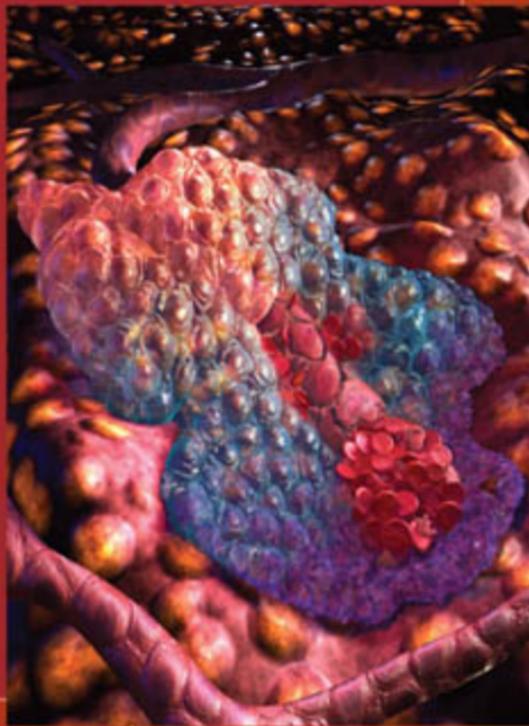


BARBARA G. WELLS  
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# Pharmacotherapy Handbook



seventh edition

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Seventh Edition

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# Pharmacotherapy Handbook

Seventh Edition

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# Preface

This seventh edition of the pocket companion to *Pharmacotherapy: A Pathophysiologic Approach*, seventh edition, is designed to provide practitioners and students with critical information that can be easily used to guide drug therapy decision making in the clinical setting. To ensure brevity and portability, the bulleted format provides the user with essential textual information, key tables and figures, and treatment algorithms.

Corresponding to the major sections in the main text, disorders are alphabetized within the following sections: Bone and Joint Disorders, Cardiovascular Disorders, Dermatologic Disorders, Endocrinologic Disorders, Gastrointestinal Disorders, Gynecologic and Obstetric Disorders, Hematologic Disorders, Infectious Diseases, Neurologic Disorders, Nutritional Disorders, Oncologic Disorders, Ophthalmic Disorders, Psychiatric Disorders, Renal Disorders, Respiratory Disorders, and Urologic Disorders. Drug-induced conditions associated with allergic and pseudoallergic reactions, hematologic disorders, liver disease, pulmonary disorders, and kidney disease appear in five tabular appendices. In the seventh edition, information on the management of pharmacotherapy in the elderly has been added as an appendix. Also in the seventh edition, chapters have been added on adrenal gland disorders and influenza.

Carrying over a popular feature from *Pharmacotherapy*, each chapter is organized in a consistent format:

- Disease state definition
- Concise review of relevant pathophysiology
- Clinical presentation
- Diagnosis
- Desired outcome
- Treatment
- Monitoring

The treatment section may include nonpharmacologic therapy, drug selection guidelines, dosing recommendations, adverse effects, pharmacokinetic considerations, and important drug–drug interactions. When more in-depth information is required, the reader is encouraged to refer to the primary text, *Pharmacotherapy: A Pathophysiologic Approach*, seventh edition.

It is our sincere hope that students and practitioners find this book helpful as they continuously strive to deliver highest quality patient-centered care. We invite your comments on how we may improve subsequent editions of this work.

Barbara G. Wells  
Joseph T. DiPiro  
Terry L. Schwinghammer  
Cecily V. DiPiro

Please provide your comments about this book, Wells et al., *Pharmacotherapy Handbook*, seventh edition, to its Authors and Publisher by writing to [pharmacotherapy@mcgraw-hill.com](mailto:pharmacotherapy@mcgraw-hill.com). Please indicate the author and title of this handbook in the subject line of your e-mail.

# Acknowledgments

The editors wish to express their sincere appreciation to the authors whose chapters in the seventh edition of *Pharmacotherapy: A Pathophysiologic Approach* served as the basis for this book. The dedication and professionalism of these outstanding practitioners, teachers, and clinical scientists are evident on every page of this work. The authors of the chapters from the seventh edition are acknowledged at the end of each respective *Handbook* chapter.

## To the Reader

Basic and clinical research provides a continuous flow of biomedical information that enables practitioners to use medications more effectively and safely. The editors, authors, and publisher of this book have made every effort to ensure accuracy of information provided. However, it is the responsibility of all practitioners to assess the appropriateness of published drug therapy information, especially in light of the specific clinical situation and new developments in the field. The editors and authors have taken care to recommend dosages that are consistent with current published guidelines and other responsible literature. However, when dealing with new and unfamiliar drug therapies, students and practitioners should consult several appropriate information sources.

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# SECTION 1 BONE AND JOINT DISORDERS

*Edited by Terry L. Schwinghammer*

## CHAPTER

# 1

## Gout and Hyperuricemia

### DEFINITIONS

- The term *gout* describes a disease spectrum including hyperuricemia, recurrent attacks of acute arthritis associated with monosodium urate crystals in leukocytes found in synovial fluid, deposits of monosodium urate crystals in tissues (tophi), interstitial renal disease, and uric acid nephrolithiasis.
- Hyperuricemia may be an asymptomatic condition, with an increased serum uric acid concentration as the only apparent abnormality. A urate concentration greater than 7.0 mg/dL is abnormal and associated with an increased risk for gout.

### PATHOPHYSIOLOGY

- In humans, uric acid is the end product of the degradation of purines. It serves no known physiologic purpose and is regarded as a waste product. The size of the urate pool is increased severalfold in individuals with gout. This excess accumulation may result from either overproduction or underexcretion.
- The purines from which uric acid is produced originate from three sources: dietary purine, conversion of tissue nucleic acid to purine nucleotides, and de novo synthesis of purine bases.
- Abnormalities in the enzyme systems that regulate purine metabolism may result in overproduction of uric acid. An increase in the activity of phosphoribosyl pyrophosphate (PRPP) synthetase leads to an increased concentration of PRPP, a key determinant of purine synthesis and thus uric acid production. A deficiency of hypoxanthine–guanine phosphoribosyl transferase (HGPRT) may also result in overproduction of uric acid. HGPRT is responsible for the conversion of guanine to guanylic acid and hypoxanthine to inosinic acid. These two conversions require PRPP as the cosubstrate and are important reutilization reactions involved in nucleic acid synthesis. A deficiency in the HGPRT enzyme leads to increased metabolism of guanine and hypoxanthine to uric acid and more PRPP to interact with glutamine in the first step of the purine pathway. Complete absence of HGPRT results in the childhood Lesch-Nyhan syndrome, characterized by choreoathetosis, spasticity, mental retardation, and markedly excessive production of uric acid.
- Uric acid may also be overproduced as a consequence of increased breakdown of tissue nucleic acids, as with myeloproliferative and lymphoproliferative disorders. Cytotoxic drugs used to treat these disorders can

also result in overproduction of uric acid due to lysis and breakdown of cellular matter.

- Dietary purines play an unimportant role in the generation of hyperuricemia in the absence of some derangement in purine metabolism or elimination.
- About two-thirds of the uric acid produced each day is excreted in the urine. The remainder is eliminated through the GI tract after enzymatic degradation by colonic bacteria. A decline in the urinary excretion of uric acid to a level below the rate of production leads to hyperuricemia and an increased miscible pool of sodium urate.
- Drugs that decrease renal clearance of uric acid through modification of filtered load or one of the tubular transport processes include diuretics, nicotinic acid, salicylates (less than 2 g/day), ethanol, pyrazinamide, levodopa, ethambutol, cyclosporine, and cytotoxic drugs.
- The average human produces 600 to 800 mg of uric acid daily and excretes less than 600 mg in urine. Individuals who excrete more than 600 mg after being on a purine-free diet for 3 to 5 days are considered overproducers. Hyperuricemic individuals who excrete less than 600 mg of uric acid per 24 hours on a purine-free diet are defined as underexcretors of uric acid. On a regular diet, excretion of more than 1,000 mg per 24 hours reflects overproduction; less than this is probably normal.
- Deposition of urate crystals in synovial fluid results in an inflammatory process involving chemical mediators that cause vasodilation, increased vascular permeability, complement activation, and chemotactic activity for polymorphonuclear leukocytes. Phagocytosis of urate crystals by leukocytes results in rapid lysis of cells and a discharge of proteolytic enzymes into the cytoplasm. The ensuing inflammatory reaction is associated with intense joint pain, erythema, warmth, and swelling.
- Uric acid nephrolithiasis occurs in 10% to 25% of patients with gout. Predisposing factors include excessive urinary excretion of uric acid, acidic urine, and highly concentrated urine.
- In acute uric acid nephropathy, acute renal failure occurs as a result of blockage of urine flow secondary to massive precipitation of uric acid crystals in the collecting ducts and ureters. This syndrome is a well-recognized complication in patients with myeloproliferative or lymphoproliferative disorders and results from massive malignant cell turnover, particularly after initiation of chemotherapy. Chronic urate nephropathy is caused by the long-term deposition of urate crystals in the renal parenchyma.
- Tophi (urate deposits) are uncommon in gouty subjects and are a late complication of hyperuricemia. The most common sites of tophaceous deposits in patients with recurrent acute gouty arthritis are the base of the great toe, helix of the ear, olecranon bursae, Achilles tendon, knees, wrists, and hands.

## CLINICAL PRESENTATION

- Acute attacks of gouty arthritis are characterized by rapid onset of excruciating pain, swelling, and inflammation. The attack is typically monoarticular

at first, most often affecting the first metatarsophalangeal joint (podagra), and then, in order of frequency, the insteps, ankles, heels, knees, wrists, fingers, and elbows. Attacks commonly begin at night, with the patient awakening from sleep with excruciating pain. The affected joints are erythematous, warm, and swollen. Fever and leukocytosis are common. Untreated attacks may last from 3 to 14 days before spontaneous recovery.

- Although acute attacks of gouty arthritis may occur without apparent provocation, attacks may be precipitated by stress, trauma, alcohol ingestion, infection, surgery, rapid lowering of serum uric acid by ingestion of uric acid–lowering agents, and ingestion of certain drugs known to elevate serum uric acid concentrations.

## DIAGNOSIS

- The definitive diagnosis is accomplished by aspiration of synovial fluid from the affected joint and identification of intracellular crystals of monosodium urate monohydrate in synovial fluid leukocytes.
- When joint aspiration is not a viable option, a presumptive diagnosis of acute gouty arthritis may be made on the basis of the presence of the characteristic signs and symptoms, as well as the response to treatment.

## DESIRED OUTCOME

- The goals in the treatment of gout are to terminate the acute attack, prevent recurrent attacks of gouty arthritis, and prevent complications associated with chronic deposition of urate crystals in tissues.

## TREATMENT

### ACUTE GOUTY ARTHRITIS

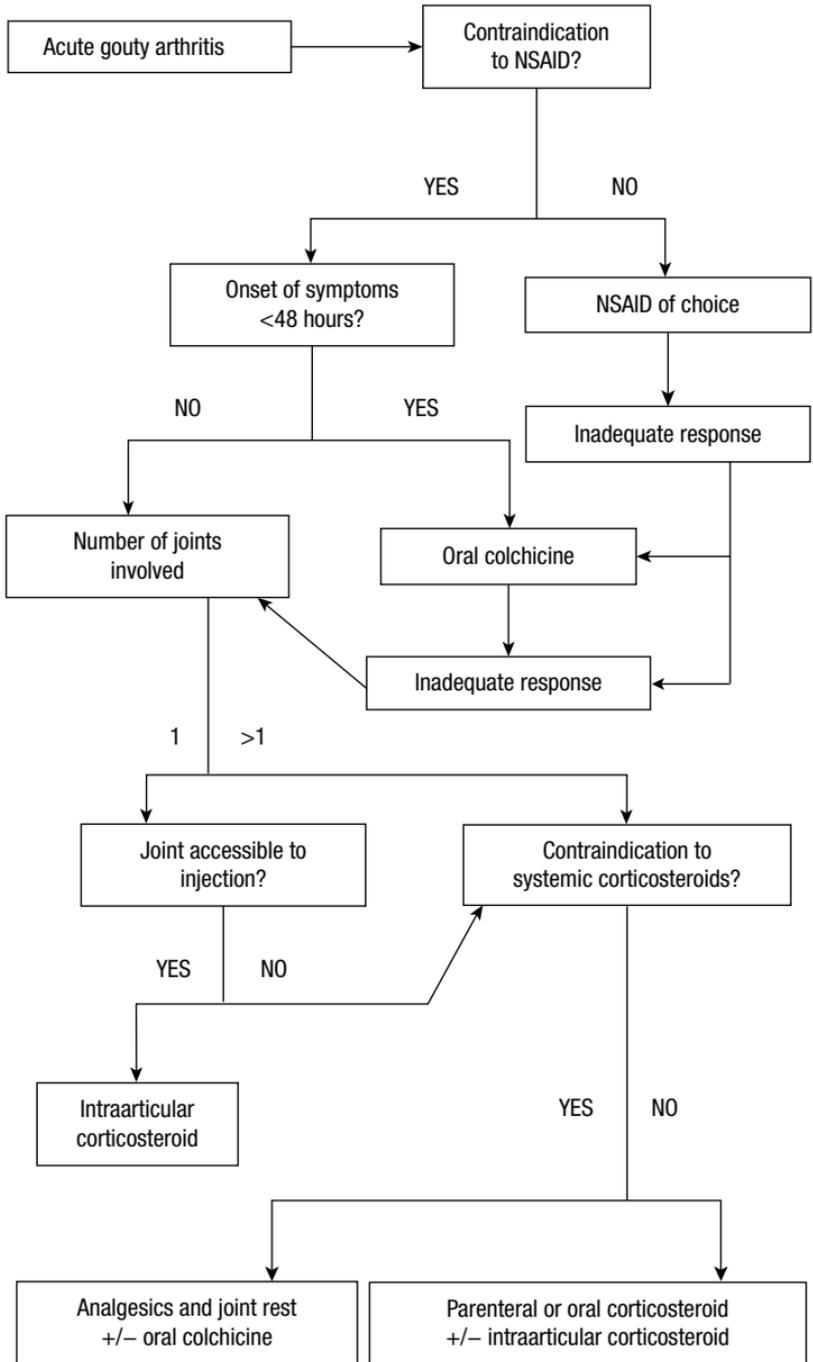
(Fig. 1-1)

#### Nonpharmacologic Therapy

- Patients may be advised to reduce their intake of foods high in purines (e.g., organ meats), avoid alcohol, increase fluid intake, and lose weight if obese.
- Joint rest for 1 to 2 days should be encouraged, and local application of ice may be beneficial.

#### Nonsteroidal Antiinflammatory Drugs

- Nonsteroidal antiinflammatory drugs (NSAIDs) are the mainstay of therapy because of their excellent efficacy and minimal toxicity with short-term use. There is little evidence to support one NSAID as more efficacious than another, and three drugs (indomethacin, naproxen, and sulindac) have FDA approval for this indication (Table 1-1).
- Therapy should be initiated with maximum recommended doses for gout at the onset of symptoms and continued for 24 hours after complete resolution of an acute attack, then tapered quickly over 2 to 3 days. Acute attacks generally resolve within 5 to 8 days after initiating therapy.



**FIGURE 1-1.** Treatment algorithm for acute gouty arthritis. (NSAID, nonsteroidal antiinflammatory drug.)

**TABLE 1-1** Dosage Regimens of Nonsteroidal Antiinflammatory Drugs for Treatment of Acute Gouty Arthritis

Generic Name	Dosage and Frequency
Etodolac	300 mg twice daily
Fenoprofen	300–600 mg three to four times daily
Ibuprofen	800 mg four times a day
Indomethacin	25–50 mg four times a day for 3 days, then taper to twice daily for 4–7 days
Ketoprofen	75 mg four times a day
Naproxen	500 mg twice daily for 3 days, then 250–500 mg daily for 4–7 days
Piroxicam	20 mg once daily or 10 mg twice daily
Sulindac	200 mg twice daily for 7–10 days

- The most common adverse effects involve the GI system (gastritis, bleeding, and perforation), kidneys (renal papillary necrosis, reduced creatinine clearance [ $CL_{CR}$ ]), cardiovascular system (sodium and fluid retention, increased blood pressure), and CNS (impaired cognitive function, headache, dizziness).
- Although the risk of GI complications is relatively small with short-term therapy, coadministration with a proton pump inhibitor should be considered in elderly patients and others at increased GI risk. NSAIDs should be used with caution in individuals with a history of peptic ulcer disease, heart failure, uncontrolled hypertension, renal insufficiency, coronary artery disease, or if they are receiving anticoagulants concurrently.
- The efficacy and safety of cyclooxygenase-2 (COX-2) selective inhibitors (e.g., celecoxib) have not been fully assessed in gouty arthritis, but they are more costly than conventional NSAIDs and are unlikely to result in fewer GI complications because of the short duration of therapy.

