diarrhea, constipation |
| **Second-Line** | | | |
| Carbamazepine | PO | 200–400 mg q 6–8 h | Cognitive changes, dizziness, leukopenia, liver dysfunction |
| Phenytoin | PO | 200–400 mg qhs | Cognitive changes, dizziness, liver dysfunction |
| Venlafaxine | PO | 37.5–150 mg/d | Asthenia, sweating, nausea, constipation, anorexia, vomiting, somnolence, dry mouth, dizziness, nervousness, anxiety, tremor, and blurred vision as well as abnormal ejaculation/orgasm and impotence |
| Tramadol | PO | 50 mg qid | Cognitive changes, gastrointestinal upset |
| **Third-Line** | | | |
| Mexiletine | PO | 200–300 mg tid | Arrhythmias |
| **Other Agents** | | | |
| EMLA cream | Apply cutaneously | qid | Local erythema |
| 2.5% lidocaine | | | |
| 2.5% prilocaine | | | |
| Capsaicin 0.025–0.075% cream | Apply cutaneously | qid | Painful burning skin |

***Source:*** Modified from AA Amato, J Russell: *Neuromuscular Disease*. New York, McGraw-Hill, 2008.

- Physical and occupational therapy is important. Proper care of denervated areas prevents skin ulceration, which can lead to poor wound healing, tissue resorption, arthropathy, and ultimately amputation.

## Specific Polyneuropathies

*AIDP* or *GBS* is an ascending, usually demyelinating, motor > sensory polyneuropathy accompanied by areflexia, motor paralysis, and elevated CSF total protein without pleocytosis. Over two-thirds are preceded by an acute respiratory or gastrointestinal infection. Maximum weakness is usually reached within 2 weeks; demyelination by EMG. Most pts are hospitalized; one-third require ventilatory assistance. 85% make a complete or near-complete recovery with supportive care. Variants of GBS include Miller Fisher syndrome (ophthalmoparesis, facial diplegia, ataxia, areflexia; associated with serum antibodies to ganglioside GQ1b) and acute motor axonal neuropathy (more severe course than demyelinating GBS; antibodies to $GM_1$ in some cases).

- IVIg (2 g/kg divided over 5 days) or plasmapheresis (40–50 mL/kg daily for 4–5 days) significantly shortens the course.
- Glucocorticoids are ineffective.

*Chronic inflammatory demyelinating polyneuropathy (CIDP)* is a slowly progressive or relapsing polyneuropathy characterized by diffuse hyporeflexia or areflexia, diffuse weakness, elevated CSF protein without pleocytosis, and demyelination by EMG.

- Begin treatment when progression is rapid or walking is compromised.
- Initial treatment is usually IVIg; most pts require periodic retreatment at 4- to 6-week intervals.
- Other first-line treatment options include plasmapheresis or glucocorticoids.
- Immunosuppressants (azathioprine, methotrexate, cyclosporine, cyclophosphamide, rituximab) used in refractory cases.

*Diabetic neuropathy* typically presents as a distal symmetric, sensorimotor, axonal polyneuropathy. A mixture of demyelination and axonal loss is frequent. Other variants include: isolated sixth or third cranial nerve palsies, asymmetric proximal motor neuropathy in the legs, truncal neuropathy, autonomic neuropathy, and an increased frequency of entrapment neuropathy (see below).

*Mononeuropathy multiplex (MM)* is defined as involvement of multiple individual peripheral nerves. When an inflammatory disorder is the cause, *mononeuritis multiplex* is the term used. Both systemic (67%) and nonsystemic (33%) vasculitis may present as MM. Immunosuppressive treatment of the underlying disease (usually with glucocorticoids and cyclophosphamide) is indicated. A tissue diagnosis of vasculitis should be obtained before initiating treatment; a positive biopsy helps to justify the necessary long-term treatment with immunosuppressive medications, and pathologic confirmation is difficult after treatment has commenced.

# MONONEUROPATHY

## Clinical Features

Mononeuropathies are usually caused by trauma, compression, or entrapment. Sensory and motor symptoms are in the distribution of a single nerve—most commonly the ulnar or median nerve in the arm or peroneal (fibular) nerve in the leg. Intrinsic factors making pts more susceptible to entrapment include arthritis, fluid retention (pregnancy), amyloid, hypothyroidism, tumors, and diabetes mellitus. Clinical features favoring conservative management of median neuropathy at the wrist (carpal tunnel syndrome) or ulnar neuropathy at the elbow include sudden onset, no motor deficit, few or no sensory findings (pain or paresthesias may be present), and no evidence of axonal loss by EMG. Surgical decompression is considered for chronic mononeuropathies that are unresponsive to conservative treatment if the site of entrapment is clearly defined. The most common mononeuropathies are summarized in **Table 193-3**.

**TABLE 193-3 MONONEUROPATHIES**

| | Symptoms | Precipitating Activities | Examination | Electro-Diagnosis | Differential Diagnosis | Treatment |
|---|---|---|---|---|---|---|
| Carpal tunnel syndrome | Numbness, pain or paresthesias in fingers | Sleep or repetitive hand activity | Sensory loss in thumb, second, and third fingers<br>Weakness in thenar muscles; inability to make a circle with thumb and index finger<br>Tinel sign, Phalen maneuver | Slowing of sensory and motor conduction across carpal tunnel | C6 radiculopathy | Splint<br>Surgery definitive treatment |
| Ulnar nerve entrapment (UNE) at the elbow | Numbness or paresthesias in ulnar aspect of hand | Elbow flexion during sleep; elbow resting on desk | Sensory loss in the little finger and ulnar half of ring finger<br>Weakness of the interossei and thumb adductor; claw-hand | Focal slowing of nerve conduction velocity at the elbow | Thoracic outlet syndrome<br>C8–T1 radiculopathy | Elbow pads<br>Avoid further injury<br>Surgery when conservative treatment fails |
| UNE at the wrist | Numbness or weakness in the ulnar distribution in the hand | Unusual hand activities with tools, bicycling | Like UNE but sensory examination spares dorsum of the hand, and selected hand muscles affected | Prolongation of distal motor latency in the hand | UNE | Avoid precipitating activities |

(*Continued*)

**TABLE 193-3 MONONEUROPATHIES (*CONTINUED*)**

| | Symptoms | Precipitating Activities | Examination | Electro-Diagnosis | Differential Diagnosis | Treatment |
|---|---|---|---|---|---|---|
| Radial neuropathy at the spiral groove | Wrist drop | Sleeping on arm after inebriation with alcohol—"Saturday night palsy" | Wrist drop with sparing of elbow extension (triceps sparing); finger and thumb extensors paralyzed; sensory loss in radial region of wrist | Early—conduction block along the spiral groove<br>Late—denervation in radial muscles; reduced radial SNAP | Posterior cord lesion; deltoid also weak<br>Posterior interosseous nerve (PIN); isolated finger drop<br>C7 radiculopathy | Splint<br>Spontaneous recovery provided no ongoing injury |
| Thoracic outlet syndrome | Numbness, paresthesias in medial arm, forearm, hand, and fingers | Lifting heavy objects with the hand | Sensory loss resembles ulnar nerve and motor loss resembles median nerve | Absent ulnar sensory response and reduced median motor response | UNE | Surgery if correctable lesion present |
| Femoral neuropathy | Buckling of knee, numbness or tingling in thigh/medial leg | Abdominal hysterectomy; lithotomy position; hematoma, diabetes | Wasting and weakness of quadriceps; absent knee jerk; sensory loss in medial thigh and lower leg | EMG of quadriceps, iliopsoas, paraspinal muscles, adductor muscles | L2–4 radiculopathy<br>Lumbar plexopathy | Physiotherapy to strengthen quadriceps and mobilize hip joint<br>Surgery if needed |
| Obturator neuropathy | Weakness of the leg, thigh numbness | Stretch during hip surgery; pelvic fracture; childbirth | Weakness of hip adductors; sensory loss in upper medial thigh | EMG—denervation limited to hip adductors sparing the quadriceps | L3–4 radiculopathy<br>Lumbar plexopathy | Conservative management<br>Surgery if needed |

| | | | | | | |
|---|---|---|---|---|---|---|
| Meralgia paresthetica | Pain or numbness in the anterior lateral thigh | Standing or walking<br>Recent weight gain | Sensory loss in the pocket of the pant distribution | Sometimes slowing of sensory response can be demonstrated across the inguinal ligament | L2 radiculopathy | Usually resolves spontaneously |
| Peroneal nerve entrapment at the fibular head | Footdrop | Usually an acute compressive episode identifiable; weight loss | Weak dorsiflexion, eversion of the foot<br>Sensory loss in the anterolateral leg and dorsum of the foot | Focal slowing of nerve conduction across fibular head<br>Denervation in tibialis anterior and peroneus longus muscles | L5 radiculopathy | Foot brace; remove external source of compression |
| Sciatic neuropathy | Flail foot and numbness in foot | Injection injury; fracture/dislocation of hip; prolonged pressure on hip (comatose pt) | Weakness of hamstring, plantar and dorsiflexion of foot; sensory loss in tibial and peroneal nerve distribution | NCS—abnormal sural, peroneal, and tibial amplitudes<br>EMG—denervation in sciatic nerve distribution sparing glutei and paraspinal | L5–S1 radiculopathies<br>Common peroneal neuropathy (partial sciatic nerve injury)<br>LS plexopathies | Conservative follow up for partial sciatic nerve injuries<br>Brace and physiotherapy<br>Surgical exploration if needed |
| Tarsal tunnel syndrome | Pain and paresthesias in the sole of the foot but not in the heel | At the end of the day after standing or walking; nocturnal | Sensory loss in the sole of the foot<br>Tinel sign at tarsal tunnel | Reduced amplitude in sensory or motor components of medial and planter nerves | Polyneuropathy, foot deformity, poor circulation | Surgery if no external cause identified |

For a more detailed discussion, see Amato AA, Barohn RJ: Peripheral Neuropathy, Chap. 459, p. 2674; and Hauser SL, Amato AA: Guillain-Barré Syndrome and Other Immune-Mediated Neuropathies, Chap. 460, p. 2694, in HPIM-19.

# 194 Myasthenia Gravis

An autoimmune neuromuscular disorder resulting in weakness and fatigability of skeletal muscles, usually due to autoantibodies directed against acetylcholine receptors (AChRs) at neuromuscular junctions (NMJs).

## CLINICAL FEATURES

May present at any age. Symptoms fluctuate throughout the day and are provoked by exertion. Characteristic distribution: cranial muscles (eyelids, extraocular muscles, facial weakness, "nasal" or slurred speech, dysphagia); in 85%, limb muscles (often proximal and asymmetric) become involved. Reflexes and sensation normal. May be limited to extraocular muscles only. Complications: aspiration pneumonia (weak bulbar muscles), respiratory failure (weak chest wall muscles), exacerbation of myasthenia due to administration of drugs with neuromuscular junction blocking effects (quinolones, macrolides, aminoglycosides, procainamide, propranolol, nondepolarizing muscle relaxants).

## PATHOPHYSIOLOGY

Anti-AChR antibodies reduce the number of available AChRs at the NMJ. Postsynaptic folds are flattened or "simplified," with resulting inefficient neuromuscular transmission. During repeated or sustained muscle contraction, decrease in amount of ACh released per nerve impulse ("presynaptic rundown," a normal occurrence), combined with disease-specific decrease in postsynaptic AChRs, results in pathologic fatigue. Thymus is abnormal in 75% of pts (65% hyperplasia, 10% thymoma). Other autoimmune diseases may coexist: Hashimoto's thyroiditis, Graves' disease, rheumatoid arthritis, systemic lupus erythematosus.

## DIFFERENTIAL DIAGNOSIS

*Lambert-Eaton syndrome* (autoantibodies to calcium channels in presynaptic motor nerve terminals): reduced ACh release; may be associated with malignancy

*Neurasthenia:* weakness/fatigue without underlying organic disorder

*Drug-induced myasthenia:* penicillamine may cause myasthenia gravis (MG); resolves weeks to months after discontinuing drug.

*Botulism:* toxin inhibits presynaptic ACh release; most common form is food-borne.

*Diplopia from an intracranial mass lesion:* compression of nerves to extraocular muscles or brainstem lesions affecting cranial nerve nuclei

*Hyperthyroidism*

*Progressive external ophthalmoplegia:* seen in rare mitochondrial disorders that can be detected with muscle biopsy

## LABORATORY EVALUATION

- AChR antibodies: levels do not correlate with disease severity; 85% of all MG pts are positive; only 50% with pure ocular findings are positive; positive antibodies are diagnostic. Muscle-specific kinase (MuSK) antibodies present in 40% of AChR antibody–negative pts with generalized MG.
- Tensilon (edrophonium) test: a short-acting anticholinesterase—look for rapid and transient improvement of strength; false-positive (placebo response, motor neuron

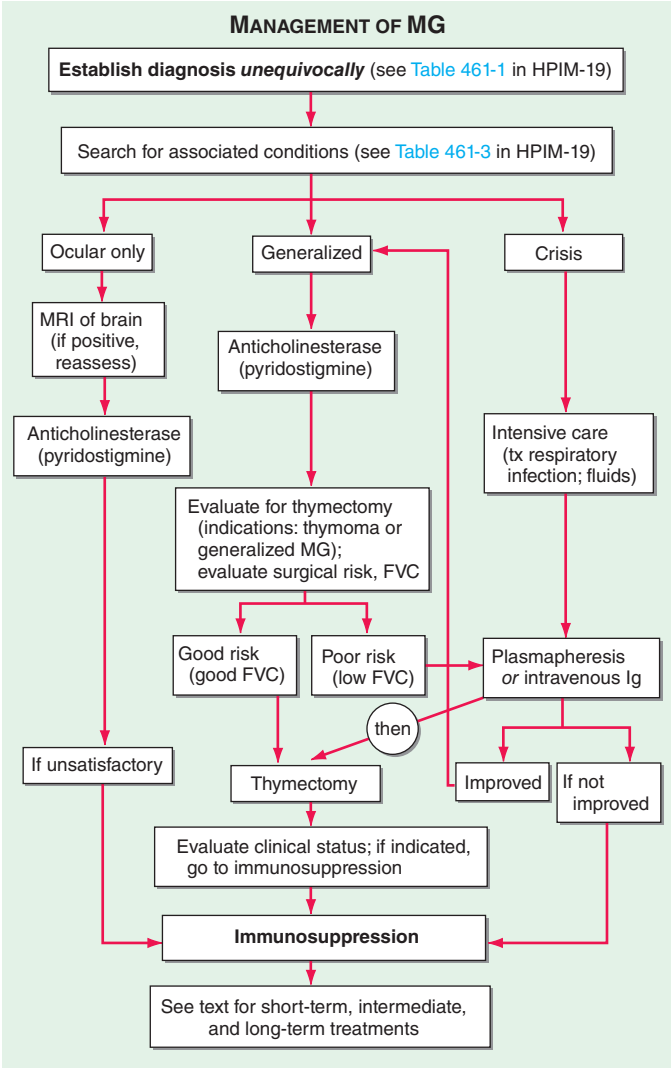


**FIGURE 194-1** Algorithm for the management of myasthenia gravis. FVC, forced vital capacity.

disease) and false-negative tests occur. Atropine IV should be on hand if symptoms such as bradycardia occur.
- EMG: low-frequency (2–4 Hz) repetitive stimulation produces rapid decrement in amplitude (>10–15%) of evoked motor responses.
- Chest CT/MRI: search for thymoma.
- Consider thyroid and other studies (e.g., ANA) for associated autoimmune disease.
- Measurements of baseline respiratory function are useful.

## TREATMENT MYASTHENIA GRAVIS (SEE FIG. 194-1)

- The anticholinesterase drug pyridostigmine (Mestinon) titrated to assist pt with functional activities (chewing, swallowing, strength during exertion); usual initial dose of 30–60 mg 3–4 times daily; long-acting tablets help at night, but have variable absorption so are not reliable during the day. Muscarinic side effects (diarrhea, abdominal cramps, salivation, nausea) blocked with atropine/diphenoxylate or loperamide if required.

**TABLE 194-1 DRUGS WITH INTERACTIONS IN MYASTHENIA GRAVIS (MG)**

| Drugs That May Exacerbate MG |
|---|
| **Antibiotics** |
| Aminoglycosides: e.g., streptomycin, tobramycin, kanamycin |
| Quinolones: e.g., ciprofloxacin, levofloxacin, ofloxacin, gatifloxacin |
| Macrolides: e.g., erythromycin, azithromycin |
| **Nondepolarizing muscle relaxants for surgery** |
| D-Tubocurarine (curare), pancuronium, vecuronium, atracurium |
| **Beta-blocking agents** |
| Propranolol, atenolol, metoprolol |
| **Local anesthetics and related agents** |
| Procaine, Xylocaine in large amounts |
| Procainamide (for arrhythmias) |
| **Botulinum toxin** |
| Botox exacerbates weakness |
| **Quinine derivatives** |
| Quinine, quinidine, chloroquine, mefloquine (Lariam) |
| **Magnesium** |
| Decreases acetylcholine release |
| **Penicillamine** |
| May cause MG |
| **Drugs with Important Interactions in MG** |
| **Cyclosporine** |
| Broad range of drug interactions, which may raise or lower cyclosporine levels. |
| **Azathioprine** |
| Avoid allopurinol—combination may result in myelosuppression. |

- Plasmapheresis or IV immune globulin (IVIg; 400 mg/kg per day for 5 days) provides temporary boost for seriously ill pts; used to improve condition prior to surgery or during myasthenic crisis (see below).
- Thymectomy improves likelihood of long-term remission in adult pts (~85% improve; of these, ~35% achieve drug-free remission); benefit is usually delayed by months to years; unclear if there is benefit in pts with pure ocular disease, children, or those age >55.
- Glucocorticoids are a mainstay of chronic immunosuppressive treatment; begin prednisone at low dose (15–25 mg/d), increase by 5 mg/d every 2–3 days until marked clinical improvement or dose of 50–60 mg/d is reached. Maintain high dose for 1–3 months, then decrease to alternate-day regimen. Immunosuppressive drugs (mycophenolate mofetil, azathioprine, cyclosporine, tacrolimus, rituximab, and occasionally cyclophosphamide) may spare dose of prednisone required long-term to control symptoms.
- Myasthenic crisis is defined as an exacerbation of weakness, usually with respiratory failure, sufficient to endanger life; expert management in an intensive care setting essential as is prompt treatment with IVIg or plasmapheresis to hasten recovery.
- A number of drugs may exacerbate MG, potentially leading to crisis, and therefore should be avoided (**Table 194-1**).

For a more detailed discussion, see Drachman DB, Amato AA: Myasthenia Gravis and Other Diseases of the Neuromuscular Junction, Chap. 461, p. 2701, in HPIM-19.

# 195 Muscle Diseases

## APPROACH TO THE PATIENT: Muscle Disease

Muscle diseases (*myopathies*) may be intermittent or persistent and usually present with proximal, symmetric weakness with preserved reflexes and sensation. An associated sensory loss suggests injury to peripheral nerve or the central nervous system rather than myopathy; on occasion, disorders affecting the anterior horn cells, the neuromuscular junction, or peripheral nerves can mimic myopathy. Any disorder causing muscle weakness may be accompanied by *fatigue*, referring to an inability to maintain or sustain a force; this must be distinguished from *asthenia*, a type of fatigue caused by excess tiredness or lack of energy. Fatigue without abnormal clinical or laboratory findings almost never indicates a true myopathy.

Muscle disorders are usually painless; however, *myalgias*, or muscle pains, may occur. Myalgias must be distinguished from *muscle cramps*, i.e., painful, involuntary muscle contractions, usually due to neurogenic disorders. A *muscle*

*contracture* due to an inability to relax after an active muscle contraction is associated with energy failure in glycolytic disorders. *Myotonia* is a condition of prolonged muscle contraction followed by slow muscle relaxation.

CK is the preferred muscle enzyme to measure in the evaluation of suspected myopathies. Electrodiagnostic studies (nerve conduction studies and electromyography, NCS/EMG) are usually necessary to distinguish myopathies from neuropathies and neuromuscular junction disorders. An approach to muscle weakness is presented in **Figs. 195-1** and **195-2**.

## MUSCULAR DYSTROPHIES

A varied group of inherited, progressive degenerations of muscle, each with unique phenotypic and genetic features.

### DUCHENNE'S MUSCULAR DYSTROPHY

X-linked recessive mutation of the dystrophin gene that affects males almost exclusively. Progressive weakness in hip and shoulder girdle muscles beginning by age 5; by age 12, the majority were nonambulatory in the era prior to the use of glucocorticoids. Survival beyond age 25 is rare. Associated problems include tendon and muscle contractures, progressive kyphoscoliosis, impaired pulmonary function, cardiomyopathy, and intellectual impairment. Palpable enlargement and firmness of some muscles. Becker dystrophy is a less severe form, with a slower course and later age of onset (5–15 years) but similar clinical, laboratory, and genetic features.

*Laboratory findings* include massive elevations (20–100 × normal) of serum CK, a myopathic pattern on EMG testing, and evidence of groups of necrotic muscle fibers with regeneration, phagocytosis, and fatty replacement of muscle on biopsy. Diagnosis is established by determination of dystrophin deficiency in muscle tissue or mutation analysis in peripheral blood. Testing is available for detecting carriers and prenatal diagnosis. Dystrophin is part of a large complex of muscle membrane glycoproteins, disruption of which weakens the cell membrane.

**TREATMENT DUCHENNE'S MUSCULAR DYSTROPHY**

- Glucocorticoids [prednisone (0.75 mg/kg)/d] slow progression of disease for up to 3 years; some pts cannot tolerate this therapy due to weight gain and increased risk of fractures.

### LIMB-GIRDLE DYSTROPHY

A constellation of diseases with proximal weakness involving the pelvic and shoulder girdle musculature. Age of onset, rate of progression, severity of manifestations, inheritance pattern (autosomal dominant or autosomal recessive), and associated complications (e.g., cardiac, respiratory) vary with the specific subtype of disease.

### MYOTONIC DYSTROPHY

Type 1 is an autosomal dominant disorder with genetic anticipation. Weakness typically becomes obvious in the second to third decade and initially involves the muscles of the face, neck, and distal extremities. This results in a distinctive facial appearance ("hatchet-faced") with ptosis, temporal wasting, drooping of the lower lip, and sagging of the jaw. Myotonia manifests as an inability to relax muscles rapidly following a strong exertion (e.g., after tight hand grip) usually by the age of 5, and by sustained contraction of muscles following percussion (e.g., of tongue or thenar eminence).

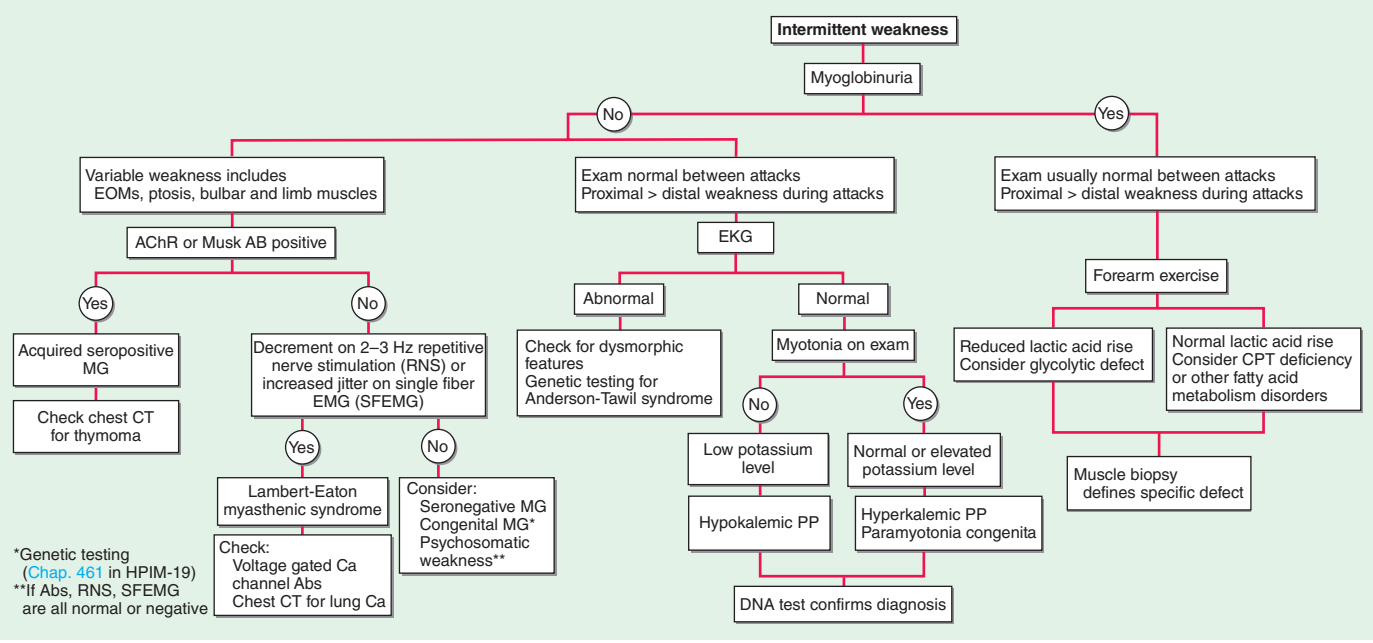


**FIGURE 195-1** Diagnostic evaluation of intermittent weakness. AChR AB, acetylcholine receptor antibody; CPT, carnitine palmitoyltransferase; EOMs, extraocular muscles; MG, myasthenia gravis; PP, periodic paralysis.

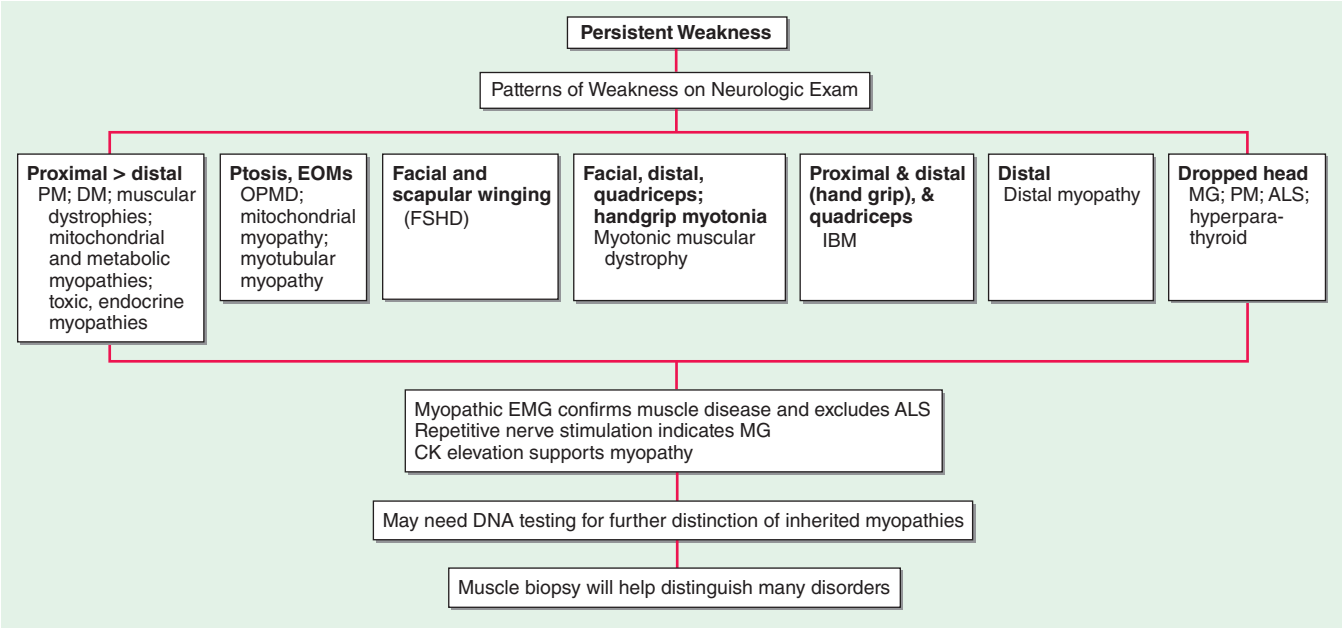


**FIGURE 195-2** Diagnostic evaluation of persistent weakness. Examination reveals one of seven patterns of weakness. The pattern or weakness in combination with the laboratory evaluation leads to a diagnosis. CK, creatinine kinase; DM, dermatomyositis; FSHD, facioscapulohumeral dystrophy; IBM, inclusion body myositis; MG, myasthenia gravis; OPMD, oculopharyngeal muscular dystrophy; PM, polymyositis.

Associated findings can include frontal baldness, posterior subcapsular cataracts, gonadal atrophy, respiratory and cardiac problems, endocrine abnormalities, intellectual impairment, and hypersomnia. Cardiac disturbances, including complete heart block, may be life-threatening. Respiratory function should be carefully followed, as chronic hypoxia may lead to cor pulmonale.

*Laboratory studies* show normal or mildly elevated CK, characteristic myotonia and myopathic features on EMG, and a typical pattern of muscle fiber injury on biopsy, including selective type 1 fiber atrophy in 50% of cases. Myotonic dystrophy type 1 is caused by an unstable expansion of a CTG trinucleotide repeat in a protein kinase gene (named *DMPK*) on chromosome 19q13.3. Genetic testing for early detection and prenatal diagnosis is possible.

**TREATMENT MYOTONIC DYSTROPHY**

- Phenytoin or mexiletine may help alleviate myotonia, although pts are rarely bothered by this symptom.
- Pacemaker insertion may be required for syncope or heart block.
- Orthoses may control foot drop, stabilize the ankle, and decrease falls.
- Excessive daytime somnolence with or without sleep apnea is not uncommon; sleep studies, noninvasive respiratory support (BiPAP), and treatment with modafinil may be beneficial.

### FACIOSCAPULOHUMERAL (FSH) DYSTROPHY

An autosomal dominant, slowly progressive disorder with onset in childhood or young adulthood. Weakness involves facial (usually the initial manifestation), shoulder girdle, and proximal arm muscles and can result in atrophy of biceps, triceps, and scapular winging. Facial weakness results in inability to smile, whistle, or fully close the eyes. Foot drop and leg weakness may cause falls and progressive difficulty with ambulation.

*Laboratory studies* reveal normal or slightly elevated CK and usually myopathic features on EMG and muscle biopsy. Type 1 FSD is caused by deletions at chromosome 4q35 leading to toic expression of the *DUX4* gene. Genetic testing is available for carrier detection and prenatal diagnosis.

**TREATMENT FACIOSCAPULOHUMERAL DYSTROPHY**

- Ankle-foot orthoses are helpful for foot drop.
- Scapular stabilization procedures may help scapular winging but may not improve function.

### OCULOPHARYNGEAL DYSTROPHY

Onset in the fourth to sixth decade of ptosis, limitation of extraocular movements, and facial and cricopharyngeal weakness. One of several disorders characterized by progressive external ophthalmoplegia. Dysphagia may be life-threatening. Most pts are of French-Canadian or Spanish-American descent. Mutation in a poly-RNA binding protein responsible.

## INFLAMMATORY MYOPATHIES

The most common group of acquired and potentially treatable skeletal muscle disorders. Three major forms: dermatomyositis (DM), inclusion body myositis (IBM), and polymyositis (PM). Usually present as progressive and symmetric muscle weakness; extraocular muscles spared but pharyngeal weakness (dysphagia) and head

drop from neck muscle weakness are common. Respiratory muscles may be affected in advanced cases. IBM is characterized by early involvement of quadriceps (leading to falls) and distal muscles; IBM may have an asymmetric pattern. Progression is over weeks or months in PM and DM, but typically over years in IBM. Skin involvement in DM may consist of a heliotrope rash (blue-purple discoloration) on the upper eyelids with edema, a flat red rash on the face and upper trunk, or erythema over knuckles (*Gottron's sign*). A variety of cancers are associated with DM. Features of each disorder are summarized in Table 195-1.

**TABLE 195-1 FEATURES ASSOCIATED WITH INFLAMMATORY MYOPATHIES**

| Characteristic | Polymyositis | Dermatomyositis | Inclusion Body Myositis |
|---|---|---|---|
| Age at onset | >18 years | Adulthood and childhood | >50 years |
| Familial association | No | No | Yes, in some rare cases |
| Extramuscular manifestations | Yes | Yes | Yes |
| Associated conditions | | | |
| Connective tissue diseases | Yes[a] | Scleroderma and mixed connective tissue disease (overlap syndromes) | Yes, in up to 20% of cases[a] |
| Systemic autoimmune diseases[b] | Frequent | Infrequent | Infrequent |
| Malignancy | No | Yes, in up to 15% of cases | No |
| Viruses | Yes[c] | Unproven | Yes[c] |
| Drugs[d] | Yes | Yes, rarely | No |
| Parasites and bacteria[e] | Yes | No | No |

[a]Systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, systemic sclerosis, mixed connective tissue disease.
[b]Crohn's disease, vasculitis, sarcoidosis, primary biliary cirrhosis, adult celiac disease, chronic graft-versus-host disease, discoid lupus, ankylosing spondylitis, Behçet's syndrome, myasthenia gravis, acne fulminans, dermatitis herpetiformis, psoriasis, Hashimoto's disease, granulomatous diseases, agammaglobulinemia, monoclonal gammopathy, hypereosinophilic syndrome, Lyme disease, Kawasaki disease, autoimmune thrombocytopenia, hypergammaglobulinemic purpura, hereditary complement deficiency, IgA deficiency.
[c]HIV (human immunodeficiency virus) and HTLV-1 (human T cell lymphotropic virus type 1).
[d]Drugs include penicillamine (dermatomyositis and polymyositis), zidovudine (polymyositis), statins (necrotizing, toxic, or autoimmune myositis), and contaminated tryptophan (dermatomyositis-like illness). Other myotoxic drugs may cause myopathy but not an inflammatory myopathy (see text for details).
[e]Parasites (protozoa, cestodes, nematodes), tropical and bacterial myositis (pyomyositis).

**TREATMENT INFLAMMATORY MYOPATHIES**

Often effective for PM and DM but not for IBM.

- Step 1: Glucocorticoids (prednisone, 1 mg/kg per day for 3–4 weeks, then tapered very gradually)
- Step 2: Approximately 75% of pts require additional therapy with other immunosuppressive drugs. Azathioprine (up to 3 mg/kg per day), methotrexate (7.5 mg/week gradually increasing to 25 mg/week), or mycophenolate mofetil (up to 2.5–3 g/day in 2 divided doses) commonly used.
- Step 3: IV immunoglobulin (2 g/kg divided over 2–5 days)
- Step 4: A trial of one of the following agents: rituximab, cyclosporine, cyclophosphamide, or tacrolimus.

## DISORDERS OF MUSCLE ENERGY METABOLISM

The two principal sources of energy for skeletal muscle are fatty acids and glucose. Abnormalities in either glucose or lipid utilization can be associated with distinct clinical presentations that can range from an acute, painful syndrome with rhabdomyolysis and myoglobinuria to a chronic, progressive muscle weakness simulating muscular dystrophy. Diagnosis usually requires biochemical-enzymatic studies of biopsied muscle.

Progressive muscle weakness usually beginning in the third or fourth decade can be due to the adult form of *acid maltase deficiency (Pompe's disease)*. Respiratory failure is often the initial manifestation; treatment with enzyme replacement may be of benefit. Progressive weakness beginning after puberty occurs with *debranching enzyme deficiency*. Glycolytic defects, including *myophosphorylase deficiency* (McArdle's disease) or *phosphofructokinase deficiency*, present as exercise intolerance with myalgias. Disorders of fatty acid metabolism present with a similar picture. In adults, the most common cause is *carnitine palmitoyltransferase deficiency*. Exercise-induced cramps and myoglobinuria are common; strength is normal between attacks. Dietary approaches (frequent meals and a low-fat high-carbohydrate diet, or a diet rich in medium-chain triglycerides) are of uncertain value.

## MITOCHONDRIAL MYOPATHIES

More accurately referred to as *mitochondrial cytopathies* because multiple tissues are usually affected, these disorders result from defects in mitochondrial DNA. Clinical presentations vary greatly: muscle symptoms may include weakness, ophthalmoparesis, pain or stiffness, or they may even be absent; age of onset ranges from infancy to adulthood; associated clinical presentations include ataxia, encephalopathy, seizures, stroke-like episodes, and recurrent vomiting. Three groups: chronic progressive external ophthalmoplegia (CPEO); skeletal muscle–central nervous system syndromes; and pure myopathy syndromes simulating muscular dystrophy. The characteristic finding on muscle biopsy is "ragged red fibers," which are muscle fibers with accumulations of abnormal mitochondria. Affected families often have a maternal pattern of inheritance because mitochondrial genes are inherited almost exclusively from the oocyte.

## PERIODIC PARALYSES

Muscle membrane excitability is affected in a group of disorders referred to as *channelopathies*. Onset is usually in childhood or adolescence. Episodes typically occur after rest or sleep, often following earlier exercise. May be due to genetic disorders of calcium (hypokalemic periodic paralysis [hypoKPP]), sodium (hyperkalemic periodic paralysis), chloride, or potassium channels.

- Attacks of hypoKPP are treated with potassium chloride (usually oral). Prophylaxis with acetazolamide (125–1000 mg/d in divided doses) is usually effective in hypoKPP type 1.
- Attacks of thyrotoxic periodic paralysis (usually in Asian men) resemble those of hypoKPP; attacks abate with treatment of the underlying thyroid condition.

## ENDOCRINE AND METABOLIC MYOPATHIES

Abnormalities of thyroid function can cause a wide array of muscle disorders. Hypothyroidism is associated with muscle cramps, pain, and stiffness, and proximal muscle weakness occurs in one-third of pts; the relaxation phase of muscle stretch reflexes is prolonged, and serum CK is often elevated (up to 10 times normal).

**TABLE 195-2 DRUG-INDUCED MYOPATHIES**

| Drugs | Major Toxic Reaction |
|---|---|
| Lipid-lowering agents<br>Fibric acid derivatives<br>HMG-CoA reductase inhibitors<br>Niacin (nicotinic acid) | Drugs belonging to all three of the major classes of lipid-lowering agents can produce a spectrum of toxicity: asymptomatic serum creatine kinase elevation, myalgias, exercise-induced pain, rhabdomyolysis, and myoglobinuria. |
| Glucocorticoids | Acute, high-dose glucocorticoid treatment can cause acute quadriplegic myopathy. These high doses of steroids are often combined with nondepolarizing neuromuscular blocking agents but the weakness can occur without their use. Chronic steroid administration produces predominantly proximal weakness. |
| Nondepolarizing neuromuscular blocking agents | Acute quadriplegic myopathy can occur with or without concomitant glucocorticoids. |
| Zidovudine | Mitochondrial myopathy with ragged red fibers |
| Drugs of abuse<br>Alcohol<br>Amphetamines<br>Cocaine<br>Heroin<br>Phencyclidine<br>Meperidine | All drugs in this group can lead to widespread muscle breakdown, rhabdomyolysis, and myoglobinuria.<br>Local injections cause muscle necrosis, skin induration, and limb contractures. |
| Autoimmune toxic myopathy<br>D-Penicillamine | Use of this drug may cause polymyositis and myasthenia gravis. |
| Amphophilic cationic drugs<br>Amiodarone<br>Chloroquine<br>Hydroxychloroquine | All amphophilic drugs have the potential to produce painless, proximal weakness associated with autophagic vacuoles in the muscle biopsy. |
| Antimicrotubular drugs<br>Colchicine | This drug produces painless, proximal weakness especially in the setting of renal failure. Muscle biopsy shows autophagic vacuoles. |

Hyperthyroidism can produce proximal muscle weakness and atrophy; bulbar, respiratory, and even esophageal muscles are occasionally involved, causing dysphagia, dysphonia, and aspiration. Other neuromuscular disorders associated with hyperthyroidism include hypoKPP, myasthenia gravis, and a progressive ocular myopathy associated with proptosis (*Graves' ophthalmopathy*).

Parathyroid, adrenal, and pituitary disorders, as well as diabetes mellitus, can also produce myopathy. Deficiencies of vitamins D and E are additional causes of muscle weakness.

## DRUG-INDUCED MYOPATHIES

Drugs (including glucocorticoids and lipid-lowering agents) and toxins (e.g., alcohol) are associated with myopathies (**Table 195-2**). In most cases, weakness is symmetric and involves proximal limb girdle muscles; myalgia and cramps may also occur. An elevated CK is often found. Diagnosis often depends on resolution of signs and symptoms with removal of offending agent.

For a more detailed discussion, see Amato AA, Brown RH Jr.: Muscular Dystrophies and Other Muscle Diseases, Chap. 462e; Dalakas MC: Polymyositis, Dermatomyositis, and Inclusion Body Myositis, Chap. 388, p. 2194, in HPIM-19.

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# 196 Psychiatric Disorders

Mental disorders are common in medical practice and may present either as a primary disorder or as a comorbid condition. The prevalence of mental or substance use disorders in the United States is ~30%, but only one-third of those individuals are currently receiving treatment.

Disorders of mood, thinking, and behavior may be due to a primary psychiatric diagnosis or a personality disorder or may be secondary to metabolic abnormalities, drug toxicities, focal cerebral lesions, seizure disorders, or degenerative neurologic disease. Any pt presenting with new onset of psychiatric symptoms must be evaluated for underlying psychoactive substance abuse and/or medical or neurologic illness. Psychiatric medications are discussed in Chap. 197.

## MAJOR PSYCHIATRIC DISORDERS (AXIS I DIAGNOSES)

### MOOD DISORDERS (MAJOR AFFECTIVE DISORDERS)

Mood disorders are characterized by a disturbance in the regulation of mood, behavior, and affect; subdivided into (1) depressive disorders, (2) bipolar disorders (depression plus manic or hypomanic episodes), and (3) depression in association with medical illness or alcohol and substance abuse (see Chaps. 199 and 200).

### Major Depression

**Clinical Features** Affects 15% of the general population at some point in life; 6–8% of all outpatients in primary care settings satisfy diagnostic criteria. Diagnosis is made when five (or more) of the following symptoms have been present for 2 weeks (at least one of the symptoms must be #1 or #2 below):

1. Depressed mood
2. Loss of interest or pleasure
3. Change in appetite or weight
4. Insomnia or hypersomnia
5. Psychomotor agitation or retardation
6. Fatigue or loss of energy
7. Feelings of worthlessness or inappropriate guilt
8. Decreased ability to concentrate and make decisions
9. Recurrent thoughts of death or suicide

A small number of pts with major depression will have psychotic symptoms (hallucinations and delusions) with their depressed mood. Negative life events can precipitate depression, but genetic factors influence the sensitivity to these events.

Onset of a first depressive episode is typically in early adulthood, although major depression can occur at any age. Untreated episodes generally resolve spontaneously in a few months to a year; however, a sizable number of pts suffer from chronic, unremitting depression, or from a partial treatment response. Half of all pts experiencing a first depressive episode will go on to a recurrent course. Untreated or partially treated episodes put the pt at risk for future problems with mood disorders. Within an individual, the nature of episodes may be similar over time. A family history of mood disorder is common and tends to predict a recurrent course. Major depression can also be the initial presentation of bipolar disorder (manic depressive illness).

**Suicide** Approximately 4–5% of all depressed pts will commit suicide, and most will have sought help from a physician within 1 month of their death. Physicians must always inquire about suicide when evaluating a pt with depression.

**Depression with Medical Illness** Virtually every class of medication can potentially induce or worsen depression. Antihypertensive drugs, anticholesterolemic agents, and antiarrhythmic agents are common triggers of depressive symptoms. Among the antihypertensive agents, β-adrenergic blockers and, to a lesser extent, calcium channel blockers are most likely to cause depressed mood. Iatrogenic depression should also be considered in pts receiving glucocorticoids, antimicrobials, systemic analgesics, antiparkinsonian medications, and anticonvulsants.

Between 20–30% of cardiac pts manifest a depressive disorder. Tricyclic antidepressants (TCAs) are contraindicated in pts with bundle branch block, and TCA-induced tachycardia is an additional concern in pts with congestive heart failure. Selective serotonin reuptake inhibitors (SSRIs) appear not to induce ECG changes or adverse cardiac events, and thus, are reasonable first-line drugs for pts at risk for TCA-related complications. SSRIs may interfere with hepatic metabolism of anticoagulants, however, causing increased anticoagulation.

In *cancer*, the prevalence of depression is 25%, but it occurs in 40–50% of pts with cancers of the pancreas or oropharynx. Extreme cachexia from cancer may be misinterpreted as depression. Antidepressant medications in cancer pts improve quality of life as well as mood.

*Diabetes mellitus* is another consideration; the severity of the mood state correlates with the level of hyperglycemia and the presence of diabetic complications. Monoamine oxidase inhibitors (MAOIs) can induce hypoglycemia and weight gain. TCAs can produce hyperglycemia and carbohydrate craving. SSRIs, like MAOIs, may reduce fasting plasma glucose, but they are easier to use and may also improve dietary and medication compliance.

Depression may also occur with *hypothyroidism* or *hyperthyroidism*, in *neurologic disorders*, in *HIV*-positive individuals, and in *chronic hepatitis C infection* (depression worsens with interferon treatment). Some chronic disorders of uncertain etiology, such as *chronic fatigue syndrome* and *fibromyalgia*, are strongly associated with depression.

## TREATMENT MAJOR DEPRESSION

- Pts with suicidal ideation require treatment by a psychiatrist and may require hospitalization.
- Most other pts with an uncomplicated unipolar major depression (a major depression that is not part of a cyclical mood disorder, such as a bipolar disorder) can be successfully treated by a nonpsychiatric physician.
- Vigorous intervention and successful treatment appear to decrease the risk of future relapse.
- Pts who do not respond fully to standard treatment should be referred to a psychiatrist.
- Antidepressant medications are the mainstay of treatment, although combined treatment with psychotherapy improves outcome. Symptoms are ameliorated after 6–8 weeks at a therapeutic dose in 60–70% of pts.
- A guideline for the medical management of depression is shown in Fig. 196-1.
- Once remission is achieved, antidepressants should be continued for 6–9 months. Pts must be monitored carefully after termination of treatment since relapse is common.
- Pts with two or more episodes of depression should be considered for indefinite maintenance treatment.

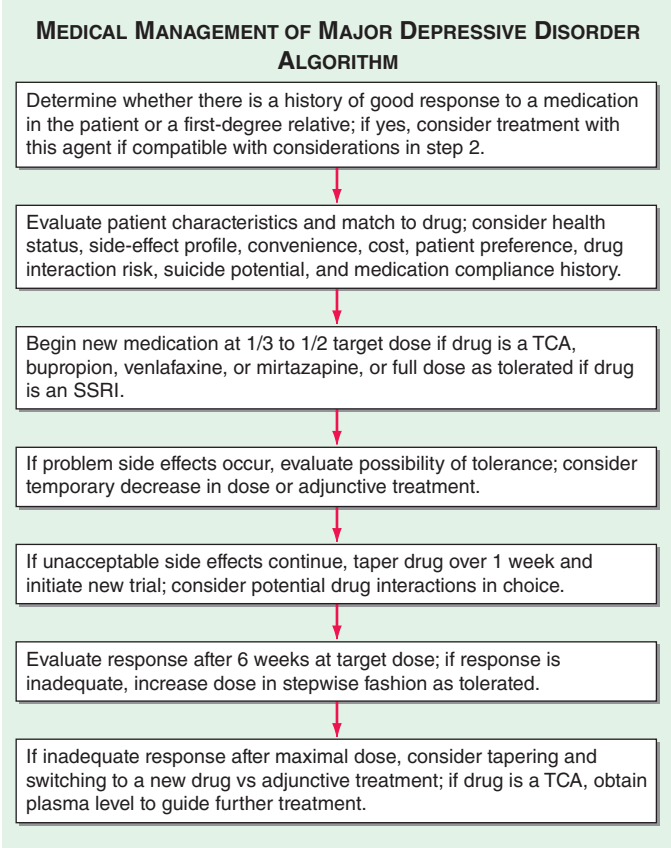



**FIGURE 196-1** A guideline for the medical management of major depressive disorder. SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

- Electroconvulsive therapy is generally reserved for treatment-resistant depression unresponsive to medication or for pts in whom the use of antidepressants is medically contraindicated.
- Transcranial magnetic stimulation (TMS) is approved for treatment-resistant depression.
- Vagus nerve stimulation (VNS) has been approved for treatment-resistant depression as well, but its degree of efficacy is controversial.

## Bipolar Disorder (Manic Depressive Illness)

**Clinical Features** A cyclical mood disorder in which episodes of major depression are interspersed with episodes of mania or hypomania; 1.5% of the population is affected. Most pts initially present with a manic episode in adolescence or young adulthood. Antidepressant therapy may provoke a manic episode; pts with a major depressive episode and a prior history of "highs" (mania or hypomania—which

can be pleasant/euphoric or irritable/impulsive) and/or a family history of bipolar disorder should not be treated with antidepressants, but instead referred promptly to a psychiatrist.

With mania, an elevated, expansive mood, irritability, angry outbursts, and impulsivity are characteristic. Specific symptoms include (1) unusual talkativeness, (2) flight of ideas and racing thoughts, (3) inflated self-esteem that can become delusional, (4) decreased need for sleep (often the first feature of an incipient manic episode), (5) increase in goal-directed activity or psychomotor agitation, (6) distractibility, and (7) excessive involvement in risky activities (buying sprees, sexual indiscretions). Pts with full-blown mania can become psychotic. Hypomania is characterized by attenuated manic symptoms and is greatly underdiagnosed, as are "mixed episodes," where both depressive and manic or hypomanic symptoms coexist simultaneously.

Untreated, a manic or depressive episode typically lasts for several weeks but can last for 8–12 months. Variants of bipolar disorder include rapid and ultrarapid cycling (manic and depressed episodes occurring at cycles of weeks, days, or hours). In many pts, especially females, antidepressants trigger rapid cycling and worsen the course of illness. Bipolar disorder has a strong genetic component; the concordance rate for monozygotic twins approaches 80%.

### TREATMENT BIPOLAR DISORDER

- Bipolar disorder is a serious, chronic illness that requires lifelong monitoring by a psychiatrist.
- Acutely manic pts often require hospitalization to reduce environmental stimulation and to protect themselves and others from the consequences of their reckless behavior.
- The recurrent nature of bipolar disorder necessitates maintenance treatment.
- Mood stabilizers (lithium, valproic acid, second-generation antipsychotic drugs, carbamazepine) are effective for the resolution of acute episodes and for prophylaxis of future episodes.

## SCHIZOPHRENIA AND OTHER PSYCHOTIC DISORDERS

### Schizophrenia

**Clinical Features** Characterized by perturbations of language, perception, thinking, social activity, affect, and volition. Occurs in 0.85% of the population worldwide; lifetime prevalence is ~1–1.5%. Pts usually present in late adolescence, often after an insidious premorbid course of subtle psychosocial difficulties. Core psychotic features last ≥6 months and include positive symptoms (such as conceptual disorganization, delusions, or hallucinations) and negative symptoms (loss of function, anhedonia, decreased emotional expression, impaired concentration, and diminished social engagement). Negative symptoms predominate in one-third and are associated with a poor long-term outcome and poor response to treatment.

Prognosis depends not on symptom severity but on the response to antipsychotic medication. A permanent remission without recurrence does occasionally occur. About 10% of schizophrenic pts commit suicide. Comorbid substance abuse is common.

### TREATMENT SCHIZOPHRENIA

- Hospitalization is required for acutely psychotic pts who may be dangerous to themselves or others.
- Conventional antipsychotic medications are effective against hallucinations, delusions, and thought disorder.

- The novel antipsychotic medications—risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, iloperidone, asenapine, lurasidone, and clozapine—are helpful in pts unresponsive to conventional neuroleptics and may also be more useful for negative and cognitive symptoms.
- Drug treatment by itself is insufficient, and educational efforts directed toward families and relevant community resources are necessary to maintain stability and optimize outcomes.

## ANXIETY DISORDERS

Characterized by severe, persistent anxiety or sense of dread or foreboding. Most prevalent group of psychiatric illnesses seen in the community; present in 15–20% of medical clinic pts.

### Panic Disorder

Occurs in 2–3% of the population; familial aggregation may occur. Onset in late adolescence or early adulthood. Initial presentation is almost always to a nonpsychiatric physician, frequently in the ER, as a possible heart attack or serious respiratory problem. The disorder is often initially unrecognized or misdiagnosed. Three-quarters of pts with panic disorder will also satisfy criteria for major depression at some point.

**Clinical Features** Characterized by panic attacks, which are sudden, unexpected, overwhelming paroxysms of terror and apprehension with multiple associated somatic symptoms. Attacks usually reach a peak within 10 min, then slowly resolve spontaneously, occurring in an unexpected fashion. Diagnostic criteria for panic disorder include recurrent panic attacks and at least 1 month of concern or worry about the attacks or a change in behavior related to them. Panic attacks are accompanied by palpitations, sweating, trembling, dyspnea, chest pain, dizziness, and a fear of impending doom or death.

When the disorder goes unrecognized and untreated, pts often experience significant morbidity: they become afraid of leaving home and may develop anticipatory anxiety, agoraphobia, and other spreading phobias; many turn to self-medication with alcohol or benzodiazepines.

Panic disorder must be differentiated from cardiovascular and respiratory disorders. Other conditions that may mimic or worsen panic attacks include hyperthyroidism, pheochromocytoma, hypoglycemia, drug ingestions (amphetamines, cocaine, caffeine, sympathomimetic nasal decongestants), and drug withdrawal (alcohol, barbiturates, opiates, minor tranquilizers).

**TREATMENT PANIC DISORDER**

- The cornerstone of drug therapy is antidepressant medication.
- SSRIs benefit the majority of pts and do not have the adverse effects of the TCAs.
- Benzodiazepines may be used in the short term while waiting for antidepressants to take effect.
- Early psychotherapeutic intervention and education aimed at symptom control enhances the effectiveness of drug treatment.
- Psychotherapy (identifying and aborting panic attacks through relaxation and breathing techniques) can be effective.

### Generalized Anxiety Disorder (GAD)

Characterized by persistent, chronic anxiety; occurs in 5–6% of the population.

**Clinical Features** Pts experience persistent, excessive, and/or unrealistic worry associated with muscle tension, impaired concentration, autonomic arousal, feeling "on edge" or restless, and insomnia. Pts worry excessively over minor matters, with life-disrupting effects; unlike panic disorder, complaints of shortness of breath, palpitations, and tachycardia are relatively rare. Secondary depression is common, as is social phobia and comorbid substance abuse.

**TREATMENT GENERALIZED ANXIETY DISORDER**

- A combination of pharmacologic and psychotherapeutic interventions is most effective; complete symptom relief is rare.
- Benzodiazepines are the initial agents of choice when generalized anxiety is severe and acute enough to warrant drug therapy; physicians must be alert to psychological and physical dependence on benzodiazepines.
- A subgroup of pts respond to buspirone, a nonbenzodiazepine anxiolytic.
- Some SSRIs also are effective at doses comparable to their efficacy in major depression.
- Anticonvulsants with GABAergic properties (gabapentin, oxcarbazepine, tiagabine, pregabalin, divalproex) may also be effective against anxiety.

## Obsessive-Compulsive Disorder (OCD)

A severe disorder present in 2–3% of the population and characterized by recurrent obsessions (persistent intrusive thoughts) and compulsions (repetitive behaviors) that impair everyday functioning. Pts are often ashamed of their symptoms; physicians must ask specific questions to screen for this disorder including asking about recurrent thoughts and behaviors.

**Clinical Features** Common obsessive thoughts and compulsive behaviors include fears of germs or contamination, handwashing, counting behaviors, and having to check and recheck such actions as whether a door is locked.

Onset is usually in early adulthood (childhood onset is not rare); more common in males and first-born children. Comorbid conditions are common, the most frequent being depression, other anxiety disorders, eating disorders, and tics. The course of OCD is usually episodic with periods of incomplete remission; some cases may show a steady deterioration in psychosocial functioning.

**TREATMENT OBSESSIVE-COMPULSIVE DISORDER**

- Clomipramine and the SSRIs (fluoxetine, fluvoxamine, sertraline) are effective, but only 50–60% of pts show adequate improvement with pharmacotherapy alone.
- A combination of drug therapy and cognitive-behavioral psychotherapy is most effective for the majority of pts.

## Posttraumatic Stress Disorder (PTSD)

Occurs in some individuals exposed to a severe life-threatening trauma. If the reaction occurs shortly after the event, it is termed *acute stress disorder*, but if the reaction is delayed and subject to recurrence, PTSD is diagnosed. Predisposing factors include a past psychiatric history and personality characteristics of extroversion and high neuroticism.

**Clinical Features** Individuals experience associated symptoms of detachment and loss of emotional responsivity. The pt may feel depersonalized and unable to recall specific events of the trauma, although it is reexperienced through intrusions in thought, dreams, or flashbacks. Comorbid substance abuse and other mood and anxiety disorders are common. This disorder is extremely debilitating; most pts require referral to a psychiatrist for ongoing care.

**TREATMENT POSTTRAUMATIC STRESS DISORDER**

- SSRIs, venlafaxine, and topiramate all are somewhat effective.
- Propranolol and opiates such as morphine given during the acute stress period may prevent the development of PTSD.
- Adjunctive naltrexone can be effective when comorbid alcoholism is present.
- Trazodone is frequently used at night to help with insomnia.
- Psychotherapeutic strategies help the pt overcome avoidance behaviors and master fear of recurrence of the trauma.

## Phobic Disorders

**Clinical Features** Recurring, irrational fears of specific objects, activities, or situations, with subsequent avoidance behavior of the phobic stimulus. Diagnosis is made only when the avoidance behavior interferes with social or occupational functioning. Affects ~10% of the population. Common phobias include fear of closed places, (claustrophobia), fear of blood, and fear of flying. Social phobia is distinguished by a specific fear of social or performance situations in which the individual is exposed to unfamiliar individuals or to possible examination and evaluation by others (e.g., having to converse at a party, use of public restrooms, meeting strangers).

**TREATMENT PHOBIC DISORDERS**

- Agoraphobia is treated as for panic disorder.
- Beta blockers (e.g., propranolol, 20–40 mg PO 2 h before the event) are particularly effective in the treatment of "performance anxiety."
- SSRIs and MAOIs are very helpful in treating social phobias. Social and simple phobias respond well to behaviorally focused psychotherapy.

## Somatic Symptom Disorder

**Clinical Features** Pts with multiple somatic complaints that cannot be explained by a known medical condition or by the effects of substances; seen commonly in primary care practice (prevalence of 5–7%). Pts may present with multiple physical complaints referable to different organ systems; pts with somatic symptom disorder can be impulsive and demanding. In *conversion disorder*, the symptoms involve voluntary motor or sensory function In *factitious illnesses*, the pt consciously and voluntarily produces physical symptoms; the sick role is gratifying. *Munchausen's syndrome* refers to individuals with dramatic, chronic, or severe factitious illness. A variety of signs, symptoms, and diseases have been simulated in factitious illnesses; most common are chronic diarrhea, fever of unknown origin, intestinal bleeding, hematuria, seizures, hypoglycemia. In *malingering*, the fabrication of illness derives from a desire for an external reward (narcotics, disability).

## TREATMENT SOMATIC SYMPTOM DISORDER

- Pts with somatic symptom disorder are usually subjected to multiple diagnostic tests and exploratory surgeries in an attempt to find their "real" illness. This approach is doomed to failure.
- Successful treatment is achieved through behavior modification, in which access to the physician is adjusted to provide a consistent, sustained, and predictable level of support that is not contingent on the pt's level of presenting symptoms or distress.
- Visits are brief, supportive, and structured and are not associated with a need for diagnostic or treatment action.
- Pts may benefit from antidepressant treatment.
- Consultation with a psychiatrist is essential.

## PERSONALITY DISORDERS

Characteristic patterns of thinking, feeling, and interpersonal behavior that are relatively inflexible and cause significant functional impairment or subjective distress for the individual. Individuals with personality disorders are often regarded as "difficult pts."

Three major categories of personality disorders; pts usually present with a combination of features.

### CLUSTER A PERSONALITY DISORDERS

Includes individuals who are odd and eccentric and who maintain an emotional distance from others. The *paranoid* personality has pervasive mistrust and suspiciousness of others. The *schizoid* personality is interpersonally isolated, cold, and indifferent, while the *schizotypal* personality is eccentric and superstitious, with magical thinking and unusual perceptual experiences.

### CLUSTER B PERSONALITY DISORDERS

Describe individuals whose behavior is impulsive, excessively emotional, and erratic. The *borderline* personality is impulsive and manipulative, with unpredictable and fluctuating intense moods and unstable relationships, a fear of abandonment, and occasional rage episodes. The *histrionic* pt is dramatic, engaging, seductive, and attention seeking. The *narcissistic* pt is self-centered and has an inflated sense of self-importance combined with a tendency to devalue or de-mean others, while pts with *antisocial* personality disorder use other people to achieve their own ends and engage in exploitative and manipulative behavior with no sense of remorse.

### CLUSTER C PERSONALITY DISORDERS

Enduring traits are anxiety and fear. The *dependent* pt fears separation, tries to engage others to assume responsibility, and often has a help-rejecting style. Pts with obsessive-*compulsive* personality disorder are meticulous and perfectionistic but also inflexible and indecisive. *Avoidant* pts are anxious about social contact and have difficulty assuming responsibility for their isolation.

For a more detailed discussion, see Reus VI: Mental Disorders, Chap. 466, p. 2708, in HPIM-19.

# 197 Psychiatric Medications

Four major classes are commonly used in adults: (1) antidepressants (ADs), (2) anxiolytics, (3) antipsychotics, and (4) mood-stabilizing agents. Nonpsychiatric physicians should become familiar with one or two drugs in each of the first three classes so that the indications, dose range, efficacy, potential side effects, and interactions with other medications are well known.