### Colchicine

- **Colchicine** is an antimetabolic drug that is highly effective in relieving acute gout attacks but has a low benefit-toxicity ratio. When colchicine is started within the first 24 hours of an acute attack, about two-thirds of patients respond within several hours. The likelihood of success decreases substantially if treatment is delayed longer than 48 hours after symptom onset.
- Oral colchicine causes dose-dependent GI adverse effects (nausea, vomiting, and diarrhea) in 50% to 80% of patients before relief of the attack. Non-GI adverse effects include neutropenia and axonal neuromyopathy, which may be worsened in patients taking other myopathic drugs (e.g., statins) or in those with renal insufficiency. Colchicine should not be used concurrently with macrolide antibiotics (especially clarithromycin) because reduced biliary excretion may lead to increased plasma colchicine levels and agranulocytosis.
- Colchicine should be reserved for patients with insufficient relief, intolerance, or contraindications to NSAIDs.
- The usual oral colchicine dose is 1 mg initially, followed by 0.5 mg every 1 hour until the joint symptoms subside, the patient develops abdominal discomfort or diarrhea, or a total dose of 8 mg has been given.

- IV colchicine should be avoided because it is associated with serious adverse effects (e.g., bone marrow suppression, tissue necrosis from local extravasation, disseminated intravascular coagulation, hepatocellular toxicity, and renal failure). If considered necessary, the recommended initial IV dose is 2 mg (if renal function is normal) diluted in 10 to 20 mL of normal saline administered slowly over 10 to 20 minutes in a secure, free-flowing IV line to avoid extravasation. This may be followed by two additional doses of 1 mg each at 6-hour intervals, with the total dose not exceeding 4 mg. After a full IV course, patients should not receive colchicine by any route for at least 7 days.

### Corticosteroids

- Corticosteroids may be used to treat acute attacks of gouty arthritis, but they are reserved primarily for patients with a contraindication or who are unresponsive to NSAID or colchicine therapy. Patients with multiple-joint involvement may also benefit.
- The recommended dose is **prednisone** 30 to 60 mg (or an equivalent dose of another corticosteroid) orally once daily for 3 to 5 days. Because rebound attacks may occur upon steroid withdrawal, the dose should be gradually tapered in 5-mg increments over 10 to 14 days and discontinued.
- A single intramuscular injection of a long-acting corticosteroid (e.g., **methylprednisolone acetate**) can be used as an alternative to the oral route if patients are unable to take oral therapy. If not contraindicated, low-dose colchicine can be used as adjunctive therapy to injectable corticosteroids to prevent rebound flare-ups.
- Intraarticular administration of **triamcinolone hexacetonide** 20 to 40 mg may be useful for acute gout limited to one or two joints.
- **Adrenocorticotropic hormone (ACTH)** gel, 40 to 80 USP units, may be given intramuscularly every 6 to 8 hours for 2 to 3 days and then discontinued. Studies with ACTH are limited, and it should be reserved for patients with contraindications to first-line therapies (e.g., heart failure, chronic renal failure, history of GI bleeding).

## PROPHYLACTIC THERAPY OF INTERCRITICAL GOUT

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### General Approach

- Prophylactic treatment can be withheld if the first episode of acute gouty arthritis was mild and responded promptly to treatment, the patient's serum urate concentration was only minimally elevated, and the 24-hour urinary uric acid excretion was not excessive (less than 1,000 mg/24 hours on a regular diet).
- If the patient had a severe attack of gouty arthritis, a complicated course of uric acid lithiasis, a substantially elevated serum uric acid (greater than 10 mg/dL), or a 24-hour urinary excretion of uric acid of more than 1,000 mg, then prophylactic treatment should be instituted immediately after resolution of the acute episode.
- Prophylactic therapy is cost-effective for patients with frequent attacks of gouty arthritis (i.e., two or more attacks per year) even if the serum uric acid concentration is normal or only minimally elevated.

## Colchicine

- **Colchicine** given in low oral doses (0.5 to 0.6 mg twice daily) may be effective in preventing recurrent arthritis in patients with no evidence of visible tophi and a normal or slightly elevated serum urate concentration. The oral dose should be reduced to no more than 0.6 mg daily or every other day in patients with renal or hepatic dysfunction. Treated patients who sense the onset of an acute attack should increase the dose to 1 mg every 2 hours; in most instances, the attack aborts after 1 or 2 mg. Discontinuation of prophylaxis may be attempted if the serum urate concentration remains normal and the patient is symptom-free for 1 year.

## Uric Acid–Lowering Therapy

- Patients with a history of recurrent acute gouty arthritis and a significantly elevated serum uric acid concentration are probably best managed with uric acid–lowering therapy.
- Colchicine, 0.5 mg twice daily, is sometimes given during the first 6 to 12 months of antihyperuricemic therapy to minimize the risk of acute attacks that may occur during initiation of uric acid–lowering therapy.
- The therapeutic objective of antihyperuricemic therapy is to achieve and maintain a serum uric acid concentration less than 6 mg/dL, and preferably below 5 mg/dL.

## Xanthine Oxidase Inhibitor

- **Allopurinol** and its major metabolite, oxypurinol, are xanthine oxidase inhibitors and impair the conversion of hypoxanthine to xanthine and xanthine to uric acid. Allopurinol also lowers the intracellular concentration of PRPP. Because of the long half-life of its metabolite, allopurinol can be given once daily orally. It is typically initiated at a dose of 100 mg/day and increased by 100 mg/day at 1-week intervals to achieve a serum uric acid level of 6 mg/dL or less. Serum levels can be checked about 1 week after starting therapy or modifying the dose. Although typical doses are 100 to 300 mg daily, occasionally doses of 600 to 800 mg/day are necessary. The dose should be reduced in patients with renal insufficiency (200 mg/day for  $CL_{Cr}$  60 mL/min or less, and 100 mg/day for  $CL_{Cr}$  30 mL/min or less).
- Allopurinol is the antihyperuricemic drug of choice in patients with a history of urinary stones or impaired renal function, in patients who have lymphoproliferative or myeloproliferative disorders and need pretreatment with a xanthine oxidase inhibitor before initiation of cytotoxic therapy to protect against acute uric acid nephropathy, and in patients with gout who are overproducers of uric acid.
- The major side effects of allopurinol are skin rash, urticaria, leukopenia, GI problems, headache, and increased frequency of acute gouty attacks with the initiation of therapy. An allopurinol hypersensitivity syndrome characterized by fever, eosinophilia, dermatitis, vasculitis, and renal and hepatic dysfunction occurs rarely but is associated with a 20% mortality rate.

## Uricosuric Drugs

- **Probenecid** and **sulfinpyrazone** increase the renal clearance of uric acid by inhibiting the renal tubular reabsorption of uric acid. They should only be

used in patients with documented underexcretion of uric acid. Therapy with uricosuric drugs should be started at a low dose to avoid marked uricosuria and possible stone formation. Maintenance of adequate urine flow and alkalinization of the urine with sodium bicarbonate or Shohl's solution during the first several days of uricosuric therapy further diminish the possibility of uric acid stone formation.

- Probenecid is given initially at a dose of 250 mg twice daily for 1 to 2 weeks, then 500 mg twice daily for 2 weeks. Thereafter, the daily dose is increased by 500-mg increments every 1 to 2 weeks until satisfactory control is achieved or a maximum dose of 2 g/day is reached.
- The initial dose of sulfipyrazone is 50 mg twice daily for 3 to 4 days, then 100 mg twice daily, increasing the daily dose by 100-mg increments each week up to 800 mg/day.
- The major side effects associated with uricosuric therapy are GI irritation, rash and hypersensitivity, precipitation of acute gouty arthritis, and stone formation. These drugs are contraindicated in patients who are allergic to them and in patients with impaired renal function ( $CL_{cr} < 50$  mL/min) or a history of renal calculi, and in patients who are overproducers of uric acid.

## EVALUATION OF THERAPEUTIC OUTCOMES

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- A serum uric acid level should be checked in patients suspected of having an acute gout attack, particularly if it is not the first attack and a decision is to be made about starting prophylactic therapy. However, acute gout can occur in the presence of normal serum uric acid concentrations. Repeat serum uric acid measurements are generally not necessary except during the titration phase of allopurinol to achieve a goal serum urate less than 6 mg/dL.
- Patients with acute gout should be monitored for symptomatic relief of joint pain as well as potential adverse effects and drug interactions related to drug therapy. The acute pain of an initial attack of gouty arthritis should begin to ease within about 8 hours of treatment initiation. Complete resolution of pain, erythema, and inflammation usually occurs within 48 to 72 hours.
- Patients receiving hypouricemic medications should have baseline assessment of renal function, hepatic enzymes, complete blood count, and electrolytes. The tests should be rechecked every 6 to 12 months in patients receiving long-term prophylaxis.
- Because of comorbidity with diabetes, dyslipidemia, hypertension, and stroke, the presence of increased serum uric acid levels or gout should prompt evaluation for cardiovascular disease and the need for appropriate risk reduction measures. Clinicians should also look for possible correctable causes of hyperuricemia (e.g., medications, obesity, and alcohol abuse).

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*See Chap. 96, Gout and Hyperuricemia, authored by Michael E. Ernst, Elizabeth C. Clark, and David W. Hawkins, for a more detailed discussion of this topic.*

## DEFINITION

- Osteoarthritis (OA) is a common, slowly progressive disorder affecting primarily the weight-bearing diarthrodial joints of the peripheral and axial skeleton. It is characterized by progressive deterioration and loss of articular cartilage, resulting in osteophyte formation, pain, limitation of motion, deformity, and progressive disability. Inflammation may or may not be present in the affected joints.

## PATHOPHYSIOLOGY

- *Primary (idiopathic) OA*, the most common type, has no known cause. Subclasses of primary OA are *localized OA* (involving one or two sites) and *generalized OA* (affecting three or more sites). The term *erosive OA* indicates the presence of erosion and marked proliferation in the proximal and distal interphalangeal (PIP and DIP) hand joints.
- *Secondary OA* is associated with a known cause such as rheumatoid arthritis or another inflammatory arthritis, trauma, metabolic or endocrine disorders, and congenital factors.
- OA usually begins with damage to articular cartilage through injury, excess joint loading from obesity or other reasons, or joint instability or injury that causes abnormal loading. Damage to cartilage increases the metabolic activity of chondrocytes, leading to increased synthesis of matrix constituents with cartilage swelling. This hypertrophic reparative response to damage does not restore cartilage to normal but instead is the first step in the process leading to further cartilage loss.
- After the hypertrophic phase, there is increased synthesis of matrix metalloproteinases (MMPs) 1, 3, 13, and 28, which causes collagen destruction to occur faster than synthesis, with a net loss of cartilage. Chondrocytes contribute to collagen loss by secreting MMPs in response to inflammatory mediators present in OA (interleukin-1 and tumor necrosis factor- $\alpha$ ). Chondrocytes also undergo apoptosis, probably as a result of induction of nitric oxide synthase and production of toxic metabolites. This leaves fewer chondrocytes to synthesize matrix components. OA chondrocytes are also less responsive to the anabolic stimulus of transforming growth factor- $\beta$ . The net result of these processes is a progressive cycle of cartilage destruction and chondrocyte loss.
- Subchondral bone adjacent to articular cartilage also undergoes pathologic changes that allow progression of damage to articular cartilage. In OA, subchondral bone releases vasoactive peptides and MMPs. Neovascularization and subsequent increased permeability of the adjacent cartilage occur, which contribute further to cartilage loss.
- Substantial loss of cartilage causes joint space narrowing and leads to painful, deformed joints. The remaining cartilage softens and develops fibrillations,

and there is splitting, further cartilage loss, and exposure of underlying bone. Cartilage is eventually eroded completely, leaving denuded subchondral bone that becomes dense, smooth, and glistening (eburnation). A more brittle, stiffer bone results, with decreased weight-bearing ability and development of sclerosis and microfractures. New bone formations (osteophytes) that arise from local and humoral factors appear at joint margins distant from cartilage destruction; evidence indicates that osteophytes help to stabilize OA joints.

- Local inflammatory changes occur in the joint capsule and synovium. The synovium becomes infiltrated with T cells, and immune complexes appear. Crystals or cartilage shards in synovial fluid may contribute to inflammation. There are also increased levels of interleukin-1, prostaglandin E<sub>2</sub>, tumor necrosis factor- $\alpha$ , and nitric oxide in synovial fluid. Inflammatory changes result in effusions and synovial thickening.
- The pain of OA arises from activation of nociceptive nerve endings within joints by mechanical and chemical irritants. OA pain may result from distension of the synovial capsule by increased joint fluid; microfracture; periosteal irritation; or damage to ligaments, synovium, or the meniscus.

## CLINICAL PRESENTATION

- The prevalence and severity of OA increase with age. Potential risk factors include obesity, repetitive use through work or leisure activities, joint trauma, and heredity.
- The clinical presentation depends on duration and severity of disease and the number of joints affected. The predominant symptom is a localized deep, aching pain associated with the affected joint. Early in OA, pain accompanies joint activity and decreases with rest. With progression, pain occurs with minimal activity or at rest.
- Joints most commonly affected are the DIP and PIP joints of the hand, the first carpometacarpal joint, knees, hips, cervical and lumbar spine, and the first metatarsophalangeal joint of the toe.
- In addition to pain, limitation of motion, stiffness, crepitus, and deformities may occur. Patients with lower extremity involvement may report a sense of weakness or instability.
- Upon arising, joint stiffness typically lasts less than 30 minutes and resolves with motion. Joint enlargement is related to bony proliferation or to thickening of the synovium and joint capsule. The presence of a warm, red, and tender joint may suggest an inflammatory synovitis.
- Joint deformity may be present in the later stages as a result of subluxation, collapse of subchondral bone, formation of bone cysts, or bony overgrowths.
- Physical examination of the affected joints reveals tenderness, crepitus, and possible joint enlargement. Heberden's and Bouchard's nodes are bony enlargements (osteophytes) of the DIP and PIP joints, respectively.

## DIAGNOSIS

- The diagnosis of OA is dependent on patient history, clinical examination of the affected joint(s), radiologic findings, and laboratory testing.

- Criteria for the classification of OA of the hips, knees, and hands were developed by the American College of Rheumatology (ACR). The criteria include the presence of pain, bony changes on examination, a normal erythrocyte sedimentation rate (ESR), and radiographs showing characteristic osteophytes or joint space narrowing.
- For hip OA, a patient must have hip pain and two of the following: (1) an ESR less than 20 mm/hour, (2) radiographic femoral or acetabular osteophytes, or (3) radiographic joint space narrowing.
- For knee OA, a patient must have knee pain and radiographic osteophytes in addition to one or more of the following: (1) age greater than 50 years, (2) morning stiffness of 30 minutes' or less duration, or (3) crepitus on motion, (4) bony enlargement, (6) bony tenderness, or (7) palpable joint warmth.
- No specific clinical laboratory abnormalities occur in primary OA. The ESR may be slightly elevated in patients with generalized or erosive inflammatory OA. The rheumatoid factor test is negative. Analysis of the synovial fluid reveals fluid with high viscosity. This fluid demonstrates a mild leukocytosis (less than 2,000 white blood cells/mm<sup>3</sup>) with predominantly mononuclear cells.

## DESIRED OUTCOME

- The major goals for the management of OA are to (1) educate the patient, caregivers, and relatives; (2) relieve pain and stiffness; (3) maintain or improve joint mobility; (4) limit functional impairment; and (5) maintain or improve quality of life.

## TREATMENT

### NONPHARMACOLOGIC THERAPY

- The first step is to educate the patient about the extent of the disease, prognosis, and management approach. Dietary counseling and a structured weight-loss program are recommended for overweight OA patients.
- Physical therapy—with heat or cold treatments and an exercise program—helps to maintain and restore joint range of motion and reduce pain and muscle spasms. Exercise programs using isometric techniques are designed to strengthen muscles, improve joint function and motion, and decrease disability, pain, and the need for analgesic use.
- Assistive and orthotic devices such as canes, walkers, braces, heel cups, and insoles can be used during exercise or daily activities.
- Surgical procedures (e.g., osteotomy, partial or total arthroplasty, joint fusion) are indicated for patients with functional disability and/or severe pain unresponsive to conservative therapy.

### PHARMACOLOGIC THERAPY

#### General Approach

- Drug therapy in OA is targeted at relief of pain. Because OA often occurs in older individuals who have other medical conditions, a conservative approach to drug treatment is warranted.