## GENERAL PRINCIPLES OF USE

1. Most treatment failures are due to undermedication and impatience. For a proper medication trial to take place, an effective dose must be taken for an adequate amount of time. For ADs, antipsychotics, and mood stabilizers, full effects may take weeks or months to occur.
2. History of a positive response to a medication usually indicates that a response to the same drug will occur again. A family history of a positive response to a specific medication is also useful.
3. Pts who fail to respond to one drug will often respond to another in the same class; one should attempt another trial with a drug that has a different mechanism of action or a different chemical structure. Treatment failures should be referred to a psychiatrist, as should all pts with psychotic symptoms or who require mood stabilizers.
4. Avoid polypharmacy; a pt who is not responding to standard monotherapy requires referral to a psychiatrist.
5. Pharmacokinetics may be altered in the elderly, with smaller volumes of distribution, reduced renal and hepatic clearance, longer biologic half-lives, and greater potential for CNS toxicity. The rule with elderly pts is to "start low and go slow."
6. Never stop treatment abruptly, especially true for ADs and anxiolytics. In general, medications should be slowly tapered and discontinued over 2–4 weeks.
7. Review possible side effects each time a drug is prescribed; educate pts and family members about side effects and need for patience in awaiting a response.

## ANTIDEPRESSANTS

Useful to group according to known actions on CNS monoaminergic systems (Table 197-1). The selective serotonin reuptake inhibitors (SSRIs) have predominant effects on serotonergic neurotransmission, also reflected in side-effect profile. The TCAs, or tricyclic ADs, affect noradrenergic and, to a lesser extent, serotonergic neurotransmission but also have anticholinergic and antihistaminic effects. Venlafaxine, desvenlafaxine, duloxetine, mirtazapine, vilazodone, vortioxetine, and levomilnacipran have mixed noradrenergic and serotonergic effects. Bupropion is a novel antidepressant that enhances noradrenergic function. Trazodone and amoxapine have mixed effects on serotonin receptors and on other neurotransmitter systems. The monoamine oxidase inhibitors (MAOIs) inhibit monoamine oxidase, the primary enzyme responsible for the degradation of monoamines in the synaptic cleft.

ADs are effective against major depression, particularly when neurovegetative symptoms and signs are present. Despite the widespread use of SSRIs, there is no convincing evidence that they are more efficacious than TCAs, although their safety profile in overdose is more favorable than that of the TCAs. ADs are also useful in treatment of panic disorder, posttraumatic stress disorder, chronic pain syndromes, and generalized anxiety disorder. The TCA clomipramine and the SSRIs successfully treat obsessive-compulsive disorder.

**TABLE 197-1 ANTIDEPRESSANTS**

| Name | Usual Daily Dose, mg | Side Effects | Comments |
|---|---|---|---|
| **SSRIs** | | | |
| Fluoxetine (Prozac) | 10–80 | Headache; nausea and other GI effects; jitteriness; insomnia; sexual dysfunction; can affect plasma levels of other medicines (except sertraline); akathisia rare | Once-daily dosing, usually in the morning; fluoxetine has very long half-life; must not be combined with MAOIs |
| Sertraline (Zoloft) | 50–200 | | |
| Paroxetine (Paxil) | 20–60 | | |
| Fluvoxamine (Luvox) | 100–300 | | |
| Citalopram (Celexa) | 20–60 | | |
| Escitalopram (Lexapro) | 10–30 | | |
| **TCAs** | | | |
| Amitriptyline (Elavil) | 150–300 | Anticholinergic (dry mouth, tachycardia, constipation, urinary retention, blurred vision); sweating; tremor; postural hypotension; cardiac conduction delay; sedation; weight gain | Once-daily dosing, usually qhs; blood levels of most TCAs available; can be lethal in overdose (lethal dose = 2 g); nortriptyline best tolerated, especially by elderly<br>FDA approved for OCD |
| Nortriptyline (Pamelor) | 50–200 | | |
| Imipramine (Tofranil) | 150–300 | | |
| Desipramine (Norpramin) | 150–300 | | |
| Doxepin (Sinequan) | 150–300 | | |
| Clomipramine (Anafranil) | 150–300 | | |
| **Mixed Norepinephrine/SNRI and Receptor Blockers** | | | |
| Venlafaxine (Effexor) | 75–375 | Nausea; dizziness; dry mouth; headaches; increased blood pressure; anxiety and insomnia | Bid-tid dosing (extended release available); lower potential for drug interactions than SSRIs; contraindicated with MAOIs |
| Desvenlafaxine (Pristiq) | 50–400 | Nausea, dizziness, insomnia | Primary metabolite of venlafaxine; no increased efficacy with higher dosing |
| Duloxetine (Cymbalta) | 40–60 | Nausea, dizziness, headache, insomnia, constipation | May have utility in treatment of neuropathic pain and stress incontinence |

| | | | |
|---|---|---|---|
| Mirtazapine (Remeron) | 15–45 | Somnolence, weight gain; neutropenia rare | Once a day dosing |
| Vilazodone (Viibryd) | 40 | Nausea, diarrhea, headache; dosage adjustment if given with CYP3A4 inhibitor/stimulator | Also 5-$HT_{1a}$ receptor partial agonist |
| Vortioxetine (Brintellix) | 5–20 | Nausea, diarrhea, sweating, headache; low incidence of sedation or weight gain | No specific p450 effects; 5-$HT_{3a}$ and 5-$HT_7$ receptor antagonist, 5-$HT_{1b}$ partial agonist, and 5-$HT_{1a}$ agonist |
| Levomilnacipran (Fetzima) | 40–120 | Nausea, constipation, sweating; rare increase in blood pressure/pulse | Most noradrenergic of SNRIs |
| **Mixed-Action Drugs** | | | |
| Bupropion (Wellbutrin) | 250–450 | Jitteriness; flushing; seizures in at-risk pts; anorexia; tachycardia; psychosis | Tid dosing, but sustained release also available; fewer sexual side effects than SSRIs or TCAs; may be useful for adult ADD |
| Trazodone (Desyrel) | 200–600 | Sedation, dry mouth, ventricular irritability, postural hypotension, priapism rare | Useful in low doses for sleep because of sedating effects with no anticholinergic side effects |
| Trazodone extended release (Oleptro) | 150–375 | Daytime somnolence, dizziness, nausea | |
| Amoxapine (Asendin) | 200–600 | Sexual dysfunction | Lethality in overdose; EPS possible |
| **MAOIs** | | | |
| Phenelzine (Nardil) | 45–90 | Insomnia; hypotension; edema; anorgasmia; weight gain; neuropathy; hypertensive crisis; toxic reactions with SSRIs; narcotics | May be more effective in pts with atypical features or treatment-refractory depression |
| Tranylcypromine (Parnate) | 20–50 | | |
| Isocarboxazid (Marplan) | 20–60 | | Less weight gain and hypotension than phenelzine |
| Transdermal selegiline (Emsam) | 6–12 | Local skin reaction hypertension | No dietary restrictions with 6-mg dose |

***Abbreviations:*** ADD, attention deficit disorder; EPS, extrapyramidal symptoms; MAOIs, monoamine oxidase inhibitors; OCD, obsessive-compulsive disorder; SNRI, serotonin norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

All ADs require at least 2 weeks at a therapeutic dose before clinical improvement is observed. All ADs also have the potential to trigger a manic episode or rapid cycling when given to a pt with bipolar disorder. The MAOIs must not be prescribed concurrently with other ADs or with narcotics, as potentially fatal reactions may occur. "Withdrawal syndromes" usually consisting of malaise can occur when ADs are stopped abruptly.

## ANXIOLYTICS

Benzodiazepines bind to sites on the γ-aminobutyric acid receptor and are cross-tolerant with alcohol and with barbiturates. Four clinical properties: (1) sedative, (2) anxiolytic, (3) skeletal muscle relaxant, and (4) antiepileptic. Individual drugs differ in terms of potency, onset of action, duration of action (related to half-life and presence of active metabolites), and metabolism (Table 197-2). Benzodiazepines have additive effects with alcohol; like alcohol, they can produce tolerance and physiologic dependence, with serious withdrawal syndromes (tremors, seizures, delirium, and autonomic hyperactivity) if discontinued too quickly, especially for those with short half-lives.

Buspirone is a nonbenzodiazepine anxiolytic that is nonsedating, is not cross-tolerant with alcohol, and does not induce tolerance or dependence. It requires at least 2 weeks at therapeutic doses to achieve full effects.

## ANTIPSYCHOTIC MEDICATIONS

These include the first-generation (typical) neuroleptics, which act by blocking dopamine $D_2$ receptors, and the second-generation (atypical) neuroleptics, which act on dopamine, serotonin, and other neurotransmitter systems. Some antipsychotic effect may occur within hours or days of initiating treatment, but full effects usually require 6 weeks to several months of daily, therapeutic dosing.

### FIRST-GENERATION ANTIPSYCHOTICS

Useful to group into high-, mid-, and low-potency neuroleptics (Table 197-3). High-potency neuroleptics are least sedating, have almost no anticholinergic side effects, and have a strong tendency to induce extrapyramidal side effects (EPSEs). The EPSEs occur within several hours to several weeks of beginning treatment and include acute dystonias, akathisia, and pseudo-parkinsonism. Extrapyramidal symptoms respond well to trihexyphenidyl, 2 mg twice daily, or benztropine mesylate, 1–2 mg twice daily. Akathisia may respond to beta blockers. Low-potency neuroleptics are very sedating, may cause orthostatic hypotension, are anticholinergic, and tend not to induce EPSEs frequently.

Up to 20% of pts treated with conventional antipsychotic agents for >1 year develop tardive dyskinesia (probably due to dopamine receptor supersensitivity), an abnormal involuntary movement disorder most often observed in the face and distal extremities. Treatment includes gradual withdrawal of the neuroleptic, with possible switch to a novel neuroleptic; anticholinergic agents can worsen the disorder.

Rarely, pts exposed to neuroleptics develop neuroleptic malignant syndrome (NMS), a life-threatening complication with a mortality rate as high as 25%; hyperpyrexia, autonomic hyperactivity, muscle rigidity, obtundation, and agitation are characteristics associated with increased WBC, increased creatine phosphokinase, and myoglobinuria. Treatment involves immediate discontinuation of neuroleptics, supportive care, and use of dantrolene and bromocriptine.

### SECOND-GENERATION ANTIPSYCHOTICS

A class of agents that has become the first line of treatment (Table 197-3); efficacious in treatment-resistant pts, tend not to induce EPSEs or tardive dyskinesia,

**TABLE 197-2 ANXIOLYTICS**

| Name | Equivalent PO Dose, mg | Onset of Action | Half-Life, h | Comments |
|---|---|---|---|---|
| Benzodiazepines | | | | |
| Diazepam (Valium) | 5 | Fast | 20–70 | Active metabolites; quite sedating |
| Flurazepam (Dalmane) | 15 | Fast | 30–100 | Flurazepam is a prodrug; metabolites are active; quite sedating |
| Triazolam (Halcion) | 0.25 | Intermediate | 1.5–5 | No active metabolites; can induce confusion and delirium, especially in elderly |
| Lorazepam (Ativan) | 1 | Intermediate | 10–20 | No active metabolites, direct hepatic glucuronide conjugation, quite sedating, FDA approved for anxiety with depression |
| Alprazolam (Xanax) | 0.5 | Intermediate | 12–15 | Active metabolites,; not too sedating, FDA approved for panic disorder and anxiety with depression, tolerance and dependence develop easily, difficult to withdraw |
| Chlordiazepoxide (Librium) | 10 | Intermediate | 5–30 | Active metabolites, moderately sedating |
| Oxazepam (Serax) | 15 | Slow | 5–15 | No active metabolites, direct glucuronide conjugation, not too sedating |
| Temazepam (Restoril) | 15 | Slow | 9–12 | No active metabolites, moderately sedating |
| Clonazepam (Klonopin) | 0.5 | Slow | 18–50 | No active metabolites, moderately sedating, FDA approved for panic disorder |
| Clorazepate (Tranxene) | 15 | Fast | 40–200 | Low sedation, unreliable absorption |
| Nonbenzodiazepines | | | | |
| Buspirone (BuSpar) | 7.5 | 2 weeks | 2–3 | Active metabolites, tid dosing—usual daily dose 10–20 mg tid, nonsedating; no additive effects with alcohol, useful for controlling agitation in demented or brain-injured pts |

**TABLE 197-3 ANTIPSYCHOTIC AGENTS**

| Name | Usual PO Daily Dose, mg | Side Effects | Sedation | Comments |
|---|---|---|---|---|
| **First-Generation Antipsychotics** | | | | |
| Low potency | | | | |
| Chlorpromazine (Thorazine) | 100–1000 | Anticholinergic effects, orthostasis, photosensitivity, cholestasis, QT prolongation | +++ | EPSEs usually not prominent; can cause anticholinergic delirium in elderly pts |
| Thioridazine (Mellaril) | 100–600 | | | |
| Midpotency | | | | |
| Trifluoperazine (Stelazine) | 2–50 | Fewer anticholinergic side effects | ++ | Well tolerated by most pts |
| Perphenazine (Trilafon) | 4–64 | Fewer EPSEs than with higher potency agents | ++ | |
| Loxapine (Loxitane) | 30–100 | Frequent EPSEs | ++ | |
| Molindone (Moban) | 30–100 | Frequent EPSEs | 0 | Little weight gain |
| High potency | | | | |
| Haloperidol (Haldol) | 5–20 | No anticholinergic side effects; EPSEs often prominent | 0/+ | Often prescribed in doses that are too high; long-acting injectable forms of haloperidol and fluphenazine available |
| Fluphenazine (Prolixin) | 1–20 | Frequent EPSEs | 0/+ | |
| Thiothixene (Navane) | 2–50 | Frequent EPSEs | 0/+ | |

| Second-Generation Antipsychotics | | | | |
|---|---|---|---|---|
| Clozapine (Clozaril) | 150–600 | Agranulocytosis (1%), weight gain, seizures, drooling, hyperthermia | + + | Requires weekly WBC count for first 6 months, then biweekly if stable |
| Risperidone (Risperdal) | 2–8 | Orthostasis | + | Requires slow titration; EPSEs observed with doses >6 mg qd |
| Olanzapine (Zyprexa) | 10–30 | Weight gain | ++ | Mild prolactin elevation |
| Quetiapine (Seroquel) | 350–800 | Sedation, weight gain, anxiety | +++ | Bid dosing |
| Ziprasidone (Geodon) | 120–200 | Orthostatic hypotension | +/++ | Minimal weight gain, increases QT interval |
| Aripiprazole (Abilify) | 10–30 | Nausea, anxiety, insomnia | 0/+ | Mixed agonist/antagonist |
| Paliperidone (Invega) | 3–12 | Restlessness, EPSEs, increased prolactin, headache | + | Active metabolite of risperidone |
| Iloperidone (Fanapt) | 12–24 | Dizziness, hypotension | 0/+ | Requires dose titration, long-acting injectable available |
| Asenapine (Saphris) | 10–20 | Dizziness, anxiety, EPSEs, minimal weight gain | ++ | Sublingual tablets; bid dosing |
| Lurasidone (Latuda) | 40–80 | Nausea, EPSEs | ++ | Uses CYP3A4 |

***Abbreviations:*** EPSEs, extrapyramidal side effects.

and appear to have uniquely beneficial properties on negative symptoms and cognitive dysfunction. Main problem is side effect of weight gain (most prominent with clozapine and in olanzapine; can induce diabetes). The CATIE study, a large-scale investigation of antipsychotic agents in the "real world," revealed a high rate of discontinuation of all medications over 18 months; olanzapine was modestly more effective than other agents but with a higher discontinuation rate due to side effects.

## MOOD-STABILIZING AGENTS

Four mood stabilizers in common use: lithium, valproic acid, carbamazepine/oxcarbazepine, and lamotrigine (Table 197-4). Lithium is the gold standard and the best studied, and along with carbamazepine and valproic acid, is used for treatment of acute manic episodes; 1–2 weeks to reach full effect. As prophylaxis, the mood stabilizers reduce frequency and severity of both manic and depressed episodes in cyclical mood disorders. In refractory bipolar disorder, combinations of mood stabilizers may be beneficial.

**TABLE 197-4 CLINICAL PHARMACOLOGY OF MOOD STABILIZERS**

| Agent and Dosing | Side Effects and Other Effects |
|---|---|
| **Lithium** | **Common side effects** |
| Starting dose: 300 mg bid or tid<br>Therapeutic blood level: 0.8–1.2 meq/L | Nausea/anorexia/diarrhea, fine tremor, thirst, polyuria, fatigue, weight gain, acne, folliculitis, neutrophilia, hypothyroidism<br>Blood level is increased by thiazides, tetracyclines, and NSAIDs<br>Blood level is decreased by bronchodilators, verapamil, and carbonic anhydrase inhibitors<br>*Rare side effects:* Neurotoxicity, renal toxicity, hypercalcemia, ECG changes |
| **Valproic acid** | **Common side effects** |
| Starting dose: 250 mg tid<br>Therapeutic blood level: 50–125 μg/mL | Nausea/anorexia, weight gain, sedation, tremor, rash, alopecia<br>Inhibits hepatic metabolism of other medications<br>*Rare side effects:* Pancreatitis, hepatotoxicity, Stevens-Johnson syndrome |
| **Carbamazepine/ Oxcarbazepine** | **Common side effects** |
| Starting dose: 200 mg bid for carbamazepine, 150 mg bid for oxcarbazepine<br>Therapeutic blood level: 4–12 μg/mL for carbamazepine | Nausea/anorexia, sedation, rash, dizziness/ataxia<br>Carbamazepine, but not oxcarbazepine, induces hepatic metabolism of other medications<br>*Rare side effects:* Hyponatremia, agranulocytosis, Stevens-Johnson syndrome |
| **Lamotrigine** | **Common side effects** |
| Starting dose: 25 mg/d | Rash, dizziness, headache, tremor, sedation, nausea<br>*Rare side effect:* Stevens-Johnson syndrome |

For a more detailed discussion, see Reus VI: Mental Disorders, Chap. 466, p. 2708, in HPIM-19.

# 198 Eating Disorders

## DEFINITIONS AND EPIDEMIOLOGY

Eating disorders constitute a group of conditions in which there is persistent disturbance of eating or associated behaviors that significantly impair an individual's physical health or psychosocial functioning. *Anorexia nervosa* is characterized by restriction of caloric intake to a degree that body weight deviates significantly from age, gender, health, and developmental norms accompanied by a fear of gaining weight and an associated disturbance in body image. *Bulimia nervosa* is characterized by recurrent episodes of binge eating followed by abnormal compensatory behaviors, such as self-induced vomiting, laxative abuse, or excessive exercise; weight is in the normal range or above. *Binge eating disorder* is similar to bulimia nervosa but lacks the compensatory behavior element.

Both anorexia nervosa and bulimia nervosa occur primarily among previously healthy young women who become overly concerned with body shape and weight. Binge eating and purging behavior may be present in both conditions, with the critical distinction between the two resting on the weight of the individual. In women, the lifetime prevalence of anorexia nervosa is up to 4% and of bulimia nervosa approximately 2%. There is at least a 10:1 female-to-male ratio for both conditions. Typically, the onset of anorexia is mid-adolescence and bulimia early adulthood. Both can occur later, but onset is uncommon after age 40.

These disorders are most common in postindustrialized and urbanized countries. Affected pts frequently exhibit perfectionist and obsessional tendencies and often have comorbid anxiety disorders. Pursuit of activities that emphasize thinness (ballet, modeling, distance running) is prevalent, as is a drive for high scholastic achievement. Risk factors are a family history of mood disturbance, childhood obesity, and psychological or physical abuse during childhood.

## CLINICAL FEATURES

### Anorexia Nervosa

- General: feeling cold
- Skin, hair, nails: alopecia, lanugo hair, acrocyanosis, edema
- Cardiovascular: bradycardia, hypotension
- Gastrointestinal: salivary gland enlargement, slow gastric emptying, constipation, elevated liver enzymes
- Hematopoietic: normochromic, normocytic anemia; leukopenia
- Fluid/electrolyte: increased blood urea nitrogen, increased creatinine, hyponatremia, hypokalemia. Hypokalemia can become life threatening.
- Endocrine: low luteinizing hormone and follicle-stimulating hormone with secondary amenorrhea, hypoglycemia, normal thyroid-stimulating hormone with low normal thyroxine, increased plasma cortisol, osteopenia

### Bulimia Nervosa

- Gastrointestinal: salivary gland enlargement, dental erosion from gastric acid exposure
- Fluid/electrolyte: hypokalemia, hypochloremia, alkalosis (from vomiting), or acidosis (from laxative abuse)
- Other: callus or scar on dorsum of hand (from repeated scraping against teeth during induced vomiting)

## TREATMENT EATING DISORDERS

### ANOREXIA NERVOSA

Maudsley family-based therapy is effective in younger individuals, with strict behavioral contingencies used when weight loss becomes critical. No pharmacologic intervention has proven to be specifically beneficial, but comorbid depression and anxiety should be treated. Weight gain should be undertaken gradually with a goal of 0.5–1 lb per week to prevent complications from rapid refeeding (fluid retention, congestive heart failure, acute gastric dilatation). Most individuals are able to achieve remission within 5 years of the original diagnosis.

### BULIMIA NERVOSA

Effective treatment approaches include selective serotonin reuptake inhibitors (SSRIs) antidepressants, usually in combination with cognitive-behavioral, emotion regulation, or interpersonal-based psychotherapies.

### PROGNOSIS

The prognosis of anorexia nervosa is variable, with some individuals recovering after a single episode, while others exhibit recurrent episodes or a chronic course. Untreated mortality is 5.1/1000 annually, the highest among psychiatric conditions. Bulimia nervosa has a more benign outcome but 10–15% will transition to anorexia.

For a more detailed discussion, see Reus VI: Mental Disorders, Chap. 466, p. 2708, in HPIM-19.

# 199 Alcohol Use Disorder

Alcohol use disorder is defined as repeated alcohol-related difficulties in at least 2 of 11 life areas that cluster together in the same 12-month period (Table 199-1). Severity is based on the number of items endorsed: mild is two or three items, moderate is four or five, and severe is six or more.

**TABLE 199-1 *DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS*, FIFTH EDITION, CLASSIFICATION OF ALCOHOL USE DISORDER (AUD)**

| Criteria |
|---|
| Two or more of the following items occurring in the same 12-month period must be endorsed for the diagnosis of an AUD[a]: |
| Drinking resulting in recurrent failure to fulfill role obligations |
| Recurrent drinking in hazardous situations |
| Continued drinking despite alcohol-related social or interpersonal problems |
| Tolerance |
| Withdrawal, or substance use for relief/avoidance of withdrawal |
| Drinking in larger amounts or for longer than intended |
| Persistent desire/unsuccessful attempts to stop or reduce drinking |
| Great deal of time spent obtaining, using, or recovering from alcohol |
| Important activities given up/reduced because of drinking |
| Continued drinking despite knowledge of physical or psychological problems caused by alcohol |
| Alcohol craving |

[a]*Mild AUD*: 2–3 criteria required; *moderate AUD*: 4–5 items endorsed; *severe AUD:* 6 or more items endorsed.

## CLINICAL FEATURES

Lifetime risk for alcohol use disorder is 10–15% for men and 5–8% for women. Typically, the first major life problem from excessive alcohol use appears in early adulthood, followed by periods of exacerbation and remission. The course is not hopeless; following treatment, between half and two-thirds of pts maintain abstinence for years and often permanently. If the alcoholic continues to drink, life span is shortened by an average of 10 years due to increased risk of death from heart disease, cancer, accidents, or suicide.

Screening for alcoholism is important given its high prevalence. Standardized questionnaires can be helpful in busy clinical practices including the 10-item Alcohol Use Disorders Identification Test (AUDIT) (Table 199-2).

Routine medical care requires attention to potential alcohol-related illness and to alcoholism itself:

1. Neurologic: blackouts, seizures, delirium tremens (DTs), cerebellar degeneration, neuropathy, myopathy
2. GI: esophagitis, gastritis, pancreatitis, hepatitis, cirrhosis, GI hemorrhage
3. Cardiovascular: hypertension, cardiomyopathy
4. Hematologic: macrocytosis, folate deficiency, thrombocytopenia, leukopenia
5. Endocrine: gynecomastia, testicular atrophy, amenorrhea, infertility
6. Skeletal: fractures, osteonecrosis
7. Cancer: breast cancer, oral and esophageal cancers, rectal cancers

### Alcohol Intoxication

Alcohol is a CNS depressant that acts on receptors for γ-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the nervous system. Behavioral, cognitive, and psychomotor changes can occur at blood alcohol levels as low as 0.02–0.03 g/dL, a level achieved after the ingestion of one or two typical drinks. “Legal intoxication” in most states requires a blood alcohol concentration of 0.08 g/dL; levels twice this can

**TABLE 199-2 THE ALCOHOL USE DISORDERS IDENTIFICATION TEST (AUDIT)[a]**

| Item | 5-Point Scale (Least to Most) |
|---|---|
| 1. How often do you have a drink containing alcohol? | Never (0) to 4+ per week (4) |
| 2. How many drinks containing alcohol do you have on a typical day? | 1 or 2 (0) to 10+ (4) |
| 3. How often do you have six or more drinks on one occasion? | Never (0) to daily or almost daily (4) |
| 4. How often during the last year have you found that you were not able to stop drinking once you had started? | Never (0) to daily or almost daily (4) |
| 5. How often during the last year have you failed to do what was normally expected from you because of drinking? | Never (0) to daily or almost daily (4) |
| 6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session? | Never (0) to daily or almost daily (4) |
| 7. How often during the last year have you had a feeling of guilt or remorse after drinking? | Never (0) to daily or almost daily (4) |
| 8. How often during the last year have you been unable to remember what happened the night before because you had been drinking? | Never (0) to daily or almost daily (4) |
| 9. Have you or someone else been injured as a result of your drinking? | No (0) to yes, during the last year (4) |
| 10. Has a relative, friend, doctor, or other health worker been concerned about your drinking or suggested that you should cut down? | No (0) to yes, during the last year (4) |

[a]The AUDIT is scored by simply summing the values associated with the endorsed response. A score ≥8 may indicate harmful alcohol use.

lead to deep but disturbed sleep. Incoordination, tremor, ataxia, confusion, stupor, coma, and even death occur at progressively higher blood alcohol levels.

## Alcohol Withdrawal

Chronic alcohol use produces CNS dependence, and the earliest sign of alcohol withdrawal is tremulousness ("shakes" or "jitters"), occurring 5–10 h after decreasing ethanol intake. This may be followed by generalized seizures in the first 24–48 h; these do not require initiation of antiseizure medications. With severe withdrawal, autonomic hyperactivity ensues (sweating, hypertension, tachycardia, tachypnea, fever), accompanied by insomnia, nightmares, anxiety, and GI symptoms.

## Delirium Tremens (DTs)

A very severe withdrawal syndrome characterized by profound autonomic hyperactivity, extreme confusion, agitation, vivid delusions, and hallucinations (often visual and tactile) that begins 3–5 days after the last drink. Mortality is 5–15%.

## Wernicke's Encephalopathy

An alcohol-related syndrome characterized by ataxia, ophthalmoplegia, and confusion, often with associated nystagmus, peripheral neuropathy, cerebellar signs, and

hypotension; there is impaired short-term memory, inattention, and emotional lability. Wernicke-Korsakoff's syndrome follows, characterized by anterograde and retrograde amnesia and confabulation. Wernicke-Korsakoff's syndrome is caused by chronic thiamine deficiency, resulting in damage to thalamic nuclei, mammillary bodies, and brainstem and cerebellar structures.

### LABORATORY FINDINGS

Include mild anemia with macrocytosis, folate deficiency, thrombocytopenia, granulocytopenia, abnormal liver function tests, hyperuricemia, and elevated triglycerides. Two blood tests with ≥60% sensitivity and specificity are γ-glutamyl transferase (GGT) (>35 U) and carbohydrate-deficient transferrin (CDT) (>20 U/L or >2.6%); the combination of the two is likely to be more accurate than either alone. A variety of diagnostic studies may show evidence of alcohol-related organ dysfunction.

## TREATMENT ALCOHOLISM

### ACUTE WITHDRAWAL

- Acute alcohol withdrawal is treated with multiple B vitamins including thiamine (50–100 mg IV or PO daily for ≥1 week) to replenish depleted stores; use the IV route if Wernicke-Korsakoff's syndrome is suspected since intestinal absorption is unreliable in alcoholics.
- CNS depressant drugs are used when seizures or autonomic hyperactivity is present to halt the rapid state of withdrawal in the CNS and allow for a slower, more controlled reduction of the substance. Low-potency benzodiazepines with long half-lives are preferred (e.g., diazepam 10 mg PO q4–6h, chlordiazepoxide 25–50 mg PO q4–6h) because they produce fairly steady blood levels of drug within a wide dose range. Risks include overmedication and oversedation, which occur less commonly with shorter-acting agents (e.g., oxazepam, lorazepam).
- In severe withdrawal or DTs, high doses of benzodiazepines are usually required. Fluid and electrolyte status and blood glucose levels should be closely followed. Cardiovascular and hemodynamic monitoring is crucial, as hemodynamic collapse and cardiac arrhythmia are not uncommon.
- Generalized withdrawal seizures rarely require aggressive pharmacologic intervention beyond that given to the usual pt undergoing withdrawal, i.e., adequate doses of benzodiazepines.

### RECOVERY AND SOBRIETY

#### Counseling, Education, and Cognitive Approaches

- First, attempts should be made to help the alcoholic achieve and maintain a high level of motivation toward abstinence. These include education about alcoholism and instructing family and/or friends to stop protecting the person from the problems caused by alcohol.
- A second goal is to help the pt to readjust to life without alcohol and to reestablish a functional lifestyle through counseling, vocational rehabilitation, and self-help groups such as alcoholics anonymous (AA).
- A third component, called *relapse prevention*, helps the pt to identify situations in which a return to drinking is likely, formulate ways of managing these risks, and develop coping strategies that increase the chances of a return to abstinence if a slip occurs.
- There is no convincing evidence that inpatient rehabilitation is more effective than outpatient care.

### Drug Therapy

Several medications may be useful in alcoholic rehabilitation; usually medications are continued for 6 months if a positive response is seen.

- The opioid-antagonist drug naltrexone (50–150 mg/d PO or monthly 380-mg injection) decreases the probability of a return to drinking and shortens periods of relapse.
- A second medication, acamprosate (2 g/d divided into three oral doses), an *N*-methyl-D-aspartate receptor inhibitor, may be used; efficacy appears similar to naltrexone.
- A combination of naltrexone and acamprosate may be superior to either drug alone, although not all studies agree.
- Disulfiram (250 mg/d), an aldehyde dehydrogenase inhibitor, produces an unpleasant and potentially dangerous reaction in the presence of alcohol.

For a more detailed discussion, see Schuckit MA: Alcohol and Alcoholism, Chap. 467, p. 2723, in HPIM-19.

# 200 Narcotic Abuse

Narcotics, or opiates, bind to specific opioid receptors in the CNS and elsewhere in the body. These receptors mediate the opiate effects of analgesia, euphoria, respiratory depression, and constipation. Endogenous opiate peptides (enkephalins and endorphins) are natural ligands for the opioid receptors and play a role in analgesia, memory, learning, reward, mood regulation, and stress tolerance.

The prototypic opiates, morphine and codeine, are derived from the juice of the opium poppy. The semisynthetic drugs produced from morphine include hydromorphone (Dilaudid), diacetylmorphine (heroin), and oxycodone (OxyContin). The purely synthetic opioids and their cousins include meperidine, propoxyphene, diphenoxylate, fentanyl, buprenorphine, tramadol, methadone, and pentazocine. All produce analgesia and euphoria as well as physical dependence when taken in high enough doses for prolonged periods of time.

## CLINICAL FEATURES

The 0.1% annual prevalence of heroin dependence in the United States is only about one-third the rate of prescription opiate abuse and is substantially lower than the 2% rate of morphine dependence in parts of Asia. Since 2007, prescription opiates have surpassed marijuana as the most common illicit drug that adolescents initially abuse.

## Acute Effects

All opiates have the following CNS effects: sedation, euphoria, decreased pain perception, decreased respiratory drive, and vomiting. In larger doses, markedly decreased respirations, bradycardia, pupillary miosis, stupor, and coma ensue. Additionally, the adulterants used to "cut" street drugs (quinine, phenacetin, strychnine, antipyrine, caffeine, powdered milk) can produce permanent neurologic damage, including peripheral neuropathy, amblyopia, myelopathy, and leukoencephalopathy; adulterants can also produce an "allergic-like" reaction characterized by decreased alertness, frothy pulmonary edema, and an elevation in blood eosinophil count.

## Chronic Effects

Tolerance and withdrawal commonly occur with chronic daily use after 6–8 weeks depending on the dose and frequency; the ever-increasing amounts of drug needed to sustain euphoriant effects and avoid discomfort of withdrawal strongly reinforce dependence once started.

## Withdrawal

Withdrawal produces nausea and diarrhea, coughing, lacrimation, mydriasis, rhinorrhea, diaphoresis, twitching muscles, piloerection, fever, tachypnea, hypertension, diffuse body pain, insomnia, and yawning.

With shorter-acting opiates such as heroin, morphine, or oxycodone, withdrawal signs begin 8–16 h after the last dose, peak at 36–72 h, and subside over 5–8 days. With longer-acting opiates such as methadone, withdrawal begins several days after the last dose, peaks at 7–10 days, and lasts several weeks.

# TREATMENT NARCOTIC ABUSE

## OVERDOSE

- High doses of opiates, whether taken in a suicide attempt or accidentally when potency is misjudged, are potentially lethal. Toxicity occurs immediately after IV administration and with a variable delay after oral ingestion. Symptoms include miosis, shallow respirations, bradycardia, hypothermia, and stupor or coma.
- Managing overdose requires support of vital functions, including intubation if needed.
- The opiate antagonist naloxone is given at 0.4–2 mg IV or IM with an expected response within 1–2 min; repeated doses, often in the form of an IV drip, may be needed for 24–72 h depending on the opiate used in overdose

## WITHDRAWAL

- Long-acting opiates such as methadone or buprenorphine can be used to treat withdrawal and achieve detoxification by slowly tapering the dose over weeks to months. Buprenorphine produces fewer withdrawal symptoms compared with methadone but does not appear to result in better outcomes.
- Several $\alpha_2$-adrenergic agonists have relieved opioid withdrawal and achieved detoxification by suppressing central noradrenergic activity. Clonidine and lofexidine are commonly used orally in three to four doses per day.
- Rapid opiate detoxification can be accomplished with naltrexone combined with an $\alpha_2$-adrenergic agonist. Completion rates are high. Ultrarapid opiate detoxification using anesthetics is an extension of this approach but is highly controversial due to medical risks including mortality.

### OPIOID MAINTENANCE

- Methadone maintenance is widely used in management of opiate addiction. Methadone is a long-acting opioid optimally dosed at 80–150 mg/d (gradually increased over time).
- The partial agonist buprenorphine can also be used; it has several advantages, including low risk of overdose, potentially easier detoxification than with methadone, and a probable ceiling effect in which higher doses do not increase euphoria. In the United States, primary care physicians can prescribe buprenorphine; this may improve access and quality of treatment.

### OPIATE ANTAGONISTS FOR OPIOID DEPENDENCE

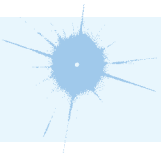
- Rationale is that blocking the action of self-administered opioids should eventually extinguish the habit; poorly accepted by many pts.
- Naltrexone can be given three times a week (100- to 150-mg dose); a depot form for monthly injection is available and improves adherence, retention, and decreases opioid use.

### DRUG-FREE PROGRAMS

- Medication-free treatments in inpatient, residential, or outpatient settings have poor 1- to 5-year outcomes compared with pharmacotherapy; exceptions are residential programs lasting 6–18 months, which require full immersion in a regimented system.

## PREVENTION

Preventing opiate abuse is a critically important challenge for physicians. In the United States, sources of opiates for adolescents are most commonly family members, not drug dealers or the Internet. Except for the terminally ill, physicians should carefully monitor opioid drug use in pts, keeping doses as low as is practical and administering them over as short a period as the level of pain requires. Pts must dispose of any remaining opiates after treatment. Physicians must be vigilant regarding their own risk for opioid abuse and dependence, never prescribing these drugs for themselves.



For a more detailed discussion, see Kosten TR, Haile CN: Opioid-Related Disorders, Chap. 468e, in HPIM-19.

# 201 Routine Disease Screening

A primary goal of health care is to prevent disease or to detect it early enough that interventions will be more effective. In general, screening is most effective when applied to relatively common disorders that carry a large disease burden and have a long latency period. Early detection of disease has the potential to reduce both morbidity and mortality; however, screening asymptomatic individuals carries some risk. False-positive results can lead to unnecessary laboratory tests and invasive procedures and can increase pt anxiety. Several measurements have been derived to better assess the potential gain from screening and prevention interventions:

- Number of subjects needed to be screened to alter the outcome in one individual
- Absolute impact of screening on disease (e.g., lives saved per thousand screened)
- Relative impact of screening on disease outcome (e.g., the % reduction in deaths)
- The cost per year of life saved
- The increase in average life expectancy for a population

As part of a routine health care examination, history should include medication use, allergies, vaccination history, dietary history, use of alcohol and tobacco, sexual practices, safety practices (seat belt and helmet use, gun possession), and a thorough family history. Routine measurements should include assessments of height, weight, body-mass index, and blood pressure. Screening should also be considered for domestic violence and depression.

Counseling by health care providers should be performed at health care visits. Tobacco and alcohol use, diet, and exercise represent the vast majority of factors that influence preventable deaths. While behavioral changes are frequently difficult to achieve, it should be emphasized that studies show even brief (<5 min) tobacco counseling by physicians results in a significant rate of long-term smoking cessation. Instruction about self-examination (e.g., skin, breast, testicular) should also be provided during preventative visits.

The top causes of age-specific mortality and corresponding preventative strategies are listed in Table 201-1. Formal recommendations from the U.S. Preventive Services Task Force are listed in Table 201-2.

In addition to the general recommendations applicable to all persons, screening for specific diseases and preventive measures need to be individualized based on family history, travel history, or occupational history. For example, when there is a significant family history of breast, colon, or prostate cancer, it is prudent to initiate screening about 10 years before the age at which the youngest family member developed cancer.

Specific recommendations for disease prevention can also be found in subsequent chapters on "Cardiovascular Disease Prevention" (Chap. 202), "Prevention and Early Detection of Cancer" (Chap. 203), "Smoking Cessation" (Chap. 204), and "Women's Health" (Chap. 205).

**TABLE 201-1 AGE-SPECIFIC CAUSES OF MORTALITY AND CORRESPONDING PREVENTATIVE OPTIONS**

| Age Group | Leading Causes of Age-Specific Mortality | Screening Prevention Interventions to Consider for Each Specific Population |
|---|---|---|
| 15–24 | 1. Accident<br>2. Homicide<br>3. Suicide<br>4. Malignancy<br>5. Heart disease | • Counseling on routine seat belt use, bicycle/motorcycle/all terrain vehicle helmets (1)<br>• Counseling on diet and exercise (5)<br>• Discuss dangers of alcohol use while driving, swimming, boating (1)<br>• Ask about vaccination status (tetanus, diphtheria, pertussis, hepatitis B, MMR, varicella, meningitis, HPV)<br>• Ask about gun use and/or gun possession (2,3)<br>• Assess for substance abuse history including alcohol (2,3)<br>• Screen for domestic violence (2,3)<br>• Screen for depression and/or suicidal/homicidal ideation (2,3)<br>• Pap smear for cervical cancer screening, discuss STD prevention (4)<br>• Recommend skin, breast, and testicular self-exams (4)<br>• Recommend UV light avoidance and regular sun screen use (4)<br>• Measurement of blood pressure, height, weight and body mass index (5)<br>• Discuss health risks of tobacco use, consider emphasis of cosmetic and economic issues to improve quit rates for younger smokers (4,5)<br>• *Chlamydia* screening and contraceptive counseling for sexually active females<br>• HIV, hepatitis B, gonorrhea, and syphilis testing if there is high-risk sexual behavior(s) or any prior history of sexually transmitted disease |

(*Continued*)

**TABLE 201-1 AGE-SPECIFIC CAUSES OF MORTALITY AND CORRESPONDING PREVENTATIVE OPTIONS**

| Age Group | Leading Causes of Age-Specific Mortality | Screening Prevention Interventions to Consider for Each Specific Population |
|---|---|---|
| 25–44 | 1. Accident<br>2. Malignancy<br>3. Heart disease<br>4. Suicide<br>5. Homicide<br>6. HIV | *As above plus consider the following*:<br>• Readdress smoking status, encourage cessation at every visit (2,3)<br>• Obtain detailed family history of malignancies and begin early screening/prevention program if pt is at significant increased risk (2)<br>• Assess all cardiac risk factors (including screening for diabetes and hyperlipidemia) and consider primary prevention with aspirin for pts at >3% 5-year risk of a vascular event (3)<br>• Assess for chronic alcohol abuse, risk factors for viral hepatitis, or other risks for development of chronic liver disease<br>• Begin breast cancer screening with mammography at age 40 (2) |
| 45–64 | 1. Malignancy<br>2. Heart disease<br>3. Accident<br>4. Diabetes mellitus<br>5. Cerebrovascular disease<br>6. Chronic lower respiratory disease<br>7. Chronic liver disease and cirrhosis<br>8. Suicide | • Consider prostate cancer screen with annual PSA and digital rectal examination at age 50 (or possibly earlier in African Americans or pts with family history) (1)<br>• Begin mammography screening by age 50 (1)<br>• Begin colorectal cancer screening at age 50 with either fecal occult blood testing, flexible sigmoidoscopy, or colonoscopy (1)<br>• Reassess vaccination status at age 50 and give special consideration to vaccines against *Streptococcus pneumoniae*, influenza, tetanus, and viral hepatitis<br>• Zoster vaccination at age 60<br>• Consider screening for coronary disease in higher risk pts (2,5) |

(*Continued*)

**TABLE 201-1 AGE-SPECIFIC CAUSES OF MORTALITY AND CORRESPONDING PREVENTATIVE OPTIONS**

| Age Group | Leading Causes of Age-Specific Mortality | Screening Prevention Interventions to Consider for Each Specific Population |
|---|---|---|
| ≥65 | 1. Heart disease<br>2. Malignancy<br>3. Cerebrovascular disease<br>4. Chronic lower respiratory disease<br>5. Alzheimer's disease<br>6. Influenza and pneumonia<br>7. Diabetes mellitus<br>8. Kidney disease<br>9. Accidents<br>10. Septicemia | *As above plus consider the following:*<br>• Readdress smoking status, encourage cessation at every visit (1,2,3)<br>• One-time ultrasound for AAA in men 65–75 who have ever smoked<br>• Consider pulmonary function testing for all long-term smokers to assess for development of chronic obstructive pulmonary disease (4,6)<br>• Vaccinate all smokers against influenza and *S. pneumoniae* at age 50 (6)<br>• Screen all postmenopausal women (and all men with risk factors) for osteoporosis<br>• Reassess vaccination status at age 65, emphasis on influenza and *S. pneumoniae* (4,6)<br>• Screen for dementia and depression (5)<br>• Screen for visual and hearing problems, home safety issues, and elder abuse (9) |

***Note:*** The numbers in parentheses refer to areas of risk in the mortality column affected by the specified intervention.
***Abbreviations:*** AAA, abdominal aortic aneurysm; HPV, human papilloma virus; MMR, measles-mumps-rubella; PSA, prostate-specific antigen; STD, sexually transmitted disease.

**TABLE 201-2 CLINICAL PREVENTIVE SERVICES FOR NORMAL-RISK ADULTS RECOMMENDED BY THE U.S. PREVENTIVE SERVICES TASK FORCE**

| Test or Disorder | Population,[a] Years | Frequency |
|---|---|---|
| Abdominal aortic aneurysm (ultrasound) | Men 65–75 who have ever smoked | Once |
| Adult immunization | | |
| Human papillomavirus (HPV) | Up to age 26 | If not done prior |
| Influenza | >50 | Yearly |
| Measles, mumps, rubella (MMR) | Women, childbearing age | One dose |
| Pneumococcal | >65 | One dose |
| Tetanus-diphtheria (Td) | >18 | Every 10 years |
| Varicella (VZV) | Susceptibles only, >18 | Two doses |
| Zoster | >60 | One dose |

(*Continued*)

**TABLE 201-2 CLINICAL PREVENTIVE SERVICES FOR NORMAL-RISK ADULTS RECOMMENDED BY THE U.S. PREVENTIVE SERVICES TASK FORCE (*CONTINUED*)**

| Test or Disorder | Population,[a] Years | Frequency |
|---|---|---|
| Alcohol use | >18 | Periodically |
| Blood pressure, height and weight | >18 | Periodically |
| Breast cancer (mammography and clinical breast examination)[a] | Women 50–75 | Every 2 years |
| Cervical cancer[c] | Women 21–65 | Every 3 years |
| Pap smear | Women 30–65 | Every 5 years if HPV negative |
| Pap smear and HPV testing | | |
| *Chlamydia*/Gonorrhea | Sexually active women <25 | Unknown |
| Cholesterol | Men >35 | Every 5 years |
| | Women >45 | Every 5 years |
| Colorectal cancer[a] | 50–75 | |
| fecal occult blood and/or | | Every year |
| sigmoidoscopy or | | Every 5 years |
| colonoscopy | | Every 10 years |
| Depression | All adults | Periodically[b] |
| Diabetes | >45 or earlier, if there are additional risk factors | Every 3 years |
| Hepatitis C | Adults born between 1945–1965 | Once |
| HIV | 15–65 | Once |
| Intimate partner violence | Women of childbearing age | Unknown |
| Obesity (BMI) | All adults | Unknown |
| Osteoporosis | Women >65; >60 at risk | Unknown |
| Vision, hearing | >65 | Periodically |

[a]Screening is performed earlier and more frequently when there is a strong family history. Randomized, controlled trials have documented that fecal occult blood testing (FOBT) confers a 15–30% reduction in colon cancer mortality. Although randomized trials have not been performed for sigmoidoscopy or colonoscopy, well-designed case-control studies suggest similar or greater efficacy relative to FOBT.
[b]If staff support is available.
[c]In the future, Pap smear frequency may be influenced by HPV testing and the HPV vaccine.
***Note:*** Prostate-specific antigen (PSA) testing is capable of enhancing the detection of early-stage prostate cancer, but evidence is inconclusive that it improves health outcomes. PSA testing is recommended by several professional organizations and is widely used in clinical practice, but it is not currently recommended by the U.S. Preventive Services Task Force.
***Source:*** Adapted from the U.S. Preventive Services Task Force, *Guide to Clinical Prevention Services*, 2010–2011. *www.ahrq.gov/clinic/pocketgd.htm*.

For a more detailed discussion, see Armstrong K, Martin GJ: Screening and Prevention of Disease, Chap. 4, p. 26, in HPIM-19.

# 202 Cardiovascular Disease Prevention

Cardiovascular disease is now the leading cause of death worldwide; prevention is targeted at modifiable atherosclerosis risk factors (Table 202-1). Identification and control of these attributes reduce subsequent cardiovascular event rates.

## ESTABLISHED RISK FACTORS

### Cigarette Smoking

Cigarette smoking increases the incidence of, and mortality associated with, coronary heart disease (CHD). Observational studies show that smoking cessation reduces excess risk of coronary events within months; after 3–5 years, the risk falls to that of individuals who never smoked. Pts should be asked regularly about tobacco use, followed by counseling and, as needed, antismoking pharmacologic therapy to assist cessation.

### Lipid Disorders

(See Chap. 178) Both elevated LDL and low HDL cholesterol are associated with cardiovascular events. Each 1-mg/dL increase in serum LDL correlates with a 2–3% rise in CHD risk; each 1-mg/dL decrease in HDL heightens risk by 3–4%. Fasting screening lipid profile in adults should include total cholesterol, triglycerides, HDL, and LDL (calculated or directly measured). Recommended dietary and/or pharmacologic approach depends on presence or risk of coronary artery disease (CAD); treatment should be most aggressive in pts with established CAD and in those with "equivalent risk" (e.g., presence of diabetes mellitus). Current guidelines by American Heart Association/American College of Cardiology recommend statin therapy for four specific groups of pts at highest risk (Table 202-2). In pts with isolated low HDL, encourage beneficial lifestyle measures: smoking cessation, weight loss, and increased physical activity (see Chap. 178).

### Hypertension

(See Chap. 117) Systolic or diastolic bp > "optimal" level of 115/75 mmHg is associated with increased risk of cardiovascular disease; each augmentation of 20 mmHg systolic, or 10 mmHg diastolic, above this value doubles the risk. Treatment of elevated blood pressure reduces the rate of stroke, congestive heart failure, and CHD events, with general goal of bp <140/85 mmHg. Cardiovascular event rates in elderly

**TABLE 202-1 ESTABLISHED ATHEROSCLEROTIC RISK FACTORS**

| |
|---|
| **Modifiable Risk Factors** |
| Cigarette smoking |
| Dyslipidemias (↑LDL or ↓HDL) |
| Hypertension |
| Diabetes mellitus |
| Obesity |
| Sedentary lifestyle |
| **Unmodifiable Risk Factors** |
| Premature coronary heart disease in first-degree relatives (age <55 in men, <65 in women) |
| Age (men ≥45 years; women ≥55 years) |
| Male sex |

pts with isolated systolic hypertension (systolic ≥140 but diastolic <90) are also reduced by antihypertensive therapy.

See Chap. 117 for antihypertensive treatment recommendations. Pts with "prehypertension" (systolic bp 120–139 mmHg or diastolic bp 80–89 mmHg) should receive counseling about beneficial lifestyle modifications such as those listed below (e.g., low-fat diet replete with vegetables and fruit, weight loss if overweight, increased physical activity, reduction of excessive alcohol consumption).

## Diabetes Mellitus/Insulin Resistance/Metabolic Syndrome

(See Chaps. 118 and 173) Pts with diabetes most often succumb to cardiovascular disease. LDL levels are typically near average in diabetic pts, but LDL particles are smaller, denser, and more atherogenic; low HDL and elevated triglyceride levels are common. Tight control of serum glucose in type 2 diabetics reduces microvascular diabetic complications (retinopathy, renal disease), but has less impact on macrovascular events (CAD, stroke). However, successful management of associated risk factors in diabetics (e.g., dyslipidemia and hypertension) *does* significantly reduce cardiovascular events and should be vigorously pursued. Statin therapy should be used to lower vascular risk in diabetics (Table 202-2), even if pt has no symptoms of CAD.

Individuals without overt diabetes but who have "metabolic syndrome" (constellation of insulin resistance, central obesity, hypertension, hypertriglyceridemia, low HDL—see Chap. 118) are also at high risk of cardiovascular events. Dietary counseling, weight loss, and increased physical activity are important in reducing the prevalence of this syndrome.

## Male Sex/Postmenopausal State

Coronary risk is greater in men compared to that of premenopausal women of same age, but female risk accelerates after menopause. Estrogen-replacement therapy lowers LDL and raises HDL in postmenopausal women and in observational studies has been associated with reduced coronary events. However, prospective clinical trials do not support such a benefit and hormone-replacement therapy should not be prescribed for the purpose of cardiovascular risk reduction, especially in older women.

**TABLE 202-2 GROUPS RECOMMENDED FOR STATIN THERAPY**

| Group | Recommendation |
|---|---|
| Clinical atherosclerotic disease (ASCVD) | High-intensity statin[a] |
| LDL cholesterol ≥190 mg/dL | High-intensity statin[a] |
| Diabetics (age 40–75, LDL 70–189 mg/dL) with | |
| 10 year cardiac risk[c] ≥7.5% | High-intensity statin[a] |
| 10 year cardiac risk[c] <7.5% without established ASCVD | Moderate-intensity statin[b] |
| Nondiabetics (age 40–75, LDL 70–189 mg/dL) with | |
| 10 year cardiac risk[c] ≥7.5% | Moderate-to-high intensity statin[a,b] |

[a]Atorvastatin 40–80 mg daily or rosuvastatin 20–40 mg daily; for age ≥75, or if at risk of statin adverse effect, consider moderate intensity statin.

[b]Atorvastatin 10–20 mg daily, rosuvastatin 5–10 mg daily, or simvastatin 20–40 mg daily.

[c]10 year ASCVD risk can be estimated using the online calculator: http://my.americanheart.org/cvriskcalculator.

## EMERGING RISK FACTORS

May be assessed selectively in pts without above traditional risk factors who have premature vascular disease or strong family history of premature vascular disease.

### Homocysteine

There is a graded correlation between serum homocysteine levels and risk of cardiovascular events and stroke. Supplemental folic acid and other B vitamins lower serum levels, but prospective clinical trials have not shown that such therapy reduces cardiac events.

### Inflammation

Inflammatory serum markers, such as high-sensitivity C-reactive protein (CRP), correlate with the risk of coronary events. CRP prospectively predicts risk of MI and outcomes after acute coronary syndromes; its usefulness and role in prevention as an independent risk factor is currently being defined.

Potential benefits of assessing other emerging risk factors [e.g., lipoprotein(a), fibrinogen] remain unproven and controversial.

## PREVENTION

### Antithrombotic Therapy in Primary Prevention

Thrombosis at the site of disrupted atherosclerotic plaque is the most common cause of acute coronary events. In primary prevention trials, chronic low-dose aspirin therapy has reduced the risk of a first MI in men and the risk of stroke in women. The American Heart Association recommends aspirin (75–160 mg daily) for men and women who are at high cardiovascular risk (i.e., by Framingham Study criteria, for men with ≥10% 10-year risk, or women with ≥20% 10-year risk).

### Lifestyle Modifications

Encourage beneficial exercise habits (>30 min moderate intensity physical activity daily) and sensible diet (low in saturated and trans fat; 2–3 servings of fish/week to ensure adequate intake of omega-3 fatty acids; balance caloric consumption with energy expenditure). Advise moderation in ethanol intake (no more than 1–2 drinks/day).

For a more detailed discussion, see Libby P: The Pathogenesis, Prevention, and Treatment of Atherosclerosis, Chap. 291e; Gaziano TA, Gaziano JM: Epidemiology of Cardiovascular Disease, Chap. 266e; and Armstrong K, Martin GJ: Screening and Prevention of Disease, Chap. 4, p. 26; in HPIM-19.

# 203 Prevention and Early Detection of Cancer

One of the most important functions of medical care is to prevent disease or discover it early enough that treatment might be more effective. All risk factors for cancer have not yet been defined. However, a substantial number of factors that elevate risk are within a person's control. Some of these factors are listed in Table 203-1. Every physician visit is an opportunity to teach and reinforce the elements of a

**TABLE 203-1 LIFESTYLE FACTORS THAT REDUCE CANCER RISK**

| |
|---|
| Do not use any tobacco products |
| Maintain a healthy weight; eat a well-balanced diet[a]; maintain caloric balance |
| Exercise at least 3 times a week |
| Prevent sun exposure |
| Avoid excessive alcohol intake |
| Practice safe sex; use condoms |

[a]Not precisely defined, but current recommendations include five servings of fruits and vegetables per day, 25 g fiber, and <30% of calories coming from fat.

healthy lifestyle. Cancer screening in the asymptomatic population at average risk is a complex issue. To be of value, screening must detect disease at a stage that is more readily curable than disease that is treated after symptoms appear. For cervix cancer and colon cancer, screening has been shown to save lives. For other tumors, benefit is less clear. Screening can cause harm; complications may ensue from the screening test or the tests done to validate a positive screening test or from treatments for the underlying disease. Furthermore, quality of life can be adversely affected by false-positive tests. Evaluation of screening tools can be biased and needs to rely on prospective randomized studies. *Lead-time bias* occurs when the natural history of disease is unaffected by the diagnosis, but the pt is diagnosed earlier in the course of disease than normal; thus, the pt spends more of his/her life span knowing the diagnosis. *Length bias* occurs when slow-growing cancers that might never have come to medical attention are detected during screening. *Overdiagnosis* is a form of length bias in which a cancer is detected when it is not growing and is not an influence on length of survival. *Selection bias* is the term for the fact that people who volunteer for screening trials may be different from the general population. Volunteers might have family history concerns that actually elevate their risk, or they may be generally more health-conscious, which can affect outcome.

The various groups that evaluate and recommend screening practice guidelines have used varying criteria to make their recommendations (Table 203-2). The absence of data on survival for a number of diseases has led to a lack of consensus. In particular, four areas are worth noting.

1. *Prostate cancer:* Prostate-specific antigen (PSA) levels are elevated in prostate cancer, but a substantial number of the cancers detected appear to be non-life-threatening. PSA screening has not been shown to improve survival. Efforts are underway to develop better tests (predominantly using bound vs. free and rate of increase of PSA) to distinguish lethal and nonlethal cancers. Genetic profiling has not yet provided useful distinctions.
2. *Breast cancer:* The data on annual mammography support its use in women age >50 years. However, the benefit for women age 40–49 years is quite small. One study shows some advantage for women who are screened starting at age 40 that appears 15 years later; however, it is unclear if this benefit would not have also been derived by starting screening at age 50 years. Women age 40–49 years have a much lower incidence of breast cancer and a higher false-positive rate on mammography. Nearly half of women screened during their forties will have a false-positive test. Refined methods of screening are in development.
3. *Colon cancer:* Annual fecal occult blood testing after age 50 years is felt to be useful. Colonoscopy is the gold standard in colorectal cancer detection, but it is expensive and has not been shown to be cost-effective in asymptomatic people.
4. *Lung cancer:* Chest radiographs and sputum cytology in smokers appear to identify more early-stage tumors, but paradoxically, the screened pts do not have improved survival. Low-dose spiral CT scanning performed annually for 3 years

**TABLE 203-2 SCREENING RECOMMENDATIONS FOR ASYMPTOMATIC SUBJECTS NOT KNOWN TO BE AT INCREASED RISK FOR THE TARGET CONDITION[a]**

| Cancer Type | Test or Procedure | USPSTF | ACS |
|---|---|---|---|
| Breast | Self-examination | "D" | Women ≥20 years: Breast self-exam is an option |
| | Clinical examination | Women ≥40 years: "I" (as a stand-alone without mammography) | Women 20–39 years: Perform every 3 years<br>Women ≥40 years: Perform annually |
| | Mammography | Women 40–49 years: The decision should be an individual one, and take pt context/values into account ("C")<br>Women 50–74 years: Every 2 years ("B")<br>Women ≥75 years: "I" | Women ≥40 years: Screen annually for as long as the woman is in good health |
| | Magnetic resonance imaging (MRI) | "I" | Women with >20% lifetime risk of breast cancer: Screen with MRI plus mammography annually<br>Women with 15–20% lifetime risk of breast cancer: Discuss option of MRI plus mammography annually<br>Women with <15% lifetime risk of breast cancer: Do not screen annually with MRI |
| Cervical | Pap test (cytology) | Women 21–65 years: Screen every 3 years ("A")<br>Women <21 years: "D"<br>Women >65 years, with adequate, normal prior Pap screenings: "D" | Women 21–29 years: Screen every 3 years<br>Women 30–65 years: Acceptable approach to screen with cytology every 3 years (see HPV test below)<br>Women <21 years: No screening<br>Women >65 years: No screening following adequate negative prior screening |
| | | Women after total hysterectomy for noncancerous causes: "D" | Women after total hysterectomy for noncancerous causes: Do not screen |

(*Continued*)

**TABLE 203-2 SCREENING RECOMMENDATIONS FOR ASYMPTOMATIC SUBJECTS NOT KNOWN TO BE AT INCREASED RISK FOR THE TARGET CONDITION[a] (*CONTINUED*)**

| Cancer Type | Test or Procedure | USPSTF | ACS |
|---|---|---|---|
| | HPV test | Women 30–65 years: Screen in combination with cytology every 5 years if woman desires to lengthen the screening interval (see Pap test, above) ("A")<br>Women <30 years: "D"<br>Women >65 years, with adequate, normal prior Pap screenings: "D"<br>Women after total hysterectomy for noncancerous causes: "D" | Women 30–65 years: Preferred approach to screen with HPV and cytology co-testing every 5 years (see Pap test above)<br>Women <30 years: Do not use HPV testing<br>Women >65 years: No screening following adequate negative prior screening<br>Women after total hysterectomy for noncancerous causes: Do not screen |
| Colorectal | Sigmoidoscopy | Adults 50–75 years: every 5 years in combination with high-sensitivity FOBT every 3 years ("A")[b]<br>Adults 76–85 years: "C"<br>Adults ≥85 years: "D" | Adults ≥50 years: Screen every 5 years |
| | Fecal occult blood testing (FOBT) | Adults 50–75 years: Annually, for high-sensitivity FOBT ("A")<br>Adults 76–85 years: "C"<br>Adults ≥85 years: "D" | Adults ≥50 years: Screen every year |
| | Colonoscopy | Adults 50–75 years: every 10 years ("A")<br>Adults 76–85 years: "C"<br>Adults ≥85 years: "D" | Adults ≥50 years: Screen every 10 years |
| | Fecal DNA testing | "I" | Adults ≥50 years: Screen, but interval uncertain |
| | Fecal immunochemical testing (FIT) | "I" | Adults ≥50 years: Screen every year |
| | CT colonography | "I" | Adults ≥50 years: Screen every 5 years |

(*Continued*)

**TABLE 203-2 SCREENING RECOMMENDATIONS FOR ASYMPTOMATIC SUBJECTS NOT KNOWN TO BE AT INCREASED RISK FOR THE TARGET CONDITION[a] (*CONTINUED*)**

| Cancer Type | Test or Procedure | USPSTF | ACS |
|---|---|---|---|
| Lung | Low-dose computed tomography (CT) scan | Adults 55–80 years, with a ≥30 pack-year smoking history, still smoking or have quit within past 15 years. Discontinue once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability to have curative lung surgery: "B" | Men and women, 55–74 years, with ≥30 pack-year smoking history, still smoking or have quit within past 15 years: Discuss benefits, limitations, and potential harms of screening; only perform screening in facilities with the right type of CT scanner and with high expertise/specialists |
| Ovarian | CA-125<br>Transvaginal ultrasound | "D"<br>"D" | There is no sufficiently accurate test proven effective in the early detection of ovarian cancer. For women at high risk of ovarian cancer and/or who have unexplained, persistent symptoms, the combination of CA-125 and transvaginal ultrasound with pelvic exam may be offered. |
| Prostate | Prostate-specific antigen (PSA) | Men, all ages: "D" | Starting at age 50, men should talk to a doctor about the pros and cons of testing so they can decide if testing is the right choice for them. If African American or have a father or brother who had prostate cancer before age 65, men should have this talk starting at age 45. How often they are tested will depend on their PSA level. |

(*Continued*)

**TABLE 203-2 SCREENING RECOMMENDATIONS FOR ASYMPTOMATIC SUBJECTS NOT KNOWN TO BE AT INCREASED RISK FOR THE TARGET CONDITION[a] (*CONTINUED*)**

| Cancer Type | Test or Procedure | USPSTF | ACS |
|---|---|---|---|
| | Digital rectal examination (DRE) | No individual recommendation | As for PSA; if men decide to be tested, they should have the PSA blood test with or without a rectal exam |
| Skin | Complete skin examination by clinician or pt | "I" | Self-examination monthly; clinical exam as part of routine cancer-related checkup |

[a]Summary of the screening procedures recommended for the general population by the USPSTF and the ACS. These recommendations refer to asymptomatic persons who are not known to have risk factors, other than age or gender, for the targeted condition.
[b]USPSTF lettered recommendations are defined as follows: "A": The USPSTF recommends the service, because there is high certainty that the net benefit is substantial; "B": The USPSTF recommends the service, because there is high certainty that the net benefit is moderate or moderate certainty that the net benefit is moderate to substantial; "C": The USPSTF recommends selectively offering or providing this service to individual pts based on professional judgment and pt preferences; there is at least moderate certainty that the net benefit is small; "D": The USPSTF recommends against the service because there is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits; "I": The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service.
***Abbreviations:*** ACS, American Cancer Society; USPSTF, U.S. Preventive Services Task Force.

reduces lung cancer death in older smokers by 20% compared with annual chest x-ray. However, 96% of the positive tests are false-positives and overall survival is improved by only 6.7%.