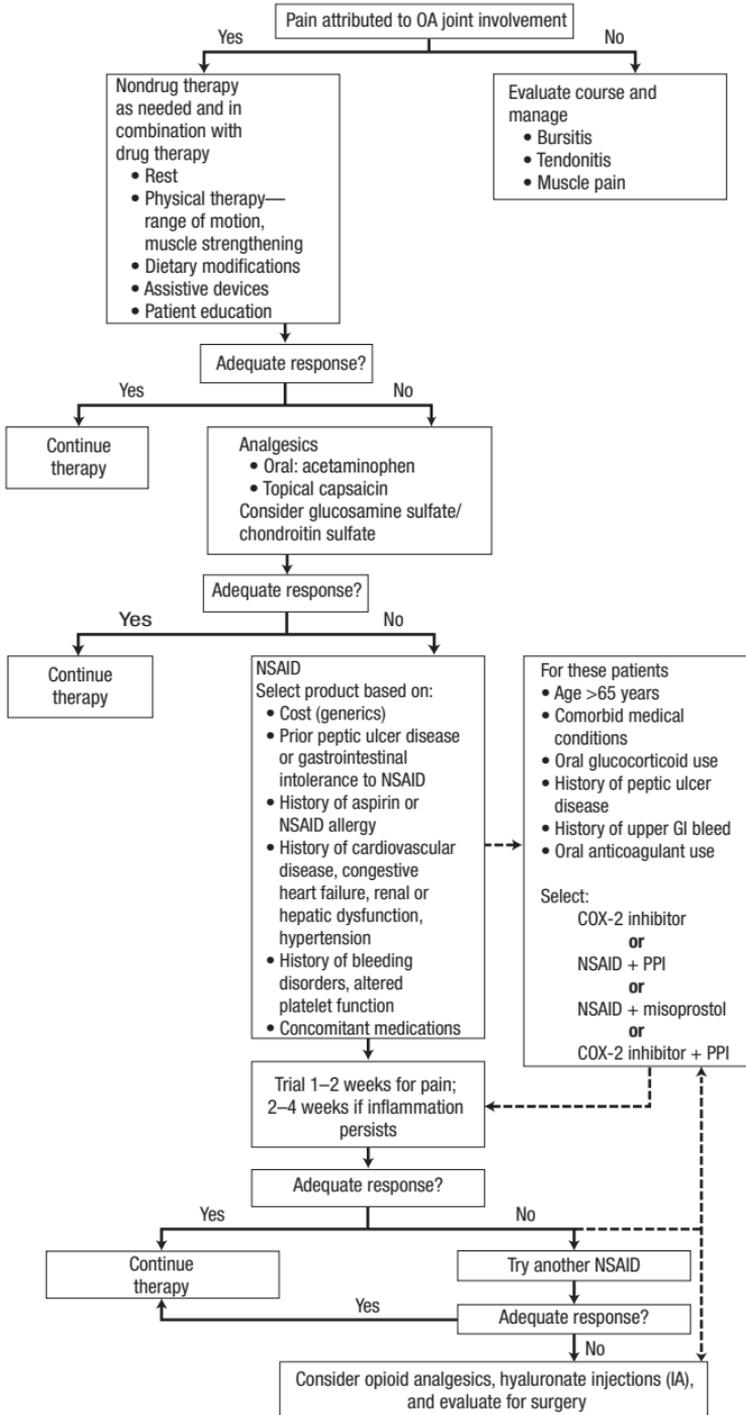
- An individualized approach to treatment is necessary (Fig. 2-1). For mild or moderate pain, topical analgesics or acetaminophen can be used. If these measures fail or if there is inflammation, nonsteroidal antiinflammatory drugs (NSAIDs) may be useful. Appropriate nondrug therapies should be continued when drug therapy is initiated.

### Acetaminophen

- **Acetaminophen** is recommended by the ACR as first-line drug therapy for pain management of OA. The dose is 325 to 650 mg every 4 to 6 hours on a scheduled basis (maximum dose 4 g/day; maximum 2 g/day if chronic alcohol intake or underlying liver disease). Comparable relief of mild to moderate OA pain has been demonstrated for acetaminophen (2.6 to 4 g/day) compared with aspirin (650 mg four times daily), ibuprofen (1,200 or 2,400 mg daily), and naproxen (750 mg daily). However, some patients respond better to NSAIDs.
- Acetaminophen is usually well tolerated, but potentially fatal hepatotoxicity with overdose is well documented. It should be used with caution in patients with liver disease and those who chronically abuse alcohol. Chronic alcohol users (three or more drinks daily) should be warned about an increased risk of liver damage or GI bleeding with acetaminophen. Other individuals do not appear to be at increased risk for GI bleeding. Renal toxicity occurs less frequently than with NSAIDs.

### Nonsteroidal Antiinflammatory Drugs

- NSAIDs at prescription strength are often prescribed for OA patients after treatment with acetaminophen proves ineffective, or for patients with inflammatory OA. Analgesic effects begin within 1 to 2 hours, whereas antiinflammatory benefits may require 2 to 3 weeks of continuous therapy.
- All NSAIDs have similar efficacy in reducing pain and inflammation in OA (Table 2-1), although individual patient response differs among NSAIDs.
- Selection of an NSAID depends on prescriber experience, medication cost, patient preference, toxicities, and adherence issues. An individual patient should be given a trial of one drug that is adequate in time (2 to 3 weeks) and dose. If the first NSAID fails, another agent in the same or another chemical class can be tried; this process may be repeated until an effective drug is found. Combining two NSAIDs increases adverse effects without providing additional benefit.
- Cyclooxygenase-2 (COX-2) selective inhibitors (e.g., celecoxib) demonstrate analgesic benefits that are similar to traditional nonselective NSAIDs. Although COX-2 selective inhibition was designed to reduce NSAID-induced gastropathy (e.g., ulcers, bleeding, perforation), concerns about adverse cardiovascular events (e.g., myocardial infarction, stroke) have led authorities to recommend their use only in selected patients who are at high risk for NSAID-related GI effects and low risk for cardiovascular toxicity.
- GI complaints are the most common adverse effects of NSAIDs. Minor complaints such as nausea, dyspepsia, anorexia, abdominal pain, flatulence, and diarrhea occur in 10% to 60% of patients. NSAIDs should be taken with food or milk, except for enteric-coated products (milk or antacids may destroy the enteric coating and cause increased GI symptoms in some patients).



**FIGURE 2-1.** Treatment for osteoarthritis. (COX, cyclooxygenase; IA, intraarticular; NSAID, nonsteroidal antiinflammatory drug; OA, osteoarthritis; PPI, proton pump inhibitor.)

**TABLE 2-1** Medications Commonly Used in the Treatment of Osteoarthritis

Medication	Dosage and Frequency	Maximum Dosage (mg/day)
<b>Oral analgesics</b>		
Acetaminophen	325–650 mg every 4–6 hours or 1 g three to four times/day	4,000
Tramadol	50–100 mg every 4–6 hours	400
Acetaminophen/codeine	300–1,000 mg/15–60 mg every 4 hours as needed	4,000/360
Acetaminophen/oxycodone	325–650 mg/2.5–10 mg every 6 hours as needed	4,000/40
<b>Topical analgesics</b>		
Capsaicin 0.025% or 0.075%	Apply to affected joint three to four times/day	—
<b>Nutritional supplements</b>		
Glucosamine sulfate/chondroitin sulfate	500 mg/400 mg three times/day	1,500/1,200
<b>Nonsteroidal antiinflammatory drugs (NSAIDs)</b>		
<i>Carboxylic acids</i>		
<i>Acetylated salicylates</i>		
Aspirin, plain, buffered, or enteric-coated	325–650 mg every 4–6 hours for pain; antiinflammatory doses start at 3,600 mg/day in divided doses	3,600 <sup>d</sup>
<i>Nonacetylated salicylates</i>		
Salsalate	500–1,000 mg two to three times/day	3,000 <sup>d</sup>
Diflunisal	500–1,000 mg two times/day	1,500
Choline salicylate <sup>b</sup>	500–1,000 mg two to three times/day	3,000 <sup>d</sup>
Choline magnesium salicylate	500–1,000 mg two to three times/day	3,000 <sup>d</sup>
<i>Acetic acids</i>		
Etodolac	800–1,200 mg/day in divided doses	1,200
Diclofenac	100–150 mg/day in divided doses	200
Indomethacin	25 mg two to three times/day; 75 mg SR once daily	200; 150
Ketorolac <sup>c</sup>	10 mg every 4–6 hours	40
Nabumetone <sup>d</sup>	500–1,000 mg one to two times/day	2,000
<i>Propionic acids</i>		
Fenoprofen	300–600 mg three to four times/day	3,200
Flurbiprofen	200–300 mg/day in 2–4 divided doses	300
Ibuprofen	1,200–3,200 mg/day in 3–4 divided doses	3,200
Ketoprofen	150–300 mg/day in 3–4 divided doses	300
Naproxen	250–500 mg twice a day	1,500
Naproxen sodium	275–550 mg twice a day	1,375
Oxaprozin	600–1,200 mg daily	1,800
<i>Fenamates</i>		
Meclofenamate	200–400 mg/day in 3–4 divided doses	400
Mefenamic acid <sup>e</sup>	250 mg every 6 hours	1,000
<i>Oxicams</i>		
Piroxicam	10–20 mg daily	20
Meloxicam	7.5 mg daily	15
<i>Coxibs</i>		
Celecoxib	100 mg twice daily or 200 mg once daily	200 (400 for RA)

RA, rheumatoid arthritis; SR, sustained-release.

<sup>a</sup>Monitor serum salicylate levels over 3–3.6 g/day.<sup>b</sup>Only available as a liquid; 870 mg salicylate/5 mL.<sup>c</sup>Not approved for treatment of OA for more than 5 days.<sup>d</sup>Nonorganic acid but metabolite is an acetic acid.<sup>e</sup>Not approved for treatment of OA.

- All NSAIDs have the potential to cause gastric and duodenal ulcers and bleeding through direct (topical) or indirect (systemic) mechanisms. Risk factors for NSAID-associated ulcers and ulcer complications (perforation, gastric outlet obstruction, GI bleeding) include increased age, comorbid medical conditions (e.g., cardiovascular disease), concomitant corticosteroid or anticoagulant therapy, and history of peptic ulcer disease or upper GI bleeding.
- For OA patients who need an NSAID but are at high risk for GI complications, the ACR recommendations include either a COX-2 selective inhibitor or a nonselective NSAID in combination with either a proton pump inhibitor or misoprostol.
- NSAIDs may also cause kidney diseases, hepatitis, hypersensitivity reactions, rash, and CNS complaints of drowsiness, dizziness, headaches, depression, confusion, and tinnitus. All nonselective NSAIDs inhibit COX-1-dependent thromboxane production in platelets, thereby increasing bleeding risk. NSAIDs should be avoided in late pregnancy because of the risk of premature closure of the ductus arteriosus.
- The most potentially serious drug interactions include the concomitant use of NSAIDs with lithium, warfarin, oral hypoglycemics, high-dose methotrexate, antihypertensives, angiotensin-converting enzyme inhibitors,  $\beta$ -blockers, and diuretics.

### Topical Therapies

- **Capsaicin**, an extract of red peppers that causes release and ultimately depletion of substance P from nerve fibers, has been beneficial in providing pain relief in OA when applied topically over affected joints. It may be used alone or in combination with oral analgesics or NSAIDs.
- To be effective, capsaicin must be used regularly, and it may take up to 2 weeks to work. It is well tolerated, but some patients experience temporary burning or stinging at the site of application. Patients should be warned not to get the cream in their eyes or mouth and to wash their hands after application.
- Application of the cream, gel, or lotion is recommended four times daily, but tapering to twice-daily application may enhance long-term adherence with adequate pain relief.
- **Topical diclofenac** in a dimethyl sulfoxide carrier (Pennsaid) is a safe and effective treatment for OA pain. It is thought to act primarily by local inhibition of COX-2 enzymes. The product was under review by the U.S. FDA at the time of this writing.
- Topical rubefacients containing **methyl salicylate**, **trolamine salicylate**, and other salicylates may have modest, short-term efficacy for treating acute pain associated with OA.

### Glucosamine and Chondroitin

- **Glucosamine** and **chondroitin** are dietary supplements that were shown to stimulate proteoglycan synthesis from articular cartilage in vitro. Although their excellent safety profile makes them appealing for patients at high risk of adverse drug events, enthusiasm waned after results of a large, well-controlled, National Institutes of Health-sponsored clinical trial demonstrated no significant clinical response to glucosamine alone, chon-

droitin alone, or combination therapy when compared to placebo across all patients. In subgroup analyses, patients with moderate to severe knee pain showed a response to combination glucosamine–chondroitin therapy superior to placebo, but this finding did not reach the predetermined threshold for pain reduction.

- Because of their relative safety, a trial of glucosamine–chondroitin may be reasonable in patients considering alternatives to traditional OA treatment. Dosing should be at least glucosamine sulfate 1,500 mg/day and chondroitin sulfate 1,200 mg/day in divided doses.
- Glucosamine adverse effects are mild and include GI gas, bloating, and cramps; it should not be used in patients with shellfish allergies. The most common adverse effect of chondroitin is nausea.

### Corticosteroids

- Systemic corticosteroid therapy is not recommended in OA, given the lack of proven benefit and the well-known adverse effects with long-term use.
- Intraarticular corticosteroid injections can provide relief, particularly when a joint effusion is present. Average doses for injection of large joints in adults are **methylprednisolone acetate** 20 to 40 mg or **triamcinolone hexacetonide** 10 to 20 mg. After aseptic aspiration of the effusion and corticosteroid injection, initial pain relief may occur within 24 to 72 hours, with peak relief occurring in about 1 week and lasting for 4 to 8 weeks. The patient should minimize joint activity and stress on the joint for several days after the injection. Therapy is generally limited to three or four injections per year because of the potential systemic effects of the drugs and because the need for more frequent injections indicates poor response to therapy.

### Hyaluronate Injections

- High-molecular-weight hyaluronic acid is a constituent of normal cartilage that provides lubrication with motion and shock absorbency during rapid movements. Because the concentration and molecular size of endogenous hyaluronic acid decrease in OA, exogenous administration has been studied in an attempt to reconstitute synovial fluid and reduce symptoms.
- Hyaluronic acid injections temporarily and modestly increase synovial fluid viscosity and were reported to decrease pain, but many studies were short term and poorly controlled with high placebo response rates.
- Four intraarticular hyaluronic acid preparations are available for treating pain associated with OA of the knee: **sodium hyaluronate** (Hyalgan 20 mg/2 mL; Supartz 25 mg/2.5 mL), **hylan polymers** (Synvisc 16 mg/2 mL), and **hyaluronan** (Orthovisc 30 mg/2 mL). Hyalgan and Supartz are administered once weekly for five injections, whereas Synvisc and Orthovisc are administered once weekly for three injections.
- Injections are well tolerated, but acute joint swelling and local skin reactions (e.g., rash, ecchymoses, or pruritus) have been reported.
- These products may be beneficial for OA of the knee that is unresponsive to other therapy, but they are expensive because treatment includes both drug and administration costs.

## Opioid Analgesics

- Low-dose opioid analgesics (e.g., **oxycodone**) may be useful for patients who experience no relief with acetaminophen, NSAIDs, intraarticular injections, or topical therapy.
- They are particularly useful in patients who cannot take NSAIDs because of renal failure, or for patients in whom all other treatment options have failed and who are at high surgical risk, precluding joint arthroplasty.
- Low-dose opioids should be used initially, usually in combination with acetaminophen. Sustained-release compounds usually offer better pain control throughout the day and are used when simple opioids are ineffective.

## Tramadol

- Tramadol with or without acetaminophen has modest analgesic effects in patients with OA. It may also be effective as add-on therapy in patients taking concomitant NSAIDs or COX-2 selective inhibitors. As with opioids, tramadol may be helpful for patients who cannot take NSAIDs or COX-2 selective inhibitors.
- Tramadol should be initiated at a lower dose (100 mg/day in divided doses) and may be titrated as needed for pain control to a dose of 200 mg/day. It is available in a combination tablet with acetaminophen and as a sustained-release tablet.
- Opioid-like adverse effects such as nausea, vomiting, dizziness, constipation, headache, and somnolence are common.

## EVALUATION OF THERAPEUTIC OUTCOMES

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- To monitor efficacy, the patient's baseline pain can be assessed with a visual analog scale, and range of motion for affected joints can be assessed with flexion, extension, abduction, or adduction.
- Depending on the joint affected, measurement of grip strength and 50-foot walking time can help assess hand and hip/knee OA, respectively.
- Baseline radiographs can document the extent of joint involvement and follow disease progression with therapy.
- Other measures include the clinician's global assessment based on the patient's history of activities and limitations caused by OA, the Western Ontario and McMaster Universities Arthrosis Index, Stanford Health Assessment Questionnaire, and documentation of analgesic or NSAID use.
- Patients should be asked if they are having adverse effects from their medications. They should also be monitored for any signs of drug-related effects, such as skin rash, headaches, drowsiness, weight gain, or hypertension from NSAIDs.
- Baseline serum creatinine, hematology profiles, and serum transaminases with repeat levels at 6- to 12-month intervals are useful in identifying specific toxicities to the kidney, liver, GI tract, or bone marrow.

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*See Chap. 95, Osteoarthritis, authored by Lucinda M. Buys and Mary Elizabeth Elliott, for a more detailed discussion of this topic.*

## DEFINITION

- Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing individuals to an increased fracture risk.
- Categories of osteoporosis include: (1) postmenopausal osteoporosis, (2) age-related osteoporosis, and (3) secondary osteoporosis.

## PATHOPHYSIOLOGY

- Bone loss occurs when bone resorption exceeds bone formation, usually from high bone turnover when the number and/or depth of bone resorption sites greatly exceed the rate and ability of osteoblasts to form new bone.
- In addition to reduced bone mineral density (BMD), bone quality and structural integrity are impaired because of the increased quantity of immature bone that is not yet adequately mineralized.
- Men and women begin to lose a small amount of bone mass starting in the third or fourth decade as a consequence of reduced bone formation. Estrogen deficiency during menopause increases proliferation, differentiation, and activation of new osteoclasts and prolongs survival of mature osteoclasts; this increases bone resorption more than formation. Men do not undergo a period of accelerated bone resorption similar to menopause. The etiology of male osteoporosis is multifactorial; secondary causes and aging are the most common contributing factors.
- Age-related osteoporosis occurs mainly because of hormone, calcium, and vitamin D deficiencies leading to accelerated bone turnover and reduced osteoblast formation.
- Drug-induced osteoporosis may result from systemic corticosteroids (prednisone doses greater than 7.5 mg/day), thyroid hormone replacement, some antiepileptic drugs (e.g., phenytoin, phenobarbital), depot medroxyprogesterone acetate, and other agents.