## CANCER PREVENTION IN HIGH-RISK GROUPS

### BREAST CANCER

Risk factors include age, early menarche, nulliparity or late first pregnancy, high body-mass index, radiation exposure before age 30 years, hormone-replacement therapy (HRT), alcohol consumption, family history, presence of mutations in *BRCA1* or *BRCA2*, and prior history of breast neoplasia. Models are able to predict a woman's risk level (see *www.cancer.gov/cancertopics/pdq/treatment/breast/healthprofessional#Section_627*).

#### Diagnosis

MRI scanning is a more effective screening tool than mammography in women with a familial breast cancer risk.

## Interventions

Women whose risk exceeds 1.66% in the next 5 years have been shown to have a 50% reduction in breast cancer from taking tamoxifen or raloxifene. Aromatase inhibitors have generally been superior to tamoxifen in the adjuvant treatment of hormone-sensitive breast cancer, and one of them (exemestane) reduces the risk of breast cancer by 65% in postmenopausal women at increased risk. Women with strong family histories should undergo testing for mutations in *BRCA1* and *BRCA2*. Mutations in these genes carry a lifetime probability of >80% for developing breast cancer. Bilateral prophylactic mastectomy prevents at least 90% of these cancers but is a more radical prevention than the usual treatment for the disease. In addition, bilateral salpingo-oophorectomy reduces ovarian and fallopian tube cancer risk by about 96% in women with *BRCA1* or *BRCA2* mutations.

### COLORECTAL CANCER

Risk factors include diets high in saturated fats and low in fruits and vegetables, smoking, and alcohol consumption. Stronger but less prevalent risk factors are the presence of inflammatory bowel disease or genetic disorders such as familial polyposis (autosomal dominant germline mutation in *APC*) and hereditary nonpolyposis colorectal cancer (mutations in DNA mismatch repair genes *hMSH2* and *hMLH1*).

## Interventions

Pts with ulcerative colitis and familial polyposis generally undergo total colectomy. In familial polyposis, nonsteroidal anti-inflammatory drugs (NSAIDs) reduce the number and size of polyps. Celecoxib, sulindac, and even aspirin appear to be effective, and celecoxib is approved by the U.S. Food and Drug Administration for this indication. Calcium supplementation can lead to a decrease in the recurrence of adenomas, but it is not yet clear that the risk of colorectal cancer is decreased and survival increased. The Women's Health Study noted a significant reduction in the risk of colorectal cancer in women taking HRT, but the increase in thrombotic events and breast cancers counterbalanced this benefit. Studies are underway to assess NSAIDs with and without inhibitors of the epidermal growth factor (EGF) receptor in other risk groups.

### LUNG CANCER

Risk factors include smoking, exposure to radiation, asbestos, radon.

## Interventions

Smoking cessation is the only effective prevention (Chap. 204). NSAIDs and EGF receptor inhibitors are being evaluated. Carotenoids, selenium, retinoids, and α-tocopherol do not work.

### PROSTATE CANCER

Risk factors include age, family history, and possibly dietary fat intake. African Americans are at increased risk. The disease is highly prevalent, with autopsy studies finding prostate cancer in 70–80% of men over age 70.

## Interventions

In a group of men age ≥55 years with normal rectal examinations and PSA levels <3 ng/mL, daily finasteride reduced the incidence of prostate cancer by 25%. Finasteride also prevents the progression of benign prostate hyperplasia. However, some men experience decreased libido as a side effect. The Gleason grade of tumors seen in men taking finasteride prevention was somewhat higher than the controls; however, androgen deprivation alters the morphology of the cells and it is not yet clear that the Gleason grade is a reliable indicator of tumor aggressiveness in the setting of androgen deprivation. Dutasteride, another 5α-reductase inhibitor, had similar effects. The

FDA has reviewed the data and concluded that the reduction in risk is primarily in the group of pts with low-grade tumors whose risk from prostate cancer is unclear. One additional high-grade tumor emerges for every 3–4 low-grade tumors averted. More follow-up is necessary to see if higher-grade tumors emerging on preventive therapy have the same aggressive behavior as those occurring in the absence of preventive hormone blockade.

### CERVICAL CANCER

Risk factors include early age at first intercourse, multiple sexual partners, smoking, and infection with human papillomavirus (HPV) types 16, 18, 45, and 56.

#### Interventions

Regular Pap testing can detect nearly all cases of the premalignant lesion called *cervical intraepithelial neoplasia*. Untreated, the lesion can progress to carcinoma in situ and invasive cervical cancer. Surgical removal, cryotherapy, or laser therapy is used to treat the disease and is effective in 80%. Risk of recurrence is highest in women over age 30, those with prior HPV infection, and those who have had prior treatment for the same condition. A vaccine (Gardasil) containing antigens of strains 6, 11, 16, and 18 has been shown to be 100% effective in preventing HPV infections from those strains. The vaccine is recommended for all females and males age 9–26 years and could prevent up to 70% of all cervical cancer. The vaccine is not effective after infection has been established.

### HEAD AND NECK CANCER

Risk factors include smoking, alcohol consumption, and possibly HPV infection.

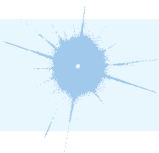
#### Interventions

Oral leukoplakia, white lesions of the oral mucosa, occur in 1–2 persons in 1000, and 2–3% of these pts go on to develop head and neck cancer. Spontaneous regression of oral leukoplakia is seen in 30–40% of pts. Retinoid treatment (13-*cis* retinoid acid) can increase the regression rate. Vitamin A induces complete remission in ~50% of pts. The use of retinoids in pts who have been diagnosed with head and neck cancer and received definitive local therapy has not produced consistent results. Initial studies claimed that retinoids prevented the development of second primary tumors, a common feature of head and neck cancer. However, large randomized studies did not confirm this benefit. Other studies are underway combining retinoids and NSAIDs with and without EGF receptor inhibitors.

## PATIENT EDUCATION IN EARLY DETECTION

Pts can be taught to look for early warning signals. The American Cancer Society has identified seven major warning signs of cancer:

- A change in bowel or bladder habits
- A sore that does not heal
- Unusual bleeding or discharge
- A lump in the breast or other parts of the body
- Chronic indigestion or difficulty in swallowing
- Obvious changes in a wart or mole
- Persistent coughing or hoarseness



For a more detailed discussion, see Crosswell JM, Brawley OW, Kramer BS: Prevention and Early Detection of Cancer, Chap. 100, p. 475, in HPIM-19.

# 204 Smoking Cessation

Over 400,000 individuals die prematurely each year in the United States from cigarette use: one out of every five deaths nationwide. Approximately 40% of smokers will die prematurely unless they are able to quit; major diseases caused by cigarette smoking are listed in Table 204-1.

## APPROACH TO THE PATIENT: Nicotine Addiction

All pts should be asked whether they smoke, how much they smoke, how long they have smoked, their past experience with quitting, and whether they are currently interested in quitting; even those who are not interested should be encouraged and motivated to quit. Provide a clear, strong, and personalized message that smoking is an important health concern. A quit date should be negotiated within a few weeks of the visit, and a follow-up contact by office staff around the time of the quit date should be provided. Incorporation of cessation assistance into a practice requires a change of the care delivery infrastructure. Simple changes include:

- Adding questions about smoking and interest in cessation on pt-intake questionnaires
- Asking pts whether they smoke as part of the initial vital sign measurements made by office staff
- Listing smoking as a problem in the medical record
- Automating follow-up contact with the pt on the quit date

**TABLE 204-1 RELATIVE RISKS FOR CURRENT SMOKERS OF CIGARETTES**

| | Current Smokers | |
|---|---|---|
| **Disease or Condition** | **Males** | **Females** |
| Coronary heart disease | | |
| Age 35–64 | 2.8 | 3.1 |
| Age ≥65 | 1.5 | 1.6 |
| Cerebrovascular disease | | |
| Age 35–64 | 3.3 | 4 |
| Age ≥65 | 1.6 | 1.5 |
| Aortic aneurysm | 6.2 | 7.1 |
| Chronic airway obstruction | 10.6 | 13.1 |
| Cancer | | |
| Lung | 23.3 | 12.7 |
| Larynx | 14.6 | 13 |
| Lip, oral cavity, pharynx | 10.9 | 5.1 |
| Esophagus | 6.8 | 7.8 |
| Bladder, other urinary organs | 3.3 | 2.2 |
| Kidney | 2.7 | 1.3 |
| Pancreas | 2.3 | 2.3 |
| Stomach | 2 | 1.4 |
| Liver | 1.7 | 1.7 |
| Colorectal | 1.2 | 1.2 |
| Cervix | | 1.6 |
| Acute myeloid leukemia | 1.4 | 1.4 |
| Sudden infant death syndrome | | 2.3 |
| Infant respiratory distress syndrome | | 1.3 |
| Low birth weight at delivery | | 1.8 |

## TREATMENT NICOTINE ADDICTION

- Clinical practice guidelines suggest a variety of pharmacologic and nonpharmacologic interventions to aid in smoking cessation (Table 204-2).
- Numerous nicotine-replacement products exist, including over-the-counter nicotine patches, gum, and lozenges, as well as nicotine nasal and oral inhalers available by prescription; these products can be used for 3–6 months with a gradual step-down in dosage with increasing duration of abstinence.
- Prescription medications that have been shown to be effective include antidepressants such as bupropion (300 mg/d in divided doses for up to 6 months) and varenicline, a partial agonist for the nicotinic acetylcholine receptor (initial dose 0.5 mg daily increasing to 1 mg twice daily at day 8; treatment duration up to 6 months). Antidepressants are more effective in pts with a history of depressive symptoms.
- Clonidine or nortriptyline may be useful for pts who have failed first-line therapies.
- Current recommendations are to offer pharmacologic treatment, usually with nicotine replacement therapy or varenicline, to all who will accept it and to provide counseling and other support as a part of the cessation attempt.

## PREVENTION

Approximately 85% of individuals who will become cigarette smokers initiate the behavior during adolescence; prevention must begin early, preferably in the elementary school years. Physicians who treat adolescents should be sensitive to the

**TABLE 204-2 CLINICAL PRACTICE GUIDELINES**

| |
|---|
| **Physician Actions** |
| Ask: Systematically identify all tobacco users at every visit |
| Advise: Strongly urge all smokers to quit |
| Identify smokers willing to quit |
| Assist the patient in quitting |
| Arrange follow-up contact |
| **Effective Pharmacologic Interventions**[a] |
| First-line therapies |
| Nicotine gum (1.5) |
| Nicotine patch (1.9) |
| Nicotine nasal inhaler (2.7) |
| Nicotine oral inhaler (2.5) |
| Nicotine lozenge (2.0) |
| Bupropion (2.1) |
| Varenicline (2.7) |
| Second-line therapies |
| Clonidine (2.1) |
| Nortriptyline (3.2) |
| **Other Effective Interventions**[a] |
| Physician or other medical personnel counseling (10 min) (1.3) |
| Intensive smoking cessation programs (at least 4–7 sessions of 20- to 30-min duration lasting at least 2 and preferably 8 weeks) (2.3) |
| Clinic-based smoking status identification system (3.1) |
| Counseling by nonclinicians and social support by family and friends |
| Telephone counseling (1.2) |

[a]Numerical value following the intervention is the multiple for cessation success compared to no intervention.

prevalence of this problem and screen for tobacco use, reinforcing the fact that most adolescents and adults do not smoke, and explaining that all forms of tobacco are both addictive and harmful.

For a more detailed discussion, see Burns DM: Nicotine Addiction, Chap. 470, p. 2729, in HPIM-19.

# 205 Women's Health

The most common causes of death in both men and women are heart disease and cancer, with lung cancer the top cause of cancer death, despite common misperceptions that breast cancer is the most common cause of death in women. These misconceptions perpetuate inadequate attention to modifiable risk factors in women, such as dyslipidemia, hypertension, and cigarette smoking. Furthermore, since women in the Unites States live on average 5.1 years longer than men, the majority of the disease burden for many age-related disorders (e.g., hypertension, Alzheimer's disease) rests in women.

## SEX DIFFERENCES IN HEALTH AND DISEASE

### ALZHEIMER'S DISEASE (SEE ALSO CHAP. 182)

Alzheimer's disease (AD) affects approximately twice as many women as men, due to larger numbers of women surviving to older ages and to sex differences in brain size, structure, and functional organization. The impact of postmenopausal hormone therapy on cognitive function and the development of AD is inconclusive, though some studies suggest increased risk.

### CORONARY HEART DISEASE (SEE ALSO CHAPS. 119-121)

Coronary heart disease (CHD) presents differently in women, who are usually 10–15 years older than men with CHD and are more likely to have comorbidities, such as hypertension, congestive heart failure, and diabetes. Women more often have atypical symptoms, such as nausea, vomiting, indigestion, and upper back pain, and are less likely to recognize these and call 9-1-1. Physicians are less likely to suspect heart disease in women with chest pain and are less likely to perform diagnostic and therapeutic cardiac procedures in women. The conventional risk factors for CHD are the same in both men and women, though women receive fewer interventions for modifiable risk factors than do men. The prevalence of CHD is increasing in middle-aged women, at a time when the prevalence in men is unchanged or declining. The marked increase in CHD occurring after menopause or oophorectomy suggests that endogenous estrogens are cardioprotective. However, hormone replacement therapy in postmenopausal women was not shown to be cardioprotective in controlled trials such as the Women's Health Initiative and other randomized trials. Therapy with estrogen plus progestin therapy was associated with *increased* cardiovascular events. The discrepancy between endogenous and exogenous estrogen effects is poorly

understood but may be related to deleterious effects of late re-exposure to estrogen after a period of estrogen deficiency.

## DIABETES MELLITUS (SEE ALSO CHAP. 173)

The prevalence of type 2 diabetes mellitus (DM) is similar between men and women. Polycystic ovary syndrome and gestational diabetes mellitus are both common conditions in premenopausal women that carry an increased risk for type 2 DM. Premenopausal women with DM have identical rates of CHD to those of males.

## HYPERTENSION (SEE ALSO CHAP. 117)

Hypertension, as an age-related disorder, is more common in women than in men after age 60. Antihypertensive drugs appear to be equally effective in women and men; however, women may experience more side effects.

## AUTOIMMUNE DISORDERS (SEE ALSO CHAP. 158)

Most autoimmune disorders occur more commonly in women than in men; these include autoimmune thyroid and liver diseases, lupus, rheumatoid arthritis, scleroderma, multiple sclerosis, and idiopathic thrombocytopenic purpura. The mechanism for these sex differences remains obscure.

## HIV INFECTION (SEE ALSO CHAP. 105)

Heterosexual contact with an at-risk partner is the fastest-growing transmission category of HIV, and women are more susceptible to HIV infection than men. Women account for about 50% of the 34 million persons infected with HIV-1 worldwide. Women with HIV have more rapid decreases in their CD4 cell counts than men do. Other sexually transmitted diseases, such as chlamydial infection and gonorrhea, are important causes of infertility in women, and papilloma virus infection predisposes to cervical cancer.

## OBESITY (SEE ALSO CHAP. 172)

The prevalence of obesity is higher in women than in men, in part due to the unique risk factors of pregnancy and menopause. More than 80% of patients who undergo bariatric surgery are women. The distribution of body fat differs by sex, with a gluteal and femoral (gynoid) pattern in women and a central and upper body (android) pattern in men. The android distribution of fat carries a higher risk for metabolic syndrome, diabetes mellitus, and cardiovascular disease. Obesity increases a woman's risk for postmenopausal breast and endometrial cancer, in part because of adipose tissue aromatization of androgens to estrone.

## OSTEOPOROSIS (SEE ALSO CHAP. 177)

Osteoporosis is much more prevalent in postmenopausal women than in age-matched men, since men accumulate more bone mass in their youth and lose bone more slowly than do women, in particular after age 50, when accelerated postmenopausal bone loss occurs in women. In addition, differences in calcium intake, vitamin D, and estrogen levels contribute to sex differences in bone formation and bone loss. Vitamin D insufficiency is present in a large proportion of elderly women living in Northern latitudes. Osteoporotic hip fracture is a major cause of morbidity and an important cause of mortality in elderly women.

## PHARMACOLOGY

On average, women have lower body weights, smaller organs, higher percent body fat, and lower total-body water than men do. Gonadal steroids, menstrual cycle phase, and pregnancy can all affect drug metabolism and action. Women also take more medications than men do, including over-the-counter formulations and supplements. The greater use of medications, combined with biologic differences, may account for the reported higher frequency of adverse drug reactions in women.

## PSYCHOLOGICAL DISORDERS (SEE ALSO CHAPS. 196 AND 198)

Depression, anxiety, and eating disorders (bulimia and anorexia nervosa) are more common in women than in men. Depression occurs in 10% of women during pregnancy and 10–15% of women during the postpartum period.

## SLEEP DISORDERS (SEE ALSO CHAP. 56)

During sleep, women have an increased amount of slow-wave activity, differences in timing of delta activity, and an increase in the number of sleep spindles. They have a decreased prevalence of sleep apnea compared to men, a feature that may be related to lower androgen levels.

## SUBSTANCE ABUSE AND TOBACCO (SEE ALSO CHAPS. 199 AND 204)

Substance abuse is more common in men than women. However, women alcoholics are less likely to be diagnosed than men and are less likely to seek help. When they do seek help, it is more likely to be from a physician than from a treatment facility. Alcoholic women drink less than alcoholic men but exhibit the same degree of impairment. Alcohol abuse poses special risks to a woman, adversely affecting fertility and the health of the baby (fetal alcohol syndrome). Even moderate alcohol use increases the risk of breast cancer, hypertension, and stroke in women. More men than women smoke tobacco, but the prevalence of smoking is declining faster in men than women. The effects of smoking on pulmonary disease (COPD and cancer) and osteoporosis are more pronounced in women than in men.

## VIOLENCE AGAINST WOMEN

Domestic violence is the most common cause of physical injury in women. More than one in three women in the United States have experienced rape, physical violence, and/or stalking by an intimate partner. Women may present with symptoms of chronic abdominal pain, headaches, substance abuse, and eating disorders, in addition to obvious manifestations such as trauma. Sexual assault is one of the most common crimes against women (reported by one in five women in the United States) and is more likely committed by a spouse, ex-spouse, or acquaintance than by a stranger.

For a more detailed discussion, see Dunaif A: Women's Health, Chap. 6e, HPIM-19.

# 206 Adverse Drug Reactions

Adverse drug reactions are among the most frequent problems encountered clinically and represent a common cause for hospitalization. They occur most frequently in pts receiving multiple drugs and are caused by:

- Errors in self-administration of prescribed drugs (quite common in the elderly);
- Exaggeration of intended pharmacologic effect (e.g., hypotension in a pt given antihypertensive drugs);
- Concomitant administration of drugs with synergistic effects (e.g., aspirin and warfarin);
- Cytotoxic reactions (e.g., hepatic necrosis due to acetaminophen);
- Immunologic mechanisms (e.g., quinidine-induced thrombocytopenia, hydralazine-induced SLE);
- Genetically determined enzymatic defects (e.g., primaquine-induced hemolytic anemia in G6PD deficiency); or
- Idiosyncratic reactions (e.g., chloramphenicol-induced aplastic anemia).

## Recognition

History is of prime importance. Consider the following:

- Nonprescription drugs and topical agents as potential offenders
- Previous reaction to identical drugs
- Temporal association between drug administration and development of clinical manifestations
- Subsidence of manifestations when the agent is discontinued or reduced in dose
- Recurrence of manifestations with cautious readministration (for less hazardous reactions)
- *Rare*: (1) biochemical abnormalities, e.g., red cell G6PD deficiency as cause of drug-induced hemolytic anemia; (2) abnormal serum antibody in pts with agranulocytosis, thrombocytopenia, or hemolytic anemia.

Table 206-1 lists a number of clinical manifestations of adverse effects of drugs. It is not designed to be complete or exhaustive. The table can be accessed via the following link: www.accessmedicine.com.

For a more detailed discussion, see Roden DM: Principles of Clinical Pharmacology, Chap. 5, p. 31, in HPIM-19; Wood AJJ: Adverse Reactions to Drugs, Chap. 71, p. 430, in HPIM-15.

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# INDEX

Note: Page numbers followed by *f* or *t* denote figures or tables, respectively.


**A**
abacavir, for HIV infection, 561*t*, 566
abatacept, for rheumatoid arthritis, 847
abciximab, for thrombotic disorders, 283
abdominal angina, 797
abdominal aortic aneurysm, 693–694, 1090*t*
abdominal infections, actinomycosis, 480
abdominal pain, 154–158
  acute, catastrophic, 157–158
  approach to, 154–157
  causes of, 155*t*
  clinical manifestations of, 156–157
abdominal radiography, 23, 804
abdominal wall disorders, pain in, 155*t*
abdominoperineal resection, for anal cancer, 330
ABG. *See* arterial blood gases
*Abiotrophia* infections, 439–440
abiraterone, for prostate cancer, 343
abortion, 922
abscess
  brain, 478, 1020, 1029–1030
  epidural. *See* epidural abscess
  intraabdominal, 384–385
  liver, 384–385
  lung, 726, 729–730
  nerve, in leprosy, 491
  *Nocardia*, 478
  pancreatic, 807
  perinephric, 385
  peritonsillar, 475
  renal, 385
  splenic, 385
  streptococcal, 439
  visceral, 385
absence (petit mal) seizures, 956. *See also* seizures
ABU (asymptomatic bacteriuria), 776, 778
ABVD regimen, for Hodgkin's disease, 304
acamprosate, for alcoholic rehabilitation, 1084
acanthocytes, 202, 265
acarbose, for diabetes mellitus, 908*t*
accelerated idioventricular rhythm (AIVR), 663, 682*t*
accessory nerve (CN XI)
  disorders of, 1000
  examination of, 948
accident prevention, 1088–1090*t*
ACE inhibitors. *See* angiotensin-converting enzyme inhibitors
acetaminophen
  for back pain, 211
  for fever, 128
  for migraine, 217*t*
  for osteoarthritis, 862
  for pain, 37, 38*t*
  for tension-type headache, 218
  toxicity of, 815
acetazolamide, for periodic paralysis, 1060
*N*-acetylcysteine, for acetaminophen overdose, 815
acetylsalicylic acid. *See* aspirin
achalasia, 164
acid maltase deficiency, 1059
acid-base disorders, 13–22
  metabolic acidosis. *See* metabolic acidosis
  metabolic alkalosis, 20–21, 21*f*
  mixed, 22
  nomogram for, 17*f*
  respiratory acidosis, 21
  respiratory alkalosis, 21–22
acid-fast bacilli, 482
acidosis, 14
*Acinetobacter* infections, 457
acitretin, for psoriasis, 259
ACMV (assist-control mandatory ventilation), 75*t*
acne, 262–263
acne rosacea, 256*f*, 263
acne vulgaris, 256*f*, 262–263
acoustic neuroma, 227, 997
acrodermatitis chronica atrophicans, 495
acromegaly, 349*t*, 350, 880–881
ACTH. *See* adrenocorticotropic hormone
actinic keratosis, 256*f*
*Actinobacillus actinomycetemcomitans* infections. *See* HACEK group infection
actinomycetoma, 478, 480*t*
actinomycosis, 479–480, 1034*t*
activated charcoal
  for erythropoietic protoporphyria, 945

activated charcoal (*Cont.*):
for paralytic shellfish poisoning, 122
for toxic and drug-induced hepatitis, 815
acupuncture, for chronic back pain, 211
acute, catastrophic abdominal pain, 157–158
acute coronary syndrome (ACS), 668, 668*f*. *See also* ST-segment elevation myocardial infarction; unstable angina/non-ST-elevation myocardial infarction
acute disseminated encephalomyelitis (ADEM), 1020
acute intermittent porphyria (AIP), 944, 991
acute interstitial nephritis (AIN), 771–772, 771*t*
acute interstitial pneumonia (AIP), 736
acute kidney injury (AKI), 771–772
acute low back pain (ALBP). *See* low back pain
acute lymphoblastic leukemia and lymphoblastic lymphoma (ALL), 295*t*, 296*f*, 299–300
acute myeloid leukemia (AML), 283–287
classification of, 284*t*, 286*f*
clinical manifestations of, 285
incidence of, 285
treatment of, 285–287, 286*f*
acute promyelocytic leukemia, 284*t*, 285
acute renal failure (ARF), 747–751
clinical manifestations of, 749–750
in critically ill patient, 35
definition of, 747
dialysis for, 751
differential diagnosis of, 747–749
etiology of, 747, 747–748*t*
intrinsic, 748–749, 748*t*, 750*t*
laboratory testing in, 749–750
postrenal, 748*t*, 749
prerenal, 747–748, 747*t*, 750*t*
treatment for, 751
acute respiratory distress syndrome (ARDS), 71–73, 72*f*
acute retroviral syndrome, 555, 557, 558*t*
acute stress disorder, 1068
acute uric acid nephropathy, 864
acyclovir
for Bell's palsy, 997
for Epstein-Barr virus infections, 529
for genital HSV infections, 412, 415*t*
for herpes zoster infections, 415*t*
for HSCT patients, 367
for HSV infections, 519, 520–522*t*
for viral encephalitis, 1029
for viral esophagitis, 165
for viral meningitis, 1027
for VZV infections, 524
AD. *See* Alzheimer's disease
adalimumab
for ankylosing spondylitis, 857
for inflammatory bowel disease, 794
for psoriasis, 259
for psoriatic arthritis, 858
for rheumatoid arthritis, 846
adaptive immune system, deficiencies of, 841*t*
Addison's disease, 898–899
adefovir, for chronic hepatitis B, 817, 818–819*t*
ADEM (acute disseminated encephalomyelitis), 1020
adenoma
adrenal, 896
colonic, 326
gastric, 325
hepatocellular, 330
pituitary. *See* pituitary adenoma
small-bowel, 325
thyroid, 893–895, 894*f*
adenosine
for arrhythmias, 684*t*
for tachyarrhythmias, 680*t*
for Wolff-Parkinson-White syndrome, 686
adenosine deaminase deficiency, 840
adenovirus infections, 534*t*, 537
adenylate kinase 2 deficiency, 840
ADH (antidiuretic hormone), 883
adnexal mass, 338
ADPKD (autosomal dominant polycystic kidney disease), 773–774
adrenal gland disease, 895–900
Addison's disease, 898–899
adenoma, 896
carcinoma, 896
Cushing's syndrome. *See* Cushing's syndrome
hyperaldosteronism. *See* hyperaldosteronism

hypoaldosteronism, 899–900
incidental masses, 900, 900*f*
adrenal insufficiency
paraneoplastic, 112
primary, 898
secondary, 898
adrenalectomy, for prostate cancer, 343
adrenocorticotropic hormone (ACTH), 878*f*
deficiency of, 882, 883*t*, 898
ectopic hypersecretion of, 348–350, 349*t*, 351
hypersecretion of, 896
for inflammatory bowel disease, 792
production of, 877
adrenomyeloneuropathy, 1007
adult inclusion conjunctivitis (AIC), 514–515
adult T cell leukemia/lymphoma (ATL), 301
advance directives, 49
advanced sleep-wake phase syndrome, 245
adverse drug reactions, 1107. *See also* drug-induced illness
AED (automated external defibrillator), 57
*Aeromonas* infections, 458
aflatoxin, hepatocellular carcinoma and, 331–332
African tick-bite fever, 501*t*, 504–505
agammaglobulinemia, 843
agglutination, 586
*Aggregatibacter actinomycetemcomitans* infections, 452, 453*t*
*Aggregatibacter aphrophilus* infections, 452, 453*t*
aggressive lymphoma, 295*t*, 296, 298–299
agitation, in terminally ill patient, 56*t*
agoraphobia, 1067, 1069
AIC (adult inclusion conjunctivitis), 514–515
AIDS, 554. *See also* HIV infection
AIN (acute interstitial nephritis), 771–772, 771*t*
AION (anterior ischemic optic neuropathy), 230*f*, 231
AIP (acute intermittent porphyria), 944, 991
AIP (acute interstitial pneumonia), 736
airborne precautions, 357
airway obstruction, 142–143
AIVR (accelerated idioventricular rhythm), 663, 682*t*
AKI (acute kidney injury), 771–772
alanine aminotransferase (ALT), 183, 184*t*
albendazole
for ascariasis, 601
for echinococcosis, 609
for enterobiasis, 603
for giardiasis, 391
for hookworm infections, 601
for larva migrans, 600
for lymphatic filariasis, 604
for strongyloidiasis, 602
for taeniasis solium and cysticercosis, 607
for trichinellosis, 599
ALBP (acute low back pain). *See* low back pain
albumin
intravenous, 188, 189
for peritonitis, 382
serum, in liver disease, 184*t*, 185
serum-ascites gradient, 188*f*
urine, 200–201
albuterol
for anaphylaxis, 114
for COPD, 720, 721
for hyperkalemia, 16*t*
alcohol intoxication, 1081–1082
alcohol use disorder, 1080–1084
chronic, 807
clinical manifestations of, 1081–1083
definition of, 1080, 1081*t*
laboratory testing in, 1083
metabolic consequences of, 828
screening for, 1088–1090*t*, 1091*t*
treatment of, 1083–1084
in women, 1106
Alcohol Use Disorders Identification Test (AUDIT), 1082*t*
alcohol withdrawal, 1082, 1083
alcoholic ketoacidosis, 17, 18*t*
alcoholic liver disease, 827–828
alcoholic polyneuropathy, 991
alemtuzumab
for CLL, 297
for multiple sclerosis, 1018
alendronate, for osteoporosis, 934
alkali therapy, for nephrolithiasis, 782*t*
alkaline phosphatase, 183, 184*t*, 804
alkaline-encrusted cystitis, 443

alkalosis, 14
ALL (acute lymphoblastic leukemia and lymphoblastic lymphoma), 295*t*, 296*f*, 299–300
allergic bronchopulmonary aspergillosis, 572, 574*t*
allergy
  anaphylaxis in, 114–115
  to insect sting, 124–125
allodynia, 36, 991
alloimmunization, 46
allopurinol
  for CML, 289
  for gout, 865
  for nephrolithiasis, 781–782*t*
  for tumor lysis syndrome, 113
allylamines, for dermatophyte infections, 262
almotriptan, for migraine, 217*t*, 219*t*
alogliptin, for diabetes mellitus, 908*t*
alosetron, for irritable bowel syndrome, 795, 796*t*
$\alpha_1$-antitrypsin deficiency, 720
alpha-adrenergic antagonists, for vasospastic disorders, 698
alphavirus infections, 550–551
alprazolam, 1075*t*
alprostadil injection, for erectile dysfunction, 916
ALS. *See* amyotrophic lateral sclerosis
ALT (alanine aminotransferase), 183, 184*t*
alteplase, for thrombotic disorders, 282
aluminum phosphate binders, for hyperphosphatemia, 929
alveolar hemorrhage syndromes, 739
alveolar ventilation, 707
alveolar-arterial oxygen gradient, 707–708
Alzheimer's disease (AD)
  approach to, 968
  clinical manifestations of, 972–973
  differential diagnosis of, 969*t*, 970*t*
  familial, 971
  pathogenesis of, 973
  treatment of, 973–974
  in women, 1104
amantadine
  for influenza, 532, 532*t*
  for Parkinson's disease, 980
amaurosis fugax, 82, 230
AmB. *See* amphotericin B
ambrisentan, for pulmonary hypertension, 702
amebiasis, 396–397
amenorrhea, 917–918, 917*f*
amikacin
  for community-acquired pneumonia, 725*t*
  for enteric GNB infections, 458
  for extraintestinal *E. coli* infections, 454
  for health care–associated pneumonia, 727*t*
  for *Klebsiella* infections, 456
  for nocardiosis, 479
  for nontuberculous mycobacterial infections, 494
  for *P. aeruginosa* infections, 460*t*
  for *Proteus* infections, 457
amiloride
  for diabetes insipidus, 6
  for edema, 153*t*
  for hyperaldosteronism, 898
  for hypertension, 652*t*
  for Liddle's syndrome, 20
aminoglutethimide, for prostate cancer, 343
aminoglycosides
  for *Aeromonas* infections, 458
  for brucellosis, 464
  for enterococcal infections, 440–441
  for HACEK group infections, 453*t*
  for infective endocarditis, 376*t*, 379
  for nontuberculous mycobacterial infections, 494
  for *P. aeruginosa* infections, 460–461*t*
aminophylline, for anaphylaxis, 114
5-aminosalicylic acid (5-ASA), for inflammatory bowel disease, 792
aminotransferases, 183, 184*t*
amiodarone
  for arrhythmias, 684*t*
  for dilated cardiomyopathy, 641
  for hypertrophic cardiomyopathy, 643
  for tachyarrhythmias, 681*t*
  thyrotoxicosis induced by, 892
  for ventricular fibrillation, 59*f*
  for ventricular tachycardia, 662
amitriptyline
  for ciguatera poisoning, 121
  dosage and side effects of, 39*t*, 1072*t*
  for irritable bowel syndrome, 795
  for migraine prevention, 220*t*
  for multiple sclerosis, 1019

for pain, 39*t*
for postherpetic neuralgia, 524
for tension-type headache, 218
AML. *See* acute myeloid leukemia
amlodipine, for pulmonary hypertension, 702
ammonia, blood, in liver disease, 184*t*
amodiaquine, for malaria, 588*t*
amoxapine, 1071, 1073*t*
amoxicillin
for community-acquired pneumonia, 725*t*
for COPD exacerbations, 721
for *H. pylori* eradication, 787*t*
for infective endocarditis prophylaxis, 381*t*
for Lyme borreliosis, 496
for otitis media, 252*t*
for pneumococcal infections, 424
for sinusitis, 249*t*
amoxicillin-clavulanate
for animal bite infections, 116*t*, 415*t*
for community-acquired pneumonia, 725*t*
for *H. influenzae* infections, 449
for *M. catarrhalis*, 452
for nocardiosis, 479
for otitis media, 252*t*
for sinusitis, 249*t*
amphotericin B, 569
for aspergillosis, 574*t*
for blastomycosis, 581
for candidiasis, 571
for coccidioidomycosis, 580
for cryptococcosis, 576
for febrile neutropenia in cancer patient, 113
for fusariosis, 582
for histoplasmosis, 579*t*
for leishmaniasis, 594
for *Malassezia* infections, 581
for mucormycosis, 577
for paracoccidioidomycosis, 582
for penicilliosis, 582
for scedosporiosis, 582
for sepsis/septic shock, 68*t*
for sporotrichosis, 581
ampicillin
for actinomycosis, 481
for bacterial meningitis, 1024*t*, 1025*t*
for clostridial infections, 474*t*
for community-acquired pneumonia, 725*t*
for diverticulitis, 796–797
for enterococcal infections, 440
for Epstein-Barr virus infections, 528
for extraintestinal *E. coli* infections, 454
for *H. influenzae* infections, 449
for HACEK group infections, 453*t*
for infective endocarditis, 376, 377*t*, 378*t*, 379
for infective endocarditis prophylaxis, 381*t*
for listerial infections, 447
for *M. catarrhalis*, 452
for mixed anaerobic infections, 476*t*
for necrotizing fasciitis, 416*t*
for peritonitis, 382
for streptococcal infections, 438
for urinary tract infections, 778
ampicillin-clavulanate, for diverticulitis, 797
ampicillin-sulbactam
for animal bite infections, 116*t*, 415*t*
for cellulitis, 415*t*
for cholecystitis, 801
for epiglottitis, 254
for HACEK group infections, 453*t*
for health care–associated pneumonia, 727*t*
for human bite infections, 116*t*
for infective endocarditis, 378*t*
for myositis/myonecrosis, 418
for snakebite, 117*t*
amylase, serum, 804
amylase-creatinine clearance ratio, urinary, 804
amyloid angiopathy, 84*t*
amyloidosis, 873–875
AA (secondary), 873, 874*f*
AL (primary), 772–773, 773*t*, 873, 874*f*
autonomic involvement in, 991
classification of, 873
clinical manifestations of, 873–874
definition of, 873
diagnosis of, 874, 874*f*
familial, 873
glomerular disease in, 768*t*
treatment of, 875
amyotrophic lateral sclerosis (ALS), 984–988
clinical manifestations of, 985
familial, 984
laboratory testing in, 986
pathophysiology of, 985
treatment of, 987–988

ANA (antinuclear antibodies), 700, 736, 824, 825
anaerobic bacteria, 469
anaerobic infections, 469–477
  bone and joint, 476
  clostridial. *See* clostridial infections
  mixed, 474–477, 476*t*
  of mouth, head, and neck, 475
  pelvic, 475
  skin and soft tissue, 476
anagliptin, for diabetes mellitus, 908*t*
anagrelide, for essential thrombocytosis, 293
anakinra
  for fever of unknown origin, 129
  for gout, 864
  for rheumatoid arthritis, 847
anal cancer, 330, 414
anal condyloma, 798
anal fissure, 798
analgesia, 36
analgesic nephropathy, 772
analgesics, 38–39*t*
anaphylaxis, 114–115, 125
anaplasmosis, 122, 502*t*, 508
anaplastic large cell lymphoma, 294, 296*f*
anastrozole, for breast cancer, 321
ANCA (antineutrophil cytoplasmic autoantibodies), 762, 852
*Ancylostoma braziliense* infections, 600
*Ancylostoma duodenale* infections, 601
androgen abuse, 915
androgen deficiency
  approach to, 914*f*
  clinical manifestations of, 913
  etiology of, 912–913
  treatment of, 914–915
androgen deprivation, for prostate cancer, 343
androgen excess, in female, 920
anemia, 194. *See also specific types*
  blood loss and, 269
  in critical illness, 34
  drug-induced, 269, 272*t*
  in hypometabolic states, 270*t*
  hypoproliferative, 194, 267–269, 270*t*
  in inflammation, 270*t*, 271*t*
  microcytic, 268*f*, 269, 271*t*
  in parvovirus infections, 542
  physiologic classification of, 194, 195*f*
  refractory, 269, 292*t*
  in renal failure, 270*t*
  treatment of, 273–274
anemia of chronic disease, 268–269, 273
anesthetics, for delirium, 52*t*
aneurysm
  aortic, 693–694, 1090*t*
  intracranial, 84*t*, 91
  ventricular, 91
angina
  chronic stable. *See* chronic stable angina
  in myocardial ischemia, 138
  Prinzmetal's variant, 676
  recurrent, 667
  unstable. *See* unstable angina/non-ST-elevation myocardial infarction
angiodysplasia, 175, 178, 798
angioedema
  classification of, 836, 836*t*
  diagnosis of, 836–837
  etiology of, 150
  treatment of, 837
angiography, hepatobiliary, 186
angioma, senile, 256*f*
angiotensin receptor blockers (ARBs)
  for diabetic nephropathy, 766
  for dilated cardiomyopathy, 640
  for glomerulonephritis, 764
  for heart failure, 664, 688, 689*t*, 690*t*
  for hypertension, 651, 653*t*, 654*t*, 655*f*
  for slowing renal disease progression, 754
  for STEMI, 662, 667
  for UA/NSTEMI, 671
angiotensin-converting enzyme (ACE) inhibitors
  for aortic regurgitation, 638
  for chronic stable angina, 675
  for diabetic nephropathy, 766
  for dilated cardiomyopathy, 640
  for focal glomerulosclerosis, 765
  for heart failure, 664, 688, 689*t*, 690*t*, 692
  for hypertension, 651, 653*t*, 654*t*, 655*f*
  for membranous glomerulonephritis, 764
  for slowing renal disease progression, 754
  for STEMI, 662, 667
  for systemic sclerosis, 848
  for UA/NSTEMI, 671

anidulafungin, 569
animal bite, 415*t*, 417
anion gap, 15, 18*t*, 19, 22
anisocytosis, 265
anistreplase, for thrombotic disorders, 282
ankle-brachial index, 613, 697
ankylosing spondylitis, 854–857
  clinical manifestations of, 855–856
  definition of, 854–855, 855*t*
  diagnosis of, 856*t*, 857–858
  treatment of, 857
Ann Arbor staging system, for Hodgkin's disease, 304, 305*t*
annular skin lesion, 255
anomia, 239*t*
anorectal disease, 798
anorectal gonorrhea, 405
anorexia, in terminally ill patient, 54*t*
anorexia nervosa, 1079–1080
anosmia, 976
anosognosia, 82
ANS. *See* autonomic nervous system
antacids
  for erosive gastropathies, 788
  for indigestion, 161
  for peptic ulcer disease, 787
  for systemic sclerosis, 848
anterior ischemic optic neuropathy (AION), 230*f*, 231
antiarrhythmics, 683–684*t*
  for dilated cardiomyopathy, 641
  for hypertrophic cardiomyopathy, 643
  for pain, 39*t*, 40
  for tachyarrhythmia, 686
antibacterial therapy
  for acute renal failure, 751
  for bronchiectasis, 729
  for *C. difficile* infections, 398
  for campylobacteriosis, 395
  for cholera, 389
  for COPD, 721
  for cor pulmonale, 693
  for diverticular disease, 796–797
  for epididymitis, 400
  for febrile neutropenic patients, 365–366, 365*f*
  for HSCT patients, 366
  for infective endocarditis, 374, 376–378*t*, 378–380, 381*t*
  for intestinal pseudoobstruction, 797
  for intraabdominal abscess, 384–385
  for irritable bowel syndrome, 795
  for lung abscess, 730
  for peritonitis, 382–384
  resistance to, 361
  for salmonellosis, 394
  for shigellosis, 396
  for transplant recipients, 368
  for typhoid fever, 393
  for urethritis in men, 399–400
anticholinergics
  for asthma, 713–715
  for COPD, 720
  for diverticular disease, 797
  for dystonia, 237
  for irritable bowel syndrome, 795
  for nausea and vomiting, 160
  for Parkinson's disease, 980
  for vertigo, 228*t*
anticholinesterase drugs, for myasthenia gravis, 1052
anticoagulants
  for deep venous thrombosis, 732–733
  for dilated cardiomyopathy, 641
  for pulmonary embolism, 732–733
  for restrictive cardiomyopathy, 642
  for STEMI, 662
  for stroke, 87
  for stroke prevention, 89–90*t*, 90
  for thrombotic disorders, 281–282
  for UA/NSTEMI, 670
  for venous thromboembolism, 732–733
anticonvulsants
  for brain tumor, 1008
  for generalized anxiety disorder, 1068
  for migraine prevention, 220*t*
  for pain, 37, 39*t*, 40
  for polyneuropathy, 1044
  for status epilepticus, 102*f*, 103
  for subarachnoid hemorrhage, 92
antidepressants, 1071, 1074
  for Alzheimer's disease, 973–974
  for bulimia nervosa, 1080
  for chronic fatigue syndrome, 135
  for depression, 1064
  dosage and side effects, 1072–1073*t*
  for fibromyalgia, 868
  for irritable bowel syndrome, 795, 796*t*
  for narcolepsy, 244
  for pain, 37, 39*t*, 40
  for panic disorder, 1067
  for PTSD, 1069
  selective serotonin reuptake inhibitors, 1071, 1072*t*

antidepressants (*Cont.*):
for smoking cessation, 1103
tricyclic. *See* tricyclic antidepressants
withdrawal syndromes, 1074
antidiuretic hormone (ADH), 883
antiepileptic drugs, 961–966*t*, 967*t*
antifungal agents, 569–570
antigenic drift, 530
antigenic shift, 530
anti-glomerular basement membrane disease, 762–763
antihistamines
for allergic rhinitis, 838
for antivenom reaction, 119
for carcinoid tumor, 332
for cough, 148
for erythema multiforme, 263
for hymenoptera sting, 125
for nausea and vomiting, 160
for pityriasis rosea, 259
for scombroid poisoning, 122
for systemic mastocytosis, 839
for urticaria/angioedema, 837
for vertigo, 228*t*
antihypertensives
for aortic dissection, 695
for slowing renal disease progression, 754
antileukotrienes, for asthma, 714
anti-LKM antibodies, 825
antimalarials
for malaria prophylaxis, 590–591*t*
for malaria treatment, 588*t*
for psoriatic arthritis, 859
for SLE, 845
antimonial compounds, for leishmaniasis, 594
antineuronal antibodies, paraneoplastic, 352, 353*t*, 354*t*
antineutrophil cytoplasmic autoantibodies (ANCA), 762, 852
antinuclear antibodies (ANA), 700, 736, 825
antiphospholipid syndrome (APS), 849–850
antiplatelet agents
for membranoproliferative glomerulonephritis, 765
for myocardial infarction, 667
for STEMI, 662
for stroke, 87
for stroke prevention, 89–90
for thrombotic disorders, 283
antiprotozoal agents
for cryptosporidiosis, 393
for cystoisosporiasis, 392
for giardiasis, 391
antipsychotics
for Alzheimer's disease, 974
for bipolar disorder, 1066
dosage and side effects of, 1076–1077*t*
first-generation, 1074, 1076*t*
for schizophrenia, 1066–1067
second-generation, 1074, 1077*t*, 1078
antipyretics, 128
antiretroviral therapy, 559, 566–567
entry inhibitors, 559, 564*t*
initiation of, 557
integrase inhibitors, 559, 564–565*t*
nonnucleoside reverse transcriptase inhibitors, 559, 561–563*t*
nucleoside/nucleotide analogues, 559, 560–561*t*
protease inhibitors, 559, 563*t*
resistance testing for, 557
selection of, 559, 566*t*
antisocial personality disorder, 1070
antithrombotic drugs, for UA/NSTEMI, 670
antithymocyte globulin, for aplastic anemia, 274
antitoxin
botulism, 472
for diphtheria, 442
for tetanus, 470
$\alpha_1$-antitrypsin deficiency, 720
antitussive agents, 148
antivenom
for snakebite, 119–120
sources of, 119
antiviral agents
for acute viral hepatitis, 814
for HSCT patients, 367–368
for transplant recipients, 368–369
for vasculitis, 854
antrectomy, 788*t*
anuria, 199
anxiety attack, 225
anxiety disorders, 1067–1070
anxiolytics, 1074
for delirium, 52*t*
dosage of, 1075*t*
for dyspnea, 51*t*
pharmacology of, 1075*t*
aorta
abdominal, 696
coarctation of, 630–631, 649
echocardiography of, 624, 626*t*

aortic aneurysm, 693–694
aortic dissection
chest pain in, 138, 140*f*
classification of, 694, 695*f*
clinical manifestations of, 694
diagnosis of, 694
etiology of, 694
treatment of, 695, 696*t*
aortic regurgitation (AR), 616*t*, 624*f*, 637–638
aortic stenosis (AS)
clinical manifestations of, 636
echocardiography in, 624*f*, 636
etiology of, 636
heart sounds in, 615*f*, 616*t*, 636
treatment of, 636, 637*f*
aortic valve disease, antithrombotic therapy for, 89*t*
aortography, 694
aphasia, 239–240, 239*t*
aphthous stomatitis, 256*f*
apixaban, for thrombotic disorders, 282
aplastic anemia, 267, 277
aplastic crisis, in parvovirus infections, 542
apnea, 55*t*, 745
apo A-V deficiency, 937*t*
apo B-100, familial defective, 936, 937*t*
apo CII deficiency, 937*t*, 940
apomorphine, for Parkinson's disease, 980*t*
apraxia, 233
apremilast
for psoriasis, 259
for psoriatic arthritis, 859
aprepitant, for nausea and vomiting, 51, 160
APS (antiphospholipid antibody syndrome), 849–850
AR (aortic regurgitation), 616*t*, 624*f*, 637–638
arachnoiditis, lumbar adhesive, 210
ARBs. *See* angiotensin receptor blockers
*Arcanobacterium haemolyticum* infections, 443
ARDS. *See* acute respiratory distress syndrome
ARF. *See* acute renal failure
argatroban
for heparin-induced thrombocytopenia, 280
for thrombotic disorders, 282
arginine vasopressin (AVP), 1, 883
aripiprazole
dosage and side effects of, 1077*t*
for schizophrenia, 1067
armodafinil, 245
aromatase inhibitors, for breast cancer, 320, 321
arrhythmia
bradyarrhythmias. *See* bradyarrhythmias
serum magnesium and, 662
in STEMI, 662–663
syncope in, 222, 224*t*
tachyarrhythmias. *See* tachyarrhythmias
arsenic trioxide, for AML, 287
artemether, for malaria, 588*t*
artemether-lumefantrine, for malaria, 588*t*
artemisinin derivatives, for malaria, 587, 588*t*
arterial blood gases (ABG), 708
in acid-base disorders, 15, 20
analysis of, in ICU, 34
arterial embolism, 697
arteriography
for colonic angiodysplasia, 798
coronary, 671, 673
mesenteric, 175
arteriovenous fistula, dural, 84*t*
arteriovenous malformation, 1006, 1007*f*
intracranial hemorrhage in, 84*t*
subarachnoid hemorrhage in, 91
artesunate, for malaria, 587, 588–589*t*
arthritis. *See also specific types*
in alphavirus infections, 550–551
gonococcal, 406, 419
infectious, 418–420
in Lyme disease, 495, 496
*S. aureus*, 430
septic, 427
arthritis mutilans, 858
arthropathy, chronic, 865
arthropod bite/sting, 122–124
arthropod-borne viral diseases
with arthritis and rash, 550–551
encephalitis, 550
with fever and myalgia, 548–550
microbiology of, 548
pathogenesis of, 548
pulmonary, 551
viral hemorrhagic fever, 551–552
arthroscopic therapy, for osteoarthritis, 862

AS. *See* aortic stenosis
5-ASA (5-aminosalicylic acid), for inflammatory bowel disease, 792
asbestos-related disease, 716
ascariasis, 600–601
ascites, 150, 187–189
  cirrhotic, 188
  complications of, 188–189
  fluid characteristics, 188*f*
  pancreatic, 807
  paracentesis in, 30–31
  primary bacterial peritonitis and, 382
  refractory, 188
  serum-ascites albumin gradient, 188*f*
ASD (atrial septal defect), 627–628
asenapine, 1077*t*
L-asparaginase, for ALL, 300
aspartate aminotransferase (AST), 183, 184*t*, 804
aspergilloma, 572, 574*t*
aspergillosis, 571–573
  clinical manifestations of, 572
  diagnosis of, 572–573
  disseminated, 572
  meningitis in, 1035*t*
  microbiology and epidemiology of, 571–572
  pulmonary, 572
  sinusitis, 572
  treatment of, 573, 574–575*t*
aspiration, of bone marrow, 266
aspirin
  for antiphospholipid antibody syndrome, 850
  for atrial fibrillation, 686
  for cardiovascular disease prevention, 1094
  for chronic stable angina, 675
  for colon cancer prevention, 1100
  for fever, 128
  for migraine, 217*t*
  for pain, 37, 38*t*
  for pericarditis, 645
  Reye's syndrome and, 532
  for rheumatoid arthritis, 846
  for STEMI, 659, 662, 667
  for stroke, 87
  for stroke prevention, 89–90
  for superficial thrombophlebitis, 698
  for tension-type headache, 218
  for thrombotic disorders, 283
  for UA/NSTEMI, 670, 671
assist-control mandatory ventilation (ACMV), 75*t*
assist-control ventilation, 74
assisted reproductive technology, 924
AST (aspartate aminotransferase), 183, 184*t*
asterixis, 238
asthma
  clinical evaluation of, 712
  cough in, 147
  definition and epidemiology of, 711–712
  differential diagnosis of, 713
  dyspnea in, 142
  intrinsic, 711
  occupational, 711, 716–718
  physical examination in, 712
  pulmonary function tests in, 712
  sleep disorders in, 242
  treatment for, 712–714, 714*f*
asthma exacerbations, 714–715
astrocytoma, 1009, 1009*f*
asymptomatic bacteriuria (ABU), 776, 778
asystole, 60, 60*f*
ataxia, 981–984
  approach to, 981, 983
  clinical manifestations of, 981
  diagnosis of, 984
  etiology of, 982*t*
  inherited, 983–984, 983*f*
  treatment of, 984
ataxia-telangiectasia, 842
atazanavir, for HIV infection, 563*t*
atenolol
  for hypertension, 652*t*
  for thyrotoxicosis, 890
atheroembolism, 697–698
atherosclerosis
  *C. pneumoniae* infections and, 513
  of peripheral arteries, 696–697
  prevention of complications of, 941–942
  risk factors for, 1092–1094, 1092*t*
athetosis, 237
ATL (adult T cell leukemia/lymphoma), 301
atorvastatin
  for dyslipidemia, 938*t*
  for STEMI, 667
  for UA/NSTEMI, 671
atovaquone
  for ANCA-associated glomerulonephritis, 762

for babesiosis, 592
for *Pneumocystis* infections, 584*t*
for *Pneumocystis* prophylaxis, 585*t*
for toxoplasmosis, 598
atovaquone-proguanil
for malaria, 588*t*
for malaria prophylaxis, 590*t*
atrial fibrillation
anticoagulants for stroke prevention in, 89*t*, 90
chronic, 686
clinical and ECG features of, 681*t*
atrial flutter, 681*t*
atrial premature beats, 680*t*
atrial septal defect (ASD), 627–628
atrial tachycardia, 680*t*, 681*t*
atrioventricular (AV) block
drug-induced, 678*t*
etiology of, 678*t*
first degree, 677, 679*f*
second degree, 677, 679*f*
in STEMI, 663
third degree (complete), 678, 679*f*
atrophy (skin lesion), 257*t*
atropine
for bradycardia, 60*f*, 659
for inflammatory bowel disease, 792
for tachyarrhythmias, 681–682*t*
atypical parkinsonism, 977, 977*t*
AUDIT (Alcohol Use Disorders Identification Test), 1082*t*
Auer rods, 266
auscultation, 614–615
autoantibody disorders, 48
autoimmune autonomic neuropathy, 991
autoimmune disease
leukopenia in, 276
thrombocytopenia in, 278
in women, 1105
autoimmune hemolysis, 274
autologous transfusion, 46
automated external defibrillator (AED), 57
autonomic dysfunction, paraneoplastic, 354
autonomic nervous system (ANS)
actions of, 988, 990*t*
anatomy of, 989*f*
testing of, 990–991
autonomic nervous system (ANS) disorders, 988–995
approach to, 988, 990–991
classification of, 992–993*t*
clinical manifestations of, 991
drug-induced, 988
treatment of, 994–995, 994*t*
autosomal dominant polycystic kidney disease (ADPKD), 773–774
AV block. *See* atrioventricular block
avascular necrosis (osteonecrosis), 869, 934
avoidant personality disorder, 1070
AVP (arginine vasopressin), 1, 883
5-azacytidine, for myelodysplastic syndromes, 289
azathioprine
for ANCA-associated glomerulonephritis, 762
for autoimmune hepatitis, 825
for immunosuppression after renal transplantation, 758
for inflammatory bowel disease, 794
for inflammatory myopathy, 1059
for multiple sclerosis, 1019
for myasthenia gravis, 1053
for polyneuropathy, 1046
for reactive arthritis, 860
for SLE, 845
for vasculitis, 854
azelastine, for allergic rhinitis, 838
azidothymidine. *See* zidovudine
azithromycin
for adult inclusion conjunctivitis, 515
for babesiosis, 592
for *Bartonella* infections, 467*t*
for *C. pneumoniae* infections, 513
for campylobacteriosis, 395
for chancroid, 413
for cholera, 389
for community-acquired pneumonia, 725*t*
for COPD exacerbation prophylaxis, 721
for donovanosis, 413
for endemic treponematosis, 497
for gonococcal infections, 406*t*
for *H. influenzae* infections, 449
for infective endocarditis prophylaxis, 381*t*
for *Legionella* infections, 512–513
for leptospirosis, 498
for *M. catarrhalis*, 452
for *M. pneumoniae* infections, 511
for meningococcal prophylaxis, 1025
for nontuberculous mycobacterial infections, 494
for otitis media, 252*t*

azithromycin (*Cont.*):
for pertussis, 451
for pneumococcal infections, 424
for scrub typhus, 507
for shigellosis, 396
for typhoid fever, 393
for urethritis in men, 399
azoles
for candidiasis, 262, 571
pharmacology of, 569
for scedosporiosis, 582
azotemia, 197–199, 198*f*, 198*t*. *See also* acute renal failure
AZT. *See* zidovudine