## CLINICAL PRESENTATION

- Many patients are unaware that they have osteoporosis and only present after fracture. Fractures can occur after bending, lifting, or falling, or independent of any activity.
- The most common osteoporosis-related fractures involve the vertebrae, proximal femur, and distal radius (wrist or Colles' fracture). Two-thirds of patients with vertebral fractures are asymptomatic; the remainder present with moderate to severe back pain that radiates down a leg after a new vertebral fracture. The pain usually subsides significantly after 2 to 4 weeks, but residual, chronic, low-back pain may persist. Multiple vertebral fractures decrease height and sometimes curve the spine (kyphosis or lordosis) with or without significant back pain.

- Patients with a nonvertebral fracture frequently present with severe pain, swelling, and reduced function and mobility at the fracture site.

## DIAGNOSIS

- A patient history should be obtained to identify history of adult fractures, comorbidities, surgeries, falls, and the presence of risk factors for osteoporosis.
- Major risk factors include current smoker, low body weight (<127 lb in postmenopausal women), history of osteoporotic fracture in a first-degree relative, and personal history of low-trauma fracture as an adult. Other independent risk factors include age, high bone turnover, low body mass index (<19 kg/m<sup>2</sup>), rheumatoid arthritis, and glucocorticoid use. Decision tools may help identify individuals who should undergo BMD testing, such as the Osteoporosis Risk Assessment Instrument and the Simple Calculated Osteoporosis Risk Estimation.
- A complete physical examination and laboratory analysis are needed to rule out secondary causes and to assess kyphosis and back pain. Laboratory testing may include complete blood count, liver function tests, creatinine, urea nitrogen, calcium, phosphorus, alkaline phosphatase, albumin, thyroid-stimulating hormone, free testosterone, 25-hydroxyvitamin D, and 24-hour urine concentrations of calcium and phosphorus. Urine or serum biomarkers (e.g., cross-linked N-telopeptides of type I collagen, osteocalcin) are sometimes used.
- Measurement of central (hip and spine) BMD with dual-energy x-ray absorptiometry (DXA) is the gold standard for osteoporosis diagnosis. Measurement at peripheral sites (forearm, heel, and phalanges) with ultrasound or DXA is used only for screening purposes and to determine the need for further testing.
- A T-score is a comparison of the patient's measured BMD to the mean BMD of a healthy, young (20- to 29-year-old), sex-matched, white reference population. The T-score is the number of standard deviations from the mean of the reference population.
- The diagnosis of osteoporosis based on a low-trauma fracture or central hip and/or spine DXA using World Health Organization T-score thresholds. Normal bone mass is a T-score greater than -1, osteopenia is a T-score of -1 to -2.4, and osteoporosis is a T-score at or below -2.5.

## DESIRED OUTCOME

- The primary goal of osteoporosis management is prevention. Optimizing skeletal development and peak bone mass accrual in childhood, adolescence, and early adulthood will reduce the future incidence of osteoporosis.
- Once osteopenia or osteoporosis develops, the objective is to stabilize or improve bone mass and strength and prevent fractures.
- Goals in patients who have already suffered osteoporotic fractures include reducing future falls and fractures, improving functional capacity, reducing pain and deformity, and improving quality of life.

## PREVENTION AND TREATMENT

Management algorithms that incorporate both nonpharmacologic and pharmacologic approaches are shown in Fig. 3-1 (women) and Fig. 3-2 (men).

## NONPHARMACOLOGIC THERAPY

- All individuals should have a balanced diet with adequate intake of **calcium** and **vitamin D** (Table 3-1). Table 3-2 lists dietary sources of calcium and vitamin D. If adequate dietary intake cannot be achieved, calcium supplements are necessary.
- Because excessive caffeine consumption increases calcium excretion, caffeine intake should ideally be limited to two servings per day. Moderate caffeine intake (2 to 4 servings per day) should not be a concern if adequate calcium intake is achieved.
- Smoking cessation can help to optimize peak bone mass, minimize bone loss, and ultimately reduce fracture risk.
- Weight-bearing aerobic and strengthening exercises can decrease the risk of falls and fractures by improving muscle strength, coordination, balance, and mobility.

## PHARMACOLOGIC THERAPY

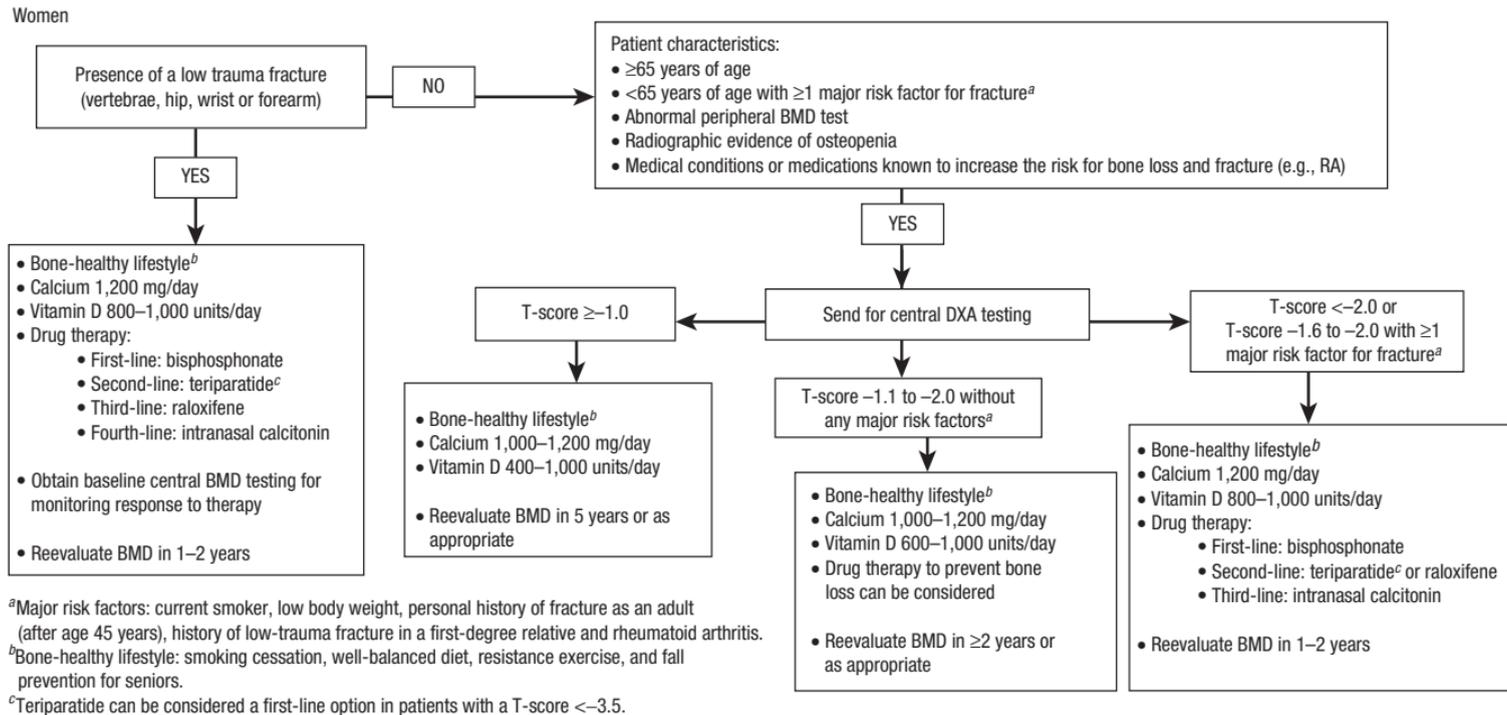
### ANTIRESORPTIVE THERAPY

#### Calcium

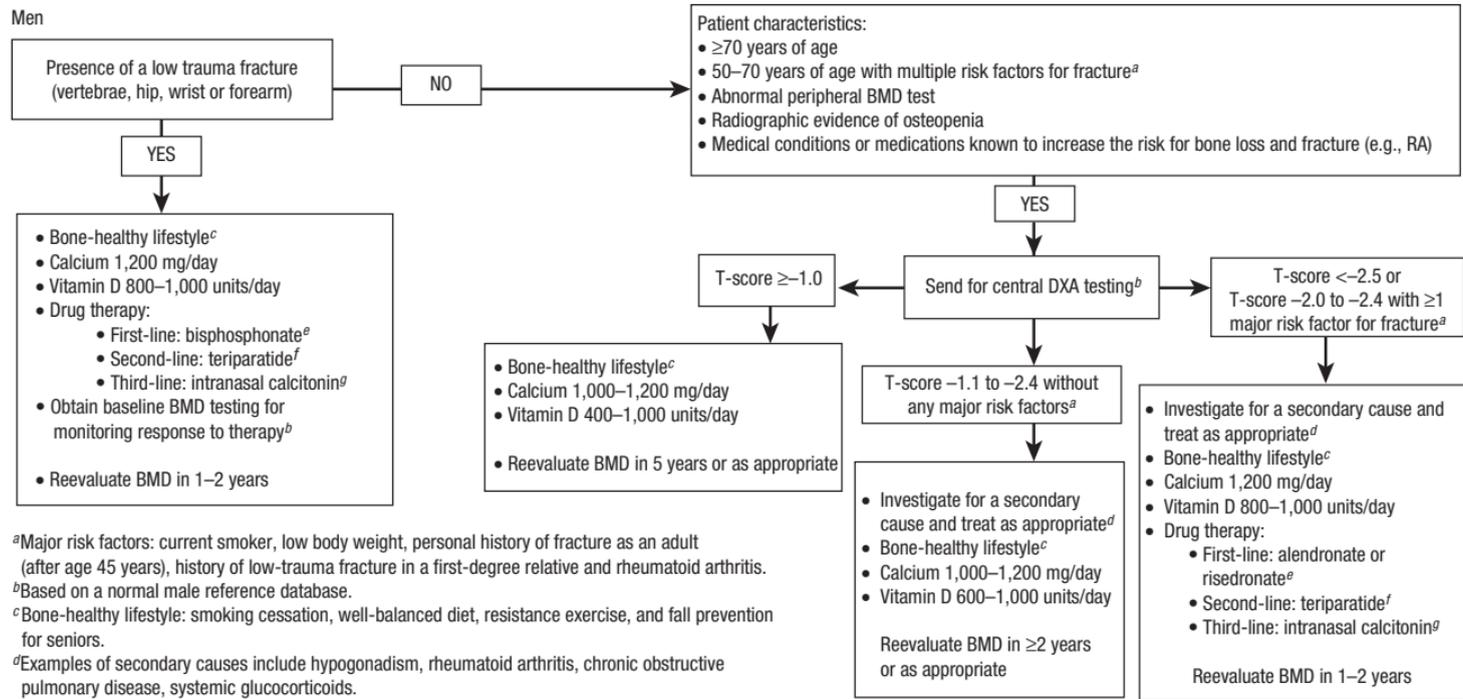
- **Calcium** should be ingested in adequate amounts to prevent secondary hyperparathyroidism and bone destruction. Although calcium increases BMD, fracture prevention is minimal. It should be combined with vitamin D and osteoporosis medications when needed.
- **Calcium carbonate** is the salt of choice because it contains the highest concentration of elemental calcium (40%) and is the least expensive (Table 3-3). It should be ingested with meals to enhance absorption from increased acid secretion. **Calcium citrate** absorption is acid independent and need not be taken with meals. Because the fraction of calcium absorbed decreases with increasing dose, maximum single doses of 600 mg or less of elemental calcium are recommended.
- Constipation is the most common adverse reaction; it can be treated with increased water intake, dietary fiber (given separately from calcium), and exercise. Calcium carbonate can create gas, sometimes causing flatulence or upset stomach.

#### Vitamin D Supplementation

- **Vitamin D** deficiency results from insufficient intake, decreased sun exposure, decreased skin production, decreased liver and renal metabolism, and winter residence in northern climates.
- Supplemental vitamin D maximizes intestinal calcium absorption and has been shown to increase BMD; it may also reduce fractures.



**FIGURE 3-1.** Bone health therapeutic algorithm for women. (BMD, bone mineral density; CBC, complete blood count; DXA, dual-energy x-ray absorptiometry; PTH, parathyroid hormone; RA, rheumatoid arthritis; TSH, thyroid-stimulating hormone.)



<sup>a</sup>Major risk factors: current smoker, low body weight, personal history of fracture as an adult (after age 45 years), history of low-trauma fracture in a first-degree relative and rheumatoid arthritis.

<sup>b</sup>Based on a normal male reference database.

<sup>c</sup>Bone-healthy lifestyle: smoking cessation, well-balanced diet, resistance exercise, and fall prevention for seniors.

<sup>d</sup>Examples of secondary causes include hypogonadism, rheumatoid arthritis, chronic obstructive pulmonary disease, systemic glucocorticoids.

<sup>e</sup>Alendronate and risedronate are FDA approved in men. Intravenous bisphosphonates are an option if patient cannot tolerate oral bisphosphonates or has significant adherence problems.

<sup>f</sup>Teriparatide is FDA approved for use in men and can be considered a first-line option in men with a T-score  $< -3.5$ .

<sup>g</sup>Calcitonin is not FDA approved for use in men.

**FIGURE 3-2.** Bone health therapeutic algorithm for men. (BMD, bone mineral density; CBC, complete blood count; DXA, dual-energy x-ray absorptiometry; PTH, parathyroid hormone; RA, rheumatoid arthritis; TSH, thyroid-stimulating hormone.)

**TABLE 3-1** Daily Calcium and Vitamin D Recommendations

Group and Ages	Institute of Medicine Adequate Intake	
	Elemental Calcium (mg) <sup>a</sup>	Vitamin D (units) <sup>a,b</sup>
Infants		
Birth to 6 months	210	200
6–12 months	270	200
Children		
1–3 years	500	200
4–8 years	800	200
9–13 years	1,300	200
Adolescents		
14–18 years	1,300	200
Adults		
19–50 years	1,000	200
51–70 years	1,200	400
>70 years	1,200	600

<sup>a</sup>U.S. Institute of Medicine of the National Academy of Sciences recommends no more than 2,500 mg/day elemental calcium and 2,000 units/day vitamin D.

<sup>b</sup>Most experts believe the recommended adequate intakes for vitamin D are too low.

- Although the vitamin D intakes included in Table 3-1 are usually recommended, many experts feel that adult intake should be 800 to 1,000 units daily.

## Bisphosphonates

(Table 3-4)

- Bisphosphonates bind to hydroxyapatite in bone and decrease resorption by inhibiting osteoclast adherence to bone surfaces. All bisphosphonates become incorporated into bone, giving them long biologic half-lives of up to 10 years.
- Of the antiresorptive agents available, bisphosphonates provide the greatest BMD increases and fracture risk reductions. Fracture reductions are demonstrated as early as 6 months, with the greatest fracture reduction seen in patients with lower initial BMD and in those with the greatest BMD changes with therapy.
- BMD increases are dose dependent and greatest in the first 6 to 12 months of therapy. Small increases continue over time at the lumbar spine but plateau after 2 to 5 years at the hip. After discontinuation, the increased BMD is sustained for a prolonged period that varies depending on the bisphosphonate used.
- **Alendronate**, **risedronate**, and **oral ibandronate** are FDA approved for prevention and treatment of postmenopausal osteoporosis. **IV ibandronate** and **zoledronic acid** are indicated only for treatment of postmenopausal women. Risedronate and alendronate are also approved for male and glucocorticoid-induced osteoporosis.
- Bisphosphonates must be administered carefully to optimize the clinical benefit and minimize the risk of adverse GI effects. All bisphosphonates are

**TABLE 3-2** Dietary Sources of Calcium and Vitamin D<sup>a</sup>

Food	Serving Size	Calcium Content (mg)	Vitamin D Content (units)
Milk	1 cup	300	100
Powdered nonfat milk	1 teaspoon	50	—
Ice cream	1 cup	200	—
Yogurt, fortified	1 cup	240–415	60
American cheese	1 oz	150	—
Cheddar cheese	1 oz	211	—
Cottage cheese	1/2 cup	100	—
Swiss cheese	1 oz	250	—
Parmesan cheese	1 tablespoonful	70	—
Cheese pizza	1 slice	150	—
Macaroni and cheese	1 cup	360	—
Slim Fast	11 oz	400	140
Orange juice, fortified	1 cup	350	100
Soymilk, fortified	1 cup	80–300	100
Bread, fortified	1 slice	100	—
Cereals, fortified	1 cup	100–250	60
Sardines with bones	3 oz	370	230
Salmon with bones	3 oz	170–210	310
Catfish	3 oz	—	570
Halibut	3 oz	—	680
Tuna	4 oz	—	260
Almonds	1 oz	80	—
Bok choy	1/2 cup	125	—
Broccoli	1 cup	130–160	—
Collards	1/2 cup	180	—
Corn bread	1 slice	85	—
Egg, medium	1	55	25
Figs, dried	5 medium	125	—
Kale	1/2 cup	95	—
Orange	1	52	—
Soybeans	1 cup	130	—
Spinach	1/2 cup	110	—
Tofu	4 oz	140	—
Turnip greens	1/2 cup	125	—

<sup>a</sup>To calculate calcium content, multiply percentage on package by 1,000. To calculate vitamin D content, multiply percentage on package by 400.

poorly absorbed (bioavailability 1% to 5%) even under optimal conditions. Each oral tablet should be taken in the morning with at least 6 oz of plain tap water (not coffee, juice, mineral water, or milk) at least 30 minutes (60 minutes for oral ibandronate) before consuming any food, supplement, or medication. The patient should remain upright (sitting or standing) for at least 30 minutes after alendronate and risedronate and 1 hour after ibandronate administration to prevent esophageal irritation and ulceration.

- Most patients prefer once-weekly or once-monthly bisphosphonate administration over daily therapy. If a patient misses a weekly dose, it can be taken the next day. If more than 1 day has elapsed, that dose is skipped until the next scheduled ingestion. If a patient misses a monthly dose, it can be taken up to 7 days before the next scheduled dose.

**TABLE 3-3** Calcium and Vitamin D Product Selection

Product (% calcium) <sup>a</sup>	Elemental Calcium (mg)	Vitamin D (units)
<i>Calcium carbonate (40%)<sup>b</sup></i>	—	—
Trade and generic products	200–600	100–200
Mylanta Supreme liquid (5 mL)	160	—
Tums Chewable	200	—
Tums E-X	300	—
Tums Ultra	400	—
Rolaids chewable	471	—
Os-Cal sugar-free chewable	500	400
Viactiv chews <sup>c</sup>	500	200
CalMax powder (10 mL)	400	—
Bayer's Women <sup>d</sup>	300	—
Ensure high calcium <sup>c</sup> (8 oz)	400	140
<i>Calcium citrate (24%)</i>	—	—
Generic	315	200
Citracal + Vit D	200–315	200
Citracal chew	500	200
<i>Tricalcium phosphate (39%)</i>	—	—
Posture-D	600	125
<i>Vitamin D<sub>3</sub> (cholecalciferol)</i>	0	400, 700, 800, or 1,000
<i>Ergocalciferol (D<sub>2</sub>)<sup>e</sup></i>	—	—
Liquid (1 mL)	—	8,000
Tablets/capsules	—	25,000 or 50,000
Intramuscular	—	500,000

<sup>a</sup>Many products are adding magnesium, boron, zinc, copper, vitamin K, and/or manganese; sometimes adding "Plus" or "Ultra" to their name. These products are not listed here.

<sup>b</sup>There are many trade-name products for calcium carbonate (e.g., Calci-D, Caltrate, Os-Cal). Only calcium carbonate alternative dosage forms (i.e., chewable, liquid, power) are specifically listed.

<sup>c</sup>Contains vitamin K.

<sup>d</sup>Contains aspirin 81 mg.

<sup>e</sup>Prescription products.

- The most common bisphosphonate adverse effects are nausea, abdominal pain, and dyspepsia. Esophageal, gastric, or duodenal irritation, perforation, ulceration, or bleeding may occur when administration directions are not followed or when bisphosphonates are prescribed for patients with contraindications. The most common adverse effects of IV bisphosphonates include fever, flu-like symptoms, and local injection-site reactions. Osteonecrosis of the jaw occurs rarely; if it develops, oral chlorhexidine washes, systemic antibiotics, and systemic analgesics are used based on severity.

### Mixed Estrogen Agonists/Antagonists

- **Raloxifene** is an estrogen agonist on bone but an antagonist on the breast and uterus. It is approved for prevention and treatment of postmenopausal osteoporosis. Other estrogen agonists/antagonists may be approved soon (e.g., bazedoxifene, lasofoxifene).
- Raloxifene decreases vertebral fractures and increases spine and hip BMD, but to a lesser extent than bisphosphonates. After discontinuation, the beneficial effect is lost and bone loss returns to age- or disease-related rates.

**TABLE 3-4** Medications Used to Prevent and Treat Osteoporosis

Drug	Adult Dosage	Pharmacokinetics	Adverse Effects	Drug Interactions
Calcium	Adequate intake (Table 3-1) in divided doses	Absorption—predominantly active transport with some passive diffusion, fractional absorption 10–60%, fecal elimination for the unabsorbed and renal elimination for the absorbed calcium	Constipation, gas, upset stomach, rare kidney stones	Carbonate salts—decreased absorption with proton pump inhibitors Decrease absorption of iron, tetracycline, quinolones, bisphosphonates, phenytoin, and fluoride when given concomitantly Might antagonize verapamil Might induce hypercalcemia with thiazide diuretics Fiber laxatives (variable), oxalates, phytates, and sulfates can decrease calcium absorption if given concomitantly Phenytoin, barbiturates, carbamazepine, rifampin increase vitamin D metabolism
D <sub>3</sub> (cholecalciferol)	Adequate intake (Table 3-1); if malabsorption or multiple anticonvulsants might require higher doses (~≥4,000 or more units daily)	Hepatic metabolism to 25(OH) vitamin D and then renal metabolism to active compound 1,25(OH) <sub>2</sub> vitamin D, other active and inactive metabolites	Hypercalcemia, (weakness, headache, somnolence, nausea, cardiac rhythm disturbance), hypercalciuria	Cholestyramine, colestipol, orlistat, or mineral oil decrease vitamin D absorption Might induce hypercalcemia with thiazide diuretics in hypoparathyroid patients
D <sub>2</sub> (ergocalciferol)	For vitamin D deficiency, 50,000 units once weekly or once monthly; dosed dependent on serum calcium			
1,25(OH) <sub>2</sub> vitamin D (calcitriol, Rocaltrol po, Calcijex IV)	0.25–0.5 mcg orally or 1–2 mcg/mL intravenously daily for renal osteodystrophy, hypoparathyroidism, and refractory rickets			
Oral bisphosphonates		Poorly absorbed—<1% decreasing to zero with food or beverage intake—long T <sub>1/2</sub> (<10 years); renal elimination (of absorbed) and fecal elimination (unabsorbed)	Nausea; heartburn; GI pain, irritation, perforation, ulceration, and/or bleeding; transient flu-like illness; muscle pains; black box warning for rare osteonecrosis of the jaw	Do not coadminister with any other medication or supplements (including calcium and vitamin D)
Alendronate (Fosamax, Fosamax plus D)	5 mg daily, 35 mg weekly (prevention) 10 mg daily, 70 mg tablet, 70 mg tablet with vitamin D 2,800 or 5,600 units, or 75 mL liquid weekly (treatment)			
Risedronate (Actonel)	5 mg daily, 35 mg weekly, 75 mg on 2 consecutive days once monthly, 150 mg monthly			
Ibandronate (Boniva)	2.5 mg daily, 150 mg once monthly			

Intravenous bisphosphonates Ibandronate (Boniva) Zoledronic acid <sup>a</sup> (Reclast)	5 mg IV infusion yearly		Muscle pains, transient flu-like illness, redness or swelling at injection site, black-box warning for rare osteonecrosis of the jaw	
Mixed estrogen agonist/antagonist Raloxifene (Evista)	60 mg daily	Hepatic metabolism	Hot flushes, leg cramps, venous thromboembolism, peripheral edema, rare cataracts and gallbladder disease; black box warning for fatal stroke	None
Calcitonin (Miacalcin)	200 units intranasal daily, alternating nares every other day	Renal elimination 3% nasal availability	Rhinitis, epistaxis	None
Teriparatide (1–34 units, Forteo)	20 mcg subcutaneously daily for up to 2 years	95% bioavailability T <sub>max</sub> ~ 30 minutes T <sub>1/2</sub> ~ 60 minutes Hepatic metabolism	Pain at injection site, nausea, dizziness, leg cramps, rare increase in uric acid, slightly increased calcium	None
Testosterone products		10% gel absorption (5 mg absorbed from 50 mg testosterone in 5 g of gel)	Weight gain, acne, hirsutism, dyslipidemia, hepatic consequences, gynecomastia, priapism, prostate disorders, testicular atrophy, sleep apnea, and skin reactions with patches	
Transdermal patch (Testoderm TTS, Androderm, Testim)	5 mg patch applied to arm, back, or thigh every evening (patches 2.5, 4, 5, & 6 mg) <sup>a</sup>			
Testoderm (R) with or without adhesive)	6 mg applied to scrotal skin every evening			
Gel (AndroGel 1%, Testim 1%)	5 g gel applied to shoulder, upper arm, or abdomen every morning			
Buccal system (Striant 30 mg)	Place one system in gum area twice a day. Alternate sides of mouth. Do not crush or swallow			
Injection				
Cypionate (100 or 200 mg/mL) or enanthate (200 mg/mL) salt	200–300 mg IM every 2–3 weeks			
Methyltestosterone (for women)	1.25–2.5 mg with esterified estrogen			

GI, gastrointestinal; IM, intramuscular; T<sub>max</sub>, time to maximum concentration; T<sub>1/2</sub>, half life.

<sup>a</sup>No abdomen patch placement for Testim; none of these patches can be applied to the genitals.

- Raloxifene (like tamoxifen) is associated with decreased breast cancer risk. Raloxifene is associated with decreases in total and low-density lipoprotein cholesterol, neutral effects on high-density lipoprotein cholesterol, but slight increases in triglycerides; no beneficial cardiovascular effects have yet been demonstrated.
- Raloxifene is well tolerated overall. Hot flushes occur more frequently in women recently finishing menopause or discontinuing estrogen therapy (ET). Endometrial bleeding occurs rarely. Raloxifene is contraindicated in women with an active or past history of venous thromboembolism. Therapy should be stopped if a patient anticipates extended immobility.

### Calcitonin

- **Calcitonin** is released from the thyroid gland when serum calcium is elevated. Salmon calcitonin is used clinically because it is more potent and longer lasting than the mammalian form. Calcitonin is reserved as a third-line agent because efficacy is less robust than with the other antiresorptive therapies.
- Calcitonin is indicated for osteoporosis treatment for women at least 5 years past menopause. Although limited data suggest beneficial effects in men and concomitantly with glucocorticoids, these indications are not FDA approved.
- Only vertebral fractures have been documented to decrease with intranasal calcitonin therapy. Calcitonin does not consistently affect hip BMD and does not decrease hip fracture risk.
- Calcitonin may provide pain relief to some patients with acute vertebral fractures. If used, it should be prescribed for short-term treatment (4 weeks) and should not be used in place of other more effective and less expensive analgesics, nor should it preclude the use of more appropriate osteoporosis therapy.
- The intranasal dose is 200 units daily, alternating nares every other day. Subcutaneous administration of 100 units daily is available but rarely used because of adverse effects and cost.

### Estrogen Therapy

- Estrogens are FDA approved for prevention of osteoporosis, but they should only be used short-term in women who need ET for the management of menopausal symptoms such as hot flushes. The risks of long-term ET outweigh the potential bone benefits.
- The enhanced BMD effects from ET and combined estrogen-progestin hormonal therapy (HT) significantly reduce fracture risk but are less than those from bisphosphonates or teriparatide but greater than those from raloxifene or calcitonin. Oral and transdermal estrogens at equivalent doses and continuous or cyclic HT regimens have similar BMD effects. Effect on BMD is dose dependent with some benefit seen with lower estrogen doses. When ET or HT is discontinued, bone loss accelerates and fracture protection is lost.
- The lowest effective dose of ET and HT should still be used for preventing and controlling menopausal symptoms with use discontinued with symptom abatement. Many contraindications to ET and HT exist and must be identified before starting therapy.

### Testosterone

- Testosterone replacement is not FDA approved for the prevention or treatment of osteoporosis. It should not be used solely for these indications

but might be beneficial to reduce bone loss in patients needing therapy for hypogonadal symptoms. In a few studies, women receiving oral **methyltestosterone** 1.25 or 2.5 mg daily or **testosterone** implants 50 mg every 3 months had increased BMD. Various salt forms of testosterone were associated with increased BMD in some studies of hypogonadal men or senior men with normal hormone levels or mild hormonal deficiency. Transdermal gel, oral, intramuscular, and pellet testosterone products are available.

- The virilizing and estrogenic adverse effects of these products are listed in Table 3-4. Patients using them should be evaluated within 1 to 2 months of initiation and then every 3 to 6 months thereafter.

### Thiazide Diuretics

- Thiazide diuretics increase urinary calcium reabsorption; two controlled trials demonstrated small increases in bone mass over placebo.
- Prescribing thiazide diuretics solely for osteoporosis is not recommended but is a reasonable choice for patients with osteoporosis who require a diuretic and for patients on glucocorticoids with a 24-hour urinary calcium excretion >300 mg.

## ANABOLIC THERAPY

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### Teriparatide

- **Teriparatide** is a recombinant product representing the first 34 amino acids in human parathyroid hormone. Teriparatide increases bone formation, the bone remodeling rate, and osteoblast number and activity. Both bone mass and architecture are improved.
- Teriparatide is FDA approved for postmenopausal women and men who are at high risk for fracture. Candidates for therapy include patients with a history of osteoporotic fracture, multiple risk factors for fracture, very low bone density (e.g., T-score <-3.5), or those who have failed or are intolerant of previous bisphosphonate therapy.
- The drug reduces fracture risk in postmenopausal women, but no fracture data are available in men. Lumbar spine BMD increases are higher than with any other osteoporosis therapy. Although wrist BMD is decreased, wrist fractures are not increased.
- Discontinuation of therapy results in a decrease in BMD, but some antifracture efficacy appears to be maintained. Sequential therapy with teriparatide followed by an antiresorptive agent (e.g., bisphosphonate) should be considered to maintain BMD gains.
- The dose is 20 mcg administered subcutaneously in the thigh or abdominal area (see Table 3-4). The initial dose should be given with the patient either lying or sitting, in case orthostatic hypotension occurs. Each prefilled 3-mL pen device delivers a 20-mcg dose each day for up to 28 days; the pen device should be kept refrigerated.
- Transient hypercalcemia rarely occurs. A trough serum calcium concentration is recommended 1 month after initiation of therapy.
- Teriparatide is contraindicated in patients at baseline increased risk for osteosarcoma (e.g., Paget's bone disease, unexplained alkaline phosphatase elevations, pediatric patients, young adults with open epiphyses, or patients with prior radiation therapy involving the skeleton).

## GLUCOCORTICOID-INDUCED OSTEOPOROSIS

- Glucocorticoids decrease bone formation through decreased proliferation and differentiation, and enhanced apoptosis of osteoblasts. They also increase bone resorption, decrease calcium absorption, increase renal calcium excretion, and result in secondary hyperparathyroidism.
- Bone losses are rapid, with the greatest decrease occurring during the first 6 to 12 months of therapy. Low to medium doses of inhaled glucocorticoids have no appreciative effect on BMD or fracture risk. Patients using high-dose, inhaled glucocorticoids should be evaluated for osteopenia or osteoporosis.
- Guidelines for managing corticosteroid-induced osteoporosis recommend measuring BMD at the beginning of chronic therapy (prednisone 5 mg or more daily or equivalent for at least 6 months) and followup monitoring with DXA in 6 to 12 months. BMD should be measured in patients taking chronic therapy whose baseline values were not obtained.
- All patients starting or receiving long-term systemic glucocorticoid therapy should receive at least 1,500 mg elemental calcium and 800 to 1,200 units of vitamin D daily and practice a bone-healthy lifestyle.
- Both alendronate and risedronate have documented efficacy and are FDA approved for glucocorticoid-induced osteoporosis. The American College of Rheumatology guidelines recommend that all patients newly starting on systemic glucocorticoids ( $\geq 5$  mg/day of prednisone equivalent) for an anticipated duration of at least 3 months should receive preventive bisphosphonate therapy. Patients starting or receiving long-term glucocorticoid therapy with documented low bone density (T-score below  $-1$ ) or evidence of a low-trauma fracture should also receive bisphosphonate treatment.
- Teriparatide can be used if bisphosphonates are not tolerated or contraindicated. Testosterone replacement therapy should be considered in men, and high-dose hormonal oral contraceptives can be considered for premenopausal women with documented hypogonadism.

## EVALUATION OF THERAPEUTIC OUTCOMES

- Patients receiving pharmacotherapy for low bone mass should be examined at least annually.
- Patients should be asked about possible fracture symptoms (e.g., bone pain, disability) at each visit.
- Medication adherence and tolerance should be evaluated at each visit.
- Central DXA BMD measurements can be obtained every 1 to 2 years for monitoring bone loss and treatment response. More frequent monitoring may be warranted in patients with conditions associated with higher rates of bone loss (e.g., glucocorticoid use, after transplantation).

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See Chap. 93, *Osteoporosis and Other Metabolic Bone Diseases*, authored by Mary Beth O'Connell and Sheryl F. Vondracek, for a more detailed discussion of this topic.

## DEFINITION

- Rheumatoid arthritis (RA) is a chronic and usually progressive inflammatory disorder of unknown etiology characterized by polyarticular symmetric joint involvement and systemic manifestations.