**B**
B cell deficiency, 843
B cell receptors, defective rearrangements of, 840
B cells, 189
babesiosis, 122, 592
Babinski sign, 233*t*, 951
bacillary angiomatosis, 415*t*, 467*t*, 468
bacillary peliosis, 467*t*, 468
bacille Calmette-Guérin (BCG), 334, 490
*Bacillus cereus* infections, 387
back pain. *See also* low back pain
in ankylosing spondylitis, 855
in cancer patient, 111*f*
baclofen
for dystonia, 237
for multiple sclerosis, 1019
bacteremia
clostridial, 473
*E. coli*, 454
*Klebsiella*, 456
listerial, 446–447
*P. aeruginosa*, 459, 460*t*
*S. aureus*, 427
streptococcal, 437, 439
bacterial food poisoning, 386–389, 388*f*
bacterial infections. *See also specific bacteria and diseases*
chronic meningitis in, 1033–1034*t*
in HSCT patients, 366
lymphadenopathy and, 190*t*
bacterial vaginosis, 401
bacteriuria, asymptomatic, 776, 778
*Bacteroides fragilis* infections, 474, 475
BAL (bronchoalveolar lavage), 710
Balkan endemic nephropathy (BEN), 772
balloon dilatation, for esophageal disorders, 164
balloon tamponade, for esophageal varices, 832
barbiturate coma, 95*t*
bariatric surgery, 902–903, 903*f*
barium contrast study, 170
barium enema, 328, 330
barium radiography, for GI bleeding, 175
barium swallow, 162, 165, 323
Barmah Forest virus infections, 551
barotrauma, 76
Barrett's esophagus, 161, 322
barrier contraception, 922
*Bartonella* infections, 466–469, 467*t*
bacillary angiomatosis, 468
bacillary peliosis, 468
Carrión's disease, 468–469
cat-scratch disease, 467–468
endocarditis, 378*t*, 468
trench fever, 468
basal cell carcinoma (BCC), 256*f*, 307
basal energy expenditure (BEE), 40, 41*f*
basic life support (BLS), 57–58, 58*f*, 59*f*, 60*f*
basophilia, 276
basophilic stippling, 265
BCG (bacille Calmette-Guérin), 334, 490
Becker dystrophy, 1054
beclomethasone, for allergic rhinitis, 838
bee sting, 124–125
beer potomania, 2
Behçet's syndrome, 1039*t*
belimumab, for SLE, 845
Bell's palsy, 517, 997
Belsey procedure, 161
BEN (Balkan endemic nephropathy), 772
benign paroxysmal positional vertigo (BPPV), 227, 227*t*, 228*t*, 229
benserazide/levodopa, for Parkinson's disease, 980*t*
bentiromide test, 170
benzathine penicillin
for diphtheria, 442
for endemic treponematosis, 497
for pharyngitis, 253
for rheumatic fever prophylaxis, 632
for streptococcal infections, 436*t*
for syphilis, 411*t*
benzene derivative poisoning, 815
benznidazole, for Chagas' disease, 595

benzodiazepines
for alcohol withdrawal, 1083
dosage and action of, 1075*t*
for fibromyalgia, 868
for generalized anxiety disorder, 1068
for panic disorder, 1067
sleep disorders with, 242
for tetanus, 470
for vertigo, 228*t*
benzonatate, for cough, 148
benzoyl peroxide, for acne, 262
berylliosis, 717
beta agonists
for asthma, 713–715
for COPD, 720, 721
beta blockers
for aortic dissection, 695, 696*t*
for atrial fibrillation, 686
for chronic stable angina, 674
for dilated cardiomyopathy, 640
for esophageal varices, 832
for heart failure, 688, 689*t*, 690, 690*t*, 692
for hypertension, 651, 652*t*, 654*t*
for hypertrophic cardiomyopathy, 643
for migraine prevention, 220*t*
for mitral stenosis, 632
for mitral valve prolapse, 636
for sinus tachycardia, 663
for STEMI, 661–662, 667
for supraventricular arrhythmias, 663
for tachyarrhythmias, 680–681*t*
for thyrotoxicosis, 890
for toxic multinodular goiter, 893
for UA/NSTEMI, 670, 671
for Wolff-Parkinson-White syndrome, 686
beta-carotene, for erythropoietic protoporphyria, 945
beta-lactams
for *Corynebacterium* infections, 443
for enterococcal infections, 440
for HACEK group infections, 453*t*
for *P. aeruginosa* infections, 459, 460*t*
for pneumococcal infections, 424
for staphylococcal infections, 430, 431*t*
for urinary tract infections, 777*t*, 778
bethanechol, for bladder hyporeflexia, 1019
bevacizumab
for cervical cancer, 341
for colorectal cancer, 328
for renal cancer, 335
BFM regimen, for Burkitt's lymphoma/leukemia, 301
bicarbonate, renal retention of, 20
bicarbonate therapy
for metabolic acidosis, 20
for renal tubular acidosis, 775
for tumor lysis syndrome, 113
bicuspid aortic valve, congenital, 630
biguanides, for diabetes mellitus, 908*t*
bilastine, for allergic rhinitis, 838
bile ducts, diagnostic evaluation of, 800*t*
bile salt deficiency, 173*t*
biliary colic, 801
bilirubin, serum, 804
conjugated fraction (direct), 179
unconjugated fraction (indirect), 179
binge eating disorder, 1079
Binswanger's disease (diffuse white matter disease), 974, 975*f*
biopsy
bone marrow, 266–267
liver, 186
lung, 737
pleural, 710
prostate, 343, 344*f*
sentinel node, 320
skin, 256
bioterrorism, 361
bipolar disorder, 1065–1066
bisacodyl, for constipation, 50*t*
bismuth subsalicylate, for *H. pylori* eradication, 787*t*
bisoprolol, for heart failure, 690*t*
bisphosphonates
actinomycosis and, 479
for breast cancer, 321
for hypercalcemia, 351
for osteoporosis, 934
for primary biliary cirrhosis, 829
for prostate cancer, 345
bite
arthropod, 122–124
mammalian, 115, 116*t*, 118
snakebite, 117*t*, 118
wound infection from, 116–117*t*
bivalirudin
for STEMI, 662
for UA/NSTEMI, 670

bladder
cancer, 333–334
hyper/hyporeflexia in multiple sclerosis, 1019
pain, 246
Blakemore-Sengstaken tube, for esophageal varices, 832
blastomycosis, 580–582, 1035*t*
bleeding disorders, 277–281
blood vessel wall defects, 279
coagulation disorders, 279–280
platelet disorders, 277–278
treatment of, 280–281
bleomycin, for testicular cancer, 336
blepharospasm, 997
blood loss
anemia and, 194
anemia in, 269
symptoms of, 174
blood smear, 265–266
erythrocyte abnormalities, 265
leukocyte abnormalities, 266
platelet abnormalities, 266
blood urea nitrogen (BUN), 197
blood vessel wall defects, 279
BLS (basic life support), 57–58, 58*f*, 59*f*, 60*f*
blue toe syndrome, 697
BNP. *See* B-type natriuretic peptide
body louse, 610–611
body mass index (BMI), 41, 901
body temperature, 127
bone density testing, 933, 934*t*
bone disease
neck pain in, 212
osteoporosis. *See* osteoporosis
bone infections
anaerobic, 476
osteomyelitis. *See* osteomyelitis
*P. aeruginosa*, 459, 460*t*
septic arthritis, 418–420, 427, 430
in tuberculosis, 484
bone marrow
cellularity of, 267
damage causing anemia, 268
erythroid:granulocytic ratio, 267
examination of, 194, 266–267
bone marrow aspirate, 266–267
bone marrow failure, 277
bone marrow transplant. *See* hematopoietic stem cell transplant (HSCT)
bone metastasis, osteoblastic, in men, 348
borderline personality disorder, 1070
*Bordetella pertussis* infections. *See* pertussis
Bornholm disease, 544
*Borrelia burgdorferi* infections. *See* Lyme borreliosis
*Borrelia miyamotoi* infections, 499
*Borrelia recurrentis* infections, 498–499
bortezomib, for multiple myeloma, 302
bosentan
for pulmonary hypertension, 702
for systemic sclerosis, 848
botulinum toxin
for achalasia, 164
for anal fissures, 798
for dystonia, 237
for hemifacial spasm or blepharospasm, 998
botulism, 471–472, 991, 1050
bounding (hyperkinetic) pulse, 613, 614*f*
Bowen's disease, 308
BPPV (benign paroxysmal positional vertigo), 227, 227*t*, 228*t*, 229
brachial neuritis, acute, 212–213
brachial plexus, injury to, 212–213
bradyarrhythmias
approach to, 60, 60*f*
in AV block, 677–678, 678*t*
in sinoatrial node dysfunction, 677
in STEMI, 663
bradycardia, 677
bradykinesia, 233, 236
brain abscess, 478, 1020, 1029–1030
brain death, 81–82
brain herniation, 94, 94*f*
brain mass, in cancer patients, 364
brain metastasis, 1001*t*, 1010–1011
brain tumor, 971
approach to, 1008
headache in, 215*t*
intracranial, 1009–1010
metastatic, 84*t*
treatment of, 1008
brainstem encephalitis, 353
brainstem lesion, 234*t*
*BRCA* genes, 317, 321, 338, 1100
break-bone fever, 550
breast cancer, 316–321
in axillary lymph node, 348
diagnosis of, 317–318, 317*f*
epidemiology of, 316
genetic factors in, 317
incidence of, 316
infections in, 363*t*

metastatic, 321
oncologic emergencies, 110–111
paraneoplastic syndromes in, 349*t*, 353*t*, 354*t*
prevention of, 321, 1100
prognosis of, 320*t*
risk factors for, 1099
screening for, 1089–1090*t*, 1091*t*, 1095, 1096*t*
staging of, 318–320, 319–320*t*
treatment of, 320–321
breast mass, approach to, 317–318, 317*f*
Brenner tumor, 338
Brill-Zinsser disease, 506
Broca's aphasia, 239*t*, 240
bromocriptine
for acromegaly, 881
for hyperprolactinemia, 880
bronchiectasis, 727–729
bronchitis, hemoptysis in, 148
bronchoalveolar lavage (BAL), 710
bronchodilators
for asthma, 713
for bronchiectasis, 729
for COPD, 720, 721
for cor pulmonale, 693
bronchoscopy, 149, 149*f*, 710
Brown-Séquard syndrome, 235*t*, 1002
brucellosis, 462–464, 463*t*, 1034*t*
Brugada syndrome, 679
Brugia infections. *See* filariasis
Bruton's tyrosine kinase gene, 843
B-type natriuretic peptide (BNP)
in dilated cardiomyopathy, 640
in heart failure, 688
bubonic plague, 465–466
Budd-Chiari syndrome, 188*f*
bulimia nervosa, 1079, 1080
bullae (skin lesion), 257*t*, 416
bumetanide
for edema, 153*t*
for heart failure, 690*t*
for hypertension, 655
BUN (blood urea nitrogen), 197
bundle branch block
left, 619*f*, 621*t*
right, 619*f*
bundled interventions, 358, 359*t*
buprenorphine
abuse, 1084
for opioid maintenance, 1086
bupropion
as antidepressant, 1071
dosage and side effects of, 1073*t*
for smoking cessation, 720, 1103
*Burkholderia cepacia* infections, 461*t*, 462
*Burkholderia mallei* infections, 461*t*, 462
*Burkholderia pseudomallei* infections, 461*t*, 462
Burkitt's lymphoma/leukemia, 294, 296*f*, 300–301, 528
burn patient, neutrophilia in, 274
bursitis, 869
buspirone
as anxiolytic, 1074
dosage and action of, 1075*t*
for generalized anxiety disorder, 1068
butorphanol
for migraine, 218*t*
for pain, 39*t*
byssinosis, 717

**C**

cabazitaxel, for prostate cancer, 343
cabergoline
for acromegaly, 881
for hyperprolactinemia, 880
CABG (coronary artery bypass grafting), 664, 671, 676, 676*t*
cabozantinib, for renal cancer, 335
CAD (coronary artery disease), 627*f*. *See also* chronic stable angina
caffeine, for migraine, 217*t*
calamine lotion, for insect stings, 125
calcipotriol, for psoriasis, 259
calcitonin, for hypercalcemia, 351, 927*t*
calcitriol
for hypoparathyroidism, 929
for osteomalacia, 935
calcium antagonists, for tetanus, 470
calcium apatite deposition disease, 866–867, 866*t*
calcium carbonate, for hyperphosphatemia, 754
calcium channel blockers
for atrial fibrillation, 686
for chronic stable angina, 674–675
for hypertension, 651, 653*t*, 654*t*
for mitral stenosis, 632
for pulmonary hypertension, 702
for systemic sclerosis, 848
for vasospastic disorders, 698
calcium docusate, for constipation, 50*t*
calcium gluconate
for GI bleeding, 178
for hypocalcemia, 929
for muscle spasms, 120

calcium oxalate deposition disease, 867
calcium oxalate stones, 780, 781*t*
calcium phosphate stones, 780, 781*t*
calcium polycarbophil, for irritable bowel syndrome, 796*t*
calcium pyrophosphate dihydrate (CPPD) deposition disease, 865–866
calcium therapy
  for colon cancer prevention, 1100
  for hyperkalemia, 16*t*
  for hypermagnesemia, 930
  for hypocalcemia, 929
  for hypoparathyroidism, 929
  for osteoporosis, 934
  for primary biliary cirrhosis, 829
  for primary sclerosing cholangitis, 803
calicivirus infections, 389–390
Calvert formula, 339
campylobacteriosis, 394–395, 403
canagliflozin, for diabetes mellitus, 909*t*
cancer. *See also specific types and sites*
  depression in, 1064
  fatigue in, 133*t*
  hemoptysis in, 148
  infections in patients with, 362–366, 363*t*, 365*f*
  leukocytosis in, 275
  meningitis in, 1038*t*
  neck pain in, 212
  nervous system metastases in, 1011*t*, 1012
  oncologic emergencies, 109–113
  paraneoplastic syndromes
    endocrine, 348–351
    neurologic, 352–355, 352*t*
  prevention of, 1095*t*
  screening for, 1088–1090*t*, 1095–1096
  spinal cord compression in, 98–99
  vaccination of patients with, 369–370*t*, 369–371
  warning signs of, 1101
  weight loss with, 135
cancer chemotherapy
  leukopenia and, 276
  nausea and vomiting in, 160
cancer of unknown primary site (CUPS), 345–348
  biopsy in, 346–347*t*
  clinical manifestations of, 345
  cytogenetics in, 346–347*t*
  cytokeratin markers in, 347*f*
  histology of, 346*t*, 347
  prognosis for, 347
cancrum oris, 475
candesartan
  for heart failure, 690*t*
  for hypertension, 653*t*
  for migraine prophylaxis, 220*t*
  for STEMI, 662
candidiasis, 570–571
  in cancer patients, 364
  in catheter-associated urinary tract infections, 778
  cutaneous, 258, 262
  deeply invasive, 570–571
  esophageal, 166
  meningitis in, 1035*t*
  microbiology and epidemiology of, 570
  mucocutaneous, 570
  prevention of, 571
  treatment of, 262
  vulvovaginal, 262, 400–401, 570
CAP. *See* community-acquired pneumonia
CAPD-associated peritonitis, 383–384
capecitabine
  for breast cancer, 321
  for gastric carcinoma, 323
  for pancreatic cancer, 331
capillary telangiectasia, 84*t*
*Capnocytophaga canimorsus* infections, 115, 116*t*
capsaicin cream
  for osteoarthritis, 862
  for polyneuropathy, 1044, 1045*t*
capsulitis, adhesive, 870
captopril
  for heart failure, 688, 690*t*
  for hypertension, 653*t*
  for STEMI, 662, 667
carbamazepine
  for bipolar disorder, 1066
  dosage and side effects of, 1078*t*
  for glossopharyngeal neuralgia, 1000
  for multiple sclerosis, 1019
  for pain, 37, 39*t*
  for polyneuropathy, 1045*t*
  for seizures, 967*t*
  for trigeminal neuralgia, 995
carbapenems
  for *Aeromonas* infections, 458
  for enteric GNB infections, 458
  for extraintestinal *E. coli* infections, 454

for *Klebsiella* infections, 456
for nontuberculous mycobacterial infections, 494
for *P. aeruginosa* infections, 460*t*
carbidopa/levodopa, for Parkinson's disease, 978, 980*t*
carbidopa/levodopa/entacapone, for Parkinson's disease, 980*t*
carbimazole, for thyrotoxicosis, 890
carbohydrate requirements, 41
carbon monoxide poisoning, 100, 717
carbon tetrachloride poisoning, 815
carboplatin
for bladder cancer, 334
for head and neck cancer, 309
for ovarian cancer, 339
carbuncle, 427
carcinoid syndrome, 331, 332*t*
carcinoid tumor, 331–332, 349*t*
carcinomatosis, peritoneal, in women, 348
cardiac arrest, 57–60
follow-up of, 60
management of, 57–60, 58*f*, 59*f*, 60*f*
cardiac biomarkers
in STEMI, 658
in UA/NSTEMI, 688
cardiac catheterization
in cardiac tamponade, 647
in cardiomyopathy, 641*t*, 642
in constrictive pericarditis, 648
in pulmonary hypertension, 700
cardiac tamponade, 645, 647
*Cardiobacterium hominis* infections, 452, 453*t*
cardiogenic shock
approach to, 32, 33*f*
characteristics of, 62*t*
etiology of, 61*t*
treatment of, 64, 664, 665*t*, 666*f*
cardiomyopathy, 639–643
clinical and laboratory features of, 640*t*
dilated, 639–642
hypertrophic. *See* hypertrophic cardiomyopathy
restrictive, 640*t*, 642, 648*t*
cardiopulmonary resuscitation, 57–60, 58*f*
cardiorenal syndrome, 749
cardiovascular disease. *See* heart disease
carnitine palmitoyltransferase deficiency, 1059
carotene, serum, 178
carotid artery pulse, 613, 614*f*
carotid endarterectomy, 90–91
carotid stenosis, 90–91
carpal tunnel syndrome, 1046, 1047*t*
Carrión's disease, 468–469
carvedilol
for heart failure, 688, 690*t*
for hypertension, 652*t*
CASPAR criteria, for psoriatic arthritis, 858*t*
caspofungin
for aspergillosis, 574*t*
for *Candida* esophagitis, 166
pharmacology of, 569
for sepsis/septic shock, 68*t*
cast nephropathy, 772–773, 773*t*
Castleman's disease, 525
cat bite, 115, 116*t*, 417
cataplexy, 225, 243, 244*t*
catfish envenomation, 120–121
catheter-related infections
in cancer patients, 362, 364
urinary tract, 778
cat-scratch disease, 115, 467–468, 467*t*
cauda equina syndrome, 209, 1004
causalgia, 36, 994
cavernous angioma, 84*t*
cavernous sinus, 1001*f*
cavernous sinus syndrome, 1001–1002
CBT. *See* cognitive behavioral therapy
CD (Crohn's disease), 791. *See also* inflammatory bowel disease
CD40 ligand deficiency, 843
cefazolin
for cellulitis, 415*t*
for infective endocarditis, 377*t*
for infective endocarditis prophylaxis, 381*t*
for peritonitis, 383
for staphylococcal infections, 431*t*
for streptococcal infections, 431*t*, 439
cefdinir, for otitis media, 252*t*
cefepime
for bacterial meningitis, 1024*t*, 1025*t*
for brain abscess, 1030
for community-acquired pneumonia, 725*t*
for health care–associated pneumonia, 727*t*
for osteomyelitis, 421*t*
for *P. aeruginosa* infections, 460–461*t*
for sepsis/septic shock, 68*t*

cefixime, for gonococcal infections, 406*t*, 407*t*
cefotaxime
for bacterial meningitis, 1024*t*, 1025*t*
for bacterial peritonitis, 188
for brain abscess, 1030
for community-acquired pneumonia, 725*t*
for gonococcal infections, 406*t*, 407*t*
for *H. influenzae* infections, 449
for infectious arthritis, 420
for leptospirosis, 498
for Lyme borreliosis, 496
for meningococcal infections, 445
for nocardiosis, 479
for peritonitis, 382
for pneumococcal infections, 424
for sepsis/septic shock, 68*t*
cefotetan
for gonococcal infections, 406*t*
for pelvic inflammatory disease, 403, 407*t*
cefoxitin
for animal bite infections, 415*t*
for clostridial infections, 474*t*
for gas gangrene, 416*t*
for gonococcal infections, 406*t*
for human bite infections, 116*t*
for nontuberculous mycobacterial infections, 494
for pelvic inflammatory disease, 403
cefpodoxime, for community-acquired pneumonia, 725*t*
ceftaroline, for staphylococcal infections, 431*t*, 432*t*
ceftazidime
for bacterial meningitis, 1024*t*, 1025*t*
for brain abscess, 1030
for febrile neutropenia in cancer patient, 113
for glanders, 461*t*
for health care–associated pneumonia, 727*t*
for melioidosis, 461*t*
for neutropenia, 287
for osteomyelitis, 421*t*
for *P. aeruginosa* infections, 460–461*t*
for peritonitis, 383
ceftizoxime, for gonococcal infections, 406*t*
ceftriaxone
for bacterial meningitis, 1024*t*, 1025*t*
for *Bartonella* infections, 467*t*
for brain abscess, 1030
for brucellosis, 464
for chancroid, 413
for community-acquired pneumonia, 725*t*
for epididymitis, 400
for gonococcal infections, 406*t*, 407*t*
for *H. influenzae* infections, 449
for HACEK group infections, 453*t*
for health care–associated pneumonia, 727*t*
for infectious arthritis, 420
for infective endocarditis, 376–378*t*, 379
for infective endocarditis prophylaxis, 381*t*
for leptospirosis, 498
for Lyme borreliosis, 496
for meningococcal infections, 445
for meningococcal prophylaxis, 1025
for nocardiosis, 479
for osteomyelitis, 421*t*
for otitis media, 252*t*
for pelvic inflammatory disease, 403, 406t
for peritonitis, 382
for pneumococcal infections, 424
for proctitis, proctocolitis, enterocolitis, and enteritis, 405
for sepsis/septic shock, 68*t*
for shigellosis, 396
for typhoid fever, 393
for urethritis in men, 399
for Whipple's disease, 482
cefuroxime
for community-acquired pneumonia, 725*t*
for Lyme borreliosis, 496
for otitis media, 252*t*
celecoxib
for colon cancer prevention, 1100
for pain, 38*t*
celiac arteriography, 832
cellulitis
auricular, 249
in cancer patients, 362, 363*t*
clinical manifestations of, 417
clostridial, 473
diagnosis of, 436
*E. coli*, 454
*Klebsiella*, 456
microbiology of, 417
*Nocardia*, 478, 480*t*
pathogenesis of, 417
streptococcal, 436, 436*t*
treatment of, 415*t*

central catheter, clotted, 110
central nervous system (CNS) infections
after HSCT, 367*t*
approach to, 1020, 1021–1022*f*
brain abscess, 478, 1020, 1029–1030
in cancer patients, 364
cryptococcal, 572
encephalitis. *See* encephalitis
listerial, 446
meningitis. *See* meningitis
*P. aeruginosa*, 459, 460*t*
progressive multifocal leukoencephalopathy, 1030–1031
toxoplasmosis, 597
central pontine myelinolysis, 4
central sleep apnea (CSA), 243, 746
central venous catheter infections, 359*t*, 360
cepacia syndrome, 462
cephalexin
for infective endocarditis prophylaxis, 381*t*
for staphylococcal infections, 433*t*
for streptococcal infections, 436
cephalosporins
for *Aeromonas* infections, 458
for cholecystitis, 801
for epiglottitis, 254
for extraintestinal *E. coli* infections, 454
for *H. influenzae* infections, 449
for infectious arthritis, 420
for *M. catarrhalis*, 452
for meningococcal infections, 445
for necrotizing fasciitis, 416*t*
for peritonitis, 382–383
for pneumococcal infections, 424
for *Proteus* infections, 457
for salmonellosis, 394
for staphylococcal infections, 430
for urinary tract infections, 778
cerebellar degeneration, paraneoplastic, 352*t*, 353*t*, 354
cerebral angiography, 91
cerebral aspergillosis, 572
cerebral herniation, 94, 94*f*
cerebral palsy, 237
cerebral perfusion pressure (CPP), 93
cerebral salt wasting, 92
cerebritis, 1020, 1029
cerebrospinal fluid analysis
in bacterial meningitis, 1023, 1023*t*
in chronic meningitis, 1032
lumbar puncture, 28–30
lumbar puncture for, 29*f*
in viral meningitis, 1026–1027
Cernunnos deficiency, 840
certolizumab
for psoriatic arthritis, 858
for rheumatoid arthritis, 46
ceruloplasmin, serum, 946
Cervarix, 414
cervical angina syndrome, 212
cervical cancer, 340–341
clinical manifestations of, 414
incidence and epidemiology of, 340–341
paraneoplastic syndromes in, 349*t*
prevention of, 341, 414, 1101
risk factors for, 1101
screening for, 341, 1091*t*, 1096–1097*t*
staging and prognosis in, 339*t*, 340
cervical intraepithelial neoplasia, 1101
cervical lymph node metastasis, 348
cervical spine disease, pain in, 139*f*, 141, 212
cervicitis, mucopurulent, 401–402
cestode infections, 606–610
cetirizine
for allergic rhinitis, 838
for urticaria/angioedema, 837
cetuximab
for colorectal cancer, 328
for head and neck cancer, 309
cevimeline, for Sjögren's syndrome, 849
CFS (chronic fatigue syndrome), 134–135, 134*t*, 1064
Chagas' disease, 594–595
chagoma, 594
chancre, syphilitic, 409
chancroid, 404*t*, 413
channelopathy, 1059–1060
Charcot's joint, 867
Charcot's triad, 802
chelation therapy
for hemochromatosis, 944
for Wilson's disease, 946
chest pain, 137–141
in ankylosing spondylitis, 856
approach to, 141
causes of, 137–141, 138*t*
differential diagnosis of, 139*f*, 140*f*
noncardiac, 164
in STEMI, 658
chest wall disease, 138*t*, 143
chest wall pain, 139*f*, 141

chest x-ray (CXR)
in aortic disease, 694
in cardiac tamponade, 647
in cardiomyopathy, 641*t*
in congenital heart disease, 628–630
in cor pulmonale, 692
in heart failure, 687
in hemoptysis, 149, 149*f*
indications for, 23
in interstitial lung disease, 736
in mitral stenosis, 632
normal, 24*f*
in pericarditis, 645
in pneumonia, 724
in pulmonary edema, 144
in pulmonary embolism, 731
in pulmonary hypertension, 700
in respiratory disease, 709
in superior vena cava syndrome, 110
utility of, 23
Cheyne-Stokes respiration, 55*t*, 81
chickenpox, 361, 523
Chikungunya virus infections, 550
Child-Pugh classification, of cirrhosis, 827*t*
Chinese herbal nephropathy, 772
chlamydial infections
adult inclusion conjunctivitis, 514–515
*C. pneumoniae*, 513
cervicitis, 401–402
clinical manifestations of, 408
diagnosis of, 408
epidemiology of, 408
epididymitis, 400
microbiology of, 408
pelvic inflammatory disease, 402–403
proctitis, proctocolitis, enterocolitis, and enteritis, 403, 405
psittacosis, 515–516
trachoma, 514–515
treatment of, 408
urethritis, 400
vulvovaginal infections, 400–401
chloramphenicol
for anaerobic infections, 476*t*
for *Bartonella* infections, 467*t*
for plague, 466
for Rocky Mountain spotted fever, 504
for scrub typhus, 507
for tick-borne spotted fevers, 505
chlordiazepoxide
for alcohol withdrawal, 1083
dosage and action of, 1075*t*
chloroquine
for inflammatory bowel disease, 794
for malaria, 588*t*
for malaria prophylaxis, 590*t*
for porphyria cutanea tarda, 945
for Whipple's disease, 482
chlorpheniramine
for allergic rhinitis, 838
for urticaria/angioedema, 837
chlorpromazine
for delirium, 52*t*
dosage and side effects of, 1076*t*
for migraine, 218*t*
for tetanus, 470
chlorthalidone, for hypertension, 652*t*
cholangiography, 186, 800*t*
cholangiopancreatography, 800*t*, 802
cholangitis, 802–803
cholecystectomy, 800, 801, 803
cholecystitis, 801–802
choledocholithiasis, 802–803
cholelithiasis, 799–800, 800*t*
cholera, 387, 389
cholestasis, liver function tests in, 184*t*
cholesterol, 936. *See also* hypercholesterolemia
cholesterol gallstones, 799
cholestyramine
for acute viral hepatitis, 814
for dyslipidemia, 938*t*
for erythropoietic protoporphyria, 945
for irritable bowel syndrome, 795, 796*t*
for nephrolithiasis, 781*t*
for primary biliary cirrhosis, 829
for primary sclerosing cholangitis, 803
for toxic and drug-induced hepatitis, 815
cholinesterase inhibitors, for Alzheimer's disease, 973
chondrocalcinosis, 865
CHOP regimen
for aggressive lymphoma, 299
for follicular lymphoma, 298
for gastric carcinoma, 324
choreoathetosis, 237
choriocarcinoma, 336, 349*t*
chorioretinitis, in toxoplasmosis, 597
chronic, 802
chronic fatigue syndrome (CFS), 134–135, 134*t*, 1064
chronic interstitial nephritis, 772
chronic kidney disease (CKD)
classification of, 198*t*

differential diagnosis of, 752–753
epidemiology of, 752
etiology of, 752*t*
laboratory testing in, 753
renal transplantation for. *See* renal transplantation
slowing progression of, 754
treatment of, 753–754
uremic syndrome in, 753
chronic low back pain (CLBP), 211. *See also* low back pain
chronic lymphocytic leukemia (CLL)
clinical manifestations of, 296–297
staging of, 296–297, 297*t*
treatment of, 297
chronic lymphoid leukemia/lymphoma, 295*t*, 296*f*
chronic myeloid leukemia (CML), 287–289
clinical manifestations of, 287–288
incidence of, 287
natural history of, 288
response criteria for, 288*t*
treatment of, 288–289
chronic obstructive pulmonary disease (COPD), 718–722
clinical manifestations of, 719
dyspnea in, 142
*H. influenzae* infection in, 448–449
*M. catarrhalis* infections in, 451–452
pulmonary function tests in, 718*t*, 719–720
sleep disorders in, 242
treatment of, 720–721
chronic progressive external ophthalmoplegia (CPEO), 1057, 1059
chronic pulmonary aspergillosis, 572
chronic stable angina
clinical manifestations of, 672
imaging in, 673
laboratory testing in, 672
physical examination in, 672
stress testing in, 672, 673*f*, 674*t*
treatment of, 674–676, 675*t*, 676*t*
Churg-Strauss syndrome (eosinophilic granulomatosis with polyangiitis), 851
Chvostek's sign, 928
ciclopirox olamine, for dermatophyte infections, 262
cidofovir
for adenovirus infections, 537
for cytomegalovirus infections, 527
for HSV infections, 522*t*
for viral encephalitis, 1029
ciguatera poisoning, 121
cilostazol, for peripheral arteriosclerosis, 697
cimetidine
for antivenom reaction, 119
for erosive gastropathies, 788
ciprofloxacin
for *Aeromonas* infections, 458
for animal bite infections, 116*t*, 415*t*
for *Bartonella* infections, 467*t*
for chancroid, 413
for cholecystitis, 801
for cholera, 389
for clostridial infections, 474*t*
for community-acquired pneumonia, 725*t*
for diverticulitis, 796
for health care–associated pneumonia, 727*t*
for infectious arthritis, 420
for inflammatory bowel disease, 794
for intestinal pseudoobstruction, 797
for *M. pneumoniae* infections, 511
for meningococcal prophylaxis, 446
for murine typhus, 506
for necrotizing fasciitis, 416*t*
for osteomyelitis, 421*t*
for *P. aeruginosa* infections, 460–461*t*
for perichondritis, 250
for peritonitis prevention, 382
for plague, 466
for Q fever, 510
for sepsis/septic shock, 68*t*
for shigellosis, 396
for staphylococcal infections, 430
for tick-borne spotted fevers, 505
for tuberculosis, 486
for typhoid fever, 393
for urinary tract infections, 778
circadian rhythm disorder, 241
circadian rhythm sleep disorders, 245
circulatory overload, 46
cirrhosis
ascites in, 187, 188*f*
Child-Pugh classification of, 827*t*
clinical manifestations of, 826
complications of, 827, 827*t*
definition of, 826
edema in, 151, 152
etiology of, 826*t*
liver function tests in, 184*t*
primary bacterial peritonitis in, 382
primary biliary, 828–829

cisplatin
for bladder cancer, 334
for cervical cancer, 341
for endometrial cancer, 340
for esophageal carcinoma, 322
for gastric cancer, 323
for head and neck cancer, 309
for lung cancer, 313, 315
for ovarian cancer, 339
for testicular cancer, 336
citalopram, 1072*t*
citrate therapy
for nephrolithiasis, 782*t*
for renal tubular acidosis, 775
*Citrobacter* infections, 457
CJD (Creutzfeldt-Jakob disease), 970*t*, 971, 975
CKD. *See* chronic kidney disease
cladribine, for follicular lymphoma, 298
clarithromycin
for community-acquired pneumonia, 725*t*
for *H. influenzae* infections, 449
for *H. pylori* eradication, 787*t*
for infective endocarditis prophylaxis, 381*t*
for *Legionella* infections, 512–513
for *M. catarrhalis*, 452
for nontuberculous mycobacterial infections, 494
for pertussis, 451
claudication, intermittent, 696
claustrophobia, 1069
clenched-fist injury, 116*t*, 118
clindamycin
for actinomycosis, 481
for animal bite infections, 116*t*, 415*t*
for asymptomatic GAS carriage, 435
for babesiosis, 592
for bacterial vaginosis, 401
for cellulitis, 415*t*
for clostridial infections, 474*t*
for *Corynebacterium* infections, 443
for diphtheria, 442
for gas gangrene, 416*t*
for infective endocarditis prophylaxis, 381*t*
for lung abscess, 730
for malaria, 588*t*
for necrotizing fasciitis, 416*t*
for osteomyelitis, 421*t*
for otitis media, 252*t*
for pelvic inflammatory disease, 403, 407*t*
for pneumococcal infections, 424
for *Pneumocystis* infections, 584*t*
for sepsis/septic shock, 68*t*
for sinusitis, 249*t*
for snakebite, 117*t*
for staphylococcal infections, 433*t*, 434
for streptococcal infections, 436*t*, 439
for toxoplasmosis, 598
CLL. *See* chronic lymphocytic leukemia
clobazam, for seizures, 961*t*
clofazimine, for leprosy, 492
clomiphene citrate, for female infertility, 924
clomipramine
dosage and side effects of, 1072*t*
for narcolepsy, 244
for obsessive-compulsive disorder, 1068
pharmacology of, 1071
clonazepam
dosage and action of, 1075*t*
for dyspnea, 51*t*
for myoclonus, 238
for pain, 39*t*
for posthypoxic myoclonus, 101
for seizures, 961*t*, 967*t*
for vertigo, 228*t*
clonidine
for ascites, 188
for menopausal symptoms, 922
for narcotic withdrawal, 1085
for smoking cessation, 1103
for tics, 238
clonorchiasis, 606
clopidogrel
for STEMI, 662, 667
for stroke prevention, 89
for thrombotic disorders, 283
for UA/NSTEMI, 670, 671
clorazepate, 1075*t*
clostridial infections
*C. botulinum*, 471–472
*C. perfringens*, 416*t*, 418, 473, 474*t*
*C. tetani*, 469–471
enteric, 387, 473
skin and soft tissue, 473
treatment of, 474*t*
wound contamination, 473
*Clostridium difficile* infections
diarrhea, 397–398
nosocomial, 360–361
clotrimazole, for candidiasis, 401

cloxacillin, for infective endocarditis, 377*t*
clozapine
dosage and side effects of, 1077*t*
for schizophrenia, 1067
clubbing, 146, 149
cluster headache, 215, 215*t*, 219–220
CML. *See* chronic myeloid leukemia
CMV infections. *See* cytomegalovirus infections
CMV regimen, for bladder cancer, 334
CNS disease. *See* central nervous system disease
coagulase-negative staphylococci (CoNS), 428–429, 430, 431–433*t*
coagulation disorders, 279–280
intracranial hemorrhage in, 84*t*
in liver disease, 185
coal tar shampoo, 260
coal worker's pneumoconiosis, 717
coarctation of aorta, 630–631, 649
coccidioidomycosis, 578–579, 1034*t*
Cockcroft-Gault formula, 197
codeine
abuse, 1084
for cough, 148
for dyspnea, 51*t*
for pain, 38*t*
CODOX-M regimen, for Burkitt's lymphoma, 301
cognitive behavioral therapy (CBT)
for chronic back pain, 211
for chronic fatigue syndrome, 135
for insomnia, 242
for obsessive-compulsive disorder, 1068
cogwheeling, 976
colchicine
for amyloidosis, 875
for gout, 864, 865
for pericarditis, 645
for pseudogout, 866
colectomy, 327, 794
colesevelam, for dyslipidemia, 939*t*
colestipol, for dyslipidemia, 939*t*
colistin
for enteric GNB infections, 458
for *Klebsiella* infections, 456
for *P. aeruginosa* infections, 461*t*
colitis
amebic, 396–397
ischemic, 798
ulcerative, 791. *See also* inflammatory bowel disease
collagen vascular disease, 275
colon cut-off sign, 804
colonic angiodysplasia, 798
colonic polyps, 326–327, 326*t*
colonoscopy
for colonic angiodysplasia, 798
for colonic polyps, 326
for colorectal cancer diagnosis, 328
for colorectal cancer screening, 330, 1095, 1097*t*
in diarrhea, 170
for GI bleeding, 175
colorectal cancer, 327–330
clinical manifestations of, 328
diagnosis of, 328
etiology of, 327
pathology of, 328, 329*f*
prevention of, 330, 1100
risk factors for, 327–328, 1100
screening for, 330, 1089–1090*t*, 1091*t*, 1095, 1097*t*, 1100
staging and prognosis for, 329*f*
treatment of, 328
colostomy, for anal cancer, 330
coma, 76, 79–81
approach to, 79
differential diagnosis of, 80*t*
eye movements in, 81
in head trauma, 97–98
pupillary signs in, 81
respiratory patterns in, 81
responsiveness in, 79
common cold, 247, 533, 534*t*, 535
common variable immunodeficiency (CVID), 843
community-acquired pneumonia (CAP)
clinical manifestations of, 723
complications of, 725
diagnosis of, 724
epidemiology of, 723
hospitalization for, 724
microbiology of, 723
treatment of, 724–726, 725*t*
complete transposition of great arteries, 631
complex regional pain syndrome, 994
compression stockings, 92
for orthostatic hypotension, 994
for peripheral vascular disease, 699
compulsive personality disorder, 1070
computed tomography (CT)
in acute, catastrophic abdominal pain, 157
in coma, 81

computed tomography (CT) (*Cont.*):
in heart disease, 625–626, 626*t*
hepatobiliary, 800*t*
in hepatobiliary disease, 185
in increased intracranial pressure, 95
indications for, 25
for lung cancer screening, 1098*t*
in pancreatitis, 805
in respiratory disease, 709
in stroke, 85, 87
in subarachnoid hemorrhage, 91
utility of, 25
COMT inhibitors, for Parkinson's disease, 978
concussion, 96–97
conduction aphasia, 239*t*, 240
condylomata acuminata, 256*f*, 413
condylomata lata, 409
confusion, 76
congenital heart disease, 627–631
acyanotic lesions with left-to-right shunt, 627–629
acyanotic lesions without shunt, 629–631
complex heart lesions, 631
echocardiography in, 625
endocarditis prophylaxis in, 631
pulmonary hypertension in, 629
congenital rubella syndrome, 539–540
conivaptan, for SIADH, 112, 351, 886
conjunctivitis
acute hemorrhagic, 545
adult inclusion, 514–515
trachoma, 514–515
connective tissue disease, 844–845
antiphospholipid syndrome, 849–850
interstitial lung disease in, 738
mixed, 848
rheumatoid arthritis. *See* rheumatoid arthritis
Sjögren's syndrome, 848–849
systemic lupus erythematosus. *See* systemic lupus erythematosus
systemic sclerosis, 847–848
CoNS (coagulase-negative staphylococci), 428–429, 430, 431–433*t*
consciousness, disorders of, 76–82, 96
constipation, 170–174
drug-induced, 171
etiology of, 171
in irritable bowel syndrome, 795, 796*t*
in terminally ill patient, 50, 50*t*
treatment of, 172–173, 173*f*
contact precautions, 357
continuous positive airway pressure (CPAP), 746
continuous renal replacement therapy (CRRT), 751
contraception, 922–923
conversion disorder, 1069
coordination, testing of, 951
COP (cryptogenic organizing pneumonia), 736, 738
COPD. *See* chronic obstructive pulmonary disease
copper metabolism disorders, 945–946
coprolalia, 238
cor pulmonale, 692–693
coronary arteriography, 671, 673
coronary artery bypass grafting (CABG), 664, 671, 676, 676*t*
coronary artery disease (CAD), 627*f*. *See also* chronic stable angina
coronary artery spasm, 672
coronary vasospasm, 676
coronavirus infections, 533, 534*t*, 535
cortical encephalitis, 353
corticosteroid therapy. *See* glucocorticoid therapy
cortisol, excess of, 896
cortisone, for hypopituitarism, 883*t*
*Corynebacterium diphtheriae* infections, 441–442
*Corynebacterium ulcerans* infections, 443
*Corynebacterium urealyticum* infections, 443
costochondral pain, 139
cotton dust, 717
cough, 147–148
cover test, 231
COX-2 inhibitors, for osteoarthritis, 862
*Coxiella burnetii* endocarditis, 378*t*. *See also* Q fever
coxsackievirus infections, 253, 543, 544. *See also* enteroviral infections
CPAP (continuous positive airway pressure), 746
CPEO (chronic progressive external ophthalmoplegia), 1057, 1059
CPP (cerebral perfusion pressure), 93
CPPD (calcium pyrophosphate dihydrate) deposition disease, 865–866

cranial nerves
CN I. *See* olfactory nerve
CN V. *See* trigeminal nerve
CN VII. *See* facial nerve
CN X. *See* vagus nerve
CN XI. *See* accessory nerve
CN XII. *See* hypoglossal nerve
disorders of, 995–1002
examination of, 947–948
multiple cranial nerve palsies, 1001–1002
C-reactive protein (CRP), 1094
creatinine, serum, 753
creatinine clearance, 197
crescent sign, 869
CREST syndrome, 847
Creutzfeldt-Jakob disease (CJD), 970*t*, 971, 975
critical care medicine, 31–35
critically ill patient, 31–35
initial evaluation of, 31–32
limitation or withdrawal of care for, 35
mechanical ventilation, 32–34
monitoring in ICU, 34
multiorgan system failure, 34
neurologic dysfunction in, 35
prevention of complications in, 34–35
shock, 32, 33*f*
crizotinib, for lung cancer, 315
crocodile tears, 996
Crohn's disease (CD), 791. *See also* inflammatory bowel disease
cromolyn sodium
for allergic rhinitis, 838
for asthma, 714
for systemic mastocytosis, 839
Cronkhite-Canada syndrome, 325
crossed SLR sign, 207
croup, 536–537
CRP (C-reactive protein), 1094
CRRT (continuous renal replacement therapy), 751
crust (skin lesion), 257*t*, 417
cryoglobulinemia, 768*t*
cryoglobulinemic vasculitis, 851
cryoprecipitate, 47, 280
cryotherapy
for HPV infections, 414
for warts, 262
cryptococcosis
clinical manifestations of, 573
diagnosis of, 573, 576
epidemiology of, 573
meningitis, 364, 1034*t*
treatment of, 576
cryptogenic organizing pneumonia (COP), 736, 738
cryptosporidiosis, 391–392
CSA (central sleep apnea), 243, 746
CT. *See* computed tomography
Cullen's sign, 804
CUPS. *See* cancer of unknown primary site
CURB-65, 724
Cushing's syndrome
clinical manifestations of, 896
diagnosis of, 896
etiology of, 895
paraneoplastic, 348–349, 349*t*, 351
treatment of, 896
cutaneous larva migrans, 600
cutaneous leishmaniasis, 593–594
CVID (common variable immunodeficiency), 843
CXR. *See* chest x-ray
cyanide poisoning, 100
cyanosis, 145–146
approach to, 146
causes of, 146*t*
central, 145, 146*t*
peripheral, 145–146, 146*t*
cyclic adenosine monophosphate eyedrops, 849
cyclobenzaprine
for back pain, 211
for multiple sclerosis, 1019
cyclophosphamide
for acute renal failure, 751
for ANCA-associated glomerulonephritis, 762
for breast cancer, 320, 321
for Burkitt's lymphoma/leukemia, 301
for CLL, 297
for gastric carcinoma, 324
for idiopathic thrombocytopenic purpura, 280
for inflammatory myopathy, 1059
for lymphoma, 299
for multiple sclerosis, 1019
for myasthenia gravis, 1053
for polyneuropathy, 1046
for SLE, 762, 845
for systemic sclerosis, 848
for vasculitis, 854
cyclosporiasis, 392

cyclosporine
for aplastic anemia, 274
for focal glomerulosclerosis, 765
for immunosuppression after renal transplantation, 758
for inflammatory bowel disease, 794
for inflammatory myopathy, 1059
for membranous glomerulonephritis, 764
for myasthenia gravis, 1053
for polyneuropathy, 1046
for primary sclerosing cholangitis, 803
for psoriasis, 259
cyclosporine eyedrops, 849
cyproheptadine, for urticaria/angioedema, 837
cystectomy, 334
cystic fibrosis, 242
cysticercosis, 607–608, 608*t*, 1036*t*
cystine stones, 778, 782*t*
cystitis
definition of, 775
diagnosis of, 246
interstitial, 778–779
cystoisosporiasis, 392
cytarabine
for ALL, 300
for AML, 286*f*, 287
cytoadherence, 586
cytokeratin, in cancer of unknown primary site, 347, 347*f*
cytokine signaling deficiency, 840
cytokines, 275
cytomegalovirus (CMV) infections, 525–527
congenital, 526
diagnosis of, 527
epidemiology of, 525–526
in immunocompromised host, 758–759
microbiology of, 525
mononucleosis, 526
pathogenesis of, 526
perinatal, 526
pharyngitis, 253
in transplant recipients, 368–369, 526–527
treatment of, 527
cytomegalovirus immune globulin, 527
cytopenia, refractory, 290–291*t*

**D**

dabigatran
for atrial fibrillation, 686
for thrombotic disorders, 282
dacarbazine, for melanoma, 307
DAH (diffuse alveolar hemorrhage), 148, 149
dalbavancin, for staphylococcal infections, 432*t*
dalteparin
for thrombotic disorders, 281
for venous thromboembolism, 733
danazol
for autoimmune hemolysis, 274
for idiopathic thrombocytopenic purpura, 280
dantrolene, for multiple sclerosis, 1019
dapagliflozin, for diabetes mellitus, 909*t*
dapsone
for ANCA-associated glomerulonephritis, 762
for leprosy, 492
for *Pneumocystis* infections, 584*t*
for *Pneumocystis* prophylaxis, 585*t*
for toxoplasmosis, 598
daptomycin
for enterococcal infections, 440
for infective endocarditis, 379
for osteomyelitis, 421*t*
for staphylococcal infections, 430, 431*t*, 432*t*
darunavir, for HIV infection, 563*t*
dasatinib, for CML, 288
daunorubicin
for ALL, 300
for AML, 286*f*, 287
daytime sleepiness, excessive, 241, 243–245, 244*t*
DDAVP. *See* desmopressin
death. *See also* terminally ill patient
brain death, 81–82
leading causes by age group, 1088–1090*t*
rates of, 54
death rattle, 55*t*
debranching enzyme deficiency, 1059
decerebrate posturing, 81
decitabine, for myelodysplastic syndromes, 289
decorticate posturing, 79
deep-brain stimulation (DBS), 237, 981
deep-vein thrombosis (DVT)
in critically ill patient, 35
diagnosis of, 731, 732*f*
etiology of, 730

in thrombotic disorders, 281
treatment of, 281–283, 732–733
defecation, 167
deferasirox
for mucormycosis, 577
for thalassemia, 273
deferoxamine
for hemochromatosis, 944
for thalassemia, 273
dehydration, in terminally ill patient, 54*t*
delavirdine, for HIV infection, 559
delayed sleep-wake phase syndrome, 241, 245
delirium
etiologies of, 77*t*
step-wise evaluation of, 78, 78*t*
in terminally ill patient, 52, 56*t*
treatment of, 52, 52*t*, 79
delirium tremens (DTs), 1082
demeclocycline
for hyponatremia, 351
for inappropriate vasopressin secretion, 351
for SIADH, 112, 351, 886
dementia, 968–975. *See also* Alzheimer's disease
approach to, 968, 971, 972*t*
causes of, 969*t*, 974–975
clinical manifestations of, 968
definition of, 968
differential diagnosis of, 968, 969*t*, 970*t*
sleep disorders in, 242
dementia with Lewy bodies (DLB), 970*t*, 971, 974, 991
dengue fever, 550, 552
denosumab, for osteoporosis, 934
dental caries, 475
dental procedures, endocarditis prophylaxis before, 380, 381*t*
dependent personality disorder, 1070
depression
clinical manifestations of, 1064
drug-induced, 1064
with medical illness, 1064
suicide in, 1065
in terminally ill patient, 52
treatment of, 52, 1064–1065, 1065*f*, 1071
weight loss in, 135
in women, 1106
dermatitis, 259–260
allergic contact, 260
atopic, 256*f*, 259–260
contact, 256*f*
irritant contact, 260
seborrheic, 256*f*, 260
stasis, 256*f*
dermatofibroma, 256*f*
dermatomes, 954*f*
dermatomyositis (DM), 1057–1059, 1058*t*
dermatophyte infections, 258, 261–262
desipramine
dosage and side effects of, 39*t*, 1072*t*
for pain, 39*t*
desloratadine
for allergic rhinitis, 838
for urticaria/angioedema, 837
desmopressin (DDAVP)
for diabetes insipidus, 6, 884
for hypernatremia, 6
for hyponatremia, 2, 5
for hypopituitarism, 883*t*
for von Willebrand disease, 281
desquamative interstitial pneumonia (DIP), 738
desvenlafaxine, 1071, 1072*t*
device-related infections, 358–360, 359*t*
DEXA (dual-energy x-ray absorptiometry), 933
dexamethasone
for bacterial meningitis, 1024–1025
for brain tumor, 1008
for *H. influenzae* infections, 449
for hirsutism, 920, 921
for increased intracranial pressure, 95*t*
for multiple myeloma, 302
for pneumococcal infections, 425
for spinal cord compression, 99, 111
for thyroid storm, 891
for typhoid fever, 393
dexamethasone suppression test, 896
dextroamphetamine
for depression, 52
for fatigue, 52
for narcolepsy, 244
dextromethorphan, for cough, 148
DGI (disseminated gonococcal infections), 419
diabetes insipidus
central, 5, 199, 199*t*, 884
drug-induced, 5
gestational, 884
nephrogenic, 5, 199, 199*t*, 884
treatment of, 6, 884

diabetes mellitus (DM), 904–912
cardiovascular disease and, 1093, 1093*t*
clinical manifestations of, 905–906
complications of, 905–906, 907
depression in, 1064
diagnosis of, 904–905
etiology of, 904
in hospitalized patient, 911–912
hypertension in, 655
neuropathy in, 991, 1046
pancreatic cancer and, 331
prevalence of, 904
risk factors for, 905*t*
treatment of, 906–907, 907*t*, 908–910*t*, 911*f*, 1093
type 1, 904
type 2, 905
in women, 1105
diabetic ketoacidosis (DKA), 911
clinical manifestations of, 18*t*, 104
etiology of, 22, 104
laboratory values in, 104, 105*t*
pathogenesis of, 22
treatment of, 19–20, 106*t*
diabetic nephropathy, 765–766
diacetylmorphine, 1084
diagnostic imaging, 23–26
dialysis
hemodialysis. *See* hemodialysis
for hypercalcemia, 927*t*
peritoneal, 751, 755–756, 756*t*
slow low-efficiency, 751
diarrhea, 167–170
from altered intestinal motility, 168
chronic, physical examination in, 169*t*
from decreased absorptive state, 168, 173*t*
exudative, 168
infectious, 168, 386–398
approach to, 388*f*
inflammatory, 386*t*, 392–398
noninflammatory, 386–392, 386*t*
pathogens causing, 386*t*
penetrating, 386*t*
in irritable bowel syndrome, 795, 796*t*
metabolic acidosis in, 18*t*, 19
nosocomial, 360–361
osmotic, 167–168, 170
paraneoplastic, 349*t*
in patients with AIDS, 169*t*
secretory, 168
stool examination, 170
treatment of, 170, 171*f*, 172*f*
diascopy, 258
diastolic failure, 687
diazepam
for alcohol withdrawal, 1083
dosage and action of, 1075*t*
for multiple sclerosis, 1019
for muscle spasms, 120
for STEMI, 661
for vertigo, 228*t*
diazoxide therapy, for hypoglycemia, 109
DIC (disseminated intravascular coagulation), 278
dichloralphenazone, for migraine, 218*t*
diclofenac, for pain, 40
diclofenac K, for migraine, 217*t*
dicloxacillin
for staphylococcal infections, 433*t*
for streptococcal infections, 436
dicyclomine
for diverticular disease, 796
for irritable bowel syndrome, 795
dietary reference intake (DRI), 41
diethylcarbamazine, for filariasis, 603
diffuse alveolar hemorrhage (DAH), 148, 149
diffuse large B cell lymphoma, 299, 323
diffuse white matter disease, 974, 975*f*
digital rectal exam (DRE), 330, 342, 344*f*, 1099*t*
digitalis
for heart failure, 689*t*
for mitral stenosis, 632
toxicity of, 680*t*, 689–690
digoxin
for arrhythmias, 684*t*
for atrial fibrillation, 686
for cor pulmonale, 693
for heart failure, 688–689
for supraventricular arrhythmias, 663
for tachyarrhythmias, 680–681*t*
dihydroartemisinin-piperaquine, for malaria, 588*t*
dihydroergotamine, for migraine, 217*t*, 219*t*
dihydropyridine, for vasospastic disorders, 698
dilated cardiomyopathy, 639–642, 640*t*
diltiazem
for aortic dissection, 695
for arrhythmias, 684*t*

for atrial fibrillation, 686
for hypertension, 653*t*
for supraventricular arrhythmias, 663
for tachyarrhythmias, 680–681*t*
for UA/NSTEMI, 670
for Wolff-Parkinson-White syndrome, 686
dimenhydrinate
for nausea and vomiting, 160
for vertigo, 228*t*
dimethyl fumarate, for multiple sclerosis, 1018
dioctyl sodium sulfosuccinate, for hemorrhoids, 798
DIP (desquamative interstitial pneumonia), 738
diphenhydramine
for allergic rhinitis, 838
for anaphylaxis, 114
for antivenom reaction, 119
for urticaria/angioedema, 837
diphenoxylate
abuse, 1084
for diarrhea, 170
for inflammatory bowel disease, 792
for irritable bowel syndrome, 795
diphtheria, 441–442
diphtheria antitoxin, 442
diphtheria toxin, 441
diphtheria vaccine, 442
diphtheria-tetanus vaccine, 369*t*
diphyllobothriasis, 609–610
diplopia, 232, 232*t*
dipyridamole
for stroke prevention, 89
for thrombotic disorders, 283
disease prevention, 1087, 1090–1091*t*
disease-modifying antirheumatic drugs (DMARDs), for rheumatoid arthritis, 846
disequilibrium syndrome, dialysis, 755
disopyramide
for arrhythmias, 683*t*
for hypertrophic cardiomyopathy, 643
disseminated gonococcal infections (DGI), 419
disseminated intravascular coagulation (DIC), 278
distributive shock, 61*t*, 62
disulfiram, for alcoholic rehabilitation, 1084
diuresis, osmotic, 199*t*
diuretics
for ascites, 188
complications of, 8–9, 152, 154*t*, 239*t*
for cor pulmonale, 693
for diabetic nephropathy, 766
for dilated cardiomyopathy, 640
for edema, 151–152
for heart failure, 663–664, 688, 689*t*, 690*t*
for hypernatremia, 6
for hypertension, 651, 652*t*, 654*t*, 655*f*
for mitral stenosis, 632
for nephrolithiasis, 781*t*
for pulmonary hypertension, 702
for restrictive cardiomyopathy, 642
for slowing renal disease progression, 754
for STEMI, 665*t*
for tricuspid regurgitation, 639
divalproex, for generalized anxiety disorder, 1068
diverticular disease, 796
diverticulitis, 796
diverticulosis, 175, 178
Dix-Hallpike maneuver, 226
dizziness, 226
DKA. *See* diabetic ketoacidosis
DLB (dementia with Lewy bodies), 970*t*, 971, 974, 991
DLCO (diffusing capacity of lung), 707
DM (dermatomyositis), 1057–1059, 1058*t*
DM (diabetes mellitus). *See* diabetes mellitus
DMARDs (disease-modifying antirheumatic drugs), for rheumatoid arthritis, 846
DNA-dependent protein kinase gene deficiency, 840
Dobrava-Belgrade virus, 552
dobutamine
for heart failure, 91, 664, 664*t*, 691*t*
for pulmonary edema, 70
for shock, 64, 64*t*
for STEMI, 665*t*
docetaxel, for head and neck cancer, 309
docusate salts
for constipation, 50*t*, 174
in STEMI, 661
dofetilide
for arrhythmias, 684*t*
for dilated cardiomyopathy, 641

dog bite, 115, 116*t*, 417
Döhle bodies, 266
doll's head maneuver, 81
dolutegravir, for HIV infection, 559, 565*t*
domestic violence (intimate partner violence), 1091*t*, 1106
donepezil, for Alzheimer's disease, 973
donovanosis, 404*t*, 413
dopamine
  for anaphylaxis, 114
  for heart failure, 664*t*, 689*t*, 691, 691*t*
  for increased intracranial pressure, 95*t*
  for pulmonary edema, 70
  for shock, 64, 64*t*, 664
  for STEMI, 665*t*
dopamine agonists
  for acromegaly, 881
  for hyperprolactinemia, 880
  for Parkinson's disease, 978, 980*t*
doripenem, for *P. aeruginosa* infections, 460*t*
dorsal root ganglionopathy, paraneoplastic, 352*t*, 353*t*, 354*t*, 355
dosulepin, for migraine prevention, 220*t*
double vision, 232, 232*t*
doxepin
  dosage and side effects of, 39*t*, 1072*t*
  for pain, 39*t*
doxorubicin
  for bladder cancer, 334
  for breast cancer, 320, 321
  for Burkitt's lymphoma/leukemia, 301
  for carcinoid tumor, 332
  for endometrial cancer, 340
  for islet-cell tumors, 333
  for lymphoma, 299
  for multiple myeloma, 302
  for Zollinger-Ellison syndrome, 790
doxycycline
  for actinomycosis, 481
  for adult inclusion conjunctivitis, 515
  for animal bite infections, 415*t*
  for bacillary angiomatosis, 415*t*
  for *Bartonella* infections, 467*t*
  for brucellosis, 464
  for community-acquired pneumonia, 725*t*
  for COPD exacerbations, 721
  for *Corynebacterium* infections, 443
  for donovanosis, 413
  for endemic treponematosis, 497
  for enterococcal infections, 440
  for epidemic typhus, 507
  for epididymitis, 400
  for gonococcal infections, 406*t*
  for human granulocytotropic anaplasmosis, 508
  for human monocytotropic ehrlichiosis, 508
  for infective endocarditis, 378*t*
  for *Legionella* infections, 513
  for leptospirosis, 498
  for Lyme borreliosis, 496
  for Lyme disease prophylaxis, 123
  for lymphatic filariasis, 604
  for lymphogranuloma venereum, 408
  for *M. pneumoniae* infections, 511
  for malaria, 588*t*
  for malaria prophylaxis, 590*t*
  for murine typhus, 506
  for onchocerciasis, 604
  for pelvic inflammatory disease, 403, 406–407t
  for plague, 466
  for proctitis, proctocolitis, enterocolitis, and enteritis, 405
  for Q fever, 509–510
  for relapsing fever, 499
  for rickettsialpox, 505
  for Rocky Mountain spotted fever, 504
  for rodent bite infections, 117*t*
  for scrub typhus, 507
  for sinusitis, 249*t*
  for staphylococcal infections, 433*t*
  for syphilis, 411*t*
  for tick-borne spotted fevers, 505
  for tularemia, 465
  for urethritis in men, 399
  for Whipple's disease, 482
DRE (digital rectal exam), 330, 342, 344*f*, 1099*t*
DRI (dietary reference intake), 41
dronabinol, for weight loss, 137
dronedarone, for arrhythmias, 684*t*
droplet precautions, 357
drug-induced illness
  anemia, 269, 272*t*
  autonomic nervous system disease, 988
  AV block, 678*t*
  constipation/ileus, 171
  delirium, 77*t*

depression, 1064
diabetes insipidus, 5
edema, 151*t*
eosinophilia, 275
fatigue, 132, 133*t*
hepatitis, 815
hirsutism, 920
hyperkalemia, 6–7, 14*f*
hyperprolactinemia, 79
hypoglycemia, 107
hypokalemia, 7–8
insomnia, 242
intracranial hemorrhage, 84*t*
jaundice, 182*t*
leukopenia, 276
lupus, 844
metabolic acidosis, 18*t*
myopathy, 1060*t*, 1061
nausea and vomiting, 159*t*
nephritis, 771–772, 771*t*
neutropenia, 275–276
obesity, 901
pill-related esophagitis, 166
seizure, 59*t*
skin disorders, 263–264
thrombocytopenia, 278, 280
weight loss, 136*t*
DTaP vaccine, 442
DTs (delirium tremens), 1082
dual-energy x-ray absorptiometry (DEXA), 933
Duchenne's muscular dystrophy, 1054
ductal carcinoma in situ, 320
Duke criteria, for infective endocarditis, 374, 375*t*
dulaglutide, for diabetes mellitus, 909*t*
duloxetine
dosage and side effects of, 39*t*, 1072*t*
for fibromyalgia, 868
for pain, 39*t*
pharmacology of, 1071
for polyneuropathy, 1044, 1045*t*
duodenal ulcer, 785–786, 788*t*, 789*t*
durable attorney for health care, 49
Durie-Salmon staging, for multiple myeloma, 303*t*
dutasteride
for prostate cancer prevention, 345, 1100
for prostate hyperplasia, 342
DVT. *See* deep-vein thrombosis
dynamic visual acuity, for vertigo, 226
dysarthria, 83
dysbetalipoproteinemia, 937*t*, 941
dysentery, 386*t*, 389, 396–397
dysesthesia, 36
dysfunctional uterine bleeding, 917
dyskinesia, 978
dyslipidemia. *See also* hypercholesterolemia
in diabetes mellitus, 907
in metabolic syndrome, 656–657, 657*t*
treatment of, 938–939*t*
dysmenorrhea, 919, 920
dyspepsia, 160–161
dysphagia, 162–164, 1000
approach to, 162, 163*f*
esophageal, 164
oropharyngeal, 162–164
in terminally ill patient, 54*t*
dysphonia, 1000
dyspnea, 142–144
approach to, 143, 144*f*
in ARDS, 71
cardiac vs. pulmonary, 144*f*
in pulmonary edema, 144–145
in terminally ill patient, 51, 51*t*
treatment of, 51, 51*t*
dystonia, 237
dysuria, 245–246

**E**

EAEC (enteroaggregative and diffusely adherent *E. coli*) infections, 455
ear infections
anaerobic, 475
external, 249–250
middle. *See* otitis media
*P. aeruginosa*, 459, 460*t*
eastern equine encephalitis (EEE), 550
eating disorders
clinical manifestations of, 1079–1080
epidemiology of, 1079
treatment of, 1080
in women, 1106
Ebola virus infection, 552–553
Ebstein anomaly, 631
EBV infections. *See* Epstein-Barr virus infections
ECG. *See* electrocardiography
echinocandins
for candidiasis, 571
for mucormycosis, 577
pharmacology of, 569–570
for scedosporiosis, 582
echinococcosis, 608–609
echinocytes, 265

echocardiography, 622–625
in aortic disease, 624, 626*t*, 694
in aortic regurgitation, 638
in aortic stenosis, 636
in cardiac tamponade, 647
in cardiomyopathy, 641*t*
clinical uses of, 622–623, 622*t*, 624*f*
in congenital heart disease, 625, 628–630
in cor pulmonale, 692
in coronary artery disease, 672, 674*t*
Doppler, 622*t*
in endocarditis, 374
in heart failure, 688
in intracardiac mass, 624, 626*t*
in mitral regurgitation, 634
in mitral valve prolapse, 636
in myocarditis, 644
in palpitations, 142
in pericardial disease, 623–624, 626*t*
in pericarditis, 645, 648
in pulmonary embolism, 731
in pulmonary hypertension, 700
in STEMI, 659
stress, 622*t*, 625
in stroke, 87
transesophageal, 622*t*
2-D, 622*t*, 623*f*
in valvular heart disease, 623, 624*f*, 626*t*
echolalia, 238
echovirus infections, 543, 544, 1037*t*
ecstasy (MDMA), 4
ecthyma gangrenosum, 459
ectoparasites, 610–611
eczema, 256*f*, 259
eczema herpeticum, 517
edema, 150–154
approach to, 152*f*
drug-induced, 151*t*
generalized, 150–151
in heart failure, 688
idiopathic, 151
localized, 150
lymphedema, 699
treatment of, 151–152, 153*t*
EEE (eastern equine encephalitis), 550
EEG. *See* electroencephalography
efavirenz, for HIV infection, 559, 561*t*
effective circulating volume, 1*t*, 3
eflornithine, for sleeping sickness, 596
E:G (erythroid:granulocytic) ratio, bone marrow, 267
ehrlichiosis, 122
human monocytotropic, 502*t*, 507–508
EIEC (enteroinvasive *E. coli*) infections, 455
*Eikenella corrodens* infections, 452, 453*t*
Eisenmenger syndrome, 629
ejection click (heart sound), 615
elderly, joint pain in, 205–207
electrical nerve stimulation, for chronic back pain, 211
electrocardiography (ECG), 618–622
in cardiac hypertrophy, 619–620, 621*t*
in cardiac tamponade, 647
in cardiomyopathy, 641*t*, 642–643
in congenital heart disease, 628–630
in cor pulmonale, 692
in coronary artery disease, 672
heart rate, 618
in hyperkalemia, 9, 13, 14*f*, 15*f*
lead system, 618*f*
mean axis in, 618
in mitral stenosis, 632
in myocarditis, 643
in palpitations, 142
in pericarditis, 644, 645*t*, 646*f*, 647
PR interval, 618
in pulmonary hypertension, 700
QRS interval, 619
QT interval, 619
in recurrent angina, 667
rhythm, 618
in sinoatrial node dysfunction, 677
in STEMI, 141, 620, 621*f*, 621*t*, 645*t*, 658, 659
ST-T waves, 620, 622
in subarachnoid hemorrhage, 91
in tachyarrhythmias, 679, 680–682*t*
in variant angina, 676
electroconvulsive therapy, 1065
electrodiagnosis
in mononeuropathy, 1047–1049*t*
in muscle disease, 1054
in peripheral neuropathy, 1044
electroencephalography (EEG)
in brain death, 82
in coma, 81
in seizure, 958
in status epilepticus, 103
electrolyte balance, 1, 133*t*
elephantiasis, 603
eletriptan, for migraine, 217*t*, 219*t*
elliptocytes, 265

eltrombopag, for idiopathic thrombocytopenic purpura, 280
elvitegravir, for HIV, 565*t*
embolectomy, 733
embryonal carcinoma, 336
emergencies, medical, 57–60
  anaphylaxis, 114–115
  ARDS, 71–73
  bites, venoms, stings, and marine poisonings, 115–125
  cardiovascular collapse, 57–60
  diabetic ketoacidosis, 104, 106*t*
  head trauma, 96–98
  hyperglycemic hyperosmolar state, 104–105
  hypoglycemia, 107–109
  hypoxic-ischemic encephalopathy, 100–101
  increased intracranial pressure, 93–96
  oncologic, 109–113
  pulmonary edema, acute, 69–70
  respiratory failure, 73–76
  sepsis and septic shock, 65–68
  shock, 61–65
  spinal cord compression, 98–100
  status epilepticus, 101–103
  stroke, 82–91
  stupor and coma, 76–82
  subarachnoid hemorrhage, 91–93
emergency contraceptive pills, 923
emerging disease, 360–361
empagliflozin, for diabetes mellitus, 909*t*
emphysema
  dyspnea in, 143
  mediastinal, chest pain in, 138
empyema
  anaerobic, 475
  streptococcal, 423, 436*t*
emtricitabine, for HIV infection, 561*t*, 566
enalapril/enalaprilat
  for heart failure, 690*t*
  for malignant hypertension, 656*t*
encephalitis
  approach to, 1020, 1021–1022*f*
  in cancer patients, 364
  in measles, 538
  paraneoplastic, 352*t*, 353, 353*t*, 354*t*
  in rabies, 547
  viral
    clinical manifestations of, 1027
    cytomegalovirus, 527
    diagnosis of, 1028, 1028*f*
    differential diagnosis of, 1028–1029
    enteroviral, 544
    etiology of, 1027
    HSV, 521*t*
    prognosis of, 1029
    treatment of, 1029
encephalopathy
  hepatic, 832–833
  hypoxic-ischemic, 100–101
  Wernicke's, 1082–1083
endemic murine typhus, 502*t*, 505–506
endocarditis. *See* infective endocarditis
endocrine disease
  adrenal. *See* adrenal gland disease
  diabetes insipidus. *See* diabetes insipidus
  diabetes mellitus. *See* diabetes mellitus
  female reproductive system disorders, 917–924
  leukocytosis in, 275
  lymphadenopathy and, 190*t*
  male reproductive system disorders, 912–916
  muscle disorders in, 1060–1061
  nausea and vomiting in, 159*t*
  paraneoplastic, 348–351
  pituitary. *See* pituitary disease
  syndrome of inappropriate ADH. *See* syndrome of inappropriate ADH
  thyroid. *See* thyroid disease
  tumors of GI tract and pancreas, 331–333
  weight loss in, 136*t*
endodermal sinus tumor, 336
end-of-life care. *See* terminally ill patient
endometrial cancer, 339*t*, 340
endometritis, 402
endophthalmitis
  *Klebsiella*, 456
  *P. aeruginosa*, 461*t*
endoscopic retrograde cholangiopancreatography (ERCP), 800*t*, 802
endoscopic variceal ligation (EVL), 832
endoscopy
  in gastropathies, 788
  in GI bleeding, 175
  in peptic ulcer disease, 786
end-stage renal disease (ESRD), 752. *See also* chronic kidney disease

enfuvirtide, for HIV infection, 559, 564*t*
enoxaparin
for STEMI, 659, 662
for thrombotic disorders, 281
for UA/NSTEMI, 670
for venous thromboembolism, 733
entacapone, for Parkinson's disease, 980*t*
entecavir, for chronic hepatitis B, 817, 818–819*t*
enteral nutrition, 43–44, 44*f*
enteric bacilli, gram-negative, 453–458
*Aeromonas*, 458
extraintestinal *E. coli*, 454
intestinal pathogenic *E. coli*, 455
*Klebsiella*, 455–456
*Proteus*, 456–457
enteric fever, 386*t*, 392–394
enteritis, 403, 405
enteroaggregative and diffusely adherent *E. coli* (EAEC) infections, 455
*Enterobacter* infections, 421*t*, 457
enterobiasis (pinworm infection), 602–603
enteroclysis, 325
enterococcal infections, 434, 440–441
endocarditis, 372, 377*t*, 378–379
microbiology of, 434
osteomyelitis, 421*t*
enterocolitis, 403, 405, 792
enteroinvasive *E. coli* (EIEC) infections, 455
enteropathic arthritis, 867
enteropathogenic *E. coli* (EPEC) infections, 455
enterotoxigenic *E. coli* (ETEC) infections, 455
enteroviral infections, 534*t*, 544–546
entry inhibitors, for HIV infection, 559, 564*t*
envenomations
marine, 120–121
snakebites, 118–120
enzalutamide, for prostate cancer, 343
eosinopenia, 277
eosinophilia, 275, 738–739
eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome), 851
eosinophilic pneumonia, 738
EPEC (enteropathogenic *E. coli*) infections, 455
ependymoma, 1010
epidemic disease, 360–361
epidemic (louse-borne) typhus, 502*t*, 506–507
epidermal inclusion cyst, 256*f*
epididymitis, 400
epididymo-orchitis, in mumps, 541
epidural abscess
neck pain in, 212
*S. aureus*, 427
spinal, 99, 1005
epidural hematoma, 98, 100, 1005
epiglottitis, 254, 448–449
epilepsy. *See also* seizures
sleep disorders in, 242
status epilepticus, 101–103
treatment of, 961–966*t*, 967–968, 967*t*
epinephrine
for anaphylaxis, 114, 125
for antivenom reaction, 119
for croup, 537
for ventricular fibrillation, 59*f*
epirubicin, for gastric cancer, 323
eplerenone
for edema, 153*t*
for heart failure, 664, 688, 689*t*, 690*t*
for hyperaldosteronism, 21, 898
for hypertension, 652*t*
for STEMI, 662
Epley procedure, 229
epoprostenol
for pulmonary hypertension, 702
for systemic sclerosis, 848
eprodisate, for amyloidosis, 875
EPSEs (extrapyramidal side effects), 1074
Epstein-Barr virus (EBV) infections
cancer associated with, 294, 528–529
clinical manifestations of, 253, 528–529
diagnosis of, 529
epidemiology of, 528
in transplant recipients, 58
treatment of, 529
eptifibatide
for thrombotic disorders, 283
for UA/NSTEMI, 670
ERCP (endoscopic retrograde cholangiopancreatography), 800*t*, 802
erectile dysfunction, 915–916
ergotamine, for migraine, 217*t*, 219*t*

erlotinib
for lung cancer, 315
for pancreatic cancer, 331
erosion (skin lesion), 257*t*
ertapenem
for community-acquired pneumonia, 725*t*
for health care–associated pneumonia, 725*t*
for sepsis/septic shock, 68*t*
eruptive xanthoma, 940
erysipelas, 261, 417, 436, 436*t*
erythema infectiosum (fifth disease), 542
erythema migrans, 495
erythema multiforme, 263
in cancer patients, 362
in HSV, 522*t*
HSV infection and, 517
erythema nodosum, 263
erythema nodosum leprosum, 491, 492
erythrocytosis. *See* polycythemia
erythroid:granulocytic (E:G) ratio, bone marrow, 267
erythroleukemia, 284*t*
erythromycin
for acne, 262
for bacillary angiomatosis, 415*t*
for *Bartonella* infections, 467*t*
for *C. pneumoniae* infections, 513
for *C. psittaci* infections, 516
for campylobacteriosis, 395
for cellulitis, 415*t*
for chancroid, 413
for diphtheria, 442
for donovanosis, 413
for gastroparesis, 160
for *H. pylori* eradication, 161
for human bite infections, 116*t*
for Lyme borreliosis, 496
for lymphogranuloma venereum, 408
for pertussis, 451
for relapsing fever, 499
for streptococcal infections, 439
erythroplakia, 309
erythropoiesis, 194
erythropoietin, decreased level of, 268–269
erythropoietin therapy
for anemia, 273
for chronic kidney disease, 754
eschar, 417
*Escherichia coli* infections
enteroaggregative and diffusely adherent, 455
enteroinvasive, 455
enteropathogenic, 455
enterotoxigenic, 455
extraintestinal, 454
intestinal pathogenic, 455
Shiga toxin-producing/enterohemorrhagic, 395–396, 455
escitalopram, 1072*t*
esmolol
for aortic dissection, 695, 696*t*
for arrhythmias, 683*t*
for malignant hypertension, 656*t*
for tetanus, 470
esophageal cancer, 321–322, 349*t*
esophageal inflammation, 165–166
esophageal manometry, 264
esophageal motility disorders, 164–165
esophageal pain, 139*f*, 141
esophageal rupture, 140*f*
esophageal spasm, 165
esophageal ulcer, 161, 166
esophageal varices, 831–832
esophagitis, 165–166
*Candida*, 166
eosinophilic, 166
in HIV infection, 166
HSV, 518
HSV infections, 522*t*
pill-related, 166
viral, 165
esophagogastroscopy, 162, 322, 832
ESRD (end-stage renal disease), 752. *See also* chronic kidney disease
essential hypertension, 649
essential thrombocytosis, 293
essential tremor (ET), 236, 237*t*
estramustine, for prostate cancer, 343
estrogen therapy
for amenorrhea, 918
cardiovascular risk reduction and, 1093
for hypopituitarism, 883*t*
for menopausal symptoms, 922
oral contraceptives, 922
for osteoporosis, 934
eszopiclone, for insomnia, 242
etanercept
for ankylosing spondylitis, 857
for psoriasis, 259
for psoriatic arthritis, 858
for rheumatoid arthritis, 846

ETEC (enterotoxigenic *E. coli*) infections, 455
ethambutol
for nontuberculous mycobacterial infections, 494
for tuberculosis, 486, 487–488*t*
ethanol, for hypertrophic cardiomyopathy, 643
ethinylestradiol/norethisterone, for GI telangiectasis, 178
ethosuximide, for seizures, 962*t*, 967*t*
ethylene glycol poisoning, 17, 18*t*, 19
etoposide
for AML, 286*f*, 287
for lung cancer, 313
for testicular cancer, 336
etravirine, for HIV infection, 559, 561*t*
everolimus
for islet-cell tumors, 333
for renal cancer, 335
EVL (endoscopic variceal ligation), 832
Ewingii ehrlichiosis, 502*t*
exanthem subitum, 525
exanthems, enteroviral, 545
exchange transfusion, 46
excoriation, 257*t*
exemestane, for breast cancer, 321
exenatide, for diabetes mellitus, 906, 909*t*
exercise habits, 1094
exercise testing
in coronary artery disease, 672, 673*f*, 674*t*
for palpitations, 142
exertional headache, 215*t*, 221
extensively drug-resistant (XDR) tuberculosis, 482
extraarticular tophi, 863
extraintestinal *E. coli* (ExPEC) infections, 454
extrapyramidal side effects (EPSEs), 1074
eye disease
chlamydial infections, 514–515
HSV infections, 518, 521*t*
larva migrans, 600
in leprosy, 491
in malnutrition, 42
*Nocardia* infections, 478
*P. aeruginosa* infections, 459, 460–461*t*
paraneoplastic, 352*t*, 353*t*
toxoplasmosis, 598
eye movements, in coma, 81
ezetimibe, for dyslipidemia, 938*t*
ezogabine, for seizures, 962*t*

**F**

FAB classification
of AML, 284*t*
of lymphoid malignancy, 293
facial diplegia, 1001
facial masking, 976
facial myokymia, 996
facial nerve (CN VII)
anatomy of, 998*f*
disorders of, 996–998
examination of, 948
facial numbness, 995–996
facial pain, 221, 995–996
facial weakness, 996–998
facioscapulohumeral dystrophy, 1057
factitious illness, 1069
facultative bacteria, 469
faintness, 222, 226–227
famciclovir
for genital HSV infections, 412, 415*t*
for herpes zoster infections, 415*t*
for HSV infections, 519, 520–522*t*
for viral meningitis, 1027
for VZV infections, 524
familial amyotrophic lateral sclerosis (FALS), 984
familial combined hyperlipidemia (FCHL), 941
familial dysbetalipoproteinemia, 937*t*
familial hepatic lipase deficiency, 937*t*
familial hypercholesterolemia (FH), 936, 937*t*
familial hypocalciuric hypercalcemia (FHH), 925
familial polyposis coli (FPC), 326*t*, 327
familial spastic paraplegia, 1007
famotidine, for erosive gastropathies, 788
Fanconi syndrome, 773, 773*t*
Fanconi's anemia, 268
farmer's lung, 717
fasciculations, 233*t*, 235*t*, 951
fascioliasis, 606
fat requirements, 41
fatigability, 233
fatigue
causes of, 133*t*
chronic fatigue syndrome, 134–135, 134*t*
clinical manifestations of, 132
daytime, 241

differential diagnosis of, 132
drug-induced, 132, 133*t*
generalized, 131–134, 133*t*
laboratory testing in, 132–133
in muscle disease, 1053
in terminally ill patient, 51–52, 54*t*
treatment of, 52, 133–134
fatty liver, 827
FCHL (familial combined hyperlipidemia), 941
febrile neutrophilic dermatosis, in cancer patients, 362
febuxostat, for gout, 865
fecal antigen test, *H. pylori*, 786, 786*t*
fecal DNA testing, 1097*t*
fecal immunochemical testing, 1097*t*
fecal incontinence, 55*t*, 168
fecal occult blood test, 174, 328, 330, 1095, 1097*t*
felbamate, for seizures, 962*t*, 967*t*
female reproductive system disorders, 917–924
femoral neuropathy, 1048*t*
fenofibrate, for dyslipidemia, 939*t*
fenoprofen, for pain, 38*t*
fentanyl
abuse, 1084
for pain, 39*t*
fetal alcohol syndrome, 1106
fever, 127
approach to, 127–128, 365–366, 365*f*
in cancer patient, 113
causes of, 127
with rash, 128
treatment of, 128
fever of unknown origin (FUO), 129, 130*f*
fexofenadine
for allergic rhinitis, 838
for urticaria/angioedema, 837
FFP. *See* fresh-frozen plasma
FGS (focal glomerulosclerosis), 764–765
FH (familial hypercholesterolemia), 936, 937*t*
FHH (familial hypocalciuric hypercalcemia), 925
fiber, dietary, 172, 795
fibrinogen deficiency, 280
fibrinolytic therapy
for STEMI, 659, 661*f*
for thrombotic disorders, 282–283
for venous thromboembolism, 733
fibromyalgia, 868, 1064
fibrosing mediastinitis, 578
fifth disease (erythema infectiosum), 542
filariasis, lymphatic, 603–604
filovirus infections, 552–553
finasteride
for prostate cancer prevention, 345, 1100
for prostate hyperplasia, 342
fingolimod, for multiple sclerosis, 1018
fire coral, 120
fish oil supplementation
for IgA nephropathy, 767
for inflammatory bowel disease, 794
Fisher syndrome, 1046
Fitz-Hugh-Curtis syndrome, 402
flatworm infections, 604–606
flea-borne (murine) typhus, 502*t*, 505–506
flea-borne spotted fever, 501*t*
flecainide, for arrhythmias, 683*t*
floxuridine (FUDR), for colorectal cancer, 328
flucloxacillin, for infective endocarditis, 377–378*t*
fluconazole, 569
for blastomycosis, 581
for candidiasis, 166, 262, 401, 571
for coccidioidomycosis, 580
for cryptococcosis, 576
for *Malassezia* infections, 581
for urinary tract infections, 778
flucytosine, 570
for candidiasis, 571
for cryptococcosis, 576
fludarabine
for CLL, 297
for follicular lymphoma, 298
for idiopathic thrombocytopenic purpura, 280
fludrocortisone
for Addison's disease, 899
for adrenal insufficiency, 112
for hypoaldosteronism, 899
for orthostatic hypotension, 995
for SIADH, 886
for syncope, 225
fluid absorption, in GI tract, 167
fluid replacement, for cholera, 387
fluid restriction
for heart failure, 688
for hyponatremia, 351
for SIADH, 112, 886
fluke infections
liver (biliary) flukes, 606
lung flukes, 606

flunarizine, for migraine prevention, 220*t*
fluoroquinolones
for *Aeromonas* infections, 458
for brucellosis, 464
for *C. pneumoniae* infections, 513
for campylobacteriosis, 395
for community-acquired pneumonia, 725*t*
for *Corynebacterium* infections, 443
for enterococcal infections, 440
for extraintestinal *E. coli* infections, 454
for *H. influenzae* infections, 449
for HACEK group infections, 453*t*
for infectious arthritis, 420
for *Klebsiella* infections, 456
for *Legionella* infections, 512–513
for *M. catarrhalis* infections, 452
for *M. pneumoniae* infections, 511
for nocardiosis, 479
for peritonitis, 382–384
for pneumococcal infections, 424
for Q fever, 509–510
for shigellosis, 396
for sinusitis, 249*t*
for staphylococcal infections, 430
for tuberculosis, 486, 487–488*t*
for typhoid fever, 393
for urinary tract infections, 777*t*, 778
5-fluorouracil (5-FU)
for anal cancer, 330
for breast cancer, 321
for carcinoid tumor, 332
for cervical cancer, 341
for colorectal cancer, 328
for esophageal carcinoma, 322
for gastric cancer, 323
for head and neck cancer, 309
for pancreatic cancer, 331
for Zollinger-Ellison syndrome, 790
fluoxetine
for depression, 52
dosage and side effects of, 1072*t*
for menopausal symptoms, 922
for narcolepsy, 245
for obsessive-compulsive disorder, 1068
for systemic sclerosis, 848
fluphenazine
dosage and side effects of, 1076*t*
for postherpetic neuralgia, 524
flurazepam, 1075*t*
flutamide
for hirsutism, 920–921
for prostate cancer, 343
fluticasone
for allergic rhinitis, 838
for eosinophilic esophagitis, 166
fluvastatin, for dyslipidemia, 938*t*
fluvoxamine
dosage and side effects of, 1072*t*
for obsessive-compulsive disorder, 1068
focal glomerulosclerosis (FGS), 764–765
focal seizures, 956, 956*t*. *See also* seizures
folate, for alcoholic liver disease, 828
folate deficiency
anemia in, 269, 273
leukopenia in, 276
treatment of, 45*t*
FOLFIRI regimen, for colorectal cancer, 328
FOLFOX regimen, for colorectal cancer, 328
follicle-stimulating hormone (FSH)
deficiency of, 882, 883*t*
production of, 877, 878*f*
follicular lymphoma, 294, 296*f*, 298
folliculitis, 256*f*, 417
fondaparinux
for thrombotic disorders, 282
for UA/NSTEMI, 670
for venous thromboembolism, 733
food metabolism, 40
food poisoning
bacterial, 386–389, 388*f*
botulism, 471
*S. aureus*, 428
foot, muscles and innervation of, 950*t*
foramen magnum, lesions near, 1003
forced vital capacity, 705, 705*f*
forearm, muscles and innervation of, 949*t*
formoterol, for asthma, 713
foscarnet
for cytomegalovirus infections, 527
for HSV infections, 522*t*
for viral encephalitis, 1029
for viral esophagitis, 165
fosfomycin, for urinary tract infections, 777*t*
fosphenytoin, for status epilepticus, 102*f*
FPC (familial polyposis coli), 326*t*, 327
fracture, osteoporotic, 931, 931*t*
*Francisella tularensis*. *See* tularemia

fresh-frozen plasma (FFP), 47
for bleeding disorders, 280
for warfarin reversal, 282
Friedreich's ataxia, 983
frontotemporal dementia (FTD), 970*t*, 971, 974
frovatriptan, for migraine, 217*t*, 219*t*
frozen shoulder, 870
FSH. *See* follicle-stimulating hormone
5-FU. *See* 5-fluorouracil
FUDR (floxuridine), for colorectal cancer, 328
fungal infections, 568–582
antifungal agents, 569–570
aspergillosis. *See* aspergillosis
blastomycosis, 580–581, 1035*t*
candidiasis. *See* candidiasis
chronic meningitis in, 1034–1035*t*
coccidioidomycosis, 578–579
cryptococcosis, 573, 576, 1034*t*
fusariosis, 582
histoplasmosis, 577–578, 579*t*, 1035*t*
in HSCT patients, 366–367
lymphadenopathy and, 190*t*
*Malassezia* infections, 581
mucormycosis, 576–577
nosocomial, 361
paracoccidioidomycosis, 581–582
penicilliosis, 582
scedosporiosis, 582
sporotrichosis, 581
fungus ball, 249
FUO (fever of unknown origin), 129, 130*f*
furosemide
for ascites, 188
for edema, 153*t*
for heart failure, 663, 688, 690*t*
for hypercalcemia, 351, 927*t*
for hyperkalemia, 16*t*
for hypertension, 652*t*
for hyponatremia, 351
for pulmonary edema, 70
for SIADH, 112
for STEMI, 665*t*
furuncle, 427
furunculosis, 260
fusariosis, 582
fusidic acid, for osteomyelitis, 421*t*
*Fusobacterium* infections, 475

**G**

G6PD (glucose-6-phosphate dehydrogenase) deficiency, 269, 272*t*, 274
gabapentin
for generalized anxiety disorder, 1068
for menopausal symptoms, 922
for multiple sclerosis, 1019
for pain, 37, 39*t*
for polyneuropathy, 1044, 1045*t*
for postherpetic neuralgia, 524
for seizures, 962*t*, 967*t*
GAD (generalized anxiety disorder), 1067–1068, 1071
gait analysis, 953
galantamine, for Alzheimer's disease, 973
gallstones, 138*t*
gametocyte, 586
gamma knife radiosurgery, 996
gamma-glutamyltranspeptidase (GGT), 185
ganciclovir
for cytomegalovirus infections, 527
for viral encephalitis, 1029
for viral esophagitis, 165
Gardasil, 341, 414
*Gardnerella vaginalis* infections, 401
Gardner's syndrome, 325, 326*t*, 327
gas exchange, disturbances of, 707–708
gas gangrene (myonecrosis), 416*t*, 418, 473, 474*t*
GAS infections. *See* group A *Streptococcus* infections
gastrectomy, 323
gastric atrophy, 788
gastric carcinoma, 322–324
gastric lavage, 815
gastric tumor, benign, 325
gastric ulcer. *See* peptic ulcer disease
gastrinoma, 332, 332*t*, 789–790
gastritis, 178, 788
gastroesophageal reflux disease (GERD), 160–161
cough in, 147
evaluation of, 161
natural history of, 161
pathophysiology of, 160
sleep disorders in, 242
treatment of, 161
gastroesophageal varices, 174, 178
gastrointestinal bleeding, 174–178
anemia in, 269
in critically ill patient, 35
esophageal varices and, 832
lower, 175–178, 177*f*
upper, 175, 176*f*

gastrointestinal disease
chest pain in, 138*t*, 139*f*
cholecystitis, 801–802
choledocholithiasis/cholangitis, 802–803
cholelithiasis, 799–800
cirrhosis. *See* cirrhosis
colonic angiodysplasia, 798
colonic polyps, 326–327
diverticular disease, 796
endocrine tumors, 331–333
esophageal varices, 831–832
gastric carcinoma, 322–324, 349*t*
gastric tumors, 325
gastropathies, 788–789
hepatitis. *See* hepatitis
infections after HSCT, 367*t*
infections in cancer patients, 364
infectious diarrhea
inflammatory, 386–398, 386*t*, 388*f*
noninflammatory, 386–392
inflammatory bowel disease. *See* inflammatory bowel disease
intestinal pseudoobstruction, 797
irritable bowel syndrome, 794–795, 795*t*, 796*t*
listerial, 446
liver tumors, 330
nausea and vomiting in, 159*t*
pain in, 155*t*
pancreatitis. *See* pancreatitis
peptic ulcer disease. *See* peptic ulcer disease
portal hypertension, 831, 831*t*
primary sclerosing cholangitis, 803
small-bowel tumors, 325
in tuberculosis, 484
vascular, 797–798
weight loss in, 135, 136*t*
Zollinger-Ellison syndrome, 789–790
gastrointestinal function, normal, 167
gastrointestinal stromal cell tumor (GIST), 323, 324
gastrointestinal telangiectasis, 178
gastropathies, 788–789
gastroscopy, 323
gatifloxacin, for tuberculosis, 486
GBS (group B *Streptococcus*), 438–439
GBS (Guillain-Barré syndrome), 991, 1046
gefitinib, for lung cancer, 315
gemcitabine
for bladder cancer, 334
for breast cancer, 321
for pancreatic cancer, 331
gemfibrozil, for dyslipidemia, 939*t*
gemifloxacin, for community-acquired pneumonia, 725*t*
gemigliptin, for diabetes mellitus, 908*t*
generalized anxiety disorder (GAD), 1067–1068, 1071
generalized convulsive status epilepticus (GCSE), 101–103
generalized seizures, 956, 956*t*. *See also* seizures
genital herpes
clinical manifestations of, 404*t*, 412, 517–518
diagnosis of, 412
microbiology and epidemiology of, 412
proctitis, proctocolitis, enterocolitis, and enteritis, 403
treatment of, 412, 520–522*t*
in women, 400–401
genital lesions, ulcerative, 403, 404*t*
genital warts, 413–414, 798
genitourinary tract cancer, 333–337, 349*t*
gentamicin
for bacterial meningitis, 1024*t*, 1025*t*
for *Bartonella* infections, 467*t*
for brucellosis, 464
for enterococcal infections, 440
for health care–associated pneumonia, 727*t*
for infective endocarditis, 376–378*t*, 378
for listerial infections, 447
for pelvic inflammatory disease, 403, 407*t*
for plague, 466
for staphylococcal infections, 430, 433*t*
for streptococcal infections, 438, 440
for tularemia, 465
geographic tongue, 256*f*
GERD. *See* gastroesophageal reflux disease
germ cell tumor
extragonadal, unrecognized, 348–349
ovarian, 338
paraneoplastic syndromes in, 353*t*
German measles. *See* rubella
GFR (glomerular filtration rate), 197, 198*t*, 752, 753

GGT (gamma-glutamyltranspeptidase), 185
GH. *See* growth hormone
giant cell (temporal) arteritis, 231, 851
giant platelets, 266
giardiasis, 390–391, 403
Gilbert's syndrome, 181, 184*t*
gingivitis, 475
gingivostomatitis, HSV, 517
GIST (gastrointestinal stromal cell tumor), 323, 324
glanders, 461*t*, 462
Glasgow Coma Scale, 97*t*
glatiramer acetate, for multiple sclerosis, 1018
glaucoma, 230*f*
glibornuride, for diabetes mellitus, 908*t*
gliclazide, for diabetes mellitus, 908*t*
glimepiride, for diabetes mellitus, 908*t*
glioblastoma, 1009, 1009*f*
glioma, 1008
glipizide, for diabetes mellitus, 908*t*
gliquidone, for diabetes mellitus, 908*t*
global aphasia, 239*t*, 240
globulin, in liver disease, 185
globus pharyngeus, 162
glomerular disease, 759–766, 768*t*
glomerular filtration rate (GFR), 197, 198*t*, 752, 753
glomerulonephritis (GN)
  acute, 759–760, 760*t*
  ANCA-associated, 762
  membranoproliferative, 765
  membranous, 764
  postinfectious, 760
  poststreptococcal, 760
  rapidly progressive, 760–763, 761*t*
  in SLE, 762
glomerulosclerosis, focal, 764–765
glossopharyngeal neuralgia, 1000
glucagon, for hypoglycemia, 109
glucagonoma, 332*t*, 333
glucocorticoid therapy
  for acne, 262–263
  for acute disseminated encephalomyelitis, 1020
  for acute renal failure, 751
  for Addison's disease, 899
  for adhesive capsulitis, 869
  for adult T cell leukemia/lymphoma, 301
  for alcoholic liver disease, 828
  for amiodarone-induced thyrotoxicosis, 892
  for amyloidosis, 875
  for anaphylaxis, 114
  for ANCA-associated glomerulonephritis, 762
  for ankylosing spondylitis, 857
  for asthma, 713–715
  for ataxia, 984
  for autoimmune hemolysis, 274
  for autoimmune hepatitis, 825
  for back pain, 211
  for brain tumor, 1008
  for bursitis, 869
  for CLL, 297
  for COPD, 720–721
  for cough, 148
  for croup, 537
  for dermatitis, 259–260
  for eczema, 259–260
  for enteroviral infections, 545
  for Epstein-Barr virus infections, 529
  for erythema nodosum, 263
  for fatigue, 52
  for fever, 128
  for focal glomerulosclerosis, 765
  for glomerulonephritis, 765
  for gout, 864
  for hirsutism, 921
  for histoplasmosis, 579*t*
  for hymenoptera sting, 125
  for hypercalcemia, 112, 351, 927*t*
  for increased intracranial pressure, 95*t*
  for inflammatory bowel disease, 792
  for inflammatory myopathy, 1059
  for interstitial lung disease, 737
  for larva migrans, 600
  for leprosy, 492
  for lichen planus, 259
  lymphopenia with, 276
  for minimal change disease, 764
  monocytopenia with, 277
  for multiple myeloma, 302
  for muscular dystrophy, 1054
  for myasthenia gravis, 1053
  nasal, for allergic rhinitis, 838
  for nausea and vomiting, 160
  for optic neuritis, 231
  for osteoarthritis, 862
  for pityriasis rosea, 259
  for *Pneumocystis* infections, 584, 584*t*
  for polyneuropathy, 1046

glucocorticoid therapy (*Cont.*):
for primary sclerosing cholangitis, 803
for pseudogout, 866
for psoriasis, 259
for psoriatic arthritis, 859
for reactive arthritis, 860
for rheumatoid arthritis, 846
for sarcoidosis, 872
for schistosomiasis, 605
for Sjögren's syndrome, 849
for SLE, 762, 845
for spinal cord compression, 99
for Stevens-Johnson syndrome, 263
for systemic mastocytosis, 839
for systemic sclerosis, 848
for taeniasis solium and cysticercosis, 607
for tendinitis, 870
for trichinellosis, 600
for tuberculosis, 484
for vasculitis, 854
for vertigo, 229
gluconate, for hyperkalemia, 16*t*
glucosamine and chondroitin, for osteoarthritis, 862
glucose therapy, for hypoglycemia, 109
glucose-6-phosphate dehydrogenase (G6PD) deficiency, 269, 272*t*, 274
glucose-lowering agents, oral, 906, 908–909*t*
glulisine, for diabetes mellitus, 906
gluten-free diet, 984
glyburide, for diabetes mellitus, 908*t*
glyclopyramide, for diabetes mellitus, 908*t*
glycocholic breath test, 170
glycolytic defects, 1059
GN. *See* glomerulonephritis
GNB. *See* gram-negative bacilli
goiter, 887, 892–893
gold salts, for psoriatic arthritis, 859
golimumab
for ankylosing spondylitis, 857
for psoriatic arthritis, 858
for rheumatoid arthritis, 846
gonadotropins
deficiency of, 882, 883*t*
hypersecretion of, 881
gonorrhea
arthritis, 405–406, 419
cervicitis, 401–402, 405
clinical manifestations of, 405–406
epidemiology of, 405
epididymitis, 400
pelvic inflammatory disease, 402–403
proctitis, proctocolitis, enterocolitis, and enteritis, 403, 405
treatment of, 406–407*t*
urethritis, 400, 405
vulvovaginal infections, 400
Goodpasture's syndrome, 763, 768*t*
goserelin
for breast cancer, 320
for prostate cancer, 343
Gottron's sign, 1058
gout, 863–865
gouty arthritis, 865
GPIHBP1 deficiency, 937*t*
graded exercise therapy, for chronic fatigue syndrome, 135
graft-versus-host disease, 46, 47*t*
grain dust, 717
gram-negative bacilli (GNB)
*Bartonella*, 466–469
*Brucella*, 462–463
enteric, 453–458
*Aeromonas*, 458
extraintestinal *E. coli*, 454
intestinal pathogenic *E. coli*, 455
*Klebsiella*, 455–456
*Proteus*, 456–457
*Francisella tularensis*, 464
*Yersinia pestis*, 465
grand mal (tonic-clonic) seizures, 956. *See also* seizures
granisetron, for nausea and vomiting, 160
*Granulicatella* infections, 439–440
granuloma inguinale, 404*t*, 413
granulomatosis infantiseptica, 447
granulomatosis with polyangiitis (Wegener's granulomatosis), 851, 1039*t*
granulomatous angiitis, isolated, 1038*t*
granulomatous disease, leukocytosis in, 275
Graves' disease, 889. *See also* thyrotoxicosis
Graves' ophthalmopathy, 1061
gray hepatization, 723
griseofulvin
for dermatophyte infections, 262
for ringworm, 570
group A *Streptococcus* (GAS) infections, 434–437
bacteremia, 437

clinical manifestations of, 435–437
epidemiology of, 434–435
nosocomial, 361
pharyngitis, 253, 435
pneumonia and empyema, 437
prevention of, 437
scarlet fever, 435
skin and soft tissue infections, 435–436, 435–437, 436*t*
toxic shock syndrome, 437, 437*t*
treatment of, 436*t*
group B *Streptococcus* (GBS), 438–439
group C *Streptococcus*, 438
group D *Streptococcus*, 439
group G *Streptococcus*, 438
growth hormone (GH)
deficiency of, 882, 883*t*
hypersecretion of, 880–881
production of, 877, 878*f*
for weight loss, 137
guanfacine, for tics, 238
Guillain-Barré syndrome (GBS), 991, 1046
gumma, 410
gynecologic cancer, 339–341
gynecomastia
evaluation of, 913, 914*f*
paraneoplastic, 349*t*

**H**

$H_2$ receptor antagonists
for erosive gastropathies, 788
for peptic ulcer disease, 787
for systemic sclerosis, 848
HACEK group infections
clinical manifestations of, 452
endocarditis, 372, 378*t*, 452
microbiology of, 452
treatment of, 453*t*
*Haemophilus ducreyi* infections, 404*t*, 413
*Haemophilus influenzae* infections, 369*t*, 448–449
hallucinations, hypnagogic, 244*t*
halo sign, 573
haloperidol
for delirium, 52*t*
dosage and side effects of, 1076*t*
for nausea and vomiting, 51, 160
haloprogin, for dermatophyte infections, 262
hamartoma, gastric, 325
hand
hygiene, 357
muscles and innervation of, 949*t*
hand-foot-and-mouth disease, 545
Hantaan virus infections, 552
hantavirus pulmonary syndrome, 551
Harris and Benedict formula, 40, 41*f*
Haverhill fever, 118
HCAP. *See* health care-associated pneumonia
HD. *See* Hodgkin's disease
HDL cholesterol, 936. *See also* hypercholesterolemia
head and neck cancer, 308–309
clinical manifestations of, 309
incidence and epidemiology of, 309
infections in, 363*t*
oncologic emergencies, 110–111
paraneoplastic syndromes in, 349*t*
prevention of, 310, 1101
treatment of, 309
head and neck infections
actinomycosis, 480
anaerobic, 475
head impulse test, for vertigo, 226
head louse, 610–611
head trauma
approach to, 96–98
concussion management in sports, 97
increased intracranial pressure in, 93
intracranial hemorrhage and, 84*t*
long-term complications of, 971
post-concussion headache, 215*t*, 221
severity grading, 97*t*
subarachnoid hemorrhage in, 91
headache. *See also specific types*
approach to, 215
causes of, 215*t*
symptoms suggesting serious underlying disorder, 216*t*
health care worker, HIV infection in, 567–568
health care-associated infections, 357–361
endocarditis, 373–374. *See also* infective endocarditis
epidemic and emerging problems, 360–361
hospital-acquired, 357
nosocomial and device-related, 358–360, 359*t*, 427
prevention of, 357, 359*t*
health care-associated pneumonia (HCAP), 722
hospital-acquired pneumonia, 727
ventilator-associated pneumonia. *See* ventilator-associated pneumonia

heart
chamber size and ventricular performance, 622–623
noninvasive examination of, 622–627, 627*f*
physical examination of, 613–617
heart disease
chest pain in, 138*t*
congenital. *See* congenital heart disease
CT in, 625–626, 626*t*
cyanosis in, 145–146, 146*t*
depression in, 1064
dyspnea in, 143, 144*f*
echocardiography in, 622–623
edema in, 150–151, 152
endocarditis prophylaxis, 380, 381*t*
fatigue in, 133*t*
intracardiac mass, 624, 626*t*
in Lyme disease, 495, 496
in men, 1104
MRI in, 625, 626*t*
nausea and vomiting in, 159*t*
prevention of, 1089–1090*t*, 1092–1094, 1093*t*
risk factors for, 667, 1092–1093, 1092*t*
screening for, 1088–1090*t*
syncope in, 24*t*, 222
in syphilis, 410, 411*t*
valvular. *See* valvular heart disease
weight loss in, 136*t*
in women, 1104–1105
heart failure, 687–692
ascites in, 187, 188*f*
conditions that mimic, 688
definition of, 687
diagnosis of, 688
edema in, 150–151, 152, 688
hemodynamic profiles in, 691–692, 691*f*
lymphadenopathy and, 190*t*
precipitating factors, 687
treatment of
after STEMI, 663–664, 664*t*, 665*t*
in chronic disease, 688–692, 689*t*, 690*t*, 691*t*
heart murmurs, 615–617, 616*t*, 617*t*
heart rate, 618
heart sounds, 614–615, 615*f*, 617*t*
heart transplantation
for dilated cardiomyopathy, 642
infections after, 368–369
heartburn, 160–161
heat stroke, 129
heavy chain deposition disease, 773*t*
height, ideal weight for, 42*t*
Heinz bodies, 265
*Helicobacter pylori* infections
detection of, 786, 786*t*
eradication of, 161, 787, 787*t*
lymphoid malignancies and, 294
peptic ulcer disease and, 161, 785–787
helminth infections, 599–611
cestodes, 606–610
chronic meningitis in, 1036*t*
ectoparasites, 610–611
filarial worms, 603–604
intestinal nematodes, 600–603
tissue nematodes, 599–600
trematodes, 604–606
hemapheresis, 47–48
hematemesis, 174
hematin, for porphyria, 944
hematochezia, 174
hematocrit, 194
hematologic disease
bleeding disorders, 277–281
blood smear, 265–266
bone marrow examination, 266–267
fatigue in, 133*t*
leukocytosis, 274–276
leukopenia, 276–277
monocytosis in, 275
red cell disorders, 268–274
thrombotic disorders, 281–283
hematopoietic stem cell transplant (HSCT)
for ALL, 300
for amyloidosis, 875
for CLL, 297
for CML, 289
for follicular lymphoma, 298
infections after, 367*t*
infections in recipients, 366–368
for myelodysplastic syndromes, 289
for severe combined immunodeficiency, 842
vaccination of recipients, 369–370*t*
hematuria, 201–202
approach to, 202*f*
causes of, 201, 201*t*
of glomerular origin, 766
gross, 201
microscopic, 201
in renal cancer, 335
heme preparations
for acute intermittent porphyria, 944
for erythropoietic protoporphyria, 945

hemianopia, bitemporal, 229, 230*f*
hemiballismus, 237
hemiblock, 619*f*
hemicrania, paroxysmal, 221
hemicrania continua, 221
hemifacial spasm, 997–998
hemiparesis, 83, 97, 234*t*, 235*f*
hemochromatosis, 942–944
  clinical manifestations of, 942
  diagnosis of, 943, 943*f*
  genetic factors in, 942, 943*f*
  transfusion-associated, 46
  treatment of, 944
hemodialysis
  for acute renal failure, 751
  for chronic kidney disease, 754–755
  complications of, 755, 755*t*
  for hyperkalemia, 16*t*
  intermittent, 751
  for tumor lysis syndrome, 113
hemoglobin
  abnormal, 145, 269, 271*t*
  blood concentration, 194
  unstable variants, 269
hemolysis, 194, 275
hemolytic anemia, 269–273
  classification of, 271*t*
  etiology of, 269, 271, 273
  in G6PD deficiency, 272*t*
  laboratory testing in, 273
  pathophysiology of, 194
  treatment of, 274
hemolytic patterns, 434
hemolytic reactions, 46, 47*t*
hemolytic uremic syndrome (HUS), 271*t*
hemophilia A, 279, 280–281
hemophilia B, 279, 281
hemoptysis, 148–150, 149*f*
hemorrhage. *See also specific types and sites*
  in diverticular disease, 796
  leukoerythroblastic reaction in, 275
hemorrhagic fever with renal syndrome (HFRS), 552
hemorrhoidectomy, 798
hemorrhoids, 256*f*, 798
hemostatic disorders, 280
Henderson-Hasselbalch equation, 13–14
Henoch-Schönlein purpura (IgA vasculitis), 763, 768*t*, 851
heparin
  for antiphospholipid antibody syndrome, 850
  for arterial embolism, 697
  for DIC, 280
  for STEMI, 659, 662
  for thrombotic disorders, 281–282
  for venous thromboembolism, 733
heparin-induced thrombocytopenia, 278, 732–733
hepatic artery embolization, 332
hepatic disease. *See* liver disease
hepatic encephalopathy, 832–833
hepatic lipase deficiency, familial, 937*t*
hepatitis
  acute viral, 809, 814–815
  alcoholic, 184*t*, 828
  autoimmune, 185, 825
  chronic, 816–825, 1064
  fulminant, 815–816
  marrow damage in, 268
  toxic/drug-induced, 815
hepatitis A
  acute, 809, 810*t*, 812*f*
  chronic, 817
  prevention of, 812
hepatitis A immune globulin, 812
hepatitis A vaccine, 370*t*, 812, 817
hepatitis B
  acute, 810–811*t*, 812, 813*f*, 814
  chronic, 816–817, 818–821*t*
  hepatocellular carcinoma and, 330–331
  prevention of, 812–813
hepatitis B immune globulin, 812–813
hepatitis B vaccine, 370*t*, 813
hepatitis C
  acute, 810–811*t*, 813, 814–815, 814*f*
  chronic, 817, 822–824*t*
  hepatocellular carcinoma and, 330–331
  prevention of, 813
hepatitis D, 810–811*t*, 814
hepatitis E, 810–811*t*, 814
hepatobiliary disorders
  imaging in, 185–186, 800*t*
  liver function tests in, 184*t*
hepatocellular adenoma, 330
hepatocellular carcinoma, 330–331
hepatocellular disorders, liver function tests in, 184*t*
hepatorenal syndrome (HS), 189
hepatotoxins, 815
hereditary elliptocytosis, 271
hereditary spherocytosis, 271, 273

heroin abuse, 1084
herpangina, 545
herpes gladiatorum, 518
herpes simplex virus (HSV) infections, 516–519
  acyclovir-resistant, 522*t*
  Bell's palsy, 996
  cutaneous, 256*f*, 258, 261
  diagnosis of, 258
  eye, 518, 521*t*
  genital. *See* genital herpes
  meningitis in, 1037*t*
  neonatal, 519, 522*t*
  neurologic disease in, 518, 521*t*
  oral-facial, 517, 520–522*t*
  reactivation of, 517, 520–522*t*
  respiratory, 253, 534*t*
  treatment of, 261, 519, 520–522*t*
  visceral, 518, 522*t*
  whitlow, 518, 522*t*
herpes zoster, 523–524
herpes zoster infections
  clinical manifestations of, 256*f*, 261
  diagnosis of, 258
  neck pain in, 212
  treatment of, 261, 415*t*
herpetiform lesion, 255
heterophile test, 529, 529*f*
HFRS (hemorrhagic fever with renal syndrome), 552
HGA (human granulocytotropic anaplasmosis), 502*t*, 508
HHS (hyperglycemic hyperosmolar state), 104–105, 105*t*
5-HIAA (5-hydroxyindoleacetic acid), urinary, 332
high cardiac output/low systemic vascular resistance shock, 32, 33*f*
hirsutism, 920–921, 921*f*
histoplasmosis, 577–578, 579*t*, 1035*t*
histotoxic hypoxia, 100
histrionic personality disorder, 1070
HIV infection, 554–568
  clinical manifestations of, 557–558, 558*t*
  cytomegalovirus infections in, 526–527
  depression in, 1064
  diagnosis of, 556–557, 556*f*
  diarrhea in, 169*t*
  epidemiology of, 554
  esophagitis in, 166
  etiology and transmission of, 554
  health care workers and, 567–568
  immune abnormalities in, 555
  immune response to HIV, 555–556
  laboratory monitoring in, 557
  meningitis in, 1037*t*
  *P. aeruginosa* infections in, 459
  pathophysiology and immunopathogenesis of, 554–555
  pharyngitis in, 253
  *Pneumocystis* infections in, 583–585
  postexposure prophylaxis, 567
  prevention of, 568, 1089*t*
  secondary infections in, 567
  sepsis in, 68*t*
  treatment of, 559–567
    antiretroviral therapy, 559, 560–565*t*, 566–567, 566*t*, 567*t*
    prevention of secondary infections, 567
    principles of, 566–567, 566*t*
  tuberculosis and, 485
  vacuolar myelopathy in, 1006
  in women, 1105
HIV vaccine, 568
HIV-associated nephropathy (HIVAN), 764
HME (human monocytotropic ehrlichiosis), 502*t*, 507–508
Hodgkin's disease (HD), 302, 304
  classification of, 293, 295*t*
  Epstein-Barr virus in, 529
  infections in, 363*t*
  paraneoplastic syndromes in, 353*t*
  staging of, 304, 305*t*
  vaccination in, 369–370*t*
homocysteine, 1094
homonymous, 230*f*
hookworm infections, 601
hormone therapy, for prostate cancer, 343
hormones, ectopic production of, 348–350
hornet sting, 124–125
hospital-acquired pneumonia, 727
hospitalized patient
  care of
    acid-base balance, 13–22
    critical care medicine, 31–35
    electrolyte balance, 1–13
    end-of-life care. *See* terminally ill patient
    enteral nutrition, 43–44
    imaging, 23–26

nutritional status, 40–43
pain and its management, 35–40
parenteral nutrition, 44–45
procedures performed by internists, 26–31
transfusion and pheresis therapy, 46–48
infections in. *See* health care-associated infections
hot-tub folliculitis, 417
Howell-Jolly bodies, 265
HPV. *See* human papillomavirus
HRSV (human respiratory syncytial virus) infections, 534*t*, 535–536
HS (hepatorenal syndrome), 189
HSCT. *See* hematopoietic stem cell transplant
HSV infections. *See* herpes simplex virus infections
human bite, 116*t*, 118, 417
human granulocytotropic anaplasmosis (HGA), 502*t*, 508
human herpesvirus 6 infections, 525
human herpesvirus 7 infections, 525
human herpesvirus 8 infections, 294, 525
human metapneumovirus infections, 534*t*, 536
human monocytotropic ehrlichiosis (HME), 502*t*, 507–508
human papillomavirus (HPV) infections
cervical cancer and, 340, 1097*t*
clinical manifestations of, 414
microbiology of, 413
treatment of, 414
warts, 262, 414
human papillomavirus (HPV) vaccine, 341, 369*t*, 414, 1090*t*, 1101
human respiratory syncytial virus (HRSV) infections, 534*t*, 535–536
human T-lymphotropic virus infections, 294
Hunt-Hess Scale, for subarachnoid hemorrhage, 92*t*
Huntington's disease, 237–238, 974–975
HUS (hemolytic uremic syndrome), 271*t*
hyaluronan, for osteoarthritis, 862
hydralazine
for heart failure, 688, 690, 690*t*
for hypertension, 651
for malignant hypertension, 656*t*
hydralazine-nitrate, for dilated cardiomyopathy, 640
hydrocephalus
normal-pressure, 971, 974
in subarachnoid hemorrhage, 92
hydrochlorothiazide
for diabetes insipidus, 6
for edema, 153*t*
for heart failure, 690*t*
for hypertension, 651, 652*t*
hydrocodone, for dyspnea, 51*t*
hydrocortisone
for Addison's disease, 899
for adrenal insufficiency, 112
for hypopituitarism, 883*t*
for inflammatory bowel disease, 792
for myxedema coma, 889
for sepsis/septic shock, 67
hydroids, 120
hydromorphone
abuse, 1084
for dyspnea, 51*t*
for pain, 38*t*
hydrops fetalis, 542
hydrothorax, 150
hydroxychloroquine
for infective endocarditis, 378*t*
for malaria prophylaxis, 590*t*
for porphyria cutanea tarda, 945
for Q fever, 510
for rheumatoid arthritis, 846
for Sjögren's syndrome, 849
for SLE, 845
for Whipple's disease, 482
5-hydroxyindoleacetic acid (5-HIAA), urinary, 332
hydroxyprogesterone, for endometrial cancer, 340
hydroxyurea
for cervical cancer, 341
for essential thrombocytosis, 293
for sickle cell anemia, 273
for systemic mastocytosis, 839
hydroxyzine
for ciguatera poisoning, 121
for urticaria/angioedema, 837
hymenoptera sting, 124–125
hyoscyamine, for irritable bowel syndrome, 795
hypalgesia, 36
hyperaldosteronism
clinical manifestations of, 898
diagnosis of, 898
etiology of, 897
hypertension in, 650

hyperaldosteronism (*Cont.*):
primary, 897
secondary, 897
treatment of, 21, 898
hyperalgesia, 36
hyperalimentation, 18*t*
hyperbilirubinemia
conjugated (direct), 179
direct, 179*t*
indirect, 179*t*
unconjugated (indirect), 179
hypercalcemia, 924–928
clinical manifestations of, 924, 926
diagnosis of, 926–927, 927*t*
etiology of, 773*t*, 924–925, 925*f*, 926*t*
familial hypocalciuric, 925, 928
paraneoplastic, 111–112, 349*t*, 351, 924, 928
treatment of, 112, 927–928, 927*t*
hypercalciuria, 780, 926
hypercapnia, 21, 708–709, 744
hypercarbia, 73
hypercholesterolemia
approach to, 936
cardiovascular disease and, 1092, 1092*t*
definition of, 936
genetic causes of, 936, 937*t*
with hypertriglyceridemia, 937*t*, 940–941
isolated, 936
treatment of, 938–939*t*, 941–942, 1092, 1093*t*
hypereosinophilic syndromes, 276
hyperesthesia, 36
hyperglobulinemia, 185
hyperglycemia
in critically ill patient, 35
in metabolic syndrome, 657*t*
hyperglycemic hyperosmolar state (HHS), 104–105, 105*t*
hyperhidrosis, 988, 991
hyperkalemia, 6–7, 9–13
approach to, 14*f*
in chronic kidney disease, 754
drug-induced, 14*f*
ECG in, 9, 13, 14*f*, 15*f*
treatment of, 13, 16*t*
hyperkinetic (bounding) pulse, 613, 614*f*
hyperlipoproteinemia, 936, 937*t*. *See also* hypercholesterolemia; hypertriglyceridemia
hypermagnesemia, 930
hypernatremia, 6–7, 6*t*
hyperoxaluria, 780
hyperparathyroidism
primary, 924, 928
secondary, 925, 928
hyperpathia, 994
hyperphosphatemia, 754, 929
hyperprolactinemia, 79, 879–880
hyperpyrexia, 127
hypersegmentation, 266
hypersensitivity disorder, immediate type, 835–839
allergic rhinitis, 837–838
definition of, 835
pathophysiology of, 835, 835*f*
systemic mastocytosis, 838–839
urticaria and angioedema, 835–837, 836*t*
hypersensitivity pneumonitis, 736, 739
hypersomnia, 244*t*, 245
hypersplenism, 192, 273, 276
hypertension, 649–656
approach to, 650
cardiovascular disease and, 1092–1093
in chronic kidney disease, 754
definition of, 649
in diabetes, 655
essential, 649
in hyperaldosteronism, 898
malignant, 86, 655, 656*t*
in metabolic syndrome, 656–657, 657*t*
paraneoplastic, 349*t*
portal, 192, 831, 831*t*
in pregnancy, 651
pulmonary. *See* pulmonary hypertension
secondary, 649–650
supine, 994
treatment of, 1093
approach to, 654*t*, 655*f*
blood pressure goals for, 651
drug therapy for, 651, 652–653*t*, 654*t*
in special circumstances, 651, 655
in women, 1105
hyperthermia, 127, 129, 131
hyperthyroidism. *See also* thyrotoxicosis
depression in, 1064
muscle disorders in, 1061
paraneoplastic, 349*t*
primary, 889

secondary, 889
sleep disorders in, 242
subclinical, 893
hypertonic saline, for hyponatremia, 5
hypertransfusion therapy, 46
hypertriglyceridemia
familial combined, 941
genetic causes of, 937*t*, 940
isolated, 940
treatment of, 939*t*, 940
hypertrophic cardiomyopathy
ECG in, 619–620, 621*t*, 643
echocardiography in, 643
heart sounds in, 616*t*, 640*t*
initial evaluation of, 641*t*
presentation of, 642–643
treatment of, 643
hypertrophic osteoarthropathy, 868
hyperuricemia, 863, 864
hyperventilation
clinical manifestations of, 745
etiology of, 745
faintness with, 226–227
for increased intracranial pressure, 95, 95*t*
treatment of, 745
hyperviscosity syndrome, 48, 196, 773*t*
hypervolemia, 1
hypnozoite, 586
hypoalbuminemia, 151, 185, 187, 928
hypoaldosteronism, 899–900
hypocalcemia, 928–929
hypocupric myelopathy, 1007–1008
hypoglossal nerve (CN XII)
disorders of, 1001
examination of, 948
hypoglycemia, 107–109
clinical manifestations of, 107
diagnosis of, 107–108, 108*f*, 109*t*
etiology of, 107
faintness with, 227
paraneoplastic, 349, 349*t*
vs. syncope, 225
treatment of, 108–109
hypoglycemic unawareness, 107, 108
hypogonadism, 913. *See also* androgen deficiency
hypogonadotropic hypogonadism, 913
hypohidrosis, 988
hypokalemia, 7–9
approach to, 10–11*f*
causes of, 7–8, 7–8*t*
drug-induced, 7–8
treatment of, 8–9
hypokalemic alkalosis, 351
hypomagnesemia, 928, 930
hypomania, 1065–1066
hyponatremia, 1–5
acute symptomatic, 4
approach to, 3*f*
chronic, 4–5
euvolemic, 3*f*, 4
hypervolemic, 2–4, 3*f*, 5
hypovolemic, 2, 3*f*
paraneoplastic, 351
in subarachnoid hemorrhage, 92
treatment of, 4–5
hypoparathyroidism, 928–929
hypophysectomy, for prostate cancer, 343
hypopituitarism, 881–882, 883*t*
hypopnea, 745
hyposegmentation, 266
hyposensitization therapy, for allergic rhinitis, 838
hypotension
orthostatic. *See* orthostatic hypotension
in STEMI, 664, 667
hypothalamic hormones, 878*f*
hypothermia, therapeutic
for cardiac arrest, 60
for hypoxic-ischemic encephalopathy, 101
for increased intracranial pressure, 95*t*
for stroke, 87
hypothyroidism, 886–889
clinical manifestations of, 887–888
clinical (overt), 887
depression in, 1064
diagnosis of, 888, 888*f*
edema in, 151
etiology of, 886–887, 887*t*
muscle disorders in, 1060
subclinical (mild), 887
treatment of, 888–889
hypoventilation, 744–745
hypovolemia, 2, 665*t*
hypovolemic shock, 32, 33*f*
hypoxemia, 73
approach to, 708*f*
in ARDS, 71
mechanisms of, 708–709. *See also* respiratory disease
in pulmonary edema, 144
hypoxia, 100
histotoxic, 100

hypoxia (*Cont.*):
hypoxic-ischemic encephalopathy, 100–101
hysterectomy, 340

**I**
ibandronate, for osteoporosis, 934
IBD. *See* inflammatory bowel disease
IBM (inclusion body myositis), 1057–1058, 1058*t*
ibritumomab, for follicular lymphoma, 298
ibrutinib, for CLL, 297
IBS (irritable bowel syndrome), 794–795, 795*t*, 796*t*
ibuprofen
for migraine, 217*t*
for pain, 38*t*
for pericarditis, 645
for SLE, 845
ibutilide
for arrhythmias, 684*t*
for Wolff-Parkinson-White syndrome, 686
ICD. *See* implantable cardioverter defibrillator
ICP. *See* intracranial pressure
ICSI (intracytoplasmic sperm injection), 915, 925
icterus. *See* jaundice
ICU (intensive care unit), monitoring in, 34
ICU patient. *See* critically ill patient
idarubicin, for AML, 287
idebenone, for ataxia, 984
idiopathic myelofibrosis, 292–293
idiopathic pulmonary fibrosis (IPF), 737–738
idiopathic thrombocytopenic purpura (ITP), 278
idoxuridine, for HSV infections, 521*t*
ifosfamide, for cervical cancer, 341
IgA deficiency, isolated, 843
IgA nephropathy, 766–767
IgA vasculitis (Henoch-Schönlein purpura), 763, 768*t*, 851
IHD (intermittent hemodialysis), 751
ILD. *See* interstitial lung disease
ileal pouch-anal anastomosis, 794
ileoproctostomy, 327
iloperidone, 1077*t*
iloprost, for pulmonary hypertension, 702
imaging, diagnostic, 23–26
imatinib, for CML, 288
imidazoles, for dermatophyte infections, 262
imipenem
for cholecystitis, 801
for community-acquired pneumonia, 725*t*
for glanders, 461*t*
for health care–associated pneumonia, 727*t*
for human bite infections, 116*t*
for melioidosis, 461*t*
for mixed anaerobic infections, 476*t*
for nocardiosis, 479
for osteomyelitis, 421*t*
for *P. aeruginosa* infections, 460*t*
for peritonitis, 383
for *Proteus* infections, 457
imipenem-cilastatin, for sepsis/septic shock, 68*t*
imipramine
dosage and side effects of, 39*t*, 1072*t*
for noncardiac chest pain, 164
for pain, 39*t*
imiquimod
for HPV infections, 414
for warts, 262
immune reconstitution inflammatory syndrome (IRIS), 1031
immune-complex disorders, 48
immune-mediated myelopathy, 1006
immunization
DTaP, 442
*H. influenzae*, 449
Hib, 369*t*
HIV, 568
HPV, 369*t*, 414
of immunosuppressed patients, 369–370*t*
influenza, 370*t*, 533
measles, 370*t*, 539
meningococcal, 370*t*, 445–446
mumps, 370*t*, 539, 541
pertussis, 451
pneumococcal, 370*t*, 422, 425
poliovirus, 545–546
rabies, 548, 549*f*
recommendations for, 1088–1090*t*
rotavirus, 390
rubella, 370*t*, 539, 540
Td, 442
tetanus, 442, 471
tuberculosis, 490
VZV, 371*t*, 524

immunocompromised host
cytomegalovirus infections in, 526–527
HSV infections in, 517–519, 520–522*t*
immunization of, 369–370*t*
infections in, 362–371
cancer patients, 362–366, 363*t*, 365*f*
transplant recipients, 366–369, 367*t*
*Pneumocystis* infections in, 583–585
VZV infections in, 523
immunodeficiency disease
of adaptive immune system, 840–843, 841*t*
classification of, 841*t*
definition of, 840
diagnosis of, 842*t*
immunoglobulin deficiency syndromes, 843
of innate immune system, 840, 841*t*
leukopenia in, 276
regulatory defects, 841*t*
T cell immunodeficiency, 840, 842
immunoglobulin deficiency syndromes, 843
immunohemolytic anemia, 271
immunoproliferative small-intestinal disease (IPSID), 325
immunosuppressive agents
after renal transplantation, 758
for dilated cardiomyopathy, 42
for inflammatory bowel disease, 794
for liver transplantation, 830
for SLE, 845
for vasculitis, 854
impetigo
clinical manifestations of, 260, 417
diagnosis of, 417
microbiology of, 260, 417
pathogenesis of, 417
streptococcal, 436, 436*t*
treatment of, 261
implantable cardioverter defibrillator (ICD)
for dilated cardiomyopathy, 641
for heart failure, 692
for hypertrophic cardiomyopathy, 643
in vitro fertilization (IVF), 924
inactivated poliovirus vaccine (IPV), 546
incidentaloma, 900, 900*f*
inclusion body myositis (IBM), 1057–1058, 1058*t*
indigestion, 160–161
indolent lymphoma, 295*t*, 298
indomethacin
for pain, 38*t*
for pericarditis, 645
for reactive arthritis, 860
indomethacin-responsive headache, 221
infant botulism, 471–472
infections. *See also* antibacterial therapy; *specific diseases and pathogens*
diarrhea with, 168
fatigue in, 133*t*
headache in, 215*t*
health care-associated infections. *See* health care-associated infections
in immunocompromised host, 362–371
cancer patients, 362–366, 363*t*, 365*f*
immunization and, 369–370*t*
transplant recipients, 366–369, 367*t*, 758–759, 759*t*
leukemoid reaction in, 275
leukopenia in, 276
lymphadenopathy and, 190*t*
lymphocytosis in, 275
monocytosis in, 275
neck pain in, 212
nephritis with, 771–772, 771*t*
neutrophilia in, 274–275
sepsis and. *See* sepsis
skin, 260–262
with transfusion, 46, 47*t*
upper respiratory. *See* upper respiratory infections (URIs)
weight loss in, 136*t*
infectious mononucleosis
cytomegalovirus, 526
Epstein-Barr virus, 528–529, 529*f*
infectious myelopathy, 1006
infective endocarditis, 372–381
acute, 372
*Bartonella*, 467*t*, 468
clinical manifestations of, 373–374
diagnosis of, 374, 375*t*
epidemiology of, 372
etiology of, 72
HACEK group, 372, 378*t*, 452, 453*t*
outcome of, 380
pathogenesis of, 372–373

infective endocarditis (*Cont.*):
prevention of, 380, 381*t*, 631
*S. aureus*, 372, 427–428
streptococcal, 439
subacute, 372
treatment of, 374, 376, 378*t*, 378–380, 379–381, 379*t*
inferior vena cava filter, 733
infertility
female, 923–924, 923*f*
male, 915
inflammation
basophilia in, 276
neutropenia in, 274–275
inflammatory bowel disease (IBD), 790–794
Crohn's disease, 791
differential diagnosis of, 792
in enteropathic arthritis, 867
epidemiology of, 790–791, 790*t*
extraintestinal manifestations of, 792
treatment of, 792, 793*f*, 794
ulcerative colitis, 791
infliximab
for ankylosing spondylitis, 857
for inflammatory bowel disease, 794
for psoriasis, 259
for psoriatic arthritis, 858
for rheumatoid arthritis, 846
influenza
clinical manifestations of, 531, 534*t*
complications of, 531
epidemiology of, 530–531
laboratory testing in, 531
microbiology of, 530
nosocomial, 360
pathogenesis of, 530
prevention of, 533
treatment of, 531–532, 532*t*
influenza vaccine, 370*t*, 533, 1090*t*
innate immune system, deficiencies of, 841*t*
insomnia, 241–243
drug-induced, 242
long-term (chronic), 241
psychophysiologic, 241
rebound, 242
short-term, 241
treatment of, 242, 243*t*
insulin resistance syndrome. *See* metabolic syndrome
insulin therapy
combinations, 907*t*
for diabetes mellitus, 906–907, 907*t*, 910*t*
for diabetic ketoacidosis, 106*t*
for hyperglycemic hyperosmolar state, 105
for hyperkalemia, 16*t*
long-acting preparations, 907*t*
short-acting preparations, 907*t*
insulinoma, 107, 109*t*, 332–333, 332*t*
integrase inhibitors, for HIV infection, 559, 564–565*t*
intensive care unit (ICU), monitoring in, 34
intercostal neuritis, 141
interferon therapy
for adult T cell leukemia/lymphoma, 301
for HSV infections, 521*t*
for squamous cell carcinoma, 308
interferon-alpha therapy
for carcinoid tumor, 332
for chronic hepatitis B, 817
for essential thrombocytosis, 293
for follicular lymphoma, 298
for hepatocellular carcinoma prevention, 331
for islet-cell tumors, 333
for melanoma, 307
for renal cancer, 335
for Zollinger-Ellison syndrome, 790
interferon-beta therapy, for multiple sclerosis, 1016, 1018
interleukin-2 therapy
for melanoma, 307
for renal cancer, 335
intermittent hemodialysis (IHD), 751
internist, procedures commonly performed by, 26–31
lumbar puncture, 28–30, 29*f*
paracentesis, 30–31
thoracentesis, 27–28, 28*f*
interstitial cystitis, 778–779
interstitial lung disease (ILD), 734–739
alveolar hemorrhage syndromes, 739
approach to, 734, 736–737
classification of, 735–736*t*
in connective tissue disorders, 738
cryptogenic organizing peripheral neuropathy, 738
desquamative interstitial pneumonia, 738
hypersensitivity pneumonitis, 739

idiopathic pulmonary fibrosis, 737–738
management of, 737
nonspecific interstitial pneumonia, 738
pulmonary alveolar proteinosis, 738
pulmonary infiltrates with eosinophilia, 738–739
pulmonary Langerhans cell histiocytosis, 739
interstitial nephritis
acute, 771–772, 771*t*
chronic, 772
intestinal decompression, 797
intestinal hypermotility, paraneoplastic, 349*t*
intestinal infections
botulism, 472
pathogenic *E. coli*, 455
intestinal motility, 167, 168
intestinal pseudoobstruction, 797
intimate partner violence (domestic violence), 1091*t*, 1106
intraabdominal infections, 382–385
abscess, 384–385
clostridial, 473
peritonitis, 382–384
intra-arterial pressure monitoring, 34
intracerebral/intracranial hemorrhage. *See also* subarachnoid hemorrhage
causes of, 84*t*
clinical manifestations of, 83–85
in head trauma, 98
intracranial pressure in, 93
treatment of, 87
intracranial aneurysm, 84*t*
intracranial pressure (ICP)
increased, 93–96
clinical manifestations of, 93–94
impaired consciousness and, 81
treatment of, 94–95, 95*t*
monitoring of, 95, 95*t*, 96*f*
intracranial (saccular) aneurysm, 91
intracranial tumor, 1009–1010
intracytoplasmic sperm injection (ICSI), 915, 924
intraperitoneal abscess, 384
intrauterine contraceptive device, 479, 922
intrauterine insemination (IUI), 924
intravascular device infections, 359*t*, 360
intravenous immunoglobulin
for antiphospholipid antibody syndrome, 850
for *C. difficile* infections, 398
for CLL, 297
for enterovirus, 545
for idiopathic thrombocytopenic purpura, 280
for immunoglobulin deficiency syndromes, 843
for inflammatory myopathy, 1059
for multiple sclerosis, 1019
for myasthenia gravis, 1053
for parvovirus infection, 542
for polyneuropathy, 1044, 1046
for staphylococcal infections, 434
for streptococcal infections, 436*t*
invasive pulmonary aspergillosis, 572
iodine deficiency, 892
iodine excess, 889
iodoquinol, for amebiasis, 397
IPF (idiopathic pulmonary fibrosis), 737–738
ipilimumab, for melanoma, 307
ipratropium, for COPD, 720, 721
IPSID (immunoproliferative small-intestinal disease), 325
IPV (inactivated poliovirus vaccine), 546
irbesartan, for heart failure, 690*t*
irinotecan
for breast cancer, 321
for cervical cancer, 341
for colorectal cancer, 328
IRIS (immune reconstitution inflammatory syndrome), 1031
iris lesion, 255
iron
overload, 46
storage disorder. *See* hemochromatosis
supplementation, in chronic kidney disease, 754
iron-deficiency anemia, 268–269, 268*f*, 270*t*, 273
irritable bowel syndrome (IBS), 794–795, 795*t*, 796*t*
ischemic stroke, 82–83
causes of, 87–88, 88*t*
treatment of, 84–87, 86*t*
islet-cell tumor
pancreatic, 332–333, 332*t*
paraneoplastic syndromes in, 349*t*
isocarboxazid, 1073*t*
isolation techniques, 357
isometheptene, for migraine, 218*t*

isoniazid
for latent tuberculosis, 490*t*
for nontuberculous mycobacterial infections, 494
for tuberculosis, 485–486, 487–488*t*, 490
isoproterenol, for tachyarrhythmias, 682*t*
isosorbide dinitrate (ISDN)
for achalasia, 164
for chronic stable angina, 675*t*
for esophageal spasm, 165
for heart failure, 690, 690*t*
isosorbide mononitrate (ISMO), for chronic stable angina, 675*t*
isotretinoin, for acne, 262
itch mite, 610
ITP (idiopathic thrombocytopenic purpura), 278
itraconazole, 569
for aspergillosis, 574*t*
for blastomycosis, 581
for *Candida* esophagitis, 166
for candidiasis, 571
for coccidioidomycosis, 580
for dermatophyte infections, 262
for histoplasmosis, 579*t*
for paracoccidioidomycosis, 582
for penicilliosis, 582
for sporotrichosis, 582
IUI (intrauterine insemination), 924
IV drug use, endocarditis and, 373
ivabradine, for heart failure, 580
ivermectin
for ascariasis, 601
for cutaneous larva migrans, 600
for lymphatic filariasis, 604
for onchocerciasis, 604
for scabies, 610
for strongyloidiasis, 602
IVF (in vitro fertilization), 924
*Ixodes* ticks, 495