## PATHOPHYSIOLOGY

- RA results from a dysregulation of the humoral and cell-mediated components of the immune system. Most patients produce antibodies called rheumatoid factors; these seropositive patients tend to have a more aggressive course than patients who are seronegative.
- Immunoglobulins (Igs) can activate the complement system, which amplifies the immune response by enhancing chemotaxis, phagocytosis, and release of lymphokines by mononuclear cells that are then presented to T lymphocytes. The processed antigen is recognized by the major histocompatibility complex proteins on the lymphocyte surface, resulting in activation of T and B cells.
- Tumor necrosis factor (TNF), interleukin-1 (IL-1), and IL-6 are proinflammatory cytokines important in the initiation and continuance of inflammation.
- Activated T cells produce cytotoxins, which are directly toxic to tissues, and cytokines, which stimulate further activation of inflammatory processes and attract cells to areas of inflammation. Macrophages are stimulated to release prostaglandins and cytotoxins.
- Activated B cells produce plasma cells, which form antibodies that, in combination with complement, result in accumulation of polymorphonuclear leukocytes. Polymorphonuclear leukocytes release cytotoxins, oxygen free radicals, and hydroxyl radicals that promote cellular damage to synovium and bone.
- Vasoactive substances (histamine, kinins, prostaglandins) are released at sites of inflammation, increasing blood flow and vascular permeability. This causes edema, warmth, erythema, and pain and makes it easier for granulocytes to pass from blood vessels to sites of inflammation.
- Chronic inflammation of the synovial tissue lining the joint capsule results in tissue proliferation (pannus formation). Pannus invades cartilage and eventually the bone surface, producing erosions of bone and cartilage and leading to joint destruction. The end results may be loss of joint space, loss of joint motion, bony fusion (ankylosis), joint subluxation, tendon contractures, and chronic deformity.

## CLINICAL PRESENTATION

- Nonspecific prodromal symptoms that develop insidiously over weeks to months may include fatigue, weakness, low-grade fever, loss of appetite, and joint pain. Stiffness and myalgias may precede development of synovitis.

- Joint involvement tends to be symmetric and affect the small joints of the hands, wrists, and feet; the elbows, shoulders, hips, knees, and ankles may also be affected.
- Joint stiffness typically is worse in the morning, usually exceeds 30 minutes, and may persist all day.
- On examination, joint swelling may be visible or may be apparent only by palpation. The tissue feels soft and spongy and may appear erythematous and warm, especially early in the course of the disease. Chronic joint deformities commonly involve subluxations of the wrists, metacarpophalangeal joints, and proximal interphalangeal joints (swan-neck deformity, boutonniere deformity, ulnar deviation).
- Extra-articular involvement may include rheumatoid nodules, vasculitis, pleural effusions, pulmonary fibrosis, ocular manifestations, pericarditis, cardiac conduction abnormalities, bone marrow suppression, and lymphadenopathy.

## DIAGNOSIS

- The American Rheumatism Association criteria for classification of RA are included in Table 4-1.
- Laboratory abnormalities that may be seen include normocytic, normochromic anemia; thrombocytosis or thrombocytopenia; leukopenia; elevated erythrocyte sedimentation rate and C-reactive protein; positive

**TABLE 4-1** American Rheumatism Association Criteria for Classification of Rheumatoid Arthritis—1987 Revision

Criteria <sup>a</sup>	Definition
1. Morning stiffness	Morning stiffness in and around the joints lasting at least 1 hour before maximal improvement.
2. Arthritis of three or more joint areas	At least three joint areas simultaneously have soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible joint areas are (right or left): PIP, MCP, wrist, elbow, knee, ankle, and MTP joints.
3. Arthritis of hand joints	At least one joint area swollen as above in wrist, MCP, or PIP joint.
4. Symmetric arthritis	Simultaneous involvement of the same joint areas (as in 2) on both sides of the body (bilateral involvement of PIP, MCP, or MTP joints is acceptable without absolute symmetry).
5. Rheumatoid nodules	Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxtaarticular regions, observed by a physician.
6. Serum rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor by any method that has been positive in less than 5% of normal control subjects.
7. Radiographic changes	Radiographic changes typical of rheumatoid arthritis on posteroanterior hand and wrist x-rays, which must include erosions or unequivocal bony decalcification localized to or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify).

MCP, metacarpophalangeal; MTP, metatarsophalangeal; PIP, proximal interphalangeal.

<sup>a</sup>For classification purposes, a patient is said to have rheumatoid arthritis if he or she has satisfied at least four of these seven criteria. Criteria 1 through 4 must be present for at least 6 weeks. Patients with two clinical diagnoses are not excluded. Designation as classic, definite, or probable rheumatoid arthritis is not to be made.

rheumatoid factor (60% to 70% of patients); positive anticyclic citrullinated peptide antibody (50% to 85% of patients), and positive antinuclear antibodies (25% of patients).

- Examination of aspirated synovial fluid may reveal turbidity, leukocytosis, reduced viscosity, and normal or low glucose relative to serum concentrations.
- Radiologic findings early in the disease course may include soft tissue swelling and osteoporosis near the joint (periarticular osteoporosis). Erosions occurring later in the disease course are usually seen first in the metacarpophalangeal and proximal interphalangeal joints of the hands and metatarsophalangeal joints of the feet.

## DESIRED OUTCOME

- The ultimate goal of RA treatment is to induce a complete remission, although this may be difficult to achieve.
- The primary objectives are to reduce joint swelling, stiffness, and pain; preserve range of motion and joint function; improve quality of life; prevent systemic complications; and slow destructive joint changes.

## TREATMENT

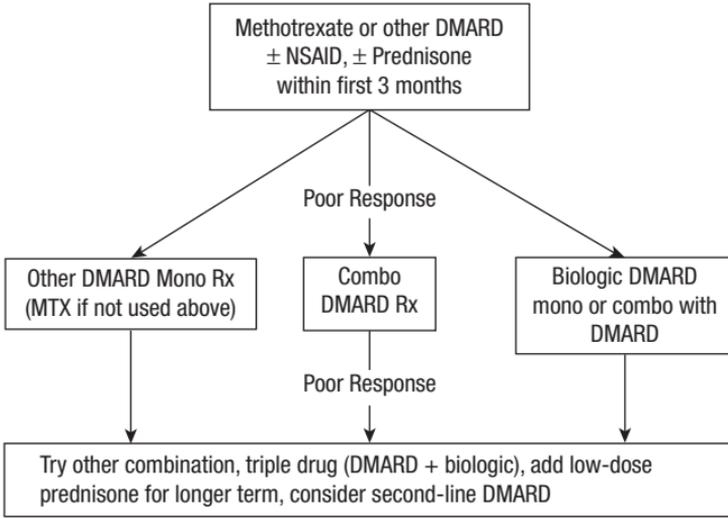
### NONPHARMACOLOGIC THERAPY

- Adequate rest, weight reduction if obese, occupational therapy, physical therapy, and use of assistive devices may improve symptoms and help maintain joint function.
- Patients with severe disease may benefit from surgical procedures such as tenosynovectomy, tendon repair, and joint replacements.
- Patient education about the disease and the benefits and limitations of drug therapy is important.

### PHARMACOLOGIC THERAPY

#### General Approach

- A disease-modifying antirheumatic drug (DMARD) should be started within the first 3 months of symptom onset (Fig. 4-1). DMARDs should be used in all patients except those with limited disease. Early use of DMARDs results in a more favorable outcome and can reduce mortality.
- First-line DMARDs include **methotrexate (MTX)**, **hydroxychloroquine**, **sulfasalazine**, and **leflunomide**. The order of agent selection is not clearly defined, but MTX is often chosen initially because long-term data suggest superior outcomes compared with other DMARDs and lower cost than biologic agents. Leflunomide appears to have long-term efficacy similar to MTX.
- Biologic agents with disease-modifying activity include the anti-TNF agents (**etanercept**, **infliximab**, **adalimumab**), the IL-1 receptor antagonist **anakinra**, and **rituximab**, which depletes peripheral B cells. Biologic agents are effective for patients who fail treatment with other DMARDs.
- DMARDs that are less frequently used include **azathioprine**, **penicillamine**, **gold salts** (including **auranofin**), **minocycline**, **cyclosporine**, and



**FIGURE 4-1.** Algorithm for treatment of rheumatoid arthritis. (DMARD, disease-modifying antirheumatic drug; MTX, methotrexate; NSAID, nonsteroidal antiinflammatory drug; Rx, therapy.)

**cyclophosphamide.** These agents have either less efficacy or higher toxicity, or both.

- Combination therapy with two or more DMARDs may be effective when single-DMARD treatment is unsuccessful. Combinations that are particularly effective include (1) MTX plus cyclosporine, and (2) MTX plus sulfasalazine and hydroxychloroquine.
- Nonsteroidal antiinflammatory drugs (NSAIDs) and/or corticosteroids may be used for symptomatic relief if needed. They provide relatively rapid improvement compared with DMARDs, which may take weeks to months before benefit is seen. However, NSAIDs have no impact on disease progression, and corticosteroids have the potential for long-term complications.
- See Tables 4-2 and 4-3 for usual dosages and monitoring parameters for DMARDs and NSAIDs used in RA.

### Nonsteroidal Antiinflammatory Drugs

- NSAIDs act primarily by inhibiting prostaglandin synthesis, which is only a small portion of the inflammatory cascade. They possess both analgesic and antiinflammatory properties and reduce stiffness but do not slow disease progression or prevent bony erosions or joint deformity. They should seldom be used as monotherapy for RA; instead, they should be viewed as adjuncts to DMARD treatment. Common NSAID dosage regimens are shown in Table 4-4.

### Methotrexate

- **MTX** inhibits cytokine production and purine biosynthesis, which may be responsible for its antiinflammatory properties. Its onset is relatively rapid

**TABLE 4-2** Usual Doses and Monitoring Parameters for Antirheumatic Drugs

Drug	Usual Dose	Initial Monitoring Tests	Maintenance Monitoring Tests
NSAIDs	See Table 4-4	S <sub>cr</sub> or BUN, CBC every 2–4 weeks after starting therapy for 1–2 months; <i>salicylates</i> : serum salicylate levels if therapeutic dose and no response	Same as initial plus stool guaiac every 6–12 months
Methotrexate	Oral or IM: 7.5–15 mg/wk	Baseline: AST, ALT, ALK-P, albumin, total bilirubin, hepatitis B and C studies, CBC with platelets, S <sub>cr</sub>	CBC with platelets, AST, albumin every 1–2 months
Leflunomide	Oral: 100 mg daily for 3 days, then 10–20 mg daily; or 10–20 mg daily without loading dose	Baseline: ALT, CBC with platelets	CBC with platelets and ALT monthly initially, and then every 6–8 weeks
Hydroxychloroquine	Oral: 200–300 mg twice daily; after 1–2 months may decrease to 200 mg once or twice daily	Baseline: color fundus photography and automated central perimetric analysis	Ophthalmoscopy every 9–12 months and Amsler grid at home every 2 weeks
Sulfasalazine	Oral: 500 mg twice daily, then increase to 1 g twice daily max	Baseline: CBC with platelets, then every week for 1 month	Same as initial every 1–2 months
Etanercept	50 mg SC once weekly	Tuberculin skin test	None
Infliximab	3 mg/kg IV at 0, 2, and 6 weeks, then every 8 weeks	Tuberculin skin test	None
Adalimumab	40 mg SC every 2 weeks	Tuberculin skin test	None
Anakinra	100 mg SC daily	None	None
Rituximab	Two 1,000-mg IV infusions separated by 2 weeks	None	None
Abatacept	30-minute IV weight-based infusion: <60 kg = 500 mg; 60–100 kg = 750 mg; >100 kg = 1,000 mg	None	None
Auranofin	Oral: 3 mg once or twice daily	Baseline: UA, CBC with platelets	Same as initial every 1–2 months
Gold thiomalate	IM: 10-mg test dose, then weekly dosing 25–50 mg; after response may increase dosing interval	Baseline and until stable: UA, CBC with platelets preinjection	Same as initial every other dose
Azathioprine	Oral: 50–150 mg daily	CBC with platelets, AST every 2 weeks for 1–2 months	Same as initial every 1–2 months
Penicillamine	Oral: 125–250 mg daily, may increase by 125–250 mg every 1–2 months; max 750 mg/day	Baseline: UA, CBC with platelets, then every week for 1 month	Same as initial every 1–2 months, but every 2 weeks if dose changes
Cyclophosphamide	Oral: 1–2 mg/kg/day	UA, CBC with platelets every week for 1 month	Same tests as initial but every 2–4 weeks

*(continued)*

**TABLE 4-2** Usual Doses and Monitoring Parameters for Antirheumatic Drugs (Continued)

Drug	Usual Dose	Initial Monitoring Tests	Maintenance Monitoring Tests
Cyclosporine	Oral: 2.5 mg/kg/day	S <sub>Cr</sub> , blood pressure every month	Same as initial
Corticosteroids	Oral, IV, IM, IA, and soft-tissue injections: variable	Glucose; blood pressure every 3–6 months	Same as initial

ALK-P, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CBC, complete blood cell count; IA, intraarticular; NSAIDs, nonsteroidal antiinflammatory drugs; S<sub>Cr</sub>, serum creatinine; UA, urinalysis.

**TABLE 4-3** Clinical Monitoring of Drug Therapy in Rheumatoid Arthritis

Drug	Toxicities Requiring Monitoring	Symptoms to Inquire About <sup>a</sup>
NSAIDs and salicylates	GI ulceration and bleeding, renal damage	Blood in stool, black stool, dyspepsia, nausea/vomiting, weakness, dizziness, abdominal pain, edema, weight gain, shortness of breath
Corticosteroids	Hypertension, hyperglycemia, osteoporosis <sup>b</sup>	Blood pressure if available, polyuria, polydipsia, edema, shortness of breath, visual changes, weight gain, headaches, broken bones or bone pain
Azathioprine	Myelosuppression, hepatotoxicity, lymphoproliferative disorders	Symptoms of myelosuppression (extreme fatigue, easy bleeding or bruising, infection), jaundice
Gold (intramuscular or oral)	Myelosuppression, proteinuria, rash, stomatitis	Symptoms of myelosuppression, edema, rash, oral ulcers, diarrhea
Hydroxychloroquine	Macular damage, rash, diarrhea	Visual changes, including a decrease in night or peripheral vision, rash, diarrhea
Methotrexate	Myelosuppression, hepatic fibrosis, cirrhosis, pulmonary infiltrates or fibrosis, stomatitis, rash	Symptoms of myelosuppression, shortness of breath, nausea/vomiting lymph node swelling, coughing, mouth sores, diarrhea, jaundice
Leflunomide	Hepatitis, GI distress, alopecia	Nausea/vomiting, gastritis, diarrhea, hair loss, jaundice
Penicillamine	Myelosuppression, proteinuria, stomatitis, rash, dysgeusia	Symptoms of myelosuppression, edema, rash, diarrhea, altered taste perception, oral ulcers
Sulfasalazine	Myelosuppression, rash	Symptoms of myelosuppression, photosensitivity, rash, nausea/vomiting
Etanercept, adalimumab, anakinra	Local injection-site reactions, infection	Symptoms of infection
Infliximab, rituximab, abatacept	Immune reactions, infection	Postinfusion reactions, symptoms of infection

NSAIDs, nonsteroidal antiinflammatory drugs.

<sup>a</sup>Altered immune function increases infection, which should be considered, particularly in patients taking azathioprine, methotrexate, corticosteroids, or other drugs that may produce myelosuppression.

<sup>b</sup>Osteoporosis is not likely to manifest early in treatment, but all patients should be taking appropriate steps to prevent bone loss.

**TABLE 4-4** Dosage Regimens for Nonsteroidal Antiinflammatory Drugs

Drug	Recommended Total Daily Antiinflammatory Dosage		Dosing Schedule
	Adult	Children	
Aspirin	2.6–5.2 g	60–100 mg/kg	Four times daily
Celecoxib	200–400 mg	—	Once or twice daily
Diclofenac	150–200 mg	—	Three to four times daily; extended release: twice daily
Diflunisal	0.5–1.5 g	—	Twice daily
Etodolac	0.2–1.2 g (max, 20 mg/kg)	—	Two to four times daily
Fenoprofen	0.9–3 g	—	Four times daily
Flurbiprofen	200–300 mg	—	Two to four times daily
Ibuprofen	1.2–3.2 g	20–40 mg/kg	Three to four times daily
Indomethacin	50–200 mg	2–4 mg/kg (max, 200 mg)	Two to four times daily; extended release: once daily
Meclofenamate	200–400 mg	—	Three to four times daily
Meloxicam	7.5–15 mg	—	Once daily
Nabumetone	1–2 g	—	Once or twice daily
Naproxen	0.5–1 g	10 mg/kg	Twice daily; extended release: once daily
Naproxen sodium	0.55–1.1 g	—	Twice daily
Nonacetylated salicylates	1.2–4.8 g	—	Two to six times daily
Oxaprozin	0.6–1.8 g (max, 26 mg/kg)	—	One to three times daily
Piroxicam	10–20 mg	—	Once daily
Sulindac	300–400 mg	—	Twice daily
Tolmetin	0.6–1.8 g	15–30 mg/kg	Two to four times daily

(as early as 2 to 3 weeks), and 45% to 67% of patients remained on it in studies ranging from 5 to 7 years.