**J**

Japanese encephalitis, 550
Jarisch-Herxheimer reaction, 410–411, 496, 499
jaundice, 178–181, 331
approach to, 180, 180*f*
causes of, 179, 179*t*
cholestatic conditions producing, 182–183*t*
definition of, 178
drug-induced, 182*t*
hepatocellular conditions producing, 182*t*
JC virus, 1030–1031
jellyfish sting, 120
jet lag, 241, 245
joint disease, neuropathic, 867–868
joint infections
anaerobic, 476
arthritis, 418–420, 427, 430
osteomyelitis. *See* osteomyelitis
*P. aeruginosa*, 459, 460*t*
in tuberculosis, 484
joint pain, 203–207
assessment of, 203
diagnosis of, 204*f*
in elderly, 205–207
historic features in, 203–204
imaging in, 205, 205*t*
laboratory testing in, 205
physical examination in, 204–205
joint replacement surgery, 862, 869
joints, muscles and innervation of, 949–950*t*
josamycin, for tick-borne spotted fevers, 505
jugular foramen syndrome, 1000
jugular venous pulsation (JVP), 613
Junin/Argentinian hemorrhagic fever, 551
juvenile polyposis, 326*t*, 327

**K**

kala-azar (visceral leishmaniasis), 593–594
kaolin-pectin, for diarrhea, 170
Kaposi's sarcoma, 525, 558
Katayama fever, 605
kayexalate, for hyperkalemia, 16*t*
Kenya tick typhus, 504
keratinolytic agents, for warts, 262
keratoconjunctivitis sicca (KCS), 849
keratosis pilaris, 256*f*
ketoconazole
for adrenal carcinoma, 896
for *Candida* esophagitis, 166
for ectopic ACTH syndrome, 351
ketorolac, for pain, 38*t*, 40
kidney cancer. *See* renal cancer
kidney disease. *See* renal disease
kidney stones, 385
*Kingella kingae* infections, 452, 453*t*
*Klebsiella* infections
enteric, 455–456
*K. granulomatosis*, 404*t*, 413
Klinefelter's syndrome, 913

Koplik's spots, 538
Kussmaul sign, 613
kwashiorkor, 41
kyphoscoliosis, 143

**L**
labetalol
for aortic dissection, 695, 696*t*
for hypertension, 651, 652*t*
for malignant hypertension, 656*t*
labyrinthine dysfunction, 227
labyrinthitis, 227
lacosamide, for seizures, 963*t*, 967*t*
lactic acidosis, 17, 18*t*, 19
lactose hydrogen breath test, 170
lactulose
for constipation, 50*t*, 174
for hepatic encephalopathy, 833
for irritable bowel syndrome, 796*t*
lacunar syndromes, 82, 83
Lambert-Eaton myasthenic syndrome (LEMS), 352*t*, 354*t*, 1050
laminectomy, decompressive, 99
lamivudine
for chronic hepatitis B, 817, 818–819*t*
for HIV infection, 560*t*, 566
lamotrigine
for bipolar disorder, 1066
dosage and side effects of, 1078*t*
for seizures, 963*t*, 967*t*
for trigeminal neuralgia, 995
lanreotide autogel, for acromegaly, 881
lansoprazole
for *H. pylori* eradication, 787*t*
for Zollinger-Ellison syndrome, 789–790
larva migrans, 600
laryngeal palsy, 1000
laryngitis, 253–254
laser therapy, for esophageal carcinoma, 322
Lassa fever, 551
Laurence-Moon-Biedl syndrome, 901
laxatives, 50*t*
for constipation, 174
for hemorrhoids, 798
LBP. *See* low back pain
LCM (lymphocytic choriomeningitis), 549, 1037*t*
LDL cholesterol, 936. *See also* hypercholesterolemia
lead-time bias, 1095
leech infestation, 611
leflunomide
for psoriatic arthritis, 859
for rheumatoid arthritis, 846
left ventricular hypertrophy, 620, 620*f*
*Legionella* infections, 361, 511–513
Legionnaires' disease, 512
leiomyoma, 325
leiomyosarcoma, 323, 324
leishmaniasis, 593–594
Lemierre's syndrome, 475
LEMS (Lambert-Eaton myasthenic syndrome), 352*t*, 354*t*, 1050
lenalidomide
for multiple myeloma, 302
for myelodysplastic syndromes, 289
length bias, 1095
lepirudin
for heparin-induced thrombocytopenia, 280
for thrombotic disorders, 282
leprosy, 490–492
clinical manifestations of, 491
complications of, 491
diagnosis of, 491
epidemiology of, 490
lepromatous, 491–492
microbiology of, 490
treatment of, 492
tuberculoid, 491
leptomeningeal metastasis, 1001*t*, 1011
leptospirosis, 497–498
Leriche syndrome, 696
letrozole, for breast cancer, 321
leucovorin
for colorectal cancer, 328
for gastric cancer, 323
for *Pneumocystis* prophylaxis, 585*t*
leukapheresis, 48
leukemia, 268. *See also specific types*
definition of, 293
infections in, 363*t*
monocytopenia in, 277
oligoblastic, 289
leukemoid reaction, 275
leukocytes
inclusion and nuclear abnormalities, 266
normal values in blood, 274*t*
leukocytosis, 274–276
leukoerythroblastic reaction, 275
leukopenia, 276–277
leukoplakia, 256*f*, 309, 528, 529, 1101
leuprolide, for prostate cancer, 343
levetiracetam
for myoclonus, 238
for seizures, 963*t*, 967*t*

levocetirizine
for allergic rhinitis, 838
for urticaria/angioedema, 837
levodopa, for Parkinson's disease, 978, 980*t*
levofloxacin
for *C. pneumoniae* infections, 513
for community-acquired pneumonia, 725*t*
for epididymitis, 400
for health care–associated pneumonia, 727*t*
for *Legionella* infections, 513
for *M. pneumoniae* infections, 511
for osteomyelitis, 421*t*
for *P. aeruginosa* infections, 461*t*
for pneumococcal infections, 424
for *S. maltophilia* infections, 461*t*
for sepsis/septic shock, 68*t*
for tuberculosis, 486
levomilnacipran, 1073*t*
levorphanol, for pain, 38*t*
levosimendan, for heart failure, 691*t*
levothyroxine
for hypothyroidism, 888–889
for myxedema coma, 889
for thyroid neoplasms, 894
for thyroiditis, 891
LH. *See* luteinizing hormone
Lhermitte's symptom, 1013
lice, human, 610–611
lichen planus, 256*f*, 259
lichen simplex chronicus, 256*f*
lichenification, 257*t*
Liddle's syndrome, 20
lidocaine
for arrhythmias, 683*t*
for polyneuropathy, 1044, 1045*t*
for postherpetic neuralgia, 524
for tachyarrhythmias, 681–682*t*
for ventricular fibrillation, 59*f*
Li-Fraumeni syndrome, 317
light chain deposition disease, 772–773, 773*t*
lightheadedness, 226–227
limb dystonia, 237
limb-girdle dystrophy, 1054
limbic encephalitis, paraneoplastic, 352*t*, 353, 353*t*, 354*t*
linagliptin, for diabetes mellitus, 908*t*
linear skin lesion, 255
linezolid
for community-acquired pneumonia, 725*t*
for enterococcal infections, 440
for health care–associated pneumonia, 727*t*
for MRSA infections, 416*t*
for nocardiosis, 479
for staphylococcal infections, 430, 431*t*, 433*t*
linitis plastica, 323
liothyronine, for thyroid neoplasms, 894–895
lipase, serum, 804
lipemia retinalis, 940
lipoma, small-bowel, 325
lipoprotein lipase deficiency, 937*t*, 940
liquid nitrogen, for warts, 262
liraglutide, for diabetes mellitus, 906, 909*t*
lisinopril
for heart failure, 690*t*
for hypertension, 653*t*
listerial infections, 446–447
lithium
for amiodarone-induced thyrotoxicosis, 892
for bipolar disorder, 1066
for cluster headache prevention, 219
dosage and side effects of, 6, 1078*t*
pharmacology of, 1078, 1078*t*
liver abscess, 384–385, 396–397
liver biopsy, percutaneous, 186
liver disease
alcoholic, 827–828
benign tumors, 330
cirrhosis. *See* cirrhosis
coagulation disorders in, 279, 281
encephalopathy in, 832–833
hepatitis. *See* hepatitis
imaging in, 185–186
jaundice in, 178–179
liver flap, 238
liver function tests, 181–185, 181*f*, 184*t*
liver transplantation
for alcoholic liver disease, 828
for amyloidosis, 875
for ascites, 188
for chronic hepatitis B, 820–821*t*
complications of, 830
contraindications to, 830*t*
donor selection for, 830
for fulminant hepatitis, 816
for hepatic encephalopathy, 833
immunosuppressive agents for, 830
indications for, 829*t*
infections after, 369

for primary biliary cirrhosis, 829
for primary sclerosing cholangitis, 803
for toxic and drug-induced hepatitis, 815
for Wilson's disease, 946
LMWH. *See* low-molecular-weight heparin
lockjaw, 470
lofexidine, for narcotic withdrawal, 1085
Löffler's syndrome, 601
Löfgren's syndrome, 871
lomitapide, for dyslipidemia, 939*t*
loperamide
for diarrhea, 170
for inflammatory bowel disease, 792
for irritable bowel syndrome, 795, 796*t*
loratadine
for allergic rhinitis, 838
for urticaria/angioedema, 837
lorazepam
for delirium, 52*t*
dosage and action of, 1075*t*
for dyspnea, 51*t*
for nausea, 51
for status epilepticus, 102*f*
for STEMI, 661
losartan
for heart failure, 690*t*
for hypertension, 653*t*
for systemic sclerosis, 848
louse-borne epidemic typhus, 502*t*, 506–507
louse-borne relapsing fever, 498–499
lovastatin, for dyslipidemia, 938*t*
low back pain (LBP), 207–307
etiology of, 209–211
examination in, 207–208, 208*t*
laboratory testing in, 208–209
risk factors for structural cause, 209*t*
treatment of, 211
types of, 207
low back strain/sprain, 210
lower esophageal sphincter, disorders of, 164–165
low-molecular-weight heparin (LMWH)
for STEMI, 662
for thrombotic disorders, 281–282
for UA/NSTEMI, 670
for venous thromboembolism, 733
loxapine, 1076*t*
lubiprostone, for irritable bowel syndrome, 796*t*
Ludwig's angina, 475
lumbar disk disease, back pain in, 209
lumbar puncture
in meningococcal infections, 445
technique for, 28–30, 29*f*
lumbar puncture headache, 221
lumpectomy, 320
lung abscess, 726, 729–730
lung biopsy, 737
lung cancer, 310–316
adenocarcinoma, 314*t*, 315
causes of, 716–718
chest pain in, 138*t*
clinical manifestations of, 311
diagnosis of, 709
etiology of, 310, 311*f*
histologic classification of, 310
incidence of, 310
non-small cell, 314*t*, 315
oncologic emergencies in, 110–111
paraneoplastic syndromes in, 349, 349–350*t*, 353*t*, 354*t*
prevention of, 1100
prognosis of, 315, 316*t*
risk factors for, 1100
screening for, 315, 1095, 1098*t*
small-cell, 314*t*, 315
staging of, 311, 312–313*t*
treatment of, 313, 314–315*t*, 315
lung disease. *See* respiratory disease
lung flukes, 606
lung transplant
for COPD, 721
infections after, 369
for interstitial lung disease, 737
lung volume reduction surgery, 721
lung volumes, 705*f*
lupus, drug-induced, 844
lupus pernio, 871
lurasidone, 1077*t*
luteinizing hormone (LH)
deficiency of, 882, 883*t*
production of, 877, 878*f*
Lyme borreliosis, 494–497
clinical manifestations of, 495
diagnosis of, 496
epidemiology of, 495
meningitis in, 1033*t*
microbiology of, 494
prevention of, 122–123, 496
treatment of, 496

lymphadenitis, in tuberculosis, 483
lymphadenopathy, 189–191
approach to, 191
diseases associated with, 190*t*
etiology of, 189, 190*t*
in HIV infection, 558
in nontuberculous mycobacterial infections, 493
treatment of, 191
lymphangiectasia, intestinal, 276
lymphedema, 699
lymphocutaneous disease, *Nocardia*, 478, 480*t*
lymphocytes, defective egress of, 840
lymphocytic choriomeningitis (LCM), 549, 1037*t*
lymphocytic leukemia, chronic. *See* chronic lymphocytic leukemia
lymphocytosis, 275
lymphoepithelioma, 309
lymphogranuloma venereum, 404*t*, 408
lymphoid malignancies, 293–305. *See also specific types*
classification of, 293–294, 295*t*
diagnosis and staging of, 294, 296
etiology of, 294
incidence and etiology of, 294, 296*f*
lymphoma, 293, 525. *See also specific types*
aggressive, 295*t*, 299
anaplastic large cell, 294, 296*f*
Burkitt's, 294, 296*f*, 300–301
definition of, 293
diffuse large B cell, 299
Epstein-Barr virus in, 529
fever of unknown origin in, 129
follicular, 294, 296*f*, 298
indolent, 295*t*, 298
infections in, 363*t*
lymphopenia with, 276
MALT, 294, 296*f*
mantle cell, 294
non-Hodgkin's, 296*f*, 298–299, 300*t*
oncologic emergencies, 110–111
primary CNS, 1010
lymphopenia, 276–277
lymphoproliferative disease, Epstein-Barr virus, 528, 529
Lynch syndrome, 326*t*, 327, 338

**M**

M component, 301
MAC (*Mycobacterium avium* complex) infections, 492–494
Machupo/Bolivian hemorrhagic fever, 551
macrolides
for *C. pneumoniae* infections, 513
for community-acquired pneumonia, 725*t*
for *Corynebacterium* infections, 443
for *H. influenzae* infections, 449
for *Legionella* infections, 513
for Lyme borreliosis, 496
for *M. catarrhalis* infections, 452
for *M. pneumoniae* infections, 511
for nontuberculous mycobacterial infections, 494
for pertussis, 451
for pneumococcal infections, 424
macular degeneration, 230*f*, 231
maculatum disease, 501*t*
macules, 257*t*, 362
magnesium citrate, for constipation, 50*t*
magnesium hydroxide (Milk of Magnesia)
for constipation, 50*t*
for irritable bowel syndrome, 796*t*
magnesium sulfate
for tetanus, 470
for ventricular fibrillation, 59*f*
magnesium therapy
for alcoholic liver disease, 828
for hypomagnesemia, 930
for torsades de pointes, 682*t*
magnetic resonance angiography (MRA), in stroke, 85, 87
magnetic resonance imaging (MRI)
for breast cancer screening, 1096*t*
in coma, 81
in heart disease, 625, 626*t*
hepatobiliary, 800*t*
in hepatobiliary disease, 186
indications for, 26
in optic neuritis, 231
in respiratory disease, 709
in spinal cord compression, 98
in spinal epidural abscess, 98
in STEMI, 659
in stroke, 87
utility of, 26
in vertigo, 227
malabsorption syndromes, 170, 173*t*
malaria, 586–591
clinical manifestations of, 587
diagnosis of, 587
microbiology and epidemiology of, 586

pathogenesis of, 586–587
in pregnancy, 587
prevention of, 589, 590–591*t*
treatment of, 587, 588–589*t*
*Malassezia* infections, 581
malathion, for pediculiasis, 611
maldigestion, 173*t*
male gender, cardiovascular disease and, 1093
male reproductive system disorders, 912–916
malingering, 1069
malnutrition, 41–43, 187
MALT lymphoma. *See* mucosa-associated lymphoid tissue lymphoma
mammography, 318, 1095, 1096*t*
mandibular positioning device, 746
mania, 1065–1066
mannitol therapy
for increased intracranial pressure, 95, 95*t*
for stroke, 87
mantle cell lymphoma, 294
MAOIs. *See* monoamine oxidase inhibitors
marasmus, 41
maraviroc, for HIV infection, 559, 564*t*
Marburg virus infection, 552–553
march hemoglobinuria, 273
Marfan's syndrome, 694
marine envenomations, 120–121
invertebrate, 120
vertebrate, 120–121
marine poisoning, 121–122
massage, for chronic back pain, 211
mastectomy
bilateral prophylactic, 1100
for breast cancer, 320
mastitis, 427
mastocytosis, systemic, 838–839, 839*t*
mastoiditis, 251
McArdle's disease, 1059
MCTD (mixed connective tissue disease), 848
MDMA (ecstasy), 4
MDR (multidrug-resistant) tuberculosis, 482
MDS. *See* myelodysplastic syndromes
measles, mumps, and rubella (MMR) vaccine, 370*t*, 539, 1090*t*
measles inclusion-body encephalitis (MIBE), 538
measles (rubeola), 538–539
measles vaccine, 370*t*, 539
mebendazole
for ascariasis, 601
for enterobiasis, 603
for hookworm, 601
for trichinellosis, 599
mechanical ventilation. *See* ventilatory support
meclizine
for nausea and vomiting, 51, 160
for vertigo, 228*t*
mediastinal mass, 743
mediastinitis, 743
mediastinitis, fibrosing, 578
mediastinoscopy, 711
medical emergencies. *See* emergencies, medical
medicinal leech, 611
Mediterranean spotted fever, 501*t*, 504
medroxyprogesterone
for amenorrhea, 918
for menopausal symptoms, 922
medulloblastomas, 1010
mefloquine, for malaria, 589, 591*t*
megakaryoblastic leukemia, 284*t*
megestrol
for endometrial cancer, 340
for weight loss, 137
meglumine antimonate, for leishmaniasis, 594
melanoma, 305–307
acral lentiginous, 306
lentigo maligna, 306
nodular, 306
paraneoplastic syndromes in, 353*t*
risk factors for, 306, 306*t*
superficial spreading, 306
melarsoprol, for sleeping sickness, 596
melasma, 256*f*
melena, 174
melioidosis, 461*t*, 462
melphalan
for amyloidosis, 875
for multiple myeloma, 302
memantine, for Alzheimer's disease, 973
membranoproliferative glomerulonephritis (MPGN), 765
MEN 1 (multiple endocrine neoplasia type 1), 332, 789, 924
Ménière's disease, 227, 228*t*, 229
meningeal syphilis, 410
meningioma, 230*f*, 1010, 1011*f*

meningitis
approach to, 1020, 1021–1022*f*
bacterial, 1022–1025
clinical manifestations of, 1022–1023
differential diagnosis of, 1023
*E. coli*, 454
etiology of, 1022, 1025*t*
*H. influenzae*, 448–449
laboratory features of, 1023, 1023*t*
listerial, 446–447
meningococcal, 444–445
pneumococcal, 423–425
prognosis of, 1025
streptococcal, 438
treatment of, 1024–1025, 1024*t*, 1025*t*
in cancer patients, 364
chronic
approach to, 1032, 1040
bacterial, 1033–1034*t*
clinical manifestations of, 1031–1032, 1032*t*
etiology of, 1032
fungal, 1034–1035*t*
helminthic, 1036*t*
noninfectious, 1038–1039*t*
protozoal, 1035–1036*t*
viral, 1037*t*
in coccidioidomycosis, 579
in poliovirus infection, 543
in tuberculosis, 484
viral
clinical manifestations of, 1025
diagnosis of, 1026–1027
differential diagnosis of, 1027
enteroviral, 544
etiology of, 1026, 1026*t*
HSV, 518, 521*t*
treatment of, 1027
meningococcal infections, 443–446
clinical manifestations of, 444–445
diagnosis of, 445
epidemiology of, 443–444
etiology of, 443
pathogenesis of, 444
prevention of, 445–446
prognosis of, 445
treatment of, 445
meningococcal vaccine, 370*t*, 445–446
meningococcemia, 444
meningoencephalitis, listerial, 446
meningovascular syphilis, 410
menopause, 242, 921–922
mental status exam, 947
meperidine
abuse, 1084
for cholecystitis, 801
for pain, 39*t*
meralgia paresthetica, 1049*t*
6-mercaptopurine
for Burkitt's lymphoma, 301
for inflammatory bowel disease, 794
meropenem
for *B. cepacia* infections, 461*t*
for bacterial meningitis, 1024*t*, 1025*t*
for brain abscess, 1030
for cholecystitis, 801
for community-acquired pneumonia, 725*t*
for glanders, 461*t*
for health care–associated pneumonia, 727*t*
for melioidosis, 461*t*
for mixed anaerobic infections, 476*t*
for *P. aeruginosa* infections, 460*t*
for sepsis/septic shock, 68*t*
for Whipple's disease, 482
merozoite, 586
MERS-CoV (Middle East respiratory syndrome coronavirus), 535
mesalamine enema, for inflammatory bowel disease, 792
mesenchymal tumors, 349*t*
mesenteric arteriography, 175, 832
mesenteric insufficiency, chronic, 797
mesenteric ischemia, 797
mesothelioma, 716
metabolic acidosis, 15–20, 18*t*
anion-gap, 17, 18*t*, 19, 22
causes of, 15, 17, 18*t*, 19
drug-induced, 18*t*
hyperchloremic, 19
nomogram for, 17*f*
non-anion-gap, 18*t*, 19, 22
metabolic alkalosis, 17*f*, 20–21, 21*f*
metabolic disease
abdominal pain in, 155*t*
fatigue with, 133*t*
muscle disorders in, 1061
nausea and vomiting in, 159*t*
neutropenia and, 275
weight loss in, 136*t*
metabolic syndrome, 905
cardiovascular disease risk and, 1093, 1093*t*
clinical manifestations of, 657
definition of, 656, 657*t*

etiology of, 656–657
treatment of, 658
metabolism, of food, 40
metformin
for diabetes mellitus, 906, 908*t*
for polycystic ovarian syndrome, 918
methadone
abuse, 1084
for narcotic withdrawal, 1085
for opioid maintenance, 1086
for pain, 38*t*
methanol poisoning, 17, 18*t*, 19
methemoglobinemia, 145
methenamine, for nephrolithiasis, 782*t*
methicillin-resistant *S. aureus* (MRSA) infections
endocarditis, 377*t*
epidemiology of, 426
osteomyelitis, 421*t*
skin and soft tissue, 416*t*, 428
treatment of, 68*t*, 430, 431–433*t*
methimazole, for thyrotoxicosis, 890
methotrexate
for ANCA-associated glomerulonephritis, 762
for ankylosing spondylitis, 857
for bladder cancer, 334
for head and neck cancer, 309
for inflammatory bowel disease, 794
for inflammatory myopathy, 1059
for multiple sclerosis, 1019
for polyneuropathy, 1046
for primary sclerosing cholangitis, 803
for psoriasis, 259
for psoriatic arthritis, 859
for reactive arthritis, 860
for rheumatoid arthritis, 846
for vasculitis, 854
methylcellulose, for irritable bowel syndrome, 796*t*
methyldopa, for hypertension, 651
methylphenidate
for depression, 52
for fatigue, 52
for narcolepsy, 244
methylprednisolone
for anaphylaxis, 114
for ANCA-associated glomerulonephritis, 762
for asthma exacerbations, 715
for multiple sclerosis, 1018, 1019
for optic neuritis, 231
for renal transplant rejection, 758
for vertigo, 228*t*
methysergide, for migraine prevention, 220*t*
metoclopramide
for *H. pylori* eradication, 161
for migraine, 218*t*
for nausea and vomiting, 51, 160
for systemic sclerosis, 848
metolazone
for edema, 152, 153*t*
for heart failure, 688, 690*t*
for hypertension, 655
metoprolol
for aortic dissection, 695
for arrhythmias, 683*t*
for heart failure, 690*t*
for hypertension, 651, 652*t*
for migraine prevention, 220*t*
for STEMI, 662, 667
for UA/NSTEMI, 670
metronidazole
for acne, 263
for amebiasis, 397
for bacterial meningitis, 1024*t*, 1025*t*
for bacterial vaginosis, 401
for brain abscess, 1030
for *C. difficile* infections, 398
for clostridial infections, 474*t*
for diverticulitis, 796
for giardiasis, 391
for *H. pylori* eradication, 787*t*
for hepatic encephalopathy, 833
for inflammatory bowel disease, 794
for intestinal pseudoobstruction, 797
for mixed anaerobic infections, 476*t*
for necrotizing fasciitis, 416*t*
for pelvic inflammatory disease, 403, 406*t*
for peritonitis, 383
for tetanus, 470
for trichomoniasis, 401
for urethritis in men, 400
metyrapone
for adrenal carcinoma, 896
for ectopic ACTH syndrome, 351
mexiletine
for arrhythmias, 683*t*
for myotonic dystrophy, 1057
for polyneuropathy, 1045*t*
MG. *See* myasthenia gravis
MGUS (monoclonal gammopathy of uncertain significance), 302

MI (myocardial infarction). *See* ST-segment elevation myocardial infarction; unstable angina/non-ST-elevation myocardial infarction
MIBE (measles inclusion-body encephalitis), 538
micafungin, 569, 574*t*
miconazole, for candidiasis, 401
microaerophilic bacteria, 469
microbial bioterrorism, 361
micrographia, 976
micronutrient deficiency, 45, 45*t*
microscopic polyangiitis, 851
midazolam
  for delirium, 52*t*
  for dyspnea, 51*t*
  for increased intracranial pressure, 95*t*
  for scorpion sting, 124
  for status epilepticus, 102*f*
Middle East respiratory syndrome coronavirus (MERS-CoV), 535
midodrine
  for ascites, 188
  for hepatorenal syndrome, 189
  for orthostatic hypotension, 994
  for syncope, 225
midsystolic click (heart sound), 615
mifepristone, for emergency contraception, 923
miglitol, for diabetes mellitus, 908*t*
migraine, 215–218
  diagnosis of, 216*t*
  epidemiology of, 215*t*
  prevention of, 220–221*t*
  sleep disorders and, 242
  treatment of, 216, 217–218*t*
  vertigo in, 228*t*, 229
  visual loss and, 231
migrating motor complex, 167
miliary disease, 484
milk alkali syndrome, 20
milnacipran, for fibromyalgia, 868
milrinone
  for heart failure, 664*t*, 691, 691*t*
  for pulmonary edema, 70
miltefosine, for leishmaniasis, 594
Milwaukee shoulder, 866
mineral deficiencies, 45*t*
mineral oil, for constipation, 174
minimal change disease, 764
Mini-Mental status examination, 947
minitransplant, 297
Minnesota tube, for esophageal varices, 832
minocycline
  for actinomycosis, 481
  for leprosy, 492
  for nocardiosis, 479
  for staphylococcal infections, 430, 433*t*
  for Whipple's disease, 482
mipomersen, for dyslipidemia, 939*t*
mirtazapine, 1071, 1073*t*
misoprostol, for erosive gastropathies, 788
mite-borne spotted fevers, 505
mitiglinide, for diabetes mellitus, 909*t*
mitochondrial myopathies, 1059
mitomycin, for anal cancer, 330
mitotane
  for adrenal carcinoma, 896
  for ectopic ACTH syndrome, 351
mitoxantrone
  for multiple sclerosis, 1018, 1019
  for prostate cancer, 343
mitral regurgitation (MR)
  clinical manifestations of, 634
  echocardiography in, 624*f*, 634
  etiology of, 634
  heart sounds in, 616*t*
  in STEMI, 667
  treatment of, 634, 635*f*
mitral stenosis (MS)
  diagnosis of, 632
  echocardiography in, 624*f*, 632
  etiology of, 632
  heart sounds in, 616*t*
  treatment of, 632, 633*f*
mitral valve disease, antithrombotic therapy for, 89*t*
mitral valve prolapse (MVP), 616*t*, 634, 636
mittelschmerz, 919
mixed connective tissue disease (MCTD), 848
MM (mononeuropathy multiplex), 1046
MMCB (multifocal motor neuropathy with conduction block), 987
MMR (measles, mumps, and rubella) vaccine, 370*t*, 539
modafinil
  for circadian rhythm sleep disorders, 245
  for depression, 52
  for narcolepsy, 244
Mohs micrographic surgery, 308

molindone, 1076*t*
Mollaret's meningitis, 1039*t*
monkey bite, 117*t*, 118
monoamine oxidase inhibitors (MAOIs)
  dosage and side effects of, 1073*t*
  for Parkinson's disease, 978
  pharmacology of, 1071
monoclonal gammopathy of uncertain significance (MGUS), 302
monoclonal immunoglobulins, renal disease and, 772–773
monocytic leukemia, 284*t*
monocytopenia, 277
monocytosis, 275
mononeuritis multiplex, 1046
mononeuropathy
  approach to, 1040–1042, 1041*f*
  clinical manifestations of, 1046, 1047–1049*t*
  definition of, 1040
  diagnosis of, 1047–1049*t*
mononeuropathy multiplex (MM), 1046
monoparesis, 235*f*
montelukast
  for allergic rhinitis, 838
  for asthma, 714
  for urticaria/angioedema, 837
mood disorders, 1063–1066
mood stabilizers, 1078, 1078*t*
MOPP regimen, for Hodgkin's disease, 304
MOPP-ABV regimen, for Hodgkin's disease, 304
*Moraxella catarrhalis* infections, 451–452
morbilliform lesion, 255
*Morganella* infections, 457
morphine
  abuse, 1084
  for dyspnea, 51*t*
  for increased intracranial pressure, 95*t*
  for pain, 38*t*
  for pulmonary edema, 70
  for STEMI, 659
  for tetanus, 470
  for UA/NSTEMI, 671
mortality, age-specific, 1088–1090*t*
motion sickness, 160, 228*t*
motor examination, 948, 949–950*t*, 951
motor fluctuations, 978
motor neuron disease, 985*t*. *See also* amyotrophic lateral sclerosis
  clinical manifestations of, 233, 233*t*, 234*t*, 235*t*
  etiology and investigation of, 986–987*t*
motor unit disorders, 233, 235*t*
movement disorders, 236–238, 242
moxifloxacin
  anaerobic infections, 476*t*
  for community-acquired pneumonia, 725*t*
  for health care–associated pneumonia, 727*t*
  for *Legionella* infections, 513
  for pneumococcal infections, 424
  for sepsis/septic shock, 68*t*
  for sinusitis, 249*t*
  for tuberculosis, 486
MPGN (membranoproliferative glomerulonephritis), 765
MR. *See* mitral regurgitation
MRA (magnetic resonance angiography), in stroke, 85, 87
MRI. *See* magnetic resonance imaging
MRSA infections. *See* methicillin-resistant *S. aureus* infections
MS. *See* mitral stenosis; multiple sclerosis
MSA (multiple system atrophy), 991
MSLT (multiple sleep latency test), 243, 244*t*
mucormycosis, 576–577
mucosa-associated lymphoid tissue (MALT) lymphoma
  epidemiology of, 296*f*
  etiology of, 294
  pathophysiology of, 323
  treatment of, 324
mucosal leishmaniasis, 593–594
mucous membranes
  dry, in terminally ill patient, 56*t*
  in malnutrition, 42
mucous patch, 409
multidrug-resistant (MDR) tuberculosis, 482
multifocal motor neuropathy with conduction block (MMCB), 987
multi-infarct dementia, 974
multiorgan system failure, 34
multiple cranial nerve palsies, 1001–1002
multiple endocrine neoplasia type 1 (MEN 1), 332, 789, 924

multiple myeloma
classification of, 295*t*
clinical manifestations of, 301–302
infections in, 301, 363*t*
oncologic emergencies, 110–111
pathogenesis of, 301–302
renal disease in, 768*t*, 772–773, 773*t*
staging of, 302, 303*t*
treatment of, 302
multiple sclerosis (MS), 1012–1020
acute (Marburg's variant), 1019
clinical manifestations of, 1012–1013
clinical variants of, 1019
diagnostic criteria for, 1013, 1013–1014*t*
disorders that mimic, 1015*t*
facial nerve involvement in, 997
imaging in, 1015, 1016*f*
laboratory features of, 1015
spinal cord involvement in, 1006
subtypes of, 1013, 1015
treatment of
acute relapses, 1018–1019
decision-making algorithm for, 1017*f*
disease-modifying therapies, 1016, 1018
progressive symptoms, 1019
symptomatic therapy, 1019
multiple sleep latency test (MSLT), 243, 244*t*
multiple system atrophy (MSA), 991
mumps, 540–541, 1037*t*
mumps vaccine, 370*t*, 539, 541
Munchausen's syndrome, 1069
mupirocin, for streptococcal infections, 436
murine (flea-borne) typhus, 502*t*, 505–506
murmur. *See* heart murmur
Murphy's sign, 801
muscle contracture, 1054
muscle cramp, 1053
muscle diseases, 1053–1061
approach to, 1053–1054, 1055*f*, 1056*f*
disorders of energy metabolism, 1059
drug-induced, 1060*t*, 1061
endocrine and metabolic myopathies, 1060–1061
inflammatory myopathies, 1057–1059, 1058*t*
mitochondrial myopathies, 1059
muscular dystrophies. *See* muscular dystrophy
paraneoplastic, 352*t*, 354*t*, 355
periodic paralysis, 1059–1060
muscular dystrophy, 1054
Duchenne's, 1054
facioscapulohumeral, 1057
limb-girdle, 1054
myotonic, 1054, 1057
oculopharyngeal, 1057
musculoskeletal complaints. *See* joint pain
musculoskeletal infections
*E. coli*, 454
*S. aureus*, 427
mushrooms, poisonous, 815
M-VAC regimen, for bladder cancer, 334
MVP (mitral valve prolapse), 616*t*, 634, 636
myalgia, 1053
myasthenia gravis (MG), 1050–1053
differential diagnosis of, 1050
diplopia in, 232
drug interactions in, 1052*t*
laboratory testing in, 1051–1052
paraneoplastic, 352*t*, 354*t*
treatment of, 1051*f*, 1052–1053
myasthenic crisis, 1053
mycetoma, 249
*Mycobacterium avium* complex (MAC) infections, 492–494
*Mycobacterium* infections
*M. abscessus*, 492–494
*M. chelonae*, 492
*M. fortuitum*, 492–494
*M. kansasii*, 492–494
*M. leprae*. *See* leprosy
*M. marinum*, 492–494
*M. tuberculosis*. *See* tuberculosis (TB)
*M. ulcerans*, 492–494
mycophenolate mofetil
for ANCA-associated glomerulonephritis, 762
for immunosuppression after renal transplantation, 758
for inflammatory myopathy, 1059
for myasthenia gravis, 1053
for SLE, 762, 845
for vasculitis, 854
*Mycoplasma pneumoniae* infections, 510–511
mycoplasmal infections, urogenital, 399, 401–402, 408–409

myelitis, paraneoplastic, 352*t*, 353*t*, 354*t*
myeloblastic leukemia, 284*t*
myelodysplastic syndromes (MDS), 284*t*, 289
classification of, 290–291*t*
with isolated del(5q), 290*t*
prognostic scoring system for, 292*t*
treatment of, 289
unclassified, 291*t*
myelofibrosis
blood abnormalities in, 268, 275
idiopathic, 292–293
myeloid leukemia
acute. *See* acute myeloid leukemia
chronic. *See* chronic myeloid leukemia
myelomonocytic leukemia, 284*t*
myelopathy
hypocupric, 1007–1008
immune-mediated, 1006
infectious, 1006
myelophthisis, 268, 275
myeloproliferative syndromes, 275, 276, 292–293
myiasis, 611
myocardial infarction. *See* ST-segment elevation myocardial infarction; unstable angina/non-ST-elevation myocardial infarction
myocardial ischemia, 138, 138*t*, 139*f*
myocarditis, 544, 643–644
myoclonus, 101, 238
myonecrosis (gas gangrene), 416*t*, 418, 473, 474*t*
myopathy, 1053
drug-induced, 1060*t*, 1061
inflammatory, 1057–1059, 1058*t*
weakness in, 233*t*, 234–235*t*
myophosphorylase deficiency, 1059
myositis, 418, 436*t*
myotonia, 1054
myotonic dystrophy, 1054, 1057
myxedema coma, 888, 889

**N**

nadolol
for esophageal varices, 832
for variceal bleeding, 178
nafcillin
for bacterial meningitis, 1024*t*, 1025*t*
for cellulitis, 415*t*
for infective endocarditis, 377*t*, 378*t*
for osteomyelitis, 421*t*
for staphylococcal infections, 430, 431*t*
nail lesions, 257
naloxone
for morphine side effects, 659
for opiate overdose, 1085
naltrexone
for alcoholic rehabilitation, 1084
for narcotic withdrawal, 1085
for opioid dependence, 1086
for primary biliary cirrhosis, 829
naproxen
for migraine, 217*t*
for pain, 38*t*
naratriptan, for migraine, 217*t*, 219*t*
narcissistic personality disorder, 1070
narcolepsy, 243–244, 244*t*
narcotic abuse, 1084–1086
clinical manifestations of, 1084–1085
prevention of, 1086
treatment of, 1085–1086
narcotics
for abdominal pain, 158
for back pain, 211
for dyspnea, 51, 51*t*
for migraine, 218*t*
for pain management, 37, 38–39*t*, 40
nasopharyngeal cancer, Epstein-Barr virus in, 528
natalizumab
for inflammatory bowel disease, 794
for multiple sclerosis, 1018
nateglinide, for diabetes mellitus, 909*t*
native valve endocarditis (NVE). *See also* infective endocarditis
etiology of, 372
HACEK group, 452, 453*t*
staphylococcal, 430
treatment of, 430
nausea and vomiting, 158–160
causes of, 159, 159*t*
complications of, 160
drug-induced, 159*t*
evaluation of, 160
in terminally ill patient, 50–51
treatment of, 50–51, 160
NBTE (nonbacterial thrombotic endocarditis), 372–373
*Necator americanus* infections, 601
neck cancer. *See* head and neck cancer
neck pain, 212–214
neck weakness, 1000

necrotizing fasciitis, 416*t*, 417–418, 436*t*, 437
necrotizing myelopathy, 352*t*
nedocromil sodium, for asthma, 714
nefazodone, 1071
Negri bodies, 547
*Neisseria gonorrhoeae* infections. *See* gonorrhea
*Neisseria meningitidis* infections. *See* meningococcal infections
nematocysts, 120
nematode infections, 599–604
  filarial worms, 603–604
  intestinal, 600–603
  tissue, 599–600
neomycin, for hepatic encephalopathy, 833
neonatal disease
  cytomegalovirus infections, 526
  generalized enteroviral infections, 544
  HSV infections, 519, 522*t*
  listerial infections, 446–447
  streptococcal infections, 438
nephrectomy, 335
nephritic syndrome, 201, 759
nephritis
  acute interstitial, 771–772, 771*t*
  chronic interstitial, 772
  drug-induced, 771, 771*t*
nephrolithiasis, 779–782
  clinical manifestations of, 780
  stone composition, 780
  treatment of, 781, 781–782*t*
  uric acid, 864
  workup for, 780–781, 781*t*
nephropathy. *See also* renal disease
  acute uric acid, 864
  analgesic, 772
  Balkan endemic, 772
  cast, 772–773, 773*t*
  diabetic, 765–766
  HIV-associated, 764
  IgA, 766–767
  thin basement membrane, 766
  urate, 864
nephrostomy tube, 784
nephrotic syndrome (NS), 201, 763–766
  ascites in, 188*f*
  etiology of, 763–764, 763*t*
  evaluation of, 766*t*
nerve abscess, in leprosy, 491
nervous system tumors, 1008–1012
  approach to, 1008
  imaging of, 1009*f*, 1011*f*
  metastatic from other locations, 1010–1012, 1011*t*
  primary intracranial, 1009–1010
  treatment of, 1008*f*, 1012
nesiritide
  for heart failure, 691, 691*t*
  for pulmonary edema, 70
neuralgia, 36
neuraminidase inhibitors, for influenza, 532
neurocysticercosis, 607
neurogenic shock, 61*t*
neuroleptic malignant syndrome (NMS), 1074
neuroleptics, for delirium, 52*t*
neurologic disease
  abdominal pain in, 155*t*
  ataxia. *See* ataxia
  autonomic nervous system disorders. *See* autonomic nervous system (ANS) disorders
  cranial nerve disorders, 995–1002
  in critically ill patient, 35
  dementia. *See* dementia
  depression in, 1064
  epilepsy. *See* epilepsy
  fatigue in, 133*t*
  in HIV infection, 558
  in HSV infection, 518, 521*t*
  infections. *See* central nervous system (CNS) infections
  in leprosy, 491
  in Lyme disease, 495
  in malnutrition, 43
  in measles, 538
  motor neuron disease. *See* amyotrophic lateral sclerosis; motor neuron disease
  multiple sclerosis. *See* multiple sclerosis
  in mumps, 541
  myasthenia gravis. *See* myasthenia gravis
  paraneoplastic, 352–355, 352*t*, 353*t*, 354*t*
  Parkinson's disease. *See* Parkinson's disease
  peripheral neuropathy. *See* peripheral neuropathy
  in rabies, 547
  seizures. *See* seizures
  sleep disorders in, 242

spinal cord disease. *See* spinal cord disease
tumors. *See* nervous system tumors
varicella-zoster virus infections, 523
weakness and paralysis in, 233
weight loss in, 136*t*
neurologic examination, 947–955
anatomic localization of problem, 953, 955*t*
coordination and gait, 951
cranial nerve exam, 947–948
in head trauma, 98
in low back pain, 208, 208*t*
mental status exam, 947
motor examination, 948, 949–950*t*, 951
reflexes, 951
sensory, 951
neuromuscular blockers, 32–33
neuromuscular junction disorders, 234*t*, 235*t*
neuromyelitis optica (NMO), 231, 1019
neuropathic pain, 36, 36*t*
neuropathy. *See specific types*
neuroprotection, for stroke, 87
neurosyphilis, 410, 411*t*, 412
neutropenia, 276
in cancer patient, 113
drug-induced, 275
febrile, 276
approach to, 365–366, 365*f*
*P. aeruginosa* infections, 460*t*
*P. aeruginosa* infections in, 459
treatment of, 276
refractory, 290*t*
sepsis and, 68*t*
treatment of, 113, 276
neutrophilia, 274–275
nevirapine, for HIV infection, 559, 561*t*
niacin deficiency, 45*t*
nicardipine, for malignant hypertension, 656*t*
nicotine, for inflammatory bowel disease, 794
nicotine addiction, 1102–1103. *See also* smoking cessation
nicotine replacement therapy, 720, 1103
nicotinic acid, for dyslipidemia, 939*t*
nifedipine
for achalasia, 164
for aortic regurgitation, 638
for esophageal spasm, 165
for hypertension, 651, 653*t*
for pulmonary hypertension, 702
for systemic sclerosis, 848
for vasospastic disorders, 698
nifurtimox, for Chagas' disease, 595
nilotinib, for CML, 288
nimodipine, for subarachnoid hemorrhage with vasospasm, 93
Nissen fundoplication, 161
nitazoxanide
for *C. difficile* infections, 398
for cryptosporidiosis, 392
for giardiasis, 391
nitrates
for chronic stable angina, 674, 675*t*
for heart failure, 688, 690*t*
nitrofurantoin, for urinary tract infections, 777, 777*t*
nitroglycerin
for anal fissures, 798
for chronic stable angina, 674, 675*t*
for heart failure, 663, 664*t*, 690–691, 691*t*
for malignant hypertension, 656*t*
for pulmonary edema, 70
for STEMI, 659, 665*t*
for systemic sclerosis, 848
for UA/NSTEMI, 670
nitroprusside
for aortic dissection, 695, 696*t*
for heart failure, 663, 664*t*, 690–691, 691*t*
for malignant hypertension, 656*t*
for mitral regurgitation, 634
for STEMI, 665*t*
for STEMI complications, 667
nits, 610
NIV (noninvasive ventilation), 74, 75*t*, 722
nivolumab
for melanoma, 307
for renal cancer, 335
NMO (neuromyelitis optica), 231, 1019
NMS (neuroleptic malignant syndrome), 1074
nocardiosis, 477–479, 480*t*, 1034*t*
nodule (skin lesion), 257*t*, 417
noma, 475
nonbacterial thrombotic endocarditis (NBTE), 372–373
non-Hodgkin's lymphoma, 296*f*, 300*t*
noninvasive ventilation (NIV), 74, 75*t*, 722

nonnucleoside reverse transcriptase inhibitors, for HIV infection, 559, 561–563*t*
nonpolyposis syndrome, 326*t*, 327
nonspecific interstitial pneumonia, 738
non-ST-elevation myocardial infarction. *See* unstable angina/non-ST-elevation myocardial infarction
nonsteroidal anti-inflammatory drugs (NSAIDs)
  for adhesive capsulitis, 870
  for ankylosing spondylitis, 857
  for bursitis, 869
  for calcium apatite deposition disease, 866
  for cholecystitis, 801
  for colon cancer prevention, 1100
  for colonic polyps, 327
  for colorectal cancer prevention, 330
  for diabetes insipidus, 6
  for enteropathic arthritis, 867
  for erythema multiforme, 263
  for erythema nodosum, 263
  for fever, 128
  for fibromyalgia, 868
  for gout, 864
  for low back pain, 211
  for migraine, 216, 217*t*, 219*t*
  for neck and back pain, 214
  for osteoarthritis, 862
  for osteonecrosis, 869
  for pain, 37, 38*t*
  for pelvic pain, 920
  for pericarditis, 645
  for pseudogout, 866
  for psoriatic arthritis, 859
  for reactive arthritis, 860
  for rheumatoid arthritis, 846
  for SLE, 845
  for systemic mastocytosis, 839
  for tendinitis, 870
  for tension-type headache, 218
  for thyroiditis, 891
nontuberculous mycobacterial (NTM) infections, 492–494
  clinical manifestations of, 493
  diagnosis of, 493
  epidemiology of, 492
  microbiology of, 492
  treatment of, 494
norepinephrine
  for increased intracranial pressure, 95*t*
  for shock, 64, 64*t*
  for subarachnoid hemorrhage with vasospasm, 93
normal-pressure hydrocephalus (NPH), 971, 974
norovirus infections
  diarrhea, 389–390
  nosocomial, 361
nortriptyline
  dosage and side effects of, 39*t*, 1072*t*
  for migraine prevention, 220*t*
  for pain, 39*t*
  for smoking cessation, 1103
nosocomial infections. *See* health care-associated infections
NS. *See* nephrotic syndrome
NSAIDs. *See* nonsteroidal anti-inflammatory drugs
NSTEMI. *See* unstable angina/non-ST-elevation myocardial infarction
NTM infections. *See* nontuberculous mycobacterial infections
nuclear cardiology, 625, 626*t*
nuclear medicine imaging, in respiratory disease, 709–710
nuclear myocardial perfusion assessment, 625, 659, 674*t*
nucleoside/nucleotide analogues, for HIV infection, 559, 560–561*t*
5'-nucleotidase (5'-NT), 183–184
nummular lesion, 255
nutcracker esophagus, 165
nutrients, absorption of, 167
nutrition
  fatigue and, 133*t*
  leukopenia and, 276
nutritional status, assessment of, 40–43
nutritional support, 43
  in critically ill patient, 35
  decision tree for initiating, 44*f*
  enteral nutrition, 43–44
  parenteral nutrition, 44–45
  in sepsis/septic shock, 67
NVE. *See* native valve endocarditis
nystagmus, 226, 227
nystatin, for candidiasis, 262, 571

**O**

obesity, 901–903
  central, 901
  classification of, 901*t*
  clinical manifestations of, 902
  drug-induced, 901
  etiology of, 901–902
  in metabolic syndrome, 656–657, 657*t*

sleep disorders in, 244*t*
treatment of, 902–903, 903*f*
in women, 1105
obinutuzumab, for CLL, 297
obsessive-compulsive disorder (OCD), 1068, 1071
obstructive shock, extracardiac, 61*t*
obstructive sleep apnea/hypopnea syndrome (OSAHS), 243, 745–746
obturator neuropathy, 1048*t*
occipital cortex lesions, 230
occipital neuralgia, 221
occlusional injury, 116*t*, 118
ocrelizumab, for multiple sclerosis, 1019
octreotide
for acromegaly, 350, 881
for carcinoid tumor, 332
for esophageal varices, 178, 832
for hepatorenal syndrome, 189
for hypoglycemia, 109
for islet-cell tumors, 333
octreotide scintigraphy, 332, 790
ocular gonorrhea, 405
ocular larva migrans, 600
ocular motor nerve palsy, 232
oculocephalic reflex, 81
oculopharyngeal dystrophy, 1057
odynophagia, 162
ofatumumab, for CLL, 297
ofloxacin
for leprosy, 492
for *M. pneumoniae* infections, 511
for meningococcal prophylaxis, 446
OH. *See* orthostatic hypotension
olanzapine
for delirium, 52*t*
dosage and side effects of, 1077*t*
for schizophrenia, 1067
olfactory nerve (CN I)
disorders of, 998, 999*t*, 1000
examination of, 947
oligemic shock, 61*t*, 62
oligoanuria, 199
oligoblastic leukemia, 289
oligodendroglioma, 1009
oligomenorrhea, 917
oliguria, 199
olopatadine, for allergic rhinitis, 838
omalizumab, for asthma, 714
omega-3 fatty acids, for dyslipidemia, 939*t*
omeprazole
for *H. pylori* eradication, 787, 787*t*
for indigestion, 161
for noncardiac chest pain, 164
for peptic ulcer disease, 787
for systemic sclerosis, 848
for Zollinger-Ellison syndrome, 789–790
onchocerciasis, 604
onchocercomata, 604
oncologic emergencies, 109–113
paraneoplastic syndromes, 111–112
structural/obstructive, 110–111
treatment complications, 112–113
ondansetron, for nausea and vomiting, 160
oophoritis, in mumps, 541
opening snap (heart sound), 614
ophthalmia neonatorum, 405
ophthalmoplegia
chronic progressive external, 1057, 1059
diffuse, 232
etiology of, 1001
ophthalmoscopic examination, 229
opioids/opiates. *See* narcotics
opisthorchiasis, 606
opsoclonus-myoclonus syndrome, 352*t*, 354
optic chiasm compression, 230*f*
optic neuritis, 230*f*, 231
optic neuropathy, 230*f*
oral contraceptives, 920, 921, 922
oral disease
actinomycosis, 480
anaerobic infections, 475
in malnutrition, 42
oral dissolution therapy, for gallstones, 800
oral hairy leukoplakia, 256*f*, 528, 529
oral leukoplakia, 1101
oral poliovirus vaccine (OPV), 546
oral rehydration solution (ORS), for cholera, 387
oral-facial HSV infections, 520–522*t*
orchiectomy, 336
orchitis, in mumps, 541
*Orientia tsutsugamushi* infections, 503*t*, 507
orlistat, for obesity, 902
Oroya fever, 467*t*, 469
orthostatic hypotension (OH)
approach to, 988, 990
definition of, 990
etiology of, 224, 224*t*
in pheochromocytoma, 649
treatment of, 994–995, 994*t*

OSAHS (obstructive sleep apnea/hypopnea syndrome), 243, 745–746
oseltamivir, for influenza, 532, 532*t*
osmolar gap, 19
osmoregulation, 1*t*
osmotic demyelination syndrome, 5
osteoarthritis, 210, 861–862
osteomalacia, 349*t*, 935
osteomyelitis
  clinical manifestations of, 420
  *Klebsiella*, 456
  neck pain in, 212
  pathogenesis and epidemiology of, 420
  *S. aureus*, 427, 430
  treatment of, 420–422, 421*t*
  vertebral, low back pain in, 210
osteonecrosis (avascular necrosis), 869, 934
osteoporosis, 931–934
  clinical manifestations of, 931
  definition of, 931
  diagnosis of, 933, 934*t*
  diseases associated with, 932–933*t*
  epidemiology of, 931
  etiology of, 931
  fracture risk in, 931, 931*t*
  low back pain in, 210
  postmenopausal, 922, 1105
  screening for, 1090*t*, 1091*t*
  treatment of, 933–934
ostium primum, 627
ostium secundum, 627
otitis externa
  acute diffuse, 250
  acute localized, 250
  chronic, 250
  malignant or necrotizing, 250
  *P. aeruginosa*, 459, 460*t*
otitis media
  acute, 250–251
  chronic, 251
  *M. catarrhalis*, 451–452
  pneumococcal, 424
  serous, 251
  treatment of, 252*t*
ovarian cancer, 339–340, 339*t*
  infections in, 363*t*
  paraneoplastic, 353*t*
  paraneoplastic syndromes in, 349*t*
  screening for, 1098*t*
  staging and prognosis in, 339*t*
ovarian cyst, 338
ovarian tumor, 338
overdiagnosis, 1095
oxacillin
  for cellulitis, 415*t*
  for infective endocarditis, 377*t*, 378*t*
  for osteomyelitis, 421*t*
  for staphylococcal infections, 430, 431*t*
oxaliplatin, for colorectal cancer, 328
oxazepam
  dosage and action of, 1075*t*
  for STEMI, 661
oxcarbazepine
  dosage and side effects of, 1078*t*
  for generalized anxiety disorder, 1068
  for pain, 39*t*
  for seizures, 964*t*, 967*t*
  for trigeminal neuralgia, 995
5-oxoprolinuria, 17–18, 18*t*, 19
oxybutynin, for bladder hyperreflexia, 1019
oxycodone
  abuse, 1084
  for dyspnea, 51*t*
  for pain, 38*t*
oxygen therapy
  for anaphylaxis, 114
  for asthma exacerbations, 715
  for cluster headache, 219
  for COPD, 721, 722
  for cor pulmonale, 693
  for heart failure, 663
  for interstitial lung disease, 737
  for pulmonary edema, 70
  for pulmonary hypertension, 702
  for shock, 64, 664
  for STEMI, 661
oxytocin, 883