- Toxicities are GI (stomatitis, diarrhea, nausea, vomiting), hematologic (thrombocytopenia, leukopenia), pulmonary (fibrosis, pneumonitis), and hepatic (elevated enzymes, rare cirrhosis). Concomitant folic acid may reduce some adverse effects without loss of efficacy. Liver injury tests (aspartate aminotransferase or alanine aminotransferase) should be monitored periodically, but a liver biopsy is recommended during therapy only in patients with persistently elevated hepatic enzymes. MTX is teratogenic, and patients should use contraception and discontinue the drug if conception is planned.
- MTX is contraindicated in pregnant and nursing women, chronic liver disease, immunodeficiency, pleural or peritoneal effusions, leukopenia, thrombocytopenia, preexisting blood disorders, and creatinine clearance <40 mL/min.

### Leflunomide

- **Leflunomide** (Arava) inhibits pyrimidine synthesis, which reduces lymphocyte proliferation and modulation of inflammation. Its efficacy for RA is similar to that of MTX.
- A loading dose of 100 mg/day for the first 3 days may result in a therapeutic response within the first month. The usual maintenance dose

of 20 mg/day may be lowered to 10 mg/day in cases of GI intolerance, complaints of hair loss, or other dose-related toxicity.

- The drug may cause liver toxicity and is contraindicated in patients with preexisting liver disease. The ALT should be monitored monthly initially and periodically thereafter. Leflunomide may cause bone marrow toxicity; a complete blood cell count with platelets is recommended monthly for 6 months and then every 6 to 8 weeks thereafter. It is teratogenic and should be avoided during pregnancy.

### Hydroxychloroquine

- **Hydroxychloroquine** lacks the myelosuppressive, hepatic, and renal toxicities seen with some other DMARDs, which simplifies monitoring. Its onset may be delayed for up to 6 weeks, but the drug should not be considered a therapeutic failure until after 6 months of therapy with no response.
- Short-term toxicities include GI (nausea, vomiting, diarrhea), ocular (accommodation defects, benign corneal deposits, blurred vision, scotomas, night blindness, preretinopathy), dermatologic (rash, alopecia, skin pigmentation), and neurologic (headache, vertigo, insomnia) effects. Periodic ophthalmologic examinations are necessary for early detection of reversible retinal toxicity.

### Sulfasalazine

- **Sulfasalazine** use is often limited by adverse effects. Antirheumatic effects should be seen in 2 months.
- Adverse effects include GI (anorexia, nausea, vomiting, diarrhea), dermatologic (rash, urticaria), hematologic (leukopenia, rare agranulocytosis), and hepatic (elevated enzymes) effects. GI symptoms may be minimized by starting with low doses, dividing the dose more evenly throughout the day, and taking the drug with food.

### Other Disease-Modifying Antirheumatic Drugs

- The drugs in this section can be effective and may be of value in certain clinical settings. However, they are used less frequently today because of toxicity, lack of long-term benefits, or both.
- **Aurothioglucose** (Solganol) (suspension in oil) and **gold sodium thiomalate** (Myochrysin, Aurolate) (aqueous solution) are intramuscular (IM) gold preparations with an onset that may be delayed for 3 to 6 months. They require weekly injections for about 22 weeks before a less frequent maintenance regimen may be initiated. **Auranofin** (Ridaura) is an oral gold preparation that is more convenient but less effective than IM gold. Adverse effects of gold salts include GI (nausea, vomiting, diarrhea), dermatologic (rash, stomatitis), renal (proteinuria, hematuria), and hematologic (anemia, leukopenia, thrombocytopenia) effects. Gold sodium thiomalate is associated with nitritoid reactions (flushing, palpitations, hypotension, tachycardia, headache, blurred vision). Patients receiving IM gold may experience a postinjection disease flare for 1 to 2 days after an injection.
- **Azathioprine** is a purine analog that is converted to 6-mercaptopurine and is thought to interfere with DNA and RNA synthesis. Antirheumatic effects

may be seen in 3 to 4 weeks. It should be discontinued if no response is observed after 12 weeks at maximal doses. Its major adverse effects are bone marrow suppression (leukopenia, macrocytic anemia, thrombocytopenia, pancytopenia), stomatitis, GI intolerance, infections, drug fever, hepatotoxicity, and oncogenic potential.

- **Penicillamine** onset may be seen in 1 to 3 months, and most responses occur within 6 months. Early adverse effects include skin rash, metallic taste, hypogeusia, stomatitis, anorexia, nausea, vomiting, and dyspepsia. Glomerulonephritis may occur, which manifests as proteinuria and hematuria. Penicillamine is usually reserved for patients who are resistant to other therapies because of the rare but potentially serious induction of autoimmune diseases (e.g., Goodpasture's syndrome, myasthenia gravis).
- **Cyclosporine** reduces production of cytokines involved in T-cell activation and has direct effects on B cells, macrophages, bone, and cartilage cells. Its onset appears to be 1 to 3 months. Important toxicities at doses of 1 to 10 mg/kg/day include hypertension, hyperglycemia, nephrotoxicity, tremor, GI intolerance, hirsutism, and gingival hyperplasia. Cyclosporine should be reserved for patients refractory to or intolerant of other DMARDs. It should be avoided in patients with current or past malignancy, uncontrolled hypertension, renal dysfunction, immunodeficiency, low white blood cell or platelet counts, or elevated liver function tests.

### Biologic Agents

- **Etanercept** (Enbrel) is a fusion protein consisting of two p75-soluble TNF receptors linked to an Fc fragment of human IgG<sub>1</sub>. It binds to and inactivates TNF, preventing it from interacting with the cell-surface TNF receptors and thereby activating cells. Most clinical trials used etanercept in patients who failed DMARDs, and responses were seen in 60% to 75% of patients. It has been shown to slow erosive disease progression to a greater degree than oral MTX in patients with inadequate response to MTX monotherapy. Adverse effects include local injection-site reactions, and there have been case reports of pancytopenia and neurologic demyelinating syndromes. No laboratory monitoring is required. The drug should be avoided in patients with preexisting infection and in those at high risk for developing infection. Treatment should be discontinued temporarily if infections develop during therapy.
- **Infliximab** (Remicade) is a chimeric anti-TNF antibody fused to a human constant-region immunoglobulin G<sub>1</sub> (IgG<sub>1</sub>). It binds to TNF and prevents its interaction with TNF receptors on inflammatory cells. To prevent formation of antibodies to this foreign protein, MTX should be given orally in doses used to treat RA for as long as the patient continues on infliximab. In clinical trials, the combination of infliximab and MTX halted progression of joint damage and was superior to MTX monotherapy. Infliximab may increase the risk of infection, especially upper respiratory infections. An acute infusion reaction with fever, chills, pruritus, and rash may occur within 1 to 2 hours after administration. Autoantibodies and lupus-like syndrome have also been reported.
- **Adalimumab** (Humira) is a human IgG<sub>1</sub> antibody to TNF that is less antigenic than infliximab. It has response rates similar to other TNF

inhibitors. Local injection site reactions were the most common adverse event reported in clinical trials. It has the same precautions regarding infections as the other biologics.

- **Anakinra** (Kineret) is an IL-1 receptor antagonist (IL-1ra) that binds to IL-1 receptors on target cells, preventing the interaction between IL-1 and the cells. IL-1 normally stimulates release of chemotactic factors and adhesion molecules that promote migration of inflammatory leukocytes to tissues. The drug is approved for moderately to severely active RA in adults who have failed one or more DMARDs. It can be used alone or in combination with any of the other DMARDs except for TNF-blocking agents. Many authorities believe that anakinra has a less robust response than TNF inhibitors and reserve it for patients who fail those agents. Injection-site reactions were the most common adverse effect (e.g., redness, swelling, pain). Infection risk and precautions are similar to those for the TNF inhibitors.
- **Abatacept** (Orencia) is a costimulation modulator approved for patients with moderate to severe disease who fail to achieve an adequate response from one or more DMARDs. By binding to CD80/CD86 receptors on antigen-presenting cells, abatacept inhibits interactions between the antigen-presenting cells and T cells, preventing T cells from activating to promote the inflammatory process. The drug is well tolerated, with infusion reactions, headache, nasopharyngitis, dizziness, cough, back pain, hypertension, dyspepsia, urinary tract infection, rash, and extremity pain reported more frequently in clinical trials.
- **Rituximab** (Rituxan) is a monoclonal chimeric antibody consisting of mostly human protein with the antigen-binding region derived from a mouse antibody to CD20 protein found on the cell surface of mature B lymphocytes. Binding of rituximab to B cells results in nearly complete depletion of peripheral B cells, with a gradual recovery over several months. Rituximab is useful in patients failing MTX or TNF inhibitors. Methylprednisolone 100 mg should be given 30 minutes prior to rituximab to reduce the incidence and severity of infusion reactions. Acetaminophen and antihistamines may also benefit patients who have a history of reactions. MTX should be given concurrently in the usual doses for RA to achieve the best therapeutic outcomes.

### Corticosteroids

- **Corticosteroids** have antiinflammatory and immunosuppressive properties. They interfere with antigen presentation to T lymphocytes, inhibit prostaglandin and leukotriene synthesis, and inhibit neutrophil and monocyte superoxide radical generation.
- Oral corticosteroids (e.g., **prednisone, methylprednisolone**) can be used to control pain and synovitis while DMARDs are taking effect (“bridging therapy”). This is often used in patients with debilitating symptoms when DMARD therapy is initiated.
- Low-dose, long-term corticosteroid therapy may be used to control symptoms in patients with difficult-to-control disease. Prednisone doses below 7.5 mg/day (or equivalent) are well tolerated but are not devoid of the long-term corticosteroid adverse effects. The lowest dose that controls

symptoms should be used. Alternate-day dosing of low-dose oral corticosteroids is usually ineffective in RA.

- High-dose oral or intravenous bursts may be used for several days to suppress disease flares. After symptoms are controlled, the drug should be tapered to the lowest effective dose.
- The IM route is preferable in nonadherent patients. Depot forms (**triamcinolone acetonide**, **triamcinolone hexacetonide**, **methylprednisolone acetate**) provide 2 to 6 weeks of symptomatic control. The onset of effect may be delayed for several days. The depot effect provides a physiologic taper, avoiding hypothalamic-pituitary axis suppression.
- Intraarticular injections of depot forms may be useful when only a few joints are involved. If effective, injections may be repeated every 3 months. No one joint should be injected more than two or three times per year.
- Adverse effects of systemic glucocorticoids limit their long-term use. Dosage tapering and eventual discontinuation should be considered at some point in patients receiving chronic therapy.

## EVALUATION OF THERAPEUTIC OUTCOMES

- Clinical signs of improvement include reduction in joint swelling, decreased warmth over actively involved joints, and decreased tenderness to joint palpation.
- Symptom improvement includes reduction in joint pain and morning stiffness, longer time to onset of afternoon fatigue, and improvement in ability to perform daily activities.
- Periodic joint radiographs may be useful in assessing disease progression.
- Laboratory monitoring is of little value in monitoring response to therapy but is essential for detecting and preventing adverse drug effects (see Table 4-2).
- Patients should be questioned about the presence of symptoms that may be related to adverse drug effects (see Table 4-3).

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*See Chap. 94, Rheumatoid Arthritis, authored by Arthur A. Schuna, for a detailed discussion of this topic.*

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## DEFINITIONS

- Acute coronary syndromes (ACSs) include all clinical syndromes compatible with acute myocardial ischemia resulting from an imbalance between myocardial oxygen demand and supply.
- In contrast to stable angina, an ACS results primarily from diminished myocardial blood flow secondary to an occlusive or partially occlusive coronary artery thrombus.
- ACSs are classified according to electrocardiographic (ECG) changes into (1) ST-segment-elevation ACS (STE ACS or STEMI) and (2) non-ST-segment-elevation ACS (NSTEMI ACS), which includes non-ST-segment-elevation myocardial infarction (NSTEMI) and unstable angina (UA).
- After a STEMI, pathologic Q waves are seen frequently on the ECG and usually indicate transmural MI. Non-Q-wave MI, which is seen predominantly in NSTEMI, is limited to the subendocardial myocardium.
- NSTEMI differs from UA in that ischemia is severe enough to produce myocardial necrosis, resulting in release of detectable amounts of biochemical markers, primarily troponin I or T and creatine kinase myocardial band (CK-MB) from the necrotic myocytes into the bloodstream.

## PATHOPHYSIOLOGY

- The formation of atherosclerotic plaques is the underlying cause of coronary artery disease (CAD) and ACS in most patients. Endothelial dysfunction leads to the formation of fatty streaks in the coronary arteries and eventually to atherosclerotic plaques. Factors responsible for development of atherosclerosis include hypertension, age, male gender, tobacco use, diabetes mellitus, obesity, and dyslipidemia.
- The cause of ACS in more than 90% of patients is rupture, fissuring, or erosion of an unstable atheromatous plaque. Plaques most susceptible to rupture have an eccentric shape, thin fibrous cap, large fatty core, high content of inflammatory cells such as macrophages and lymphocytes, limited amounts of smooth muscle, and significant compensatory enlargement.
- A partially or completely occlusive clot forms on top of the ruptured plaque. Exposure of collagen and tissue factor induce platelet adhesion and activation, which promote release of adenosine diphosphate and thromboxane A<sub>2</sub> from platelets. These produce vasoconstriction and potentiate platelet activation. A change in the conformation of the glycoprotein (GP) IIb/IIIa surface receptors of platelets occurs that cross-links platelets to each

other through fibrinogen bridges (the final common pathway of platelet aggregation).

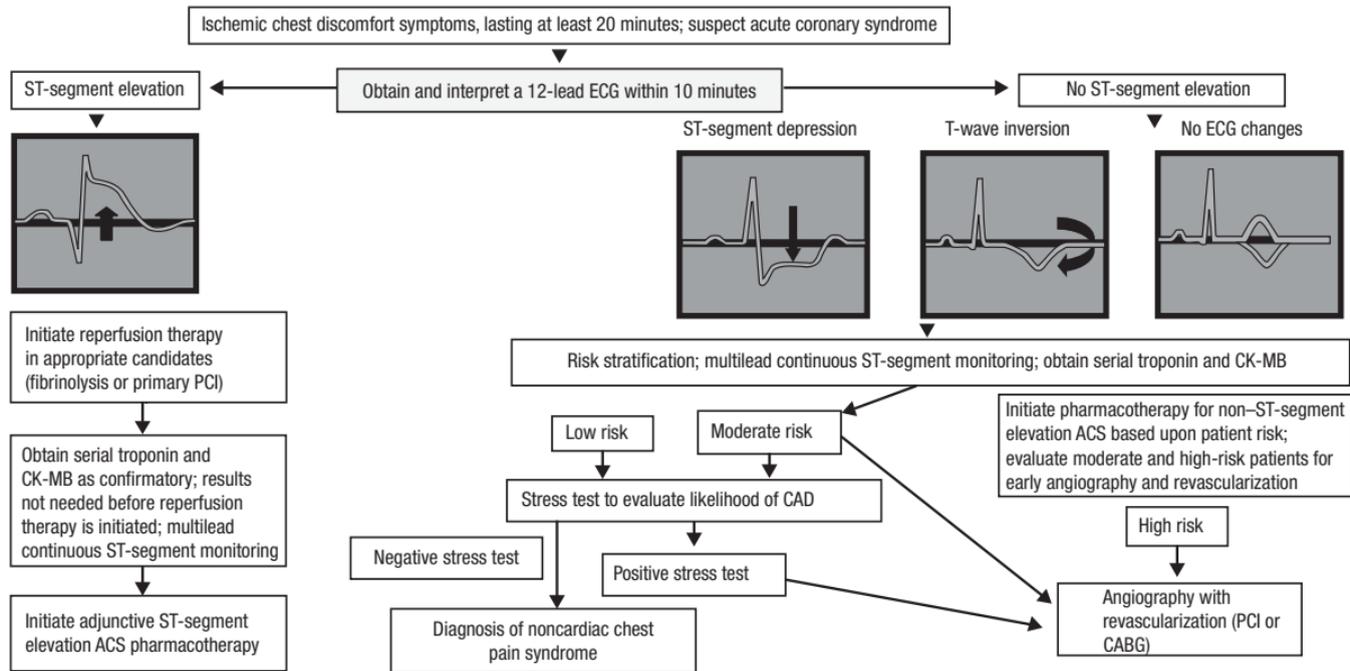
- Simultaneously, activation of the extrinsic coagulation cascade occurs as a result of exposure of blood to the thrombogenic lipid core and endothelium, which are rich in tissue factor. This pathway ultimately leads to the formation of a fibrin clot composed of fibrin strands, cross-linked platelets, and trapped red blood cells.
- Ventricular remodeling occurs after an MI and is characterized by changes in the size, shape, and function of the left ventricle that may lead to cardiac failure. Factors contributing to ventricular remodeling include neurohormonal factors (e.g., activation of the renin-angiotensin-aldosterone and sympathetic nervous systems), hemodynamic factors, mechanical factors, changes in gene expression, and modifications in myocardial matrix metalloproteinase activity and their inhibitors. This process may lead to cardiomyocyte hypertrophy, loss of cardiomyocytes, and increased interstitial fibrosis, which promote both systolic and diastolic dysfunction.
- Complications of MI include cardiogenic shock, heart failure, valvular dysfunction, various arrhythmias, pericarditis, stroke secondary to left ventricular (LV) thrombus embolization, venous thromboembolism, and LV free-wall rupture.