**P**

packed red blood cell transfusion, 46, 828
paclitaxel
  for bladder cancer, 334
  for breast cancer, 320
  for head and neck cancer, 309
  for ovarian cancer, 339
pain. *See also specific types and sites*
  approach to, 35–36
  chronic, 36, 40
  management of, 35–40, 38–39*t*, 796, 1071
  neuropathic, 36, 36*t*, 40
  pathophysiology of, 37, 37*f*
  somatic, 36, 36*t*, 156

spontaneous, 994
visceral, 36, 36*t*, 156
painful bladder syndrome, 778–779
paliperidone, 1077*t*
palivizumab, 536
palliative care. *See* terminally ill patient
palmar xanthoma, 941
palpation, precordial, 613–614
palpitations, 141–142
pamidronate, for hypercalcemia, 112, 351, 927*t*
pancreatectomy, 808
pancreatic abscess, 807
pancreatic cancer, 331, 349–350*t*
pancreatic endocrine tumors, 331–333
pancreatic enzyme replacement, 808
pancreatic exocrine insufficiency, 808*t*
pancreatic islet-cell tumor, 332–333, 349*t*
pancreatic necrosis, 807
pancreatic pseudocyst, 807
pancreatitis, 804–809
acute, 804–807
clinical manifestations of, 804
complications of, 806–807
differential diagnosis of, 805
etiology of, 805*t*
imaging in, 804–805
laboratory testing in, 804
severe, 806*t*
treatment of, 806
ascites in, 188*f*
chronic, 807–809
classification of, 808*t*
complications of, 809
laboratory testing in, 807
treatment of, 808
interstitial, 804
necrotizing, 804
pancreatic cancer and, 331
panic disorder, 1067, 1071
panitumumab, for colorectal cancer, 328
pantoprazole
for erosive gastropathies, 788
for *H. pylori* eradication, 787*t*
PAP (pulmonary alveolar proteinosis), 738
PAP (pulmonary artery pressure), 707
Pap smear, 341, 1096*t*, 1101
papillary necrosis, 776
papilledema, 230*f*, 231
Pappenheimer bodies, 265
papule (skin lesion), 257*t*, 417
papules, in cancer patients, 362
papulosquamous disorders, 258–259
paracentesis, 30–31, 188
paracoccidioidomycosis, 581–582
paragonimiasis, 148
parainfluenza virus infections, 534*t*, 536–537
paralysis, 233–235
approach to, 233
periodic, 1059–1060
site of responsible lesion, 233, 234*t*
paralytic disease, in poliovirus infections, 543–544
paralytic shellfish poisoning, 122
paraneoplastic syndromes
emergent, 111–112
endocrine, 348–351
in lung cancer, 311
neurologic, 352–355, 352*t*
in renal cancer, 335
paranoid personality disorder, 1070
paraparesis, 235*f*, 234*t*
parasitic infections
blood, 265
eosinophilia in, 275
in HSCT patients, 367
lymphadenopathy and, 190*t*
parasympathetic system, 989*f*, 990*t*
parathyroidectomy, for hyperparathyroidism, 928
parcopa, for Parkinson's disease, 980*t*
parenchymatous syphilis, 410
parenteral nutrition, 44–45, 44*f*
paresis, 233, 410
parkinsonism, 236, 976, 977, 977*t*
Parkinson's disease (PD), 976–981
autonomic dysfunction in, 991
dementia in, 971
differential diagnosis of, 976*t*, 977, 977*t*
sleep disorders in, 242
treatment of, 978–981, 979*f*, 980*t*
tremor in, 236
paromomycin
for amebiasis, 397
for leishmaniasis, 594
parotitis, in mumps, 540–541
paroxetine
for depression, 52
dosage and side effects of, 1072*t*
for irritable bowel syndrome, 795
for menopausal symptoms, 922
paroxysmal nocturnal hemoglobinuria (PNH), 268, 271, 271*t*

parvovirus B19 infections, 541–542
Pastia's lines, 435
patch (skin lesion), 257*t*
patch tests, 258
patent ductus arteriosus, 616*t*, 629
patent foramen ovale, antithrombotic therapy for, 89*t*
patient-controlled analgesia (PCA), 40
PBP (primary bacterial peritonitis), 382–383
PCA (patient-controlled analgesia), 40
PCI. *See* percutaneous coronary intervention
PCOS (polycystic ovarian syndrome), 918, 920
PD. *See* Parkinson's disease
PE. *See* pulmonary embolism
peau d'orange appearance, 261
pediculiasis, 610–611
PEEP (positive end-expiratory pressure), 72, 76
pegloticase, for gout, 865
pegvisomant, for acromegaly, 881
pegylated interferon (PEG IFN)
  for chronic hepatitis B, 817, 818–819*t*
  for chronic hepatitis C, 817, 822–824*t*
Pelger-Hüet anomaly, 266
pelvic infections
  actinomycosis, 481
  anaerobic, 475
pelvic inflammatory disease (PID), 402–403, 406–407*t*, 919
pelvic pain, 919–920, 919*t*
pemetrexed, for lung cancer, 315
pemoline, for depression, 52
penciclovir, for HSV infections, 520–522*t*
penicillamine
  for nephrolithiasis, 782*t*
  for systemic sclerosis, 848
penicillin/penicillin G/penicillin V
  for actinomycosis, 481
  for asymptomatic GAS carriage, 435
  for bacterial meningitis, 1024*t*, 1025*t*
  for clostridial infections, 474*t*
  for diphtheria, 442
  for gas gangrene, 416*t*
  for HACEK group infections, 453*t*
  for infective endocarditis, 376–377*t*
  for leptospirosis, 498
  for listerial infections, 447
  for Lyme borreliosis, 496
  for meningococcal prophylaxis, 446
  for necrotizing fasciitis, 416*t*
  for osteomyelitis, 421*t*
  for peritonitis, 383
  for pneumococcal infections, 424
  for relapsing fever, 499
  for rheumatic fever prophylaxis, 632
  for rodent bite infections, 117*t*
  for staphylococcal infections, 430, 431*t*
  for streptococcal infections, 436*t*, 438–439
  for syphilis, 411*t*
  for tetanus, 470
penicillin VK, for pharyngitis, 253
penicilliosis, 582
pentamidine
  for *Pneumocystis* infections, 584*t*
  for *Pneumocystis* prophylaxis, 585*t*
  for sleeping sickness, 596
pentamidine isethionate, for leishmaniasis, 594
pentazocine abuse, 1084
"pentobarb coma," 95*t*
pentobarbital, for status epilepticus, 102*f*
pentoxifylline
  for alcoholic liver disease, 828
  for peripheral arteriosclerosis, 697
peptic ulcer disease (PUD), 787–788
  approach to, 788
  bleeding in, 175
  causes and risk factors for, 785
  clinical manifestations of, 786
  diagnosis of, 786, 786*t*
  treatment of, 787, 787*t*, 788*t*
*Peptostreptococcus* infections, 474
peramivir, for influenza, 532
percutaneous coronary intervention (PCI)
  advantages and disadvantages of, 676*t*
  for cardiogenic shock, 665*t*
  for chronic stable angina, 675–676
  for STEMI, 659, 660*f*, 671
percutaneous needle aspiration, of lung, 710
percutaneous transhepatic cholangiogram, 800*t*
periappendicitis, 402
periarticular disorders, 869–870
pericardial disease. *See* pericarditis
pericardial effusion/tamponade, 110, 648–649
pericardial stripping/window, 110

pericardiectomy, for pericarditis, 645
pericardiocentesis, for cardiac tamponade, 647
pericarditis
acute
chest pain in, 138, 138*t*, 140*f*
etiology of, 645*t*
laboratory features of, 644–645, 645*t*, 646*f*
constrictive, 110, 647–648, 648*t*
enteroviral, 544
in STEMI, 667
in tuberculosis, 484
perichondritis, 250
perihepatitis, 402
perimenopause, 921
perinephric abscess, 385
periodic leg movements of sleep, 242
periodic limb movements of sleep (PLMS), 242
periodic paralysis, 1059–1060
periodontal disease, 475
periorbital edema, 150
peripheral nerves, cutaneous areas supplied by, 952–953*f*
peripheral neuropathy (PN), 1040–1049
approach to, 1040–1042, 1041*f*
autonomic involvement in, 933*t*, 991
in diabetes mellitus, 991, 1046
diagnosis of, 1044
mononeuropathy, 1040, 1046, 1047–1049*t*
paraneoplastic, 352*t*, 353*t*, 355
patterns of, 1043–1044*t*
polyneuropathy. *See* polyneuropathy
treatment of, 1044, 1045*t*
weakness in, 234*t*, 235*t*
peripheral vascular disease, 696–699
arterial embolism, 697
atheroembolism, 697–698
atherosclerosis, 696–697
superficial thrombophlebitis, 698
vasospastic disorders, 697–698
venous disease, 698–699
venous insufficiency, chronic, 699
peristalsis, 167
peritoneal carcinomatosis, 188*f*, 348
peritoneal dialysis, 751, 755–756, 756*t*
peritoneal disease
ascites in, 187
pain in, 155*t*
peritoneal fluid, paracentesis, 30–31
peritonitis, 382–384
bacterial, 188
CAPD-associated, 383–384
*E. coli*, 454
primary bacterial, 382–383
secondary, 383
peritonsillar abscess, 475
perleche, 256*f*
permethrin cream
for pediculiasis, 611
for scabies, 610
peroneal nerve entrapment, 1046, 1049*t*
perphenazine, 1076*t*
personality disorders, 1070
pertussis
clinical manifestations of, 450
diagnosis of, 450
epidemiology of, 450
microbiology of, 449–450
prevention of, 451
treatment of, 451
vaccine, 451
PET (positron emission tomography), 26
petit mal (absence) seizures, 956. *See also* seizures
Peutz-Jeghers syndrome, 325, 326*t*, 327
phagocytic cells, deficiencies of, 841*t*
pharmacologic stress testing, 672, 674*t*
pharyngeal gonorrhea, 405
pharyngitis
clinical manifestations of, 253
diagnosis of, 253
etiology of, 251, 253
HSV, 517
streptococcal, 253, 435, 436*t*
treatment of, 253
pharyngoconjunctival fever, 537
phenelzine, 1073*t*
phenobarbital
for seizures, 964*t*, 967*t*
for status epilepticus, 102*f*
for tetanus, 470
phentolamine, for malignant hypertension, 656*t*
phenylephrine
for increased intracranial pressure, 95*t*
for shock, 64, 64*t*
for subarachnoid hemorrhage with vasospasm, 93
phenytoin
adenopathy with, 191
for multiple sclerosis, 1019

phenytoin (*Cont.*):
for myotonic dystrophy, 1057
for polyneuropathy, 1045*t*
for seizures, 964*t*, 967*t*
for status epilepticus, 102*f*
for trigeminal neuralgia, 995
pheochromocytoma, 649–650, 895, 900
pheresis therapy, 47–48
phlebotomy
for hemochromatosis, 944
for polycythemia, 196
for polycythemia vera, 292
phobic disorders, 1069
phosphofructokinase deficiency, 1059
phosphorus therapy, for alcoholic liver disease, 828
physical activity, 40
physical therapy
for adhesive capsulitis, 870
for tendinitis, 870
for vertigo, 228*t*
PID (pelvic inflammatory disease), 402–403, 919
pigment gallstones, 799
pill rolling, 976
pilocarpine, for Sjögren's syndrome, 849
pinta, 497
pinworm infection (enterobiasis), 602–603
pioglitazone, for diabetes mellitus, 909*t*
piperacillin-tazobactam
for community-acquired pneumonia, 725*t*
for health care–associated pneumonia, 727*t*
for mixed anaerobic infections, 476*t*
for osteomyelitis, 421*t*
for *P. aeruginosa* infections, 460*t*
for peritonitis, 382
for sepsis/septic shock, 68*t*
piracetam, for myoclonus, 238
pitavastatin, for dyslipidemia, 938*t*
pitting, 191
pituitary adenoma, 877–879
ACTH-secreting, 896
clinical manifestations of, 877
diagnosis of, 879
gonadotropin-secreting, 881
growth hormone-secreting, 880
nonfunctioning, 881
prolactin-secreting, 879
thyroid-stimulating hormone-secreting, 881, 889
treatment of, 879
pituitary apoplexy, 877
pituitary disease
hormone hypersecretion syndromes, 879–881
hypopituitarism, 881–882, 883*t*
tumors. *See* pituitary adenoma
pituitary hormones, 877, 878*f*
pituitary tumor, 230*f*
pityriasis rosea, 256*f*, 259
pivmecillinam
for shigellosis, 396
for urinary tract infections, 777*t*
pizotifen, for migraine prevention, 220*t*
plague, 465–466
plantar reflex, 951
plaque (lesion of MS), 1012
plaque (skin lesion), 257*t*
plasma cell disorders, 295*t*, 296*f*, 301–305
plasma exchange
for acute renal failure, 751
for multiple sclerosis, 1019
plasmacytoma, 302
plasmapheresis, 48
for acute renal failure, 751
for ANCA-associated glomerulonephritis, 762
for autoimmune hemolysis, 274
for erythropoietic protoporphyria, 945
for myasthenia gravis, 1053
for polyneuropathy, 1044
for primary biliary cirrhosis, 829
for thrombotic thrombocytopenic purpura, 280
for vasculitis, 854
*Plasmodium*, 586. *See also* malaria
platelet clumping, 266
platelet disorders, 277–279
platelet transfusion, 47
plateletpheresis, 48
PLCH (pulmonary Langerhans cell histiocytosis), 736, 739
pleural biopsy, 710
pleural effusion, 726
approach to, 742*f*
differential diagnosis of, 740–741*t*
exudative, 740
thoracentesis for, 27–28, 28*f*
transudative, 740
pleurisy, 138
pleurodynia, enteroviral, 544

pleuropulmonary infections, anaerobic, 475
PLMS (periodic limb movements of sleep), 242
Plummer's nails, 889
PM (polymyositis), 1057–1059, 1058*t*
PML (progressive multifocal leukoencephalopathy), 1030–1031
PMR (polymyalgia rheumatica), 869
PMS (premenstrual syndrome), 919
PN. *See* peripheral neuropathy
pneumococcal infections, 422–425
  epidemiology of, 422
  meningitis, 423–425
  microbiology of, 422
  pathogenesis of, 422–423
  pneumonia, 423–425
  prevention of, 425
pneumococcal vaccine, 370*t*, 422, 425, 1090*t*
*Pneumocystis* infections, 583–585
  clinical manifestations of, 583
  diagnosis of, 584
  microbiology and epidemiology of, 583
  pathogenesis of, 583
  prevention of, 585, 585*t*
  treatment of, 584–585, 584*t*
pneumonia
  acute interstitial, 736
  aspiration, 475
  *C. pneumoniae*, 513
  in cancer patients, 364
  classification of, 722
  community-acquired. *See* community-acquired pneumonia
  cryptogenic organizing, 736, 738
  desquamative interstitial, 738
  *E. coli*, 454
  eosinophilic, 738–739
  *H. influenzae*, 448
  health care-associated, 722
  hemoptysis in, 148
  hospital-acquired, 727
  human RSV, 535
  in influenza, 531
  *Klebsiella*, 456
  *Legionella*, 511–513
  *M. catarrhalis*, 451
  *M. pneumoniae*, 510–511
  in measles, 538
  *Nocardia*, 478
  nosocomial, 358, 359*t*
  *P. aeruginosa*, 458–459, 460*t*
  pain in, 141
  pathophysiology of, 722–723
  pneumococcal, 423–425
  *Pneumocystis*, 583–585, 584*t*
  *S. aureus*, 427
  secondary bacterial, 531
  streptococcal, 436*t*, 437
  toxoplasmosis, 597
  varicella-zoster virus, 523
  ventilator-associated. *See* ventilator-associated pneumonia
Pneumonia Severity Index (PSI), 724
pneumonic plague, 466
pneumonitis
  HSV, 518, 522*t*
  hypersensitivity, 736, 739
  necrotizing, 475
pneumothorax (Ptx), 140*f*, 743
PNH (paroxysmal nocturnal hemoglobinuria), 268, 271, 271*t*
podagra, 863
podophyllin
  for HPV infections, 414
  for warts, 262
poikilocytosis, 265
poison control center, 119
poliovirus infections, 543–544
poliovirus vaccine, 370*t*, 545–546
polyarteritis, glomerular disease in, 768*t*
polyarthropathy, in parvovirus infection, 542
polychondritis, relapsing, 868
polycystic kidney disease, 773–774
polycystic ovarian syndrome (PCOS), 918, 920
polycythemia, 194–196
  causes of, 195
  complications of, 195
  differential diagnosis of, 196*f*
  treatment of, 196
polycythemia vera, 195, 292
polydipsia, 4, 884
polyene, for candidiasis, 571
polyethylene glycol-containing solution
  for constipation, 174
  for irritable bowel syndrome, 796*t*
polymyalgia rheumatica (PMR), 869
polymyositis (PM), 1057–1059, 1058*t*
polymyxin B
  for enteric GNB infections, 458
  for *Klebsiella* infections, 456

polyneuropathy
acute inflammatory demyelinating, 1046
approach to, 1040–1042, 1041*f*
chronic inflammatory demyelinating, 1046
definition of, 1040
diagnosis of, 1042, 1044
patterns of, 1043–1044*t*
treatment of, 1044, 1045*t*
polyposis syndromes, 325, 326–327, 326*t*
polyps
colonic, 326–327, 326*t*
gastric, 325
polysomnography, 244*t*
polyuria, 199, 199*t*, 200*f*, 926
Pompe's disease, 1059
ponatinib, for CML, 289
Pontiac fever, 512
porphyria cutanea tarda, 945
porphyrias, 944–945
acute intermittent, 944, 991
erythropoietic protoporphyria, 945
porphyria cutanea tarda, 945
*Porphyromonas* infections, 474
portal hypertension, 192, 831, 831*t*
Portuguese man-of-war injury, 120
posaconazole
for aspergillosis, 574*t*
for fusariosis, 582
for mucormycosis, 577
pharmacology of, 569
positive end-expiratory pressure (PEEP), 72, 76
positron emission tomography (PET), 26
post-concussion headache, 215*t*, 221
postherpetic neuralgia, 261, 523
postmeningococcal reactive disease, 444–445
postmenopausal hormone therapy, 922
postpolio syndrome, 544
postradiation fibrosis, 213
posttraumatic stress disorder (PTSD), 1068–1069, 1071
postural hypotension. *See* orthostatic hypotension
postural orthostatic tachycardia syndrome (POTS), 991
potassium, disorders of, 6–13
hyperkalemia, 6–7, 9–13, 14*f*, 15*f*
hypokalemia, 7–8*t*, 7–9, 10–11*f*
potassium chloride
for hypokalemia, 9
for periodic paralysis, 1060
potassium hydroxide preparation, 257–258
potassium iodide, for thyroid storm, 891
potassium perchlorate, for amiodarone-induced thyrotoxicosis, 892
potassium restriction, for hyperkalemia, 754
potassium therapy, for alcoholic liver disease, 828
Pott's disease, 484
Pott's puffy tumor, 248
PPMS (primary progressive multiple sclerosis), 1015
Prader-Willi syndrome, 901
pramipexole
for Parkinson's disease, 980*t*
for restless legs syndrome, 242
pramlintide, for diabetes mellitus, 906, 909*t*
prasugrel, for UA/NSTEMI, 670, 671
pravastatin, for dyslipidemia, 938*t*
praziquantel
for echinococcosis, 609
for lung fluke infections, 606
for schistosomiasis, 606
for taeniasis solium and cysticercosis, 607
for tapeworm infections, 607
prazosin, for vasospastic disorders, 698
precordial palpation, 613–614
prednisolone
for alcoholic liver disease, 828
for autoimmune hepatitis, 825
prednisone
for alcoholic liver disease, 828
for ALL, 300
for autoimmune hepatitis, 825
for Bell's palsy, 997
for Burkitt's lymphoma/leukemia, 301
for cluster headache prevention, 219
for COPD exacerbations, 722
for gastric carcinoma, 324
for hirsutism, 921
for hypercalcemia, 927*t*
for hypopituitarism, 883*t*
for idiopathic thrombocytopenic purpura, 280
for immunosuppression after renal transplantation, 758

for inflammatory bowel disease, 792
for inflammatory myopathy, 1059
for interstitial lung disease, 737
for lymphoma, 299
for multiple myeloma, 302
for multiple sclerosis, 1018
for muscular dystrophy, 1054
for myasthenia gravis, 1053
for optic neuritis, 231
for pericarditis, 645
for *Pneumocystis* infections, 584*t*
for polymyalgia rheumatica, 869
for postherpetic neuralgia, 524
for relapsing polychondritis, 868
for sarcoidosis, 872
for thyrotoxicosis, 891
for vasculitis, 854
preexcitation syndrome. *See* Wolff-Parkinson-White syndrome
pregabalin
dosage and side effects of, 39*t*
for fibromyalgia, 868
for generalized anxiety disorder, 1068
for multiple sclerosis, 1019
for polyneuropathy, 1045*t*
pregnancy
ectopic, 919
gonorrhea in, 405
hypertension in, 651
listerial infections in, 447
malaria in, 587
streptococcal infections in, 438
syphilis in, 411*t*
toxoplasmosis in, 597
urinary tract infections in, 778
prehypertension, 1093
preleukemia, 289
premenstrual syndrome (PMS), 919
pressure-control ventilation, 76
pressure-support ventilation (PSV), 74, 75*t*
preventive medicine, 1087
Preventive Services Task Force, U.S., recommendations of, 1090–1091*t*
*Prevotella* infections, 474
prilocaine, for polyneuropathy, 1045*t*
primaquine
for malaria, 587, 588*t*
for malaria prophylaxis, 591*t*
for *Pneumocystis* infections, 584*t*
primary biliary cirrhosis, 828–829
primary progressive multiple sclerosis (PPMS), 1015
primary sclerosing cholangitis (PSC), 803
primary (spontaneous) bacterial peritonitis (PBP), 382–383
primidone
for myoclonus, 238
for seizures, 965*t*, 967*t*
for tremor, 236
Prinzmetal's variant angina, 676
PRL. *See* prolactin
probenecid
for gonococcal infections, 406*t*
for gout, 865
for syphilis, 411*t*
procainamide
for arrhythmias, 683*t*
for tachyarrhythmias, 681*t*
for ventricular fibrillation, 59*f*
for Wolff-Parkinson-White syndrome, 686
procaine penicillin
for diphtheria, 442
for streptococcal infections, 436*t*
for syphilis, 411*t*
prochlorperazine
for migraine, 218*t*
for nausea and vomiting, 160
proctitis
clinical manifestations of, 403
etiology of, 403
HSV, 521*t*
treatment of, 405
proctocolitis, 403, 405
progressive multifocal leukoencephalopathy (PML), 1030–1031
prolactin (PRL)
deficiency of, 882
hypersecretion of, 879–880
production of, 877, 878*f*
prolactinoma, 879–880
promethazine, for vertigo, 228*t*
promyelocytic leukemia, acute, 284*t*, 285
propafenone, for arrhythmias, 683*t*
*Propionibacterium acnes* infections, 474
propofol
for delirium, 52*t*
for increased intracranial pressure, 95*t*
for status epilepticus, 102*f*
propoxyphene abuse, 1084

propranolol
for aortic dissection, 696*t*
for esophageal varices, 832
for hypertension, 652*t*
for hypokalemia, 9
for migraine prevention, 220*t*
for thyroid storm, 891
for thyrotoxicosis, 890
for tremor, 236
for variceal bleeding, 178
propylene glycol poisoning, 17, 18*t*, 19
propylthiouracil (PTU), for thyrotoxicosis, 890–891
Prostascint scanning, 343
prostate biopsy, transrectal ultrasound, 343, 344*f*
prostate cancer, 342–345
oncologic emergencies, 110–111
osteoblastic bone metastasis in, 348
paraneoplastic syndromes in, 349*t*
prevention of, 345, 1100–1101
risk factors for, 1100
screening for, 1090–1091*t*, 1095, 1098–1099*t*
treatment of, 343–345
prostate hyperplasia, 342
prostatectomy, radical retropubic, 343
prostate-specific antigen (PSA), 342, 343, 344*f*, 1095, 1098*t*
prostatitis, 776–777, 778
prosthetic device-related infections
coagulase-negative staphylococci, 429
joint, 420
*S. aureus*, 428
treatment of, 430
prosthetic valve endocarditis (PVE). *See also* infective endocarditis
clinical manifestations of, 374
etiology of, 372
HACEK group, 452, 453*t*
pathogenesis of, 372–373
staphylococcal, 430
treatment of, 380, 430
protamine, to reverse anticoagulation, 282, 733
protease inhibitors, for HIV infection, 559, 563*t*
protein malnutrition, 41
protein requirements, 41
protein restriction, in chronic kidney disease, 754
proteinuria, 199–201, 766–767
*Proteus* infections, 456–457
prothrombin time, 184*t*
protozoal infections, 586–598
babesiosis, 592
chronic meningitis in, 1035–1036tt
leishmaniasis, 592–594
malaria. *See* malaria
toxoplasmosis, 596–598
trypanosomiasis, 594–596
protriptyline, for narcolepsy, 244
*Providencia* infections, 457
prune juice, 50*t*
pruritus ani, 798
PS (pulmonic stenosis), 616*t*, 629–630
PSA. *See* prostate-specific antigen
PSC (primary sclerosing cholangitis), 803
pseudocyst, pancreatic, 807
pseudoephedrine
for allergic rhinitis, 838
for syncope, 225
pseudogout, 865–866
pseudohyponatremia, 2
pseudomelena, 174
*Pseudomonas aeruginosa* infections
clinical manifestations of, 458–459
epidemiology of, 458
microbiology of, 458
osteomyelitis, 421*t*, 459
treatment of, 459–461, 460–461*t*
pseudoseizures, 957
pseudothrombocytopenia, 279
pseudotumor cerebri, 231
PSI (Pneumonia Severity Index), 724
psittacosis, 515–516
psoralens, for polycythemia vera, 292
psoriasis, 256*f*, 258–259
psoriatic arthritis, 857–859
PSV (pressure-support ventilation), 74, 75*t*
psychiatric disorders, 1063–1070
anxiety disorders, 1067–1070
bipolar disorder, 1065–1066
depression. *See* depression
eating disorders, 1079–1080
fatigue in, 133*t*
nausea and vomiting in, 159*t*
personality disorders, 1070
schizophrenia, 1066–1067
sleep disorders and, 242
vs. syncope, 225
weight loss in, 136*t*
in women, 1106
psychiatric medications, 1071–1078
antidepressants. *See* antidepressants

antipsychotics. *See* antipsychotics
anxiolytics. *See* anxiolytics
mood stabilizers, 1078, 1078*t*
principles of use of, 1071
psychotic disorders, 1066–1067
psyllium
for diverticular disease, 796
for hemorrhoids, 798
for irritable bowel syndrome, 795, 796*t*
PTSD (posttraumatic stress disorder), 1068–1069
PTU (propylthiouracil), for thyrotoxicosis, 890–891
Ptx (pneumothorax), 140*f*, 743
pubic louse, 610–611
PUD. *See* peptic ulcer disease
puddle sign, 187
pulmonary alveolar proteinosis (PAP), 738
pulmonary angiography, 709
pulmonary artery catheters, 34
pulmonary artery pressure (PAP), 707
pulmonary circulation, disturbances of, 707
pulmonary disease. *See* respiratory disease
pulmonary edema, 150
cardiogenic, 69
causes of, 70*t*
cyanosis in, 145–146
dyspnea in, 144–145
noncardiogenic, 70, 70*t*
precipitants of, 69*t*
treatment of, 69–70
pulmonary embolism (PE)
chest pain in, 138, 138*t*, 140*f*
complications of, 730
diagnosis of, 731, 732*f*
dyspnea in, 143
hemoptysis in, 148
massive, 730
in thrombotic disorders, 281
treatment of, 281–283, 732–733, 734*f*
pulmonary fibrosis
idiopathic, 736, 737–738
progressive massive, 717
pulmonary function tests
in asthma, 712
in COPD, 718*t*, 719–720
in pulmonary hypertension, 700
pulmonary hypertension, 699–702
approach to, 701*f*
arterial, 700*t*
classification of, 700*t*
congenital heart disease and, 629
differential diagnosis of, 702
etiology of, 707
heart sounds in, 615*f*
laboratory features of, 702
treatment of, 702
pulmonary infiltrate, with eosinophilia, 738–739
pulmonary Langerhans cell histiocytosis (PLCH), 736, 739
pulmonary nodule, solitary, 315
pulmonary rehabilitation, 737
pulmonary thromboendarterectomy, 733
pulmonary vascular resistance (PVR), 707
pulmonic stenosis (PS), 616*t*, 629–630
pulmonic valve regurgitation, 616*t*
pulse oximetry, 708
pulseless disease, 696
pulseless electrical activity, 60, 60*f*
pulsus alternans, 613, 614*f*
pulsus bisferiens, 613, 614*f*
pulsus paradoxus, 613
pulsus parvus, 613, 614*f*
pulsus tardus, 613, 614*f*
pupillary signs, in coma, 81
pure alexia, 239*t*
pure red cell aplasia, in parvovirus infections, 542
pure word deafness, 239*t*
purging behavior, 1079
purine metabolism deficiency, 840
purpura, 264
pustule, 257*t*
Puumala virus infection, 552
PUVA, for psoriasis, 259
PVE (prosthetic valve endocarditis), 372–374, 380. *See also* infective endocarditis
PVR (pulmonary vascular resistance), 707
pyelonephritis, 385, 776
emphysematous, 776
xanthogranulomatous, 776
pyloroplasty, 788*t*
pyomyositis, 418, 427
pyrazinamide, for tuberculosis, 486, 487–488*t*
pyridostigmine
for myasthenia gravis, 1052
for orthostatic hypotension, 995
pyridoxine deficiency, 45*t*

pyrimethamine
for cystoisosporiasis, 392
for *Pneumocystis* prophylaxis, 585*t*
for toxoplasmosis, 598
pyrogen, 127
pyroglutamic aciduria, 17, 18*t*
pyruvate kinase deficiency, 269
pyuria, 203

**Q**
Q fever, 503*t*, 509–510
quadrantanopia, 234*t*
quadrantopia, 230*f*
quadriparesis, 234*t*, 235*f*
quantitative sudomotor axon reflex test (QSART), 990–991
quetiapine
dosage and side effects of, 1077*t*
for schizophrenia, 1067
quinidine
for arrhythmias, 683*t*
for malaria, 587, 589*t*
quinine
for babesiosis, 592
for malaria, 588–589*t*
quinolones. *See* fluoroquinolones
quinsy, 475
quinupristin-dalfopristin
for enterococcal infections, 440
for staphylococcal infections, 430, 431*t*

**R**
RA. *See* rheumatoid arthritis
rabies, 546–548
clinical manifestations of, 547
diagnosis of, 547–548
epidemiology of, 546
microbiology of, 546
pathogenesis of, 546–547
postexposure prophylaxis, 115, 118, 548, 549*f*
preexposure prophylaxis, 548
treatment of, 548
rabies immune globulin, 118, 548, 549*f*
rabies vaccine, 118, 548, 549*f*
radial neuropathy at spiral groove, 1048*t*
radiation therapy
for adrenal carcinoma, 896
for anal cancer, 330
for bladder cancer, 334
for brain tumor, 1008
for breast cancer, 320, 321
for cervical cancer, 341
for colorectal cancer, 328
for endometrial cancer, 340
for esophageal carcinoma, 322
for follicular lymphoma, 298
for head and neck cancer, 309
for Hodgkin's disease, 304
leukopenia in, 276
for lung cancer, 315
for multiple myeloma, 302
for nervous system tumors, complications of, 1012
for prostate cancer, 343
for spinal cord compression, 99, 111
for testicular cancer, 336
radiculopathy
cervical, 212, 213–214, 213*t*
lumbosacral, 208*t*
subacute, 212
radioiodine
for nontoxic goiter, 893
for thyroid neoplasms, 894–895
for thyrotoxicosis, 890–891
for toxic adenoma, 893
for toxic multinodular goiter, 893
radionuclide scan
in hepatobiliary disease, 186
utility of, 26
ragged red fibers, 1059
raloxifene
for breast cancer prevention, 1100
for osteoporosis, 934
raltegravir, for HIV infection, 559, 564*t*
ramipril
for heart failure, 690*t*
for hypertension, 653*t*
Ramsay Hunt syndrome, 523, 997
ramucirumab, for gastric carcinoma, 323
ranitidine
for *H. pylori* eradication, 787*t*
for indigestion, 161
for urticaria/angioedema, 837
ranolazine, for chronic stable angina, 675
rapid shallow breathing index (RSBI), 34
rapid urease test, 786, 786*t*
rasagiline, for Parkinson's disease, 980*t*
rasburicase, for tumor lysis syndrome, 113
rash
in alphavirus infections, 550–551
drug-related, 362

in measles, 538–539
in rubella, 539
rat-bite fever, 118
Raynaud's disease, 698*t*
Raynaud's phenomenon, 698, 698*t*
reactive arthritis, 859–860
*C. trachomatis*, 408
clinical manifestations of, 419, 859–860
definition of, 859
diagnosis of, 860
etiology of, 419
pathogenesis of, 859
treatment of, 860
recluse spider bite, 123
recombinase activating gene deficiency, 840
recommended dietary allowance (RDA), 41
rectal cancer, 330
red blood cells (RBCs)
disorders of, 267–274
anemia. *See* anemia
intracellular abnormalities, 269
maturation disorders, 269
membrane abnormalities, 271
polycythemia, 194–196
inclusions, 265–266
increased mass, 292
morphology of, 265
RBC indices, 194
transfusion, 46
red hepatization, 723
REE (resting energy expenditure), 40
reentrant AV nodal tachycardia, 680*t*
referred pain
abdominal, 155*t*
low back, 207
neck, 212
pathophysiology of, 36
shoulder, 214
reflex sympathetic dystrophy, 994
reflexes, testing of, 951
refractory anemia, 290*t*
refractory anemia with excess blasts, 290*t*
refractory anemia with ringed sideroblasts, 290*t*
refractory cytopenia with multilineage dysplasia, 290*t*
refractory cytopenia with unilineage dysplasia, 290*t*
refractory neutropenia, 290*t*
refractory thrombocytopenia, 290*t*
regurgitation, 158
rehydration, in diarrhea, 170
relapse prevention, 1084
relapsing fever, 498–499
relapsing polychondritis, 868
relapsing-remitting multiple sclerosis (RRMS), 1013
renal abscess, 385
renal artery stenosis, 649, 650
renal cancer, 334–335
clinical manifestations of, 335
epidemiology of, 334–335
etiology of, 335
infections in, 363*t*
oncologic emergencies, 111–112
paraneoplastic syndromes in, 349*t*
pathology of, 335
treatment of, 335
renal disease. *See also* acute renal failure; chronic kidney disease
azotemia in, 197–198, 198*f*, 198*t*
edema in, 151
fatigue in, 133*t*
glomerular, 759–766
hypertension in, 649, 650, 655
infections after HSCT, 367*t*
infections in cancer patients, 364
metabolic acidosis in, 18*t*, 19
nephrolithiasis. *See* nephrolithiasis
tubular. *See* renal tubular disease
urinary abnormalities in, 199–203
urinary tract obstruction, 782–784, 783*f*
renal transplantation, 756–759
complications of, 758–759
contraindications to, 757*t*
epidemiology of, 756–757
factors influencing graft survival, 757–758, 757*t*
focal glomerulosclerosis following, 765
immunosuppressive therapy after, 758
infections after, 368, 758–759, 759*t*
rejection after, 758
renal tubular disease, 767–775
acute interstitial nephritis, 771–772, 771*t*
chronic interstitial nephritis, 772
etiology of, 767–770*t*
monoclonal immunoglobulins and, 772–773, 773*t*
polycystic kidney disease, 773–774
renal tubular acidosis, 18*t*, 774–775
transport dysfunction in, 770*t*
repaglinide, for diabetes mellitus, 909*t*

repositioning exercises, for vertigo, 228*t*, 229
reproductive tract infections. *See* sexually transmitted infections (STI)
residual volume, 705, 705*f*
resistance, to antibacterial therapy, 361
respiratory acidosis, 17*f*, 21
respiratory alkalosis, 17*f*, 21–22
respiratory bronchiolitis, 738
respiratory disease. *See also* respiratory tract infections
  categories of, 706*t*
  in coma, 81
  cor pulmonale, 692–693
  cyanosis in, 145, 146*t*
  diagnosis of
    invasive procedures for, 710–711
    noninvasive procedures for, 709–710
  diffuse parenchymal, 143
  dyspnea in, 142–144, 144*f*
  environmental, 715–718
    inorganic dusts, 716–717
    organic dusts, 717
    toxic chemicals, 717–718
  fatigue in, 133*t*
  gas exchange disturbances, 707–708
  hypoxemia in, 708–709, 708*f*
  interstitial lung disease. *See* interstitial lung disease
  mechanisms of, 708–709
  obstructive, 706–707, 706*t*
  pulmonary circulation disturbances, 707
  pulmonary hypertension in, 700*t*
  restrictive, 706–707, 706*t*
  ventilatory function disturbances, 705–707
respiratory failure, 73–76, 75*t*
respiratory rate, 708
respiratory syncytial virus, human, 534*t*, 535–536
respiratory tract infections. *See also* pneumonia; upper respiratory infections
  actinomycosis, 480
  after HSCT, 367*t*
  aspergillosis, 572, 574*t*
  bacterial
    anaerobic, 475
    *C. pneumoniae*, 513
    diphtheria, 441–442
    *M. pneumoniae*, 510–511
    nontuberculous mycobacterial, 492–494
    *S. aureus*, 427
    tuberculosis. *See* tuberculosis
  in cancer patients, 364
  coccidioidomycosis, 579
  cryptococcal, 573
  mucormycosis, 577
  nocardiosis, 478, 480*t*
  viral
    adenovirus, 537
    clinical manifestations of, 534*t*
    coronavirus, 533, 535
    human metapneumovirus, 536
    human RSV, 535–536
    influenza. *See* influenza
    parainfluenza virus, 536–537
    rhinovirus, 533
  weight loss in, 136*t*
resting energy expenditure (REE), 40
restless legs syndrome (RLS), 242, 244*t*
restrictive cardiomyopathy, 640*t*, 642, 648*t*
retching, 158
reteplase, for thrombotic disorders, 282
reticular dysgenesis, 840
reticulocyte index (RI), 194
reticulocytes, 265
retinal artery occlusion, 230*f*
retinal detachment, 231
retinal vein occlusion, 230*f*, 231
retinitis, cytomegalovirus, 527
retinitis pigmentosa, 230*f*
retinoic acid
  for acne, 262
  for head and neck cancer, 310
  for head and neck cancer prevention, 1101
  for squamous cell carcinoma, 308
*trans*-retinoic acid, for AML, 287
retinoid, for psoriasis, 259
retinopathy, paraneoplastic, 352*t*, 353*t*, 355
reverse SLR sign, 208–209
Reye's syndrome, 531
rhabdomyolysis, 202
rheumatic fever, prophylaxis for, 632
rheumatic heart disease, 632
rheumatic mitral valve disease, 89*t*
rheumatic (Sydenham's) chorea, 237
rheumatoid arthritis (RA)
  clinical manifestations of, 845–846
  differential diagnosis of, 846–847
  evaluation of, 846
  neck pain in, 212

pathogenesis of, 845
treatment of, 846–847
rheumatoid factor, 852, 856
rhinitis, allergic, 837–838
rhinocerebral mucormycosis, 576
rhinophyma, 263
rhinosinusitis. *See* sinusitis
rhinovirus infections, 533, 534*t*
*Rhizomucor* infections. *See* mucormycosis
*Rhizopus oryzae*. *See* mucormycosis
*Rhodococcus* infections, 443
RI (reticulocyte index), 194
ribavirin
for adenovirus infections, 537
for chronic hepatitis C, 817, 822–824*t*
for croup, 537
for human RSV infections, 536
for viral encephalitis, 1029
for viral hemorrhagic fever with renal syndrome, 552
for viral hemorrhagic fevers, 552
Richter's syndrome, 296
*Rickettsia africae* infections, 501*t*, 505
*Rickettsia conorii* infections, 501*t*, 504–505
rickettsial disease, 500–510, 501–503*t*
ehrlichioses and anaplasmosis, 502*t*, 508–509
endemic murine typhus, 502*t*, 505–506
epidemic typhus, 502*t*, 506–507
lymphadenopathy and, 190*t*
Q fever, 503*t*, 509–510
rickettsialpox, 501*t*, 505
Rocky Mountain spotted fever, 500, 501*t*, 504
scrub typhus, 503*t*, 507
tick-borne spotted fevers, 501*t*, 504–505
rickettsialpox, 501*t*, 505
rifabutin
for nontuberculous mycobacterial infections, 494
for tuberculosis, 486
rifampin
for asymptomatic GAS carriage, 435
for *Bartonella* infections, 467*t*
for brucellosis, 464
for *Corynebacterium* infections, 443
for diphtheria, 442
for enterococcal infections, 440
for human granulocytotropic anaplasmosis, 508
for infectious arthritis, 420
for infective endocarditis, 377*t*, 380
for latent tuberculosis, 490*t*
for *Legionella* infections, 513
for leprosy, 492
for meningococcal prophylaxis, 446, 1025
for nontuberculous mycobacterial infections, 494
for osteomyelitis, 421*t*
for pneumococcal infections, 424
for primary biliary cirrhosis, 829
for Q fever, 510
for staphylococcal infections, 430, 433*t*
for tuberculosis, 486, 487–488*t*
rifapentine, for tuberculosis, 486, 487–488*t*, 490*t*
rifaximin
for *C. difficile* infections, 398
for hepatic encephalopathy, 833
for irritable bowel syndrome, 795
Rift Valley fever, 551
right ventricular hypertrophy, 620, 620*f*
right ventricular systolic pressure (RVSP), 622–623
rilpivirine, for HIV infection, 559, 563*t*
riluzole, for ALS, 987
rimantadine, for influenza, 532, 532*t*
Ringer's lactate, for cholera, 389
ringworm, 261
risedronate, for osteoporosis, 934
risperidone
for delirium, 52*t*
dosage and side effects of, 1077*t*
for schizophrenia, 1067
ritonavir, for HIV infection, 563*t*
rituximab
for ANCA-associated glomerulonephritis, 762
for autoimmune hemolysis, 274
for CLL, 297
for gastric carcinoma, 324
for glomerulonephritis, 765
for idiopathic thrombocytopenic purpura, 280
for inflammatory myopathy, 1059
for lymphoma, 299
for multiple sclerosis, 1019
for posttransplantation lymphoproliferative disease, 529
for rheumatoid arthritis, 847
for vasculitis, 854

rivaroxaban
for atrial fibrillation, 686
for thrombotic disorders, 282
rivastigmine, for Alzheimer's disease, 973
river blindness, 604
rizatriptan, for migraine, 217*t*, 219*t*
RLS (restless legs syndrome), 242, 244*t*
Rocky Mountain spotted fever, 500, 501*t*, 504
rodent bite, 117*t*, 118
roflumilast, for COPD exacerbation prophylaxis, 721
Romaña's sign, 594
Romberg maneuver, 951
ropinirole
for Parkinson's disease, 980*t*
for restless legs syndrome, 242
rosacea. *See* acne rosacea
rose spots, 393
roseola infantum, 525
rosetting, 586
rosiglitazone, for diabetes mellitus, 909*t*
Ross River virus infections, 551
rosuvastatin, for dyslipidemia, 938*t*
rotavirus infections, 390
rotavirus vaccine, 390
rotigotine, for Parkinson's disease, 980*t*
rouleaux formation, 265
RRMS (relapsing-remitting multiple sclerosis), 1013
RSBI (rapid shallow breathing index), 34
rubella, 539–540
rubella vaccine, 370*t*, 539, 540
rubeola (measles), 538–539
rufinamide, for seizures, 965*t*, 967*t*
rumination, 158
RVSP (right ventricular systolic pressure), 622–623

**S**

SAAG (serum-ascites albumin gradient), 187, 188*f*
*Saccharomyces boulardii* therapy, for *C. difficile* infections, 398
saccular (intracranial) aneurysm, 91
salicylates
acid-base disorders with, 17, 18*t*, 22
for osteoarthritis, 862
for seborrheic dermatitis, 260
for warts, 262
saline therapy
for diabetic ketoacidosis, 106*t*
for hypercalcemia, 112, 351, 927*t*
for hyperglycemic hyperosmolar state, 105
for hypernatremia, 5–6
for hyponatremia, 5, 351
for increased intracranial pressure, 95*t*
for metabolic alkalosis, 20
for SIADH, 112
for tumor lysis syndrome, 113
salmeterol, for asthma, 713
salmonellosis, 392–394
nontyphoidal, 394–395
typhoid fever, 393–394
salpingitis, 402
salpingo-oophorectomy, 1100
samarium-153 therapy, 345
sarcoidosis, 870–873, 872*f*, 1038*t*
sarcoma, paraneoplastic syndromes in, 349*t*
*Sarcoptes scabiei* infestation. *See* scabies
SARS (severe acute respiratory syndrome), 535
sausage digits, 857
saxagliptin, for diabetes mellitus, 908*t*
scabies, 610
scale (skin lesion), 257*t*
scar, 257*t*
scar carcinoma, 308
scarlet fever, 435
SCC. *See* squamous cell carcinoma
scedosporiosis, 582
Schilling test, 170
schistocytes, 265
schistosomiasis, 334, 605–606
schizoid personality disorder, 1070
schizophrenia, 1066–1067
schizotypal personality disorder, 1070
schwannoma, 1010
sciatic neuropathy, 1049*t*
SCID (severe combined immunodeficiency), 840
sclerodactyly, 847
scleroderma (systemic sclerosis), 165, 847–848
scombroid poisoning, 122
scopolamine
for nausea and vomiting, 51, 160
for vertigo, 228*t*
scorpion sting, 124
scorpionfish envenomation, 120–121
scotoma, 229, 230*f*
screening recommendations, 1087

scrub typhus, 503*t*, 507
sea anemone injury, 120
seborrheic keratosis, 256*f*
secondary progressive multiple sclerosis (SPMS), 1013
secretin stimulation test, 170, 807
seizures, 956. *See also* epilepsy
approach to, 956, 960*f*
classification of, 956, 956*t*
differential diagnosis of, 957, 958*t*
drug-induced, 959
EEG in, 958
etiology of, 956, 957*t*
imaging in, 960, 967
laboratory testing in, 958
vs. syncope, 225
treatment of, 961–966*t*, 967–968, 967*t*
selection bias, 1095
selective serotonin reuptake inhibitors (SSRIs), 1071, 1072*t*
selegiline
dosage and side effects of, 1073*t*
for Parkinson's disease, 980*t*
selenium sulfide, for seborrheic dermatitis, 260
semen analysis, 915
seminoma, 336, 337*f*
senna, for constipation, 50*t*
sensitization, 36
sensory examination, 951
sensory level, 110
sensory loss, 233, 234*t*
sentinel node biopsy, in breast cancer, 320
sepsis/septic shock, 65–68
approach to, 32, 33*f*, 62
clinical manifestations of, 62, 65, 66
clostridial, 473, 474*t*
complications of, 66
in critically ill patient, 35
definition of, 65
epidemiology of, 65–66
etiology of, 65
laboratory features of, 62, 62*t*, 67
pathophysiology of, 66
prevention of, 67
prognosis of, 67
*S. aureus*, 427
severe, 65
streptococcal, 438
treatment of, 67, 68*t*
septal panniculitis, 263
septicemia
listerial, 446–447
meningococcal, 444
serous otitis media (SOM), 251
*Serratia* infections, 457
sertraline
dosage and side effects of, 1072*t*
for obsessive-compulsive disorder, 1068
serum-ascites albumin gradient (SAAG), 187, 188*f*
sevelamer, for hyperphosphatemia, 929
severe acute respiratory syndrome (SARS), 535
severe combined immunodeficiency (SCID), 840
sexual assault, 1106
sexually transmitted infections (STI), 399
chancroid, 404*t*, 413
chlamydial infections. *See* chlamydial infections
donovanosis, 404*t*, 413
epididymitis, 400
genital herpes. *See* genital herpes
gonorrhea. *See* gonorrhea
HPV infections, 413–414
lymphogranuloma venereum, 404*t*, 408
mucopurulent cervicitis, 401–402
mycoplasmal infections, 399–400, 401–402, 408–409
pelvic inflammatory disease, 402–403
proctitis, proctocolitis, enterocolitis, and enteritis, 403
syphilis. *See* syphilis
urethritis
in men, 399–400
in women, 400
shift work, 241, 245
Shiga toxin-producing/enterohemorrhagic *E. coli* (STEC/EHEC), 395–396, 455
shigellosis, 395–396, 403
shingles. *See* herpes zoster
shock, 61–65. *See also specific types*
approach to, 33*f*, 62
cardiogenic, 32, 61*t*, 62*t*
forms of, 61*t*
in GI bleeding, 175
hemodynamic profiles in, 63*f*
high cardiac output/low systemic vascular resistance, 32, 33*f*
hypovolemic, 32, 33*f*
physiologic characteristics of, 62*t*
treatment of, 63–65, 63*f*, 64*t*

shoulder, muscles and innervation of, 949*t*
shoulder pain, 212–214
in adhesive capsulitis, 870
etiology of, 212–214
mechanical, 214
treatment of, 214
shunting, hypoxemia in, 708
SIADH. *See* syndrome of inappropriate ADH
sick euthyroid syndrome, 892
sick sinus syndrome (SSS), 677
sickle cell anemia, 269, 272*f*, 273
sickled cells, 265
sideroblastic anemia, 269, 271*t*
sigmoidoscopy
in colonic polyps, 327
for colorectal cancer screening, 330, 1097*t*
in diarrhea, 170
in GI bleeding, 175
"signet-ring sign," 729
sildenafil
for achalasia, 164
for erectile dysfunction, 916
for pulmonary hypertension, 702
for systemic sclerosis, 848
silent ischemia, 672
silicosis, 716–717
simple phobia, 1069
SIMV (synchronized intermittent mandatory ventilation), 74, 75*t*
simvastatin, for dyslipidemia, 938*t*
Sin Nombre virus, 551
Sindbis virus infections, 550
single photon emission computed tomography (SPECT), 26
sinoatrial node dysfunction, 677
sinus infections, 247–249
acute, 247–248, 249*t*
bacterial, 248
chronic, 248–249
fungal, 249
nosocomial, 248
treatment of, 248
viral, 248
sinus rhythm, 618
sinus tachycardia, 663, 680*t*
sinus venosus, 627
sinusitis
anaerobic, 475
aspergillosis, 572
*Klebsiella*, 456
*M. catarrhalis*, 451
pneumococcal, 424
sinusoidal obstruction syndrome, 188*f*
sipuleucel-T, for prostate cancer, 345
sirolimus, for immunosuppression after renal transplantation, 758
Sister Mary Joseph's nodule, 187
sitagliptin, for diabetes mellitus, 908*t*
sitosterolemia, 937*t*
Sjögren's syndrome, 848–849
SK. *See* streptokinase
skin biopsy, 256
skin cancer, 305–310
basal cell carcinoma, 307
melanoma. *See* melanoma
paraneoplastic syndromes in, 349*t*
prevention of, 308
screening for, 1099*t*
squamous cell carcinoma, 308
skin disease
acne, 262–263
arrangement and shape of lesions, 255, 256*f*
in cancer patients, 362
diagnosis of, 256–258
distribution of lesions, 255
drug-induced, 263–264
eczematous, 259–260
history in, 256
infections, 260–262
lesion characteristics, 255, 256*f*
in malnutrition, 42
papulosquamous, 258–259
physical examination in, 255
primary lesions, 255, 257*t*
secondary lesions, 255, 257*t*
vascular disorders, 263–264
skin infections
anaerobic, 476
aspergillosis, 572
in cancer patients, 362, 363*t*
cellulitis, 415*t*, 417
clinical manifestations of, 415–417
clostridial, 473
cryptococcal, 573
diphtheria, 441
group A *Streptococcus*, 436, 436*t*
mucormycosis, 577
necrotizing fasciitis, 416*t*, 417–418
nontuberculous mycobacterial, 493
*P. aeruginosa*, 459
*S. aureus*, 427, 430, 433*t*
in transplant recipients, 367*t*
treatment of, 415–416*t*
skin tag, 256*f*
skull fracture, 96
SLE. *See* systemic lupus erythematosus

sleep apnea, 243, 745–746
sleep disorders
approach to, 241–242
circadian rhythm, 245
excessive daytime sleepiness, 243–245, 244*t*
fatigue in, 133*t*
insomnia, 241–242, 243*t*
in women, 1106
sleep hygiene, 241, 243*t*
sleep paralysis, 243, 244, 244*t*
sleeping sickness, 595–596
slit-lamp examination, 229
slow low-efficiency dialysis (SLED), 751
SLR (straight leg raising) sign, 207–208
small-bowel tumor, 325
smell, disorders of sense of, 998, 999*t*, 1000
smoke inhalation, 717
smoking
bladder cancer and, 333
COPD and, 719
cough and, 147
lung cancer and, 310
pancreatic cancer and, 331
prevention of, 1103–1104
relative risks for current smokers, 1102*t*
in women, 1106
smoking cessation, 1087, 1102–1103
approach to, 1102
clinical practice guidelines, 1103*t*
for COPD, 720
for disease prevention, 1088–1090*t*
for head and neck cancer prevention, 310
for heart disease prevention, 1092
for interstitial lung disease, 737
for lung cancer prevention, 315
methods of, 1102–1103
for myocardial infarction prevention, 671
for osteoporosis, 934
for peripheral arteriosclerosis, 697
for vasospastic disorders, 698
snakebite
clinical manifestations of, 119
epidemiology of, 118–119
prognosis of, 119
treatment of, 117*t*, 119–120
snoring, 244*t*
SNS (specialized nutrition support), 43, 44*f*
social phobia, 1069
sodium, disorders of, 1–6
hypernatremia, 5–6, 6*t*
hyponatremia, 1–5, 3*f*
sodium bicarbonate, for metabolic acidosis, 20
sodium citrate, for metabolic acidosis, 20
sodium docusate, for constipation, 50*t*
sodium ipodate, for amiodarone-induced thyrotoxicosis, 892
sodium oxybate, for narcolepsy, 245
sodium phosphate enema, for constipation, 50*t*
sodium restriction
for aldosteronism, 898
for ascites, 188
for cor pulmonale, 693
for edema, 151–152
for heart failure, 688, 689*t*
for hypertension, 651
for restrictive cardiomyopathy, 642
for vertigo, 228*t*, 229
sodium stibogluconate, for leishmaniasis, 594
sodium tyropanoate, for amiodarone-induced thyrotoxicosis, 892
soft tissue infections
anaerobic, 476
in cancer patients, 362, 363*t*
cellulitis, 415*t*, 417
clinical manifestations of, 415–417
clostridial, 473
group A *Streptococcus*, 436, 436*t*
*Klebsiella*, 456
myositis and myonecrosis, 418
necrotizing fasciitis, 416*t*, 417–418
nontuberculous mycobacterial, 493
*P. aeruginosa*, 459
*S. aureus*, 426–427, 430, 433*t*
treatment of, 415–416*t*
SOM (serous otitis media), 251
somatic pain, 36, 36*t*
somatic symptom disorder, 1069–1070
somatostatin therapy
for acromegaly, 881
for esophageal varices, 832
somatostatinoma, 332*t*, 333
somatotropin, for hypopituitarism, 883*t*
sorafenib
for hepatocellular carcinoma, 331
for renal cancer, 335
sorbitol
for irritable bowel syndrome, 796*t*
for paralytic shellfish poisoning, 122

sotalol, for arrhythmias, 684*t*
South American blastomycosis, 581–582
soy-based products, 922
spastic colon, 794
specialized nutrition support (SNS), 43, 44*f*
SPECT (single photon emission computed tomography), 26
spectinomycin, for gonococcal infections, 407y
spermatogenesis, 915
spherocytes, 265
spider bite, 123–124
spinal cord, 004*f*
spinal cord compression, 98–100
  approach to, 98
  epidural abscess, 99
  epidural hematoma, 100
  from metastases, 1001*t*, 1012
  neoplastic, 98–99, 1005, 1005*f*
  as oncologic emergency, 110–111
  treatment of, 99, 111, 111*f*
spinal cord disease, 1002–1008
  acute and subacute, 1005–1006
  autonomic dysfunction in, 991, 1002
  cauda equina, 1004
  cervical, 1004
  chronic, 1006–1107
  complications of, 1007–1008
  extramedullary, 1005
  foramen magnum lesions, 1003
  intramedullary, 1005
  lumbar, 1004
  sacral, 1004
  thoracic, 1003
  treatable, 1003*t*
  weakness in, 234*t*
spinal cord infarction, 1005–1006
spinal manipulation, for chronic back pain, 211
spinal stenosis, 210–211
spinocerebellar ataxia, 893*f*, 983
*Spirillum minor* infections, 118
spirochetal infections
  endemic treponematosis, 497
  leptospirosis, 497–498
  Lyme borreliosis, 494–497
  relapsing fever, 498–499
spirometry, 148, 705–706, 705*f*
spironolactone
  for ascites, 188
  for edema, 152, 153*t*
  for heart failure, 664, 688, 689*t*, 690*t*
  for hirsutism, 920
  for hyperaldosteronism, 20–21, 898
  for hypertension, 652*t*
  for STEMI, 662
splenectomy, 193, 385
  for idiopathic thrombocytopenic purpura, 280
  for polycythemia vera, 292
  sepsis following, 68*t*
  for thalassemia, 273
splenic abscess, 385
splenomegaly, 191–193
  diseases associated with, 192–193*t*
  mechanism of, 192, 192–193*t*
SPMS (secondary progressive multiple sclerosis), 1013
spondylitic myelopathy, 1006
spondylolisthesis, 210
spondylosis
  cervical, 212, 214
  low back pain in, 210
spontaneous breathing trial, 33–34
sporotrichosis, 581, 1035*t*
sporozoite, 586
spotted fevers
  flea-borne, 501*t*
  tick- and mite-borne, 500–505, 501*t*
spur cell anemia, 271
sputum analysis
  in pneumonia, 724
  in respiratory disease, 710
sputum cytology, for cough, 148
squamous cell carcinoma (SCC)
  infections in, 363*t*
  location of, 256*f*
  risk factors for, 308
  treatment of, 308
  types of, 308
SSPE (subacute sclerosing panencephalitis), 538
SSRIs (selective serotonin reuptake inhibitors), 1071, 1072*t*
SSS (sick sinus syndrome), 677
SSSS (staphylococcal scalded-skin syndrome), 428
stabbing headache, primary, 215*t*, 221
standard precautions, 357
staphylococcal infections, 425–434
  arthritis, 418–420
  coagulase-negative, 428–429
  endocarditis, 372–373, 377*t*, 380
  microbiology of, 425
  osteomyelitis, 420, 421*t*. *See also* osteomyelitis

*S. aureus*. *See Staphylococcus aureus* infections
*S. moniliformis*, 118
skin, 415*t*, 417
treatment of, 430, 431–433*t*
staphylococcal scalded-skin syndrome (SSSS), 428
*Staphylococcus aureus* infections, 426–428
bacteremia and sepsis, 427
diagnosis of, 426
endocarditis, 372, 427–428, 430
epidemiology of, 426
food poisoning, 387
impetigo, 261
invasive disease, 426
methicillin-resistant. *See* methicillin-resistant *S. aureus* (MRSA) infections
musculoskeletal, 427
osteomyelitis, 430
pathogenesis of, 426
prevention of, 428
prosthetic device-related, 428
respiratory tract, 427
skin and soft tissue, 426–427, 430, 433*t*
spinal epidural abscess, 99
toxin-mediated disease, 426, 428, 429*t*, 430
treatment of, 430, 431–433*t*
urinary tract, 428
starvation, 41
stasis ulcer, 256*f*
statins
for dyslipidemia, 938*t*, 941
indications for, 1093*t*
for UA/NSTEMI, 670, 671
status epilepticus, 101–103
after hypoxic-ischemic insult, 101
clinical manifestations of, 103
etiology of, 103
nonconvulsive, 103
prognosis of, 103
treatment of, 102*f*, 103
Stauffer's syndrome, 335
steatorrhea, 170
STEC/EHEC (Shiga toxin-producing/enterohemorrhagic *E. coli*), 395–396, 455
stellate ganglion blockade, 994
STEMI. *See* ST-segment elevation myocardial infarction
*Stenotrophomonas maltophilia* infections, 461–462, 461*t*
stenting, vascular
for angina pectoris, 675–676, 676*t*
for superior vena cava syndrome, 110
stereognosis, 951
sterilization, 922
steroid therapy. *See* glucocorticoid therapy
Stevens-Johnson syndrome, 263
STI. *See* sexually transmitted infections
stiff-person syndrome, 352*t*, 353*t*, 354*t*
stingray envenomation, 120–121
stonefish envenomation, 120–121
stool analysis, 170
stool softeners, 50*t*, 798
straight leg raising (SLR) sign, 207–208
strawberry tongue, 435
*Streptobacillus moniliformis* infections, 118
streptococcal infections, 434–440
arthritis, 418–420
endocarditis, 372, 376–377*t*, 378–379
erysipelas, 261
glomerulonephritis following, 760
group A. *See* group A *Streptococcus* (GAS) infections
group B, 438
group D, 439
groups C and G, 438
hemolytic patterns, 434
microbiology of, 434
osteomyelitis, 421*t*. *See also* osteomyelitis
pharyngitis, 253
skin, 415–416*t*, 417
viridans streptococci, 439
*Streptococcus pneumoniae* infections. *See* pneumococcal infections
streptokinase (SK)
for STEMI, 659
for thrombotic disorders, 282
streptomycin
for *Bartonella* infections, 467*t*
for brucellosis, 464
for enterococcal infections, 440
for infective endocarditis, 377*t*, 378
for plague, 466
for tuberculosis, 486, 487–488*t*
for tularemia, 465
streptozotocin
for carcinoid tumor, 332
for islet-cell tumors, 333
for Zollinger-Ellison syndrome, 790

stress testing, in coronary artery disease, 672, 673*f*, 674*t*
stroke, 82–91
anatomic localization in, 83*t*
causes of, 87–88, 88*t*
hemorrhagic, 82, 85
ischemic, 82–83
causes of, 87–88, 88*t*
treatment of, 84–87, 86*t*
pathophysiology of, 82
prevention of, 89–91
risk factors for, 89
small-vessel, 82, 83
treatment of, 84–87, 85*f*
stromal tumor, 338
strongyloidiasis, 601–602
strontium-89 therapy, 345
struvite stones, 780, 782*t*
ST-segment elevation myocardial infarction (STEMI)
chest pain in, 138, 140*f*, 658
complications of
acute mechanical, 667
arrhythmias, 663–664
cardiogenic shock, 664, 665*t*, 666*f*
heart failure, 663–664, 664*t*, 665*t*
hypotension, 664, 667
hypovolemia, 665*t*
pericarditis, 667
ventricular aneurysm, 667
ECG in, 141, 620, 621*f*, 621*t*, 645*t*, 658
laboratory features of, 658–659
pericarditis following, 645*t*
physical examination in, 658
prevention of, 283, 667
risk factors for, 667
syncope in, 222
treatment of, 659–662, 660*f*, 661*f*
stupor, 76
subacute sclerosing panencephalitis (SSPE), 538
subarachnoid hemorrhage (SAH), 91–93
grading scales for, 91, 92*t*
headache in, 215*t*
with hydrocephalus, 92
treatment for, 92–93
vasospasm in, 92–93
subdural hematoma, 98
substance abuse
alcohol use disorder. *See* alcohol use disorder
narcotics. *See* narcotic abuse
in women, 1106
sucralfate
for erosive gastropathies, 788
for peptic ulcer disease, 787
sudden death, 57–60, 57*t*
suicide, 1064, 1066, 1088–1090*t*
sulfadiazine, for toxoplasmosis, 598
sulfadoxine-pyrimethamine, for malaria, 588*t*
sulfasalazine
for enteropathic arthritis, 867
for inflammatory bowel disease, 792
for psoriatic arthritis, 859
for reactive arthritis, 860
for rheumatoid arthritis, 846
sulfhemoglobinemia, 145
sulfinpyrazone, for gout, 865
sulfonamides, for nocardiosis, 479
sulfonylureas, for diabetes mellitus, 906, 908*t*
sulindac
for colon cancer prevention, 1100
for colonic polyps, 327
sumatriptan
for cluster headache, 219
for migraine, 217*t*, 219*t*
summer grippe, 544
sunitinib
for islet-cell tumors, 333
for renal cancer, 335
superior vena cava syndrome, 110
supraventricular arrhythmia, in STEMI, 663
supraventricular tachycardia (SVT), 682*t*, 685*f*
suramin, for sleeping sickness, 596
surgical wound infections, 358, 359*t*
SVR (systemic vascular resistance), 663
swallowing studies, 164
Sweet's syndrome, 362
swimmer's ear, 250, 459
swimmer's itch, 417, 605
swinging flashlight test, 229
sympathectomy, digital, for systemic sclerosis, 848
sympathetic system, 989*f*, 990*t*
sympathomimetics, for allergic rhinitis, 838
synchronized intermittent mandatory ventilation (SIMV), 74, 75*t*
syncope, 222–225
approach to, 222, 223*f*
cardiac, 224*t*
differential diagnosis of, 225
etiology of, 222–224, 223–224*t*
neurally mediated, 222, 223*t*

orthostatic hypotension, 224, 224*t*
treatment of, 225
vasodepressor, 222
vasovagal, 222, 223*t*
syndrome of inappropriate ADH (SIADH)
clinical manifestations of, 885
etiology of, 885, 885*t*
hyponatremia in, 4
paraneoplastic, 112, 351, 349*t*
treatment of, 116, 351, 886
syndrome X. *See* metabolic syndrome
synkinesis, 996
synovial fluid analysis, 205, 206*f*, 419, 864, 866
syphilis
clinical manifestations of, 403, 404*t*, 409–410
congenital, 410
diagnosis of, 410
endemic, 497
meningitis in, 1033*t*
microbiology and epidemiology of, 409
pathogenesis of, 409
phases of, 409–410
in pregnancy, 411*t*
tertiary, 1007
treatment of, 410–412, 411*t*
syringomyelia, 1006
systemic lupus erythematosus (SLE), 844–845
chorea and, 237
chronic meningitis in, 1039*t*
clinical manifestations of, 844
diagnosis of, 844
evaluation of, 844
glomerular disease in, 762, 768*t*
pathogenesis of, 844
treatment of, 845
systemic sclerosis (scleroderma), 165, 847–848
systemic vascular resistance (SVR), 663

**T**

T cell deficiency syndromes, 840, 841*t*, 842
T cell receptors, 840
T cells, 189
$T_3$ (triiodothyronine), 886
$T_4$ (thyroxine), 883*t*, 886
tabes dorsalis, 410, 1007
TAC (transient aplastic crisis), 542
tâche noire, 504
tachyarrhythmias, 679–686
clinical and ECG features of, 680–682*t*
treatment of, 685–686
tachycardia, 677
tacrine, 973
tacrolimus
for immunosuppression after renal transplantation, 758
for inflammatory bowel disease, 794
for inflammatory myopathy, 1059
for myasthenia gravis, 1053
tadalafil
for erectile dysfunction, 916
for pulmonary hypertension, 702
taeniasis asiatica, 606–607
taeniasis saginata, 606–607
taeniasis solium, 607
Takayasu arteritis, 851
Takayasu's disease, 696
tamoxifen
for breast cancer, 320, 321
for breast cancer prevention, 1100
endometrial cancer and, 340
for melanoma, 307
tapeworm infections, 606–610
tardive dyskinesia, 237, 1074
target cells, 265
target lesion, 255
tarsal tunnel syndrome, 1049*t*
TAVI (transcatheter aortic valve implantation), for aortic stenosis, 636
taxanes, for prostate cancer, 343
tazarotene, for psoriasis, 259
TB. *See* tuberculosis
TCAs. *See* tricyclic antidepressants
Td (tetanus and diphtheria toxoid) vaccine, 442, 1090*t*
teardrop cells, 265
tedizolid, for staphylococcal infections, 432*t*, 433*t*
telangiectasia, 257*t*
telavancin, for staphylococcal infections, 430
telbivudine, for chronic hepatitis B, 817, 818–819*t*
temazepam
for insomnia, 242
pharmacology of, 1075*t*
temozolomide, for melanoma, 307
temperature, 127
temporal (giant cell) arteritis, 231, 851
temsirolimus, for renal cancer, 335
tendinitis, 869–870

tendon reflexes, 233*t*
tendon xanthoma, 936
tenecteplase, for thrombotic disorders, 282
teneligliptin, for diabetes mellitus, 908*t*
tenofovir
  for chronic hepatitis B, 817, 818–819*t*
  for HIV infection, 561*t*, 566
tenosynovitis, 864
tension headache, 215*t*, 218
tension pneumothorax, 743
teratoma, 336
terazosin, for prostate hyperplasia, 342
terbinafine
  for dermatophyte infections, 262
  pharmacology of, 570
teriflunomide, for multiple sclerosis, 1018
teriparatide, for osteoporosis, 934
terminally ill patient
  care during last hours, 53, 54–56*t*
  clinical courses in last days, 53*f*
  constipation in, 50, 50*t*
  delirium in, 52, 52*t*, 56*t*
  depression in, 52
  dyspnea in, 51, 51*t*
  fatigue in, 51–52, 54*t*
  nausea and vomiting in, 51–52
  pain management in, 50
  physical symptoms of, 49–52, 49*t*
  psychological symptoms of, 49*t*
  withdrawal of care, 35
testicular cancer, 335–336, 337*f*
testosterone deficiency. *See* androgen deficiency
testosterone therapy
  for androgen deficiency, 914–915
  for hypopituitarism, 883*t*
tetanus, 469–471
tetanus and diphtheria toxoid (Td) vaccine, 442, 1090*t*
tetanus booster, 118
tetanus immune globulin, 470
tetracyclines
  for acne, 263
  for actinomycosis, 481
  for brucellosis, 464
  for *C. pneumoniae* infections, 513
  for *C. psittaci* infections, 516
  for donovanosis, 413
  for *H. pylori* eradication, 787*t*
  for human monocytotropic ehrlichiosis, 508
  for intestinal pseudoobstruction, 797
  for *Legionella* infections, 513
  for *M. pneumoniae* infections, 511
  for malaria, 588*t*
  for relapsing fever, 499
  for syphilis, 411*t*
Tetralogy of Fallot, 631
tetrathiomolybdate, for Wilson's disease, 946
thalassemia, 269, 271*t*, 273
thalidomide
  for leprosy, 492
  for multiple myeloma, 302
theophylline
  for asthma, 713
  for COPD, 720
  poisoning, 9
therapeutic hypothermia, 60
thermoregulatory sweat test (TST), 990–991
thiamine deficiency, 45*t*
thiamine therapy, for alcohol withdrawal, 1083
thiazides
  for heart failure, 688
  for hypertension, 651, 652*t*
  for nephrolithiasis, 781*t*
thiazolidinedione, for diabetes mellitus, 906
thienopyridines, for thrombotic disorders, 283
thigh, muscles and innervation of, 950*t*
thin basement membrane nephropathy, 766
thiocyanate toxicity, 690–691
thioridazine
  for delirium, 52*t*
  dosage and side effects of, 1076*t*
thiothixene, 1076*t*
thoracentesis, 27–28, 28*f*, 710–711
thoracic outlet syndrome, 212, 1048*t*
thoracic spine disease, chest pain in, 139*f*, 141
thoracic surgery, video-assisted (VATS), 711, 737
thrombocytopenia, 277–279, 278*f*
  drug-induced, 278, 280
  heparin-induced, 278
  refractory, 290*t*
  treatment of, 280
thrombocytopenic purpura
  idiopathic, 278
  thrombotic. *See* thrombotic thrombocytopenic purpura
thrombocytosis, 279, 293
thrombolytic therapy

for arterial embolism, 697
for stroke, 86, 86*t*
thrombophlebitis, superficial, 698
thrombotic disorders, 281–283
thrombotic thrombocytopenic purpura (TTP)
clinical manifestations of, 279
treatment of, 47, 280
thrush, 570
thumb, muscles and innervation of, 950*t*
thymectomy, for myasthenia gravis, 1053
thymoma, 353*t*
thymus, in myasthenia gravis, 1050
thyroid disease, 886–895
hypothyroidism. *See* hypothyroidism
neoplasms, 893–895, 894*f*
nontoxic goiter, 892–893
paraneoplastic syndromes in, 349*t*
sick euthyroid syndrome, 892
thyrotoxicosis. *See* thyrotoxicosis
toxic adenoma, 893
toxic multinodular goiter, 893
thyroid function tests, 889
thyroid nodule, 894*f*
thyroid storm (thyrotoxic crisis), 889, 891
thyroidectomy
for thyroid neoplasms, 894–895
for thyrotoxicosis, 891
for toxic multinodular goiter, 893
thyroiditis, 889, 891, 891*f*
thyroid-stimulating hormone (TSH)
deficiency of, 882, 883*t*
hypersecretion of, 881
production of, 877, 878*f*
thyrotoxic crisis (thyroid storm), 889, 891
thyrotoxicosis
amiodarone-induced, 892
clinical manifestations of, 889
diagnosis of, 889, 890*f*
etiology of, 886, 889
treatment of, 890–891
thyroxine ($T_4$), 883*t*, 886
TIA (transient ischemic attack), 82, 85*f*
tiagabine
for generalized anxiety disorder, 1068
for seizures, 965*t*, 967*t*
TIBC (total iron-binding capacity), 268, 268*f*, 270*t*
tic douloureux. *See* trigeminal neuralgia
ticagrelor, for UA/NSTEMI, 670, 671
ticarcillin-clavulanate
for mixed anaerobic infections, 476*t*
for *S. maltophilia* infections, 461*t*
tick, removal of, 123
tick bite, 122–123
tick paralysis, 123
tick-borne relapsing fever, 499
tick-borne spotted fevers, 500–505, 501*t*
ticlopidine, for thrombotic disorders, 283
tics, 238
TIGAR-O classification, of pancreatic disease, 808*t*
tigecycline
anaerobic infections, 476*t*
for *C. difficile* infections, 398
for enterococcal infections, 440
for *Klebsiella* infections, 456
for nontuberculous mycobacterial infections, 494
for staphylococcal infections, 430
tilt-table test, 990
TIMI Risk Score, 670*f*
tinea capitis, 261
tinea corporis, 261
tinea cruris, 256*f*, 261
tinea pedis, 256*f*, 261
tinea (pityriasis) versicolor, 258
tinea unguium, 261
tinidazole
for amebiasis, 397
for giardiasis, 391
for trichomoniasis, 401
tinnitus, 227
TINU (tubulointerstitial nephritis and uveitis syndrome), 772
TIPS (transjugular intrahepatic portosystemic shunt), 178, 188, 832
tirofiban
for thrombotic disorders, 283
for UA/NSTEMI, 670
tissue necrosis, 275
tissue plasminogen activator (tPA)
for stroke, 86, 86*t*
for thrombotic disorders, 282–283
for venous thromboembolism, 733
tizanidine, for multiple sclerosis, 1019
TMP-SMX. *See* trimethoprim-sulfamethoxazole

TMS (transcranial magnetic stimulation), for depression, 1065
TNM staging
for breast cancer, 318–319, 318–319*t*
for gastric carcinoma, 324*t*
for lung cancer, 311, 312–313*t*
tobramycin
for community-acquired pneumonia, 725*t*
for health care–associated pneumonia, 727*t*
for *P. aeruginosa* infections, 460–461*t*
for sepsis/septic shock, 68*t*
tocilizumab, for rheumatoid arthritis, 847
toes, muscles and innervation of, 950*t*
tofacitinib, for rheumatoid arthritis, 847
tolcapone, for Parkinson's disease, 980*t*
tolfenamic acid, for migraine, 217*t*
tolnaftate, for dermatophyte infections, 262
Tolosa-Hunt syndrome, 1002
tolvaptan, for SIADH, 112, 886
tongue paralysis, 1001
tonic-clonic (grand mal) seizures, 956. *See also* seizures
topical antifungal agents, 570
topiramate
for migraine prevention, 220*t*
for seizures, 966*t*, 967*t*
torsades de pointes, 682*t*
torsemide
for edema, 153*t*
for heart failure, 688, 690*t*
torticollis, 237
tositumomab, for follicular lymphoma, 298
total iron-binding capacity (TIBC), 268, 268*f*, 270*t*
total lung capacity, 705, 705*f*
Tourette syndrome, 238
toxic adenoma, 893
toxic chemicals, 717–718
toxic granulations, 266
toxic shock syndrome (TSS)
clostridial, 473, 474*t*
staphylococcal, 428, 429*t*, 430
streptococcal, 436*t*, 437, 437*t*
*Toxocara canis* infections, 600
toxoplasmosis, 596–598
clinical manifestations of, 597
congenital, 597
diagnosis of, 597–598
meningitis in, 1035*t*
microbiology and epidemiology of, 596–597
pathogenesis of, 597
in pregnancy, 597
prevention of, 598
treatment of, 598
tPA. *See* tissue plasminogen activator
TR (tricuspid regurgitation), 616*t*, 638–639
tracheobronchitis, 141
trachoma, 408, 514–515
"tram tracks," 729
tramadol
abuse, 1084
for osteoarthritis, 862
for pain, 39*t*
for polyneuropathy, 1045*t*
trametinib, for melanoma, 307
trandolapril, for heart failure, 690*t*
transaminases, 183, 184*t*
transcatheter aortic valve implantation (TAVI), for aortic stenosis, 636
transcranial magnetic stimulation (TMS), for depression, 1065
transfusion therapy, 46–47
autologous, 46
complications of, 46, 47*t*
plasma components, 47
platelet, 47
red blood cell, 46
whole blood, 46
transient aplastic crisis (TAC), 542
transient ischemic attack (TIA), 82, 85*f*
transient monocular blindness, 230
transjugular intrahepatic portosystemic shunt (TIPS), 178, 188, 832
transplant recipient
infections in, 366–369, 367*t*, 526–527, 758–759, 759*t*
transfusion for, 46
vaccination of, 369–370*t*
transsphenoidal surgery
for acromegaly, 881
for pituitary adenomas, 879, 896
transtubular potassium gradient (TTKG), 8, 10*f*, 13, 14*f*
transurethral microwave thermotherapy (TUMT), 342
transurethral resection of prostate (TURP), 342
tranylcypromine, 1073*t*
trastuzumab, for breast cancer, 320, 321

traveler's diarrhea, 389
trazodone
dosage and side effects of, 1073*t*
for insomnia, 242
pharmacology of, 1071
for PTSD, 1069
trematode infections, 604–606
tremor, 236–238
coarse, 236
essential, 236, 237*t*
intention, 236
parkinsonian, 236, 237*t*
postural, 236
trench fever, 467*t*, 468
trench mouth, 475
*Treponema pallidum*, 409. *See also* syphilis
treponematosis, endemic, 497
treprostinil, for pulmonary hypertension, 702
triamterene
for edema, 153*t*
for hypertension, 652*t*
triazolam
dosage and action of, 1075*t*
for insomnia, 242
triazoles
for coccidioidomycosis, 580
for dermatophyte infections, 262
trichinellosis, 599–600
*Trichomonas vaginalis* infections, 399, 401
triclabendazole, for liver flukes, 606
tricuspid regurgitation (TR), 616*t*, 638–639
tricuspid stenosis (TS), 616*t*, 638
tricuspid valve endocarditis, 372
tricuspid valve prolapse, 616*t*
tricyclic antidepressants (TCAs), 1071. *See also* antidepressants
dosage and side effects of, 1072*t*
for irritable bowel syndrome, 796*t*
for migraine prevention, 220*t*
for narcolepsy, 244
for polyneuropathy, 1044, 1045*t*
trientine, for Wilson's disease, 946
trifluoperazine, 1076*t*
trifluorothymidine, for HSV infections, 521*t*
trigeminal nerve (CN V)
examination of, 948
sensory divisions of, 996*f*
trigeminal neuralgia, 221, 995–996
trigeminal neuropathy, 996, 997*t*
trigger points, 995
triglycerides, 936. *See also* hypertriglyceridemia
trihexyphenidyl, for dystonia, 237
triiodothyronine ($T_3$), 886
trimethoprim, for *Pneumocystis* infections, 584*t*
trimethoprim-sulfamethoxazole (TMP-SMX)
for ANCA-associated glomerulonephritis, 762
for animal bite infections, 116*t*
for *B. cepacia* infections, 461*t*
for COPD exacerbations, 721
for *Corynebacterium* infections, 443
for cyclosporiasis, 392
for cystoisosporiasis, 392
for diverticulitis, 796
for donovanosis, 414
for extraintestinal *E. coli* infections, 454
for glanders, 461*t*
for HSCT patients, 367
for listerial infections, 447
for *M. catarrhalis*, 452
for melioidosis, 461*t*
for nephrolithiasis, 782*t*
for nocardiosis, 479
for osteomyelitis, 421*t*
for peritonitis prevention, 382
for pertussis, 451
for plague, 466
for *Pneumocystis* infections, 584, 584*t*
for *Pneumocystis* prophylaxis, 585, 585*t*
for *Proteus* infections, 457
for Q fever, 509–510
for *S. maltophilia* infections, 461*t*
for salmonellosis, 394
for snakebite, 117*t*
for staphylococcal infections, 430, 433*t*
for toxoplasmosis, 598
for transplant recipients, 368
for urinary tract infections, 777, 777*t*
for Whipple's disease, 482
triolein breath test, 170
triple-H therapy, for subarachnoid hemorrhage with vasospasm, 93
triptans
for migraine prophylaxis, 216
for migraine treatment, 217*t*, 219*t*
*Tropheryma whipplei*, 481–482

trophozoite, 586
troponins, cardiac-specific, 668
Trousseau's sign, 928
trypanosomiasis, 594–596, 1035*t*
TS (tricuspid stenosis), 616*t*, 638
TSH. *See* thyroid-stimulating hormone
TSS. *See* toxic shock syndrome
TST (thermoregulatory sweat test), 990–991
TTKG (transtubular potassium gradient), 8, 10*f*, 13, 14*f*
TTP. *See* thrombotic thrombocytopenic purpura
tuberculin skin test, 489*t*, 490
tuberculosis (TB), 482–490
  vs. brucellosis, 463, 463*t*
  clinical manifestations of, 483–485
  diagnosis of, 485
  epidemiology of, 482–483
  extensively drug-resistant, 482
  extrapulmonary, 483–484
  gastrointestinal disease in, 484
  genitourinary disease in, 484
  HIV infection and, 485
  latent, 489*t*, 490
  meningitis in, 484, 1033*t*
  microbiology of, 482
  miliary disease in, 484
  multidrug-resistant, 482
  nosocomial, 361
  pathogenesis of, 483
  pericarditis in, 484
  pleural involvement in, 484
  prevention of, 490, 490*t*
  pulmonary, 483
  skeletal disease in, 484
  treatment of, 485–486, 487–488*t*, 489–490
tuberoeruptive xanthoma, 941
tuberous xanthoma, 936
tubulointerstitial disease. *See* renal tubular disease
tubulointerstitial nephritis and uveitis syndrome (TINU), 772
tularemia, 115, 464–465
tumor lysis syndrome, 113
tumor (skin lesion), 257*t*
TUMT (transurethral microwave thermotherapy), 342
Turcot's syndrome, 326*t*, 327
Turner's sign, 804
TURP (transurethral resection of prostate), 342
twitching, 951
two-point discrimination, 951
typhlitis, in cancer patients, 364
typhoid fever. *See* enteric fever
typhus
  epidemic (louse-borne), 502*t*, 506–507
  Kenya tick, 504
  murine (flea-borne), 502*t*, 505–506
  scrub, 503*t*, 507
Tzanck preparation, 258

**U**

UFH. *See* unfractionated heparin
ulcer, 257*t*
  cutaneous, 417
  genital, 403, 404*t*
  skin lesion, 257*t*
ulcerative colitis (UC), 791. *See also* inflammatory bowel disease
ulnar nerve entrapment, 1046, 1047*t*
ultrasonography (US)
  diagnostic, 25
  endoscopic, 322, 800*t*
  hepatobiliary, 185, 800*t*
  in pancreatitis, 804
  renal, 752
  in stroke, 88
  venous, 731
undecylenic acid, for dermatophyte infections, 262
underweight, 901*t*
unfractionated heparin (UFH)
  for STEMI, 662
  for thrombotic disorders, 281–282
  for UA/NSTEMI, 670
  for venous thromboembolism, 732–733
unstable angina/non-ST-elevation myocardial infarction (UA/NSTEMI)
  clinical manifestations of, 668
  diagnosis of, 668, 669*f*
  ECG in, 620, 621*t*, 668
  TIMI Risk Score for, 670*f*
  treatment of, 668, 669*f*, 670–671, 671*f*
upper respiratory infections (URIs), 247–254. *See also* respiratory tract infections
  ear infections. *See* ear infections
  epiglottitis, 254
  laryngitis, 253–254
  nonspecific, 247
  pharyngitis, 251–253
  sinusitis, 247–249
urate nephropathy, 864

urea breath test, 786, 786*t*
*Ureaplasma* infections, 399, 408–409
ureidopenicillin, for cholecystitis, 801
uremia, 199
uremic syndrome, 753. *See also* chronic kidney disease
ureteral obstruction, 784
ureterosigmoidostomy, 18*t*
urethral syndrome, 400
urethritis
  in men, 399–400
  in women, 400
uric acid nephrolithiasis, 864
uric acid stones, 780, 782*t*, 864
uricosuric drugs, for gout, 865
urinalysis, 777
urinary incontinence, in terminally ill patient, 55*t*
urinary retention, 342
urinary tract infections (UTI), 775–778
  in cancer patients, 364
  catheter-associated, 778
  clinical manifestations of, 776–777
  definition of, 775–776
  diagnosis of, 777
  epidemiology of, 776
  microbiology of, 776
    *Corynebacterium*, 443
    *E. coli*, 454
    *Klebsiella*, 456
    *P. aeruginosa*, 459, 461*t*
    *Proteus*, 456–457
    *S. aureus*, 428
  nosocomial, 358, 359*t*
  pathogenesis of, 776
  recurrent, prevention of, 778
  treatment of, 777–778, 777*t*
urinary tract obstruction (UTO), 782–784, 783*f*
urine abnormalities
  asymptomatic, 766–767, 767*t*
  of composition, 199–203
  of volume, 199
URIs. *See* upper respiratory infections
urokinase, for thrombotic disorders, 282
ursodeoxycholic acid
  for gallstones, 800
  for primary biliary cirrhosis, 829
  for primary sclerosing cholangitis, 803
urticaria
  classification of, 836, 836*t*
  clinical manifestations of, 264
  diagnosis of, 836–837
  pathogenesis of, 264
  treatment of, 837
US. *See* ultrasonography
ustekinumab, for psoriasis, 259
ustekinumab, for psoriatic arthritis, 859
UTI. *See* urinary tract infections
UTO (urinary tract obstruction), 782–784, 783*f*

**V**

vaccination. *See* immunization
vaccine-associated poliomyelitis, 544
vagotomy, for peptic ulcer disease, 788*t*
vagus nerve (CN X)
  disorders of, 1000
  examination of, 948
  stimulation of, 1065
valacyclovir
  for Bell's palsy, 997
  for genital HSV infections, 412, 415*t*
  for herpes zoster infections, 415*t*
  for HSCT patients, 367
  for HSV infections, 519, 520–522*t*
  for transplant recipients, 368
  for viral esophagitis, 165
  for viral meningitis, 1027
  for VZV infections, 524
valdecoxib, for pain, 38*t*
valganciclovir
  for cytomegalovirus infections, 527
  for viral esophagitis, 165
valproate/valproic acid
  for bipolar disorder, 1066
  dosage and side effects of, 1078*t*
  for migraine prevention, 220*t*
  for myoclonus, 238
  for posthypoxic myoclonus, 101
  for seizures, 966*t*, 967*t*
  for status epilepticus, 102*f*
Valsalva maneuver, 617*t*, 990
Valsalva ratio, 990
valsartan
  for heart failure, 690*t*
  for hypertension, 653*t*
  for STEMI, 662
valvotomy, for mitral stenosis, 632
valvular heart disease, 632–639
  aortic regurgitation, 637–638
  aortic stenosis. *See* aortic stenosis
  echocardiography in, 623, 624*f*, 626*t*
  mitral regurgitation. *See* mitral regurgitation

valvular heart disease (*Cont.*):
mitral stenosis. *See* mitral stenosis
mitral valve prolapse, 634, 636
murmurs in, 616*t*
tricuspid regurgitation, 638–639
tricuspid stenosis, 638
valvuloplasty, for mitral stenosis, 632
vancomycin
for anaerobic infections, 476*t*
for bacterial meningitis, 1024*t*, 1025*t*
for brain abscess, 1030
for *C. difficile* infections, 398
for clostridial infections, 474*t*
for *Corynebacterium* infections, 443
for health care–associated pneumonia, 727*t*
for infectious arthritis, 420
for infective endocarditis, 376–378*t*, 379
for MRSA infections, 416*t*
for necrotizing fasciitis, 416*t*
for osteomyelitis, 421*t*
for peritonitis, 383
for pneumococcal infections, 424
for pyomyositis, 418
for sepsis/septic shock, 68*t*
for staphylococcal infections, 430, 431–432*t*
for streptococcal infections, 439
vancomycin-resistant enterococci (VRE), 440
VAP. *See* ventilator-associated pneumonia
vardenafil, for erectile dysfunction, 916
varenicline, for smoking cessation, 720, 1103
varicella-zoster immune globulin, 524
varicella-zoster vaccine, 371*t*, 524, 1090*t*
varicella-zoster virus (VZV) infections, 519
chickenpox, 523
herpes zoster, 523–524
nosocomial, 361
prevention of, 524
varicocele, 915
vascular dementia, 970*t*, 971, 974, 975*f*
vascular disease
abdominal pain in, 155*t*
gastrointestinal, 797–798
headache in, 215*t*
malabsorption in, 173*t*
peripheral. *See* peripheral vascular disease
skin diseases, 263–264
vascular malformation, myelopathy in, 1006, 1007*f*
vascular shunting, anatomic, 145
vasculitis, 264
approach to, 852, 852*f*
conditions that mimic, 853*t*
cutaneous, 264
definition and pathogenesis of, 851
differential diagnosis of, 853
neuropathy in, 1046
primary syndromes, 851
secondary syndromes, 852
treatment of, 264, 853–854
urticarial, 264
vasoconstrictors, for allergic rhinitis, 838
vasodilators
for acute renal failure, 751
for aortic regurgitation, 638
for heart failure, 663–664, 664*t*, 690–691, 691*t*
for pulmonary hypertension, 702
for STEMI, 662
for STEMI complications, 667
vasopressin
for asystole, 60*f*
deficiency of, 883*t*
intraarterial, for gastrointestinal bleeding, 178
for shock, 64, 64*t*
for ventricular fibrillation, 59*f*
vasopressin antagonists, for hyponatremia, 4
vasospasm, in subarachnoid hemorrhage, 92–93
vasospastic disorders, 697–698
VATS (thoracic surgery, video-assisted), 711, 737
vemurafenib, for melanoma, 307
venlafaxine, 1071
dosage and side effects of, 39*t*, 1072*t*
for menopausal symptoms, 922
for migraine prevention, 220*t*
for narcolepsy, 245
for pain, 39*t*
for polyneuropathy, 1045*t*
venous disease, 698–699
venous insufficiency, chronic, 699
venous thromboembolism, 730. *See also* deep-vein thrombosis; pulmonary embolism
ventilation, disorders of, 744–745
ventilation/perfusion lung scan, 731

ventilation/perfusion mismatch, 708
ventilator-associated pneumonia (VAP)
diagnosis of, 358, 726
etiology of, 358, 726
*P. aeruginosa*, 458–459
pathophysiology of, 76, 726, 728*t*
prevention of, 359*t*, 728*t*
risk factors for, 358
treatment of, 726–727, 727*t*
ventilatory support
in ALS, 988
in ARDS, 72, 72*f*
for asthma exacerbations, 715
complications of, 76
during COPD exacerbations, 722
for cor pulmonale, 693
for hemoptysis, 149
modes of, 74, 75*t*
patient care, 32–34, 76
in respiratory failure, 73–76, 75*t*
weaning from, 33–34
ventricular aneurysm
pseudoaneurysm, 667
in STEMI, 667
ventricular fibrillation (VF)
clinical and ECG features of, 682*t*
management of, 59*f*
in STEMI, 662–663
ventricular premature beats, 681*t*
ventricular septal defect (VSD), 616*t*, 628–629
ventricular septal rupture, 667
ventricular tachycardia (VT)
clinical and ECG features of, 681*t*
vs. supraventricular tachycardia, 685*f*
pulseless, 59*f*
in STEMI, 662
verapamil
for aortic dissection, 695
for arrhythmias, 684*t*
for atrial fibrillation, 686
for chronic stable angina, 674
for cluster headache prevention, 219
for hypertension, 651, 653*t*
for hypertrophic cardiomyopathy, 643
for mitral stenosis, 632
for supraventricular arrhythmias, 663
for tachyarrhythmias, 680–681*t*
for UA/NSTEMI, 670
for Wolff-Parkinson-White syndrome, 686
verruca plana, 256*f*
verruca vulgaris, 256*f*
verrucous carcinoma, 308
verruga peruana, 467*t*, 469
vertebral disk herniation
acute, 1005
cervical disk, 212, 214
lumbar disk, 209
vertebral fracture, 210
vertebral metastasis, 210
vertigo, 226
benign positional, 227
central, 227*t*, 228
pathologic, 227
peripheral, 227, 227*t*
physiologic, 227
provocative tests to reproduce, 226
psychogenic, 227
treatment of, 228*t*, 229
vesicle (skin lesion), 257*t*, 416
vestibular function tests, 227
vestibular neuritis, 227, 228*t*, 229
vestibular schwannomas, 227
VF. *See* ventricular fibrillation
*Vibrio cholerae* infections, 387, 389
*Vibrio parahaemolyticus* infections, 389
vidarabine, for HSV infections, 521*t*
videonystagmography, 226
vilazodone, 1073*t*
vildagliptin, for diabetes mellitus, 908*t*
vinblastine
for bladder cancer, 334
for lung cancer, 313
Vincent's stomatitis, 475
vincristine
for ALL, 300
for Burkitt's lymphoma/leukemia, 301
for gastric carcinoma, 324
for idiopathic thrombocytopenic purpura, 280
for lymphoma, 299
for multiple myeloma, 302
vindesine, for lung cancer, 313
vinorelbine
for breast cancer, 321
for lung cancer, 313
VIPoma, 332*t*, 333
viral gastroenteritis, 389–390
viral hemorrhagic fever (VHF) syndrome, 551
viral infections
animal-borne, 546–548
arthropod- and rodent-borne, 548–552

viral infections (*Cont.*):
chronic meningitis in, 1037*t*
in HSCT patients, 367–368
lymphadenopathy and, 190*t*
respiratory. *See* respiratory tract infections
viridans streptococci, 439
virilization, 920
visceral abscess, 385
visceral larva migrans, 600
visceral leishmaniasis (kala-azar), 593–594
visceral pain, 36, 36*t*
visceral spasm, 155*t*
vismodegib, for basal cell carcinoma, 307
visual acuity, 229
visual field mapping, 229, 230*f*
visual loss
acute, approach to, 229
transient or sudden, 230–231
vitamin A deficiency, 45*t*
vitamin A supplementation
for head and neck cancer prevention, 1101
for measles, 539
vitamin $B_{12}$ deficiency
anemia in, 269
in dementia, 971
leukopenia in, 276
in myelopathy, 1006
in polyneuropathy, 1044
in tapeworm infection, 610
treatment of, 273
vitamin C deficiency, 45*t*
vitamin C supplementation, for nephrolithiasis, 782*t*
vitamin D deficiency, 45*t*, 928, 935, 1105
vitamin D supplementation
for hypocalcemia, 929
in multiple sclerosis, 1018
for osteomalacia, 935
for osteoporosis, 934
for primary biliary cirrhosis, 829
for primary sclerosing cholangitis, 803
for psoriasis, 259
vitamin E deficiency, 45*t*, 983
vitamin E supplementation, for menopausal symptoms, 922
vitamin K deficiency
pathophysiology of, 279
treatment of, 45*t*, 281
vitamin K supplementation
for vitamin K deficiency, 281
for warfarin reversal, 282
vitamins. *See also specific vitamins*
for alcohol withdrawal, 1083
for alcoholic liver disease, 828
for ataxia, 984
vitiligo, 256*f*
vitreous detachment, 231
vitreous hemorrhage, 231
voglibose, for diabetes mellitus, 908*t*
Vogt-Koyanagi-Harada syndrome, 1038*t*
volume regulation, 1*t*
volume status, assessment of, 3*f*
vomiting. *See* nausea and vomiting
von Hippel-Lindau disease, 335
von Willebrand disease, 279, 281
voriconazole, 569
for aspergillosis, 574*t*
for candidiasis, 571
for fusariosis, 582
for scedosporiosis, 582
for sepsis/septic shock, 68*t*
vortioxetine, 1073*t*
VRE (vancomycin-resistant enterococci), 440
VSD (ventricular septal defect), 616*t*, 628–629
VT. *See* ventricular tachycardia
VZV infections. *See* varicella-zoster virus infections

**W**
Waldenström's macroglobulinemia, 768*t*
warfarin
for antiphospholipid antibody syndrome, 850
for atrial fibrillation, 686
for mitral stenosis, 632
for pulmonary hypertension, 702
for STEMI, 662
for venous thromboembolism, 733
warts
cutaneous, 262
genital, 413–414
wasp sting, 124–125
water requirements, 41
watery diarrhea, 386*t*
weakness, 131, 233–235
approach to, 233, 235*f*
causes of, 233*t*
diagnostic evaluation of, 1055*f*, 1056*f*
site of responsible lesion, 233, 233*t*

weaning, from mechanical ventilation, 33–34
Wegener's granulomatosis (granulomatosis with polyangiitis), 768*t*, 851, 1039*t*
weight, ideal, 42*t*
weight loss, 135–137
  clinical manifestations of, 135–137
  drug-induced, 136*t*
  etiology of, 135, 136*t*
  for hypertension, 651
  laboratory testing in, 137*t*
  in malnutrition, 41
  for metabolic syndrome, 658
  for obesity, 902–903
  for sleep apnea, 746
  treatment for, 137
Weil's syndrome, 498
Wenckebach AV block, 677, 679*f*
Wernicke-Korsakoff's syndrome, 1083
Wernicke's aphasia, 239*t*, 240–241
Wernicke's encephalopathy, 1082–1083
West Nile virus (WNV) encephalitis, 550, 1027, 1029
WFNS (World Federation of Neurosurgical Societies) Scale, for subarachnoid hemorrhage, 92*t*
wheal, 257*t*
whiplash injury, 212
Whipple's disease, 481–482, 867, 1034*t*
Whipple's triad, 107, 108*f*, 332
whitlow, herpetic, 518, 522*t*
WHO classification
  of AML, 284*t*
  of lymphoid malignancy, 294
whole blood transfusion, 46
whooping cough. *See* pertussis
widow spider bite, 123–124
Wilson's disease, 945–946
winking owl sign, 110
Winterbottom's sign, 596
Winter's formula, 15
withdrawal of care, 35
withdrawal syndrome, 1074
WNV (West Nile virus) encephalitis, 550, 1027, 1029
*Wolbachia*, 604
Wolff-Parkinson-White (WPW) syndrome, 621*t*, 679, 686
women's health, 1104–1106
  Alzheimer's disease, 1104
  autoimmune disease, 1105
  coronary heart disease, 1104–1105
  diabetes mellitus, 1105
  HIV infections, 1105
  hypertension, 1105
  nicotine addiction, 1106
  obesity, 1105
  osteoporosis, 1105
  pharmacology, 1105–1106
  psychiatric disease, 1106
  sleep disorders, 1106
  substance abuse, 1106
  violence, 1106
Wood's light examination, 258
World Federation of Neurosurgical Societies (WFNS) Scale, for subarachnoid hemorrhage, 92*t*
wound infections
  botulism, 472
  clostridial, 473
  surgical-site, 358, 359*t*
wrist, muscles and innervation of, 949*t*
*Wuchereria bancrofti* infections. *See* filariasis

**X**

xanthelasma, 256*f*, 936
xanthoma, 936, 940
XDR (extensively drug-resistant) tuberculosis, 482
xerostomia, 849
D-xylose absorption test, 170

**Y**

yaws, 497
yellow fever, 552
yellow jacket sting, 124–125
*Yersinia pestis*, 465–466
yersiniosis, 396

**Z**

zafirlukast, for urticaria/angioedema, 837
zaleplon, for insomnia, 242
zanamivir, for influenza, 532, 532*t*
zidovudine (AZT, azidothymidine)
  for adult T cell leukemia/lymphoma, 301
  for HIV infection, 560*t*
Zieve's syndrome, 826
zinc deficiency, 45*t*

zinc supplementation
for hepatic encephalopathy, 833
for Wilson's disease, 946
ziprasidone
dosage and side effects of, 1077*t*
for schizophrenia, 1067
zoledronate
for hypercalcemia, 112, 351, 927*t*
for osteoporosis, 934
Zollinger-Ellison syndrome
clinical manifestations of, 332, 332*t*, 789
diagnosis of, 789
differential diagnosis of, 789, 789*t*
treatment of, 789–790
zolmitriptan, for migraine, 217*t*, 219*t*
zolpidem, for insomnia, 242
zonisamide, for seizures, 966*t*, 967*t*
zoster ophthalmicus, 523

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**TABLE 206-1 CLINICAL MANIFESTATIONS OF ADVERSE REACTIONS TO DRUGS**

**I. MULTISYSTEM MANIFESTATIONS**

**Anaphylaxis**
- Cephalosporins
- Dextran
- Insulin
- Iodinated drugs or contrast media
- Lidocaine
- Penicillins
- Procaine

**Angioedema**
- ACE inhibitors

**Drug-induced lupus erythematosus**
- Cephalosporins
- Hydralazine
- Iodides
- Isoniazid
- Methyldopa
- Phenytoin
- Procainamide
- Quinidine
- Sulfonamides
- Thiouracil

**Fever**
- Aminosalicylic acid
- Amphotericin B
- Antihistamines
- Penicillins

**Hyperpyrexia**
- Antipsychotics

**Serum sickness**
- Aspirin
- Penicillins
- Propylthiouracil
- Sulfonamides

**II. ENDOCRINE MANIFESTATIONS**

**Addisonian-like syndrome**
- Busulfan
- Ketoconazole

**Galactorrhea (may also cause amenorrhea)**
- Methyldopa
- Phenothiazines
- Tricyclic antidepressants

**Gynecomastia**
- Calcium channel antagonists
- Digitalis
- Estrogens
- Griseofulvin
- Isoniazid
- Methyldopa
- Phenytoin
- Spironolactone
- Testosterone

**Sexual dysfunction**
- Beta blockers
- Clonidine
- Diuretics
- Guanethidine
- Lithium
- Major tranquilizers
- Methyldopa
- Oral contraceptives
- Sedatives

**Thyroid function tests, disorders of**
- Acetazolamide
- Amiodarone
- Chlorpropamide
- Clofibrate
- Colestipol and nicotinic acid
- Gold salts
- Iodides
- Lithium
- Oral contraceptives
- Phenothiazines
- Phenylbutazone
- Phenytoin
- Sulfonamides
- Tolbutamide

**III. METABOLIC MANIFESTATIONS**

**Hyperbilirubinemia**
- Rifampin

**Hypercalcemia**
- Antacids with absorbable alkali
- Thiazides
- Vitamin D

**Hyperglycemia**
- Chlorthalidone
- Diazoxide
- Encainide
- Ethacrynic acid
- Furosemide

(*Continued*)

**TABLE 206-1 CLINICAL MANIFESTATIONS OF ADVERSE REACTIONS TO DRUGS (*CONTINUED*)**

- Glucocorticoids
- Growth hormone
- Oral contraceptives
- Thiazides

**Hypoglycemia**

- Insulin
- Oral hypoglycemics
- Quinine

**Hyperkalemia**

- ACE inhibitors
- Amiloride
- Cytotoxics
- Digitalis overdose
- Heparin
- Lithium
- Potassium preparations including salt substitute
- Potassium salts of drugs
- Spironolactone
- Succinylcholine
- Triamterene

**Hypokalemia**

- Alkali-induced alkalosis
- Amphotericin B
- Diuretics
- Gentamicin
- Insulin
- Laxative abuse
- Mineralocorticoids, some glucocorticoids
- Osmotic diuretics
- Sympathomimetics
- Tetracycline
- Theophylline
- Vitamin B12

**Hyperuricemia**

- Aspirin
- Cytotoxics
- Ethacrynic acid
- Furosemide
- Hyperalimentation
- Thiazides

**Hyponatremia**

**1. Dilutional**

- Carbamazepine
- Chlorpropamide
- Cyclophosphamide
- Diuretics
- Vincristine

**2. Salt wasting**

- Diuretics
- Enemas
- Mannitol

**Metabolic acidosis**

- Acetazolamide
- Paraldehyde
- Salicylates
- Spironolactone

**IV. DERMATOLOGIC MANIFESTATIONS**

**Acne**

- Anabolic and androgenic steroids
- Bromides
- Glucocorticoids
- Iodides
- Isoniazid
- Oral contraceptives

**Alopecia**

- Cytotoxics
- Ethionamide
- Heparin
- Oral contraceptives (withdrawal)

**Eczema**

- Captopril
- Cream and lotion perservatives
- Lanolin
- Topical antihistamines
- Topical antimicrobials
- Topical local anesthetics

**Erythema multiforme or Steven Johnson syndrome**

- Barbiturates
- Chlorpropamide
- Codeine
- Penicillins
- Phenylbutazone
- Phenytoin
- Salicylates
- Sulfonamides
- Sulfones

(*Continued*)

**TABLE 206-1 CLINICAL MANIFESTATIONS OF ADVERSE REACTIONS TO DRUGS (*CONTINUED*)**

Tetracyclines
Thiazides

**Erythema nodosum**
Oral contraceptives
Penicillins
Sulfonamides

**Exfoliative dermatitis**
Barbiturates
Gold salts
Penicillins
Phenylbutazone
Phenytoin
Quinidine
Sulfonamides

**Fixed drug eruptions**
Barbiturates
Captopril
Phenylbutazone
Quinine
Salicylates
Sulfonamides

**Hyperpigmentation**
Bleomycin
Busulfan
Chloroquine and other antimalarials
Corticotropin
Cyclophosphamide
Gold salts
Hypervitaminosis A
Oral contraceptives
Phenothiazines

**Lichenoid eruptions**
Aminosalicylic acid
Antimalarials
Chlorpropamide
Gold salts
Methyldopa
Phenothiazines

**Photodermatitis**
Captopril
Chlordiazepoxide
Furosemide
Griseofulvin
Nalidixic acid
Oral contraceptives
Phenothiazines
Sulfonamides
Sulfonylureas
Tetracyclines, particularly demeclocycline
Thiazides

**Purpura (see also thrombocytopenia)**
Allopurinol
Ampicillin
Aspirin
Glucocorticoids

**Rashes (nonspecific)**
Allopurinol
Ampicillin
Barbiturates
Indapamide
Methyldopa
Phenytoin

**Skin necrosis**
Warfarin

**Toxic epidermal necrolysis (bullous)**
Allopurinol
Barbiturates
Bromides
Iodides
Nalidixic acid
Penicillins
Phenylbutazone
Phenytoin
Sulfonamides

**Urticaria**
Aspirin
Barbiturates
Captopril
Enalapril
Penicillins
Sulfonamides

**V. HEMATOLOGIC MANIFESTATIONS**

**Agranulocytosis (see also Pancytopenia)**
Captopril
Carbimazole
Chloramphenicol
Cytotoxics
Gold salts
Indomethacin
Methimazole
Oxyphenbutazone

(*Continued*)

**TABLE 206-1 CLINICAL MANIFESTATIONS OF ADVERSE REACTIONS TO DRUGS (*CONTINUED*)**

Phenothiazines
Phenylbutazone
Propylthiouracil
Sulfonamides
Tolbutamide
Tricyclic antidepressants

**Clotting abnormalities/ hypothrombinemia**
Cefamandole
Cefoperazone
Moxalactam

**Eosinophilia**
Aminosalicylic acid
Chlorpropamide
Erythromycin estolate
Imipramine
L-Tryptophan
Methotrexate
Nitrofurantoin
Procarbazine
Sulfonamides

**Hemolytic anemia**
Aminosalicylic acid
Cephalosporins
Chlorpromazine
Dapsone
Insulin
Isoniazid
Levodopa
Mefenamic acid
Melphalan
Methyldopa
Penicillins
Phenacetin
Procainamide
Quinidine
Rifampin
Sulfonamides

**Hemolytic anemias in G6PD deficiency**
See Table 62-4

**Leukocytosis**
Glucocorticoids
Lithium

**Lymphadenopathy**
Phenytoin
Primidone

**Megaloblastic anemia**
Folate antagonists
Nitrous oxide
Oral contraceptives
Phenobarbital
Phenytoin
Primidone
Triamterene
Trimethroprim

**Pancytopenia (aplastic anemia)**
Carbamazepine
Chloramphenicol
Cytotoxics
Gold salts
Mephenytoin
Phenylbutazone
Phenytoin
Quinacrine
Sulfonamides
Trimethadione
Zidovudine (AZT)

**Pure red cell aplasia**
Azathioprine
Chlorpropamide
Isoniazid
Phenytoin

**Thrombocytopenia (see also Pancytopenia)**
Acetazolamine
Aspirin
Carbamazepine
Carbenicillin
Chlorpropamide
Chlorthalidone
Furosemide
Gold salts
Heparin
Indomethacin
Isoniazid
Methyldopa
Moxalactam
Phenylbutazone
Phenytoin and other hydantoins
Quinidine
Quinine
Thiazides
Ticarcillin

(*Continued*)

**TABLE 206-1 CLINICAL MANIFESTATIONS OF ADVERSE REACTIONS TO DRUGS (*CONTINUED*)**

## VI. CARDIOVASCULAR MANIFESTATIONS

**Angina exacerbation**
- Alpha blockers
- Beta blocker withdrawal
- Ergotamine
- Excessive thyroxine
- Hydralazine
- Methysergide
- Minoxidil
- Nifedipine
- Oxytocin
- Vasopressin

**Arrhythmias**
- Adriamycin
- Antiarrhythmic drugs
- Atropine
- Anticholinesterases
- Beta blockers
- Digitalis
- Emetine
- Lithium
- Phenothiazines
- Sympathomimetics
- Thyroid hormone
- Tricyclic antidepressants
- Verapamil

**AV block**
- Clonidine
- Methyldopa
- Verapamil

**Cardiomyopathy**
- Adriamycin
- Daunorubicin
- Emetine
- Lithium
- Phenothiazines
- Sulfonamides
- Sympathomimetics

**Fluid retention or congestive heart failure**
- Beta blockers
- Calcium antagonists
- Estrogens
- Indomethacin
- Mannitol
- Minoxidil
- Phenylbutazone
- Steroids

**Hypertension**
- Clonidine withdrawal
- Corticotropin
- Cyclosporine
- Glucocorticoids
- Monoamine oxidase inhibitors with sympathomimetics
- NSAIDs
- Oral contraceptives
- Sympathomimetics
- Tricyclic antidepressants with sympathomimetics

**Hypotension**
- Calcium antagonists
- Citrated blood
- Diuretics
- Levodopa
- Morphine
- Nitroglycerin
- Phenothiazines
- Protamine
- Quinidine

**Pericarditis**
- Emetine
- Hydralazine
- Methysergide
- Procainamide

**Thromboembolism**
- Oral contraceptives

## VII. RESPIRATORY MANIFESTATIONS

**Airway obstruction**
- Beta blockers
- Cephalosporins
- Cholinergic drugs
- NSAIDs
- Penicillins
- Pentazocine
- Streptomycin
- Tartrazine (drugs with yellow dye)

**Cough**
- ACE inhibitors

**Pulmonary edema**
- Contrast media
- Heroin

(*Continued*)

**TABLE 206-1 CLINICAL MANIFESTATIONS OF ADVERSE REACTIONS TO DRUGS (*CONTINUED*)**

- Methadone
- Propoxyphene

**Pulmonary infiltrates**

- Acyclovir
- Amiodarone
- Azathioprine
- Bleomycin
- Busulfan
- Carmustine (BCNU)
- Chlorambucil
- Cyclophosphamide
- Melphalan
- Methotrexate
- Methysergide
- Mitomycin C
- Nitrofurantoin
- Procarbazine
- Sulfonamides

**VIII. GASTROINTESTINAL MANIFESTATIONS**

**Cholestatic jaundice**

- Anabolic steroids
- Androgens
- Chlorpropamide
- Erythromycin estolate
- Gold salts
- Methimazole
- Nitrofurantoin
- Oral contraceptives
- Phenothiazines

**Constipation or ileus**

- Aluminum hydroxide
- Barium sulfate
- Calcium carbonate
- Ferrous sulfate
- Ion exchange resins
- Opiates
- Phenothiazines
- Tricyclic antidepressants
- Verapamil

**Diarrhea or colitis**

- Antibiotics (broad-spectrum)
- Colchicine
- Digitalis
- Magnesium in antacids
- Methyldopa

**Diffuse hepatocellular damage**

- Acetaminophen (paracetamol)
- Allopurinol
- Aminosalicylic acid
- Dapsone
- Erythromycin estolate
- Ethionamide
- Glyburide
- Halothane
- Isoniazid
- Ketoconazole
- Methimazole
- Methotrexate
- Methoxyflurane
- Methyldopa
- Monoamine oxidase inhibitors
- Niacin
- Nifedipine
- Nitrofurantoin
- Phenytoin
- Propoxyphene
- Propylthiouracil
- Pyridium
- Rifampin
- Salicylates
- Sodium valproate
- Sulfonamides
- Tetracyclines
- Verapamil
- Zidovudine (AZT)

**Intestinal ulceration**

- Solid KCl preparations

**Malabsorption**

- Aminosalicylic acid
- Antibiotics (broad-spectrum)
- Cholestyramine
- Colchicine
- Colestipol
- Cytotoxics
- Neomycin
- Phenobarbital
- Phenytoin

**Nausea or vomiting**

- Digitalis
- Estrogens
- Ferrous sulfate
- Levodopa
- Opiates

(*Continued*)

**TABLE 206-1 CLINICAL MANIFESTATIONS OF ADVERSE REACTIONS TO DRUGS (*CONTINUED*)**

Potassium chloride
Tetracyclines
Theophylline

**Oral conditions**

**1. Gingival hyperplasia**
Calcium antagonists
Cyclosporine
Phenytoin

**2. Salivary gland swelling**
Bretylium
Clonidine
Guanethidine
Iodides
Phenylbutazone

**3. Taste Disturbances**
Biguanides
Captopril
Griseofulvin
Lithium
Metronidazole
Penicillamine
Rifampin

**4. Ulceration**
Aspirin
Cytotoxics
Gentian violet
Isoproterenol (sublingual)
Pancreatin

**Pancreatitis**
Azathioprine
Ethacrynic acid
Furosemide
Glucocorticoids
Opiates
Oral contraceptives
Sulfonamides
Thiazides

**Peptic ulceration or hemorrhage**
Aspirin
Ethacrynic acid
Glucocorticoids
NSAIDs

**IX. RENAL/URINARY MANIFESTATIONS**

**Bladder dysfunction**
Anticholinergics
Disopyramide
Monoamine oxidase inhibitors
Tricyclic antidepressants

**Calculi**
Acetazolamide
Vitamin D

**Concentrating defect with polyuria (or nephrogenic diabetes insipidus)**
Demeclocycline
Lithium
Methoxyflurane
Vitamin D

**Hemorrhagic cystitis**
Cyclophosphamide

**Interstitial nephritis**
Allopurinol
Furosemide
Penicillins, esp. methicillin
Phenindione
Sulfonamides
Thiazides

**Nephropathies**
Due to analgesics (e.g., phenacetin)

**Nephrotic syndrome**
Captopril
Gold salts
Penicillamine
Phenindione
Probenecid

**Obstructive uropathy**
Extrarenal: methysergide
Intrarenal: cytotoxics

**Renal dysfunction**
Cyclosporine
NSAIDS
Triamterene

**Renal tubular acidosis**
Acetazolamide
Amphotericin B
Degraded tetracycline

**Tubular necrosis**
Aminoglycosides
Amphotericin B
Colistin

(*Continued*)

**TABLE 206-1 CLINICAL MANIFESTATIONS OF ADVERSE REACTIONS TO DRUGS (*CONTINUED*)**

Cyclosporine
Methoxyflurane
Polymyxins
Radioiodinated contrast medium
Sulfonamides
Tetracyclines

**X. NEUROLOGIC MANIFESTATIONS**

**Exacerbation of myasthenia**
Aminoglycosides
Polymyxins

**Extrapyramidal effects**
Butyrophenones, e.g., haloperidol
Levodopa
Methyldopa
Metoclopramide
Oral contraceptives
Phenothiazines
Tricyclic antidepressants

**Headache**
Ergotamine (withdrawal)
Glyceryl trinitrate
Hydralazine
Indomethacin

**Peripheral neuropathy**
Amiodarone
Chloramphenicol
Chloroquine
Chlorpropamide
Clofibrate
Demeclocycline
Disopyramide
Ethambutol
Ethionamide
Glutethimide
Hydralazine
Isoniazid
Methysergide
Metronidazole
Nalidixic acid
Nitrofurantoin
Phenytoin
Polymyxin, colistin
Procarbazine
Streptomycin
Tolbutamide
Tricyclic antidepressants
Vincristine

**Pseudotumor cerebri (or intracranial hypertension)**
Amiodarone
Glucocorticoids, mineralocorticoids
Hypervitaminosis A
Oral contraceptives
Tetracyclines

**Seizures**
Amphetamines
Analeptics
Isoniazid
Lidocaine
Lithium
Nalidixic acid
Penicillins
Phenothiazines
Physostigmine
Theophylline
Tricyclic antidepressants
Vincristine

**Stroke**
Oral contraceptives

**XI. OCULAR MANIFESTATIONS**

**Cataracts**
Busulfan
Chlorambucil
Glucocorticoids
Phenothiazines

**Color vision alteration**
Barbiturates
Digitalis
Methaqualone
Streptomycin
Thiazides

**Corneal edema**
Oral contraceptives

**Corneal opacities**
Chloroquine
Indomethacin
Vitamin D

**Glaucoma**
Mydriatics
Sympathomimetics

**Optic neuritis**
Aminosalicylic acid

(*Continued*)

**TABLE 206-1 CLINICAL MANIFESTATIONS OF ADVERSE REACTIONS TO DRUGS (*CONTINUED*)**

| | |
|---|---|
| Chloramphenicol | Quinine |
| Ethambutol | Streptomycin |
| Isoniazid | **Retinopathy** |
| Penicillamine | Chloroquine |
| Phenothiazines | Phenothiazines |
| Phenylbutazone | |
| **XII. EAR MANIFESTATIONS** | |
| **Deafness** | Furosemide |
| Aminoglycosides | Nortriptyline |
| Aspirin | Quinine |
| Bleomycin | **Vestibular disorders** |
| Chloroquine | Aminoglycosides |
| Erythromycin | Quinine |
| Ethacrynic acid | |
| **XIII. Musculoskeletal manifestations** | |
| **Bone disorders** | **Myopathy or myalgia** |
| **1. Osteoporosis** | Amphotericin B |
| Glucocorticoids | Chloroquine |
| Heparin | Clofibrate |
| **2. Osteomalacia** | Glucocorticoids |
| Aluminum hydroxide | Oral contraceptives |
| Anticonvulsants | **Myositis** |
| Glutethimide | Gemfibrozil |
| | Lovastatin |
| **XIV. PSYCHIATRIC MANIFESTATIONS** | |
| **Delirious or confusional states** | **Drowsiness** |
| Amantadine | Antihistamines |
| Aminophylline | Anxiolytic drugs |
| Anticholinergics | Clonidine |
| Antidepressants | Major tranquilizers |
| Cimetidine | Methyldopa |
| Digitalis | Tricyclic antidepressants |
| Glucocorticoids | **Hallucinatory states** |
| Isoniazid | Amantadine |
| Levodopa | Beta blockers |
| Methyldopa | Levodopa |
| Penicillins | Meperidine |
| Phenothiazines | Narcotics |
| Sedatives and hypnotics | Pentazocine |
| **Depression** | Tricyclic antidepressants |
| Amphetamine withdrawal | **Hypomania, mania, or excited reactions** |
| Beta blockers | Glucocorticoids |
| Centrally acting antihypertensives (reserpine, methyldopa, clonidine) | Levodopa |
| Glucocorticoids | Monoamine oxidase inhibitors |
| Levodopa | Sympathomimetics |
| | Tricyclic antidepressants |

(*Continued*)

**TABLE 206-1 CLINICAL MANIFESTATIONS OF ADVERSE REACTIONS TO DRUGS (*CONTINUED*)**

| | |
|---|---|
| **Schizophrenic-like or paranoid reactions** | Monoamine oxidase inhibitors |
| Amphetamines | Tricyclic antidepressants |
| Bromides | **Sleep disturbances** |
| Glucocorticoids | Anorexiants |
| Levodopa | Levodopa |
| Lysergic acid | Monoamine oxidase inhibitors |
| | Sympathomimetics |

***Source:*** Adapted from AJJ Wood: *HPIM-15*, pp. 432-436. For a more detailed discussion, see Roden DM: *Principles of Clinical Pharmacology,* Chap 5, p. 33, *HPIM-18*; Wood AJJ: Adverse Reactions to Drugs, Chap 71, p. 430, in *HPIM-15*.

| | |
|---|---|
| **JVP** | jugular venous pressure |
| **LA** | left atrium |
| **LAD** | left axis deviation |
| **LBBB** | left bundle branch block |
| **LDH** | lactate dehydrogenase |
| **LDL** | low-density lipoprotein |
| **LFT** | liver function test |
| **LLQ** | left lower quadrant |
| **LP** | lumbar puncture |
| **LUQ** | left upper quadrant |
| **LV** | left ventricle |
| **MI** | myocardial infarction |
| **MRI** | magnetic resonance imaging |
| **NPO** | nothing by mouth |
| **NSAIDs** | nonsteroidal anti-inflammatory drugs |
| **$P_2$** | pulmonic second sound |
| **$Pa_{O_2}$** | partial pressure of $O_2$ in arterial blood |
| **$PA_{O_2}$** | partial pressure of $O_2$ in alveolar blood |
| **PCR** | polymerase chain reaction |
| **PFTs** | pulmonary function tests |
| **PMNs** | polymorphonuclear cells or leukocytes |
| **PO** | by mouth |
| **PPD** | purified protein derivative, skin test for tuberculosis |
| **prn** | as needed |
| **pt/pts** | patient/patients |
| **PT** | prothrombin time |
| **PTT** | partial thromboplastin time |
| **qAM** | every morning |
| **qd** | every day |
| **qh** | every hour |
| **qhs** | every bedtime |
| **qid** | four times daily |
| **qod** | every other day |
| **R** | respiratory rate |
| **RA** | rheumatoid arthritis |
| **RBBB** | right bundle branch block |
| **RBC** | red blood (cell) count |
| **RLQ** | right lower quadrant |
| **RUQ** | right upper quadrant |
| **RV** | right ventricle |
| **S1 . . . S4** | heart sounds, 1st to 4th |
| **SARS** | severe acute respiratory syndrome |
| **SC** | subcutaneous |
| **SL** | sublingual |
| **SLE** | systemic lupus erythematosus |
| **SVC** | superior vena cava |
| **TIA** | transient ischemic attack |
| **tid** | three times daily |
| **tiw** | thrice a week |
| **TLC** | total lung capacity |
| **TNF** | tumor necrosis factor |
| **UA** | urinalysis |
| **URI** | upper respiratory infection |
| **UTI** | urinary tract infection |
| **UV** | ultraviolet |
| **VDRL** | test for syphilis |
| **VPC** | ventricular premature contractions |
| **VZV** | varicella-zoster virus |
| **WBC** | white blood (cell) count |