## CLINICAL PRESENTATION

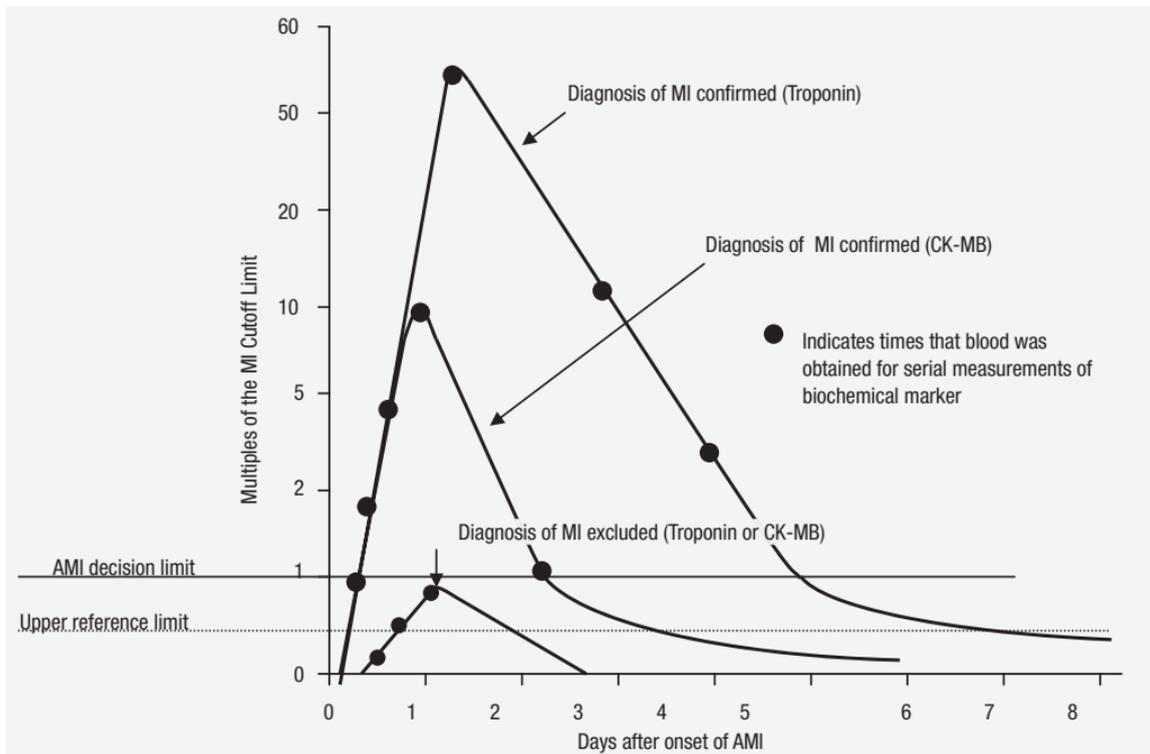
- The predominant symptom of ACS is midline anterior chest discomfort (most often occurring at rest), severe new-onset angina, or increasing angina that lasts at least 20 minutes. The discomfort may radiate to the shoulder, down the left arm, to the back, or to the jaw. Accompanying symptoms may include nausea, vomiting, diaphoresis, or shortness of breath. Elderly patients, patients with diabetes, and women are less likely to present with classic symptoms.
- There are no specific features indicative of ACS on physical examination. However, patients with ACS may present with signs of acute heart failure or arrhythmias.

## DIAGNOSIS

- A 12-lead ECG should be obtained within 10 minutes of patient presentation. Key findings indicating myocardial ischemia or MI are ST-segment elevation, ST-segment depression, and T-wave inversion (Fig. 5-1). These changes in certain groupings of leads help to identify the location of the involved coronary artery. The appearance of a new left bundle-branch block accompanied by chest discomfort is highly specific for acute MI. Some patients with myocardial ischemia have no ECG changes, so biochemical markers and other risk factors for CAD should be assessed to determine the patient's risk for experiencing a new MI or other complications.
- Biochemical markers of myocardial cell death are important for confirming the diagnosis of MI. An evolving MI is defined as a typical rise and gradual fall in troponin I or T or a more rapid rise and fall of CK-MB (Fig. 5-2). Typically, blood is obtained immediately and two additional times in



**FIGURE 5-1.** Evaluation of the acute coronary syndrome (ACS) patient. (CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; CK-MB, creatine kinase myocardial band; ECG, electrocardiogram; PCI, percutaneous coronary intervention.) (Reprinted with permission from the American College of Clinical Pharmacy. Spinler SA. Acute coronary syndromes. In: Dunsworth TS, Richardson MM, Cheng JWM, et al, eds. *Pharmacotherapy Self-Assessment Program*, 6th ed. Cardiology II module. Kansas City: American College of Clinical Pharmacy, 2007:69–70.)



**FIGURE 5-2.** Biochemical markers in suspected acute coronary syndrome. (AMI, acute myocardial infarction; CK-MB, creatine kinase myocardial band; MI, myocardial infarction.)

the first 12 to 24 hours after presentation. An MI is identified if at least one troponin value or two CK-MB values are greater than the MI decision limit set by the hospital. Both troponins and CK-MB are detectable within 6 hours of MI. Troponins remain elevated for up to 10 days, whereas CK-MB returns to normal within 48 hours.

- Patient symptoms, past medical history, ECG, and troponin or CK-MB determinations are used to stratify patients into low, medium, or high risk of death or MI or likelihood of needing urgent coronary angiography and percutaneous coronary intervention (PCI).

## DESIRED OUTCOME

- Short-term goals of therapy include: (1) early restoration of blood flow to the infarct-related artery to prevent infarct expansion (in the case of MI) or prevent complete occlusion and MI (in UA), (2) prevention of complications and death, (3) prevention of coronary artery reocclusion, (4) relief of ischemic chest discomfort, and (5) maintenance of normoglycemia.

## TREATMENT

### GENERAL APPROACH

- General treatment measures include hospital admission, oxygen administration if saturation is less than 90%, continuous multilead ST-segment monitoring for arrhythmias and ischemia, glycemic control, frequent measurement of vital signs, bedrest for 12 hours in hemodynamically stable patients, use of stools softeners to avoid Valsalva maneuver, and pain relief.
- Blood chemistry tests that should be performed include potassium and magnesium (which may affect heart rhythm), glucose (which when elevated places the patient at higher risk for morbidity and mortality), serum creatinine (to identify patients who may need drug dosing adjustments), baseline complete blood cell count and coagulation tests (because most patients receive antithrombotic therapy, which increases bleeding risk), and fasting lipid panel. The fasting lipid panel should be drawn within the first 24 hours of hospitalization because values for cholesterol (an acute phase reactant) may be falsely low after that period.
- It is important to triage and treat patients according to their risk category (see Fig. 5-1).
- Patients with STE ACS are at high risk of death, and efforts to reestablish coronary perfusion should be initiated immediately (without evaluation of biochemical markers).
- Patients with NSTEMI ACS who are considered to be at low risk (based on TIMI risk score) should have serial biochemical markers obtained. If they are negative, the patient may be admitted to a general medical floor with ECG telemetry monitoring, undergo a noninvasive stress test, or may be discharged.
- High-risk NSTEMI ACS patients should undergo early coronary angiography (within 24 to 48 hours) and revascularization if a significant coronary artery stenosis is found. Moderate-risk patients with positive biochemical

markers typically also undergo angiography and revascularization, if indicated.

- Moderate-risk patients with negative biochemical markers may initially undergo a noninvasive stress test, with only those having a positive test proceeding to angiography.

## NONPHARMACOLOGIC THERAPY

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- For patients with STE ACS, either fibrinolysis or primary PCI (with either balloon angioplasty or stent placement) is the treatment of choice for reestablishing coronary artery blood flow when the patient presents within 3 hours of symptom onset. Primary PCI may be associated with a lower mortality rate than fibrinolysis, possibly because PCI opens more than 90% of coronary arteries compared with less than 60% opened with fibrinolytics. The risks of intracranial hemorrhage (ICH) and major bleeding are also lower with PCI than with fibrinolysis. Primary PCI is generally preferred if institutions have skilled interventional cardiologists and other necessary facilities, in patients with cardiogenic shock, in patients with contraindications to fibrinolytics, and in patients presenting with symptom onset more than 3 hours prior.
- In patients with NSTEMI ACS, clinical practice guidelines recommend either PCI or coronary artery bypass grafting revascularization as an early treatment for high-risk patients, and that such an approach also be considered for moderate-risk patients. An early invasive approach results in fewer MIs, less need for revascularization procedures over the next year after hospitalization, and lower cost than the conservative medical stabilization approach.

## EARLY PHARMACOTHERAPY FOR ST-SEGMENT-ELEVATION ACUTE CORONARY SYNDROME

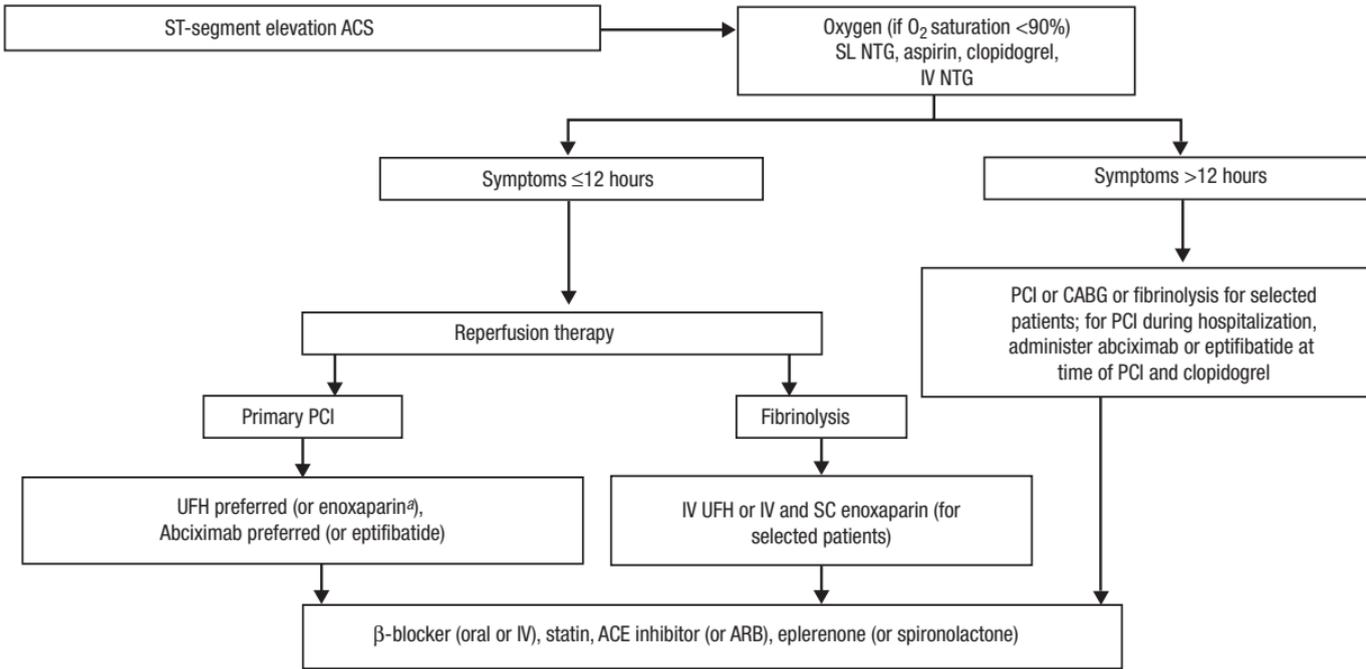
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(Fig. 5-3)

- According to the American College of Cardiology/American Heart Association (ACC/AHA) practice guidelines, early pharmacologic therapy should include: (1) intranasal oxygen (if oxygen saturation is less than 90%); (2) sublingual (SL) nitroglycerin (NTG); (3) aspirin; (4) a  $\beta$ -blocker; (5) unfractionated heparin (UFH) or enoxaparin; and (6) fibrinolysis in eligible candidates. Morphine is administered to patients with refractory angina as an analgesic and venodilator that lowers preload. These agents should be administered early, while the patient is still in the emergency department. An angiotensin-converting enzyme (ACE) inhibitor should be started within 24 hours of presentation, particularly in patients with left ventricular ejection fraction (LVEF)  $\leq 40\%$ , signs of heart failure, or an anterior wall MI, if there are no contraindications. IV NTG and  $\beta$ -blockers should be administered to selected patients without contraindications.

### Fibrinolytic Therapy

- A fibrinolytic agent is indicated in patients with STE ACS presenting within 12 hours of the onset of chest discomfort who have at least 1 mm of STE in two or more contiguous ECG leads or a new left bundle-branch



**FIGURE 5-3.** Initial pharmacotherapy for ST-segment elevation acute coronary syndromes (ACS). (ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft surgery; NTG, nitroglycerin; PCI, percutaneous coronary intervention; UFH, unfractionated heparin.) <sup>a</sup>Although recommended by the 2004 American College of Cardiology and American Heart Association practice guidelines, no dose recommendation is given. (Reprinted with permission from the American College of Clinical Pharmacy. Spinler SA. Acute coronary syndromes. In: Dunsworth TS, Richardson MM, Cheng JWM, et al., eds. *Pharmacotherapy Self-Assessment Program, 6th ed. Cardiology II module.* Kansas City: American College of Clinical Pharmacy, 2007:69–70.)

block. It should also be considered in patients with those findings and persistent symptoms of ischemia who present within 12 to 24 hours of symptom onset. Fibrinolysis is preferred over primary PCI in patients presenting within 3 hours of symptom onset when there would be a delay in performing primary PCI.

- It is not necessary to obtain the results of biochemical markers before initiating fibrinolytic therapy.
- Absolute contraindications to fibrinolytic therapy include: (1) active internal bleeding; (2) previous ICH at any time; (3) ischemic stroke within 3 months; (4) known intracranial neoplasm; (5) known structural vascular lesion; (6) suspected aortic dissection; and (7) significant closed head or facial trauma within 3 months. Primary PCI is preferred in these situations.
- Patients with relative contraindications to fibrinolytics may receive therapy if the perceived risk of death from MI is higher than the risk of major hemorrhage. These situations include: (1) severe, uncontrolled hypertension (blood pressure [BP] greater than 180/110 mm Hg); (2) history of prior ischemic stroke longer than 3 months prior, dementia, or known intracranial pathology not considered an absolute contraindication; (3) current anticoagulant use; (4) known bleeding diathesis; (5) traumatic or prolonged cardiopulmonary resuscitation or major surgery within 3 weeks; (6) non-compressible vascular puncture; (7) recent (within 2 to 4 weeks) internal bleeding; (8) pregnancy; (9) active peptic ulcer; (10) history of severe, chronic poorly controlled hypertension; and (11) for streptokinase, prior administration (>5 days) or prior allergic reactions.
- Practice guidelines indicate that a more fibrin-specific agent (alteplase, reteplase, tenecteplase) is preferred over the non-fibrin-specific agent streptokinase. Fibrin-specific agents open a greater percentage of infarct arteries, which results in smaller infarcts and lower mortality.
- Eligible patients should be treated as soon as possible, but preferably within 30 minutes from the time they present to the emergency department, with one of the following regimens:
  - ✓ **Alteplase:** 15-mg IV bolus followed by 0.75-mg/kg infusion (maximum 50 mg) over 30 minutes, followed by 0.5-mg/kg infusion (maximum 35 mg) over 60 minutes (maximum dose 100 mg).
  - ✓ **Reteplase:** 10 units IV over 2 minutes, followed 30 minutes later with another 10 units IV over 2 minutes.
  - ✓ **Tenecteplase:** A single IV bolus dose given over 5 seconds based on patient weight: 30 mg if <60 kg; 35 mg if 60 to 69.9 kg; 40 mg if 70 to 79.9 kg; 45 mg if 80 to 89.9 kg; and 50 mg if 90 kg or greater.
  - ✓ **Streptokinase:** 1.5 million units in 50 mL of normal saline or 5% dextrose in water IV over 60 minutes.
- ICH and major bleeding are the most serious side effects. The risk of ICH is higher with fibrin-specific agents than with streptokinase. However, the risk of systemic bleeding other than ICH is higher with streptokinase than with fibrin-specific agents.

### Aspirin

- **Aspirin** should be administered to all patients without contraindications within the first 24 hours of hospital admission. It provides an additional

mortality benefit in patients with STE ACS when given with fibrinolytic therapy.

- In patients experiencing an ACS, non-enteric-coated aspirin, 162 to 325 mg, should be chewed and swallowed as soon as possible after the onset of symptoms or immediately after presentation to the emergency department regardless of the reperfusion strategy being considered.
- A daily maintenance dose of 75 to 162 mg is recommended thereafter and should be continued indefinitely.
- For patients undergoing PCI and receiving stents, the recommended dose is 325 mg once daily for at least 30 days with bare metal stents, for 3 months with a sirolimus-eluting stent, and for 6 months with a paclitaxel-eluting stent, followed by 75 to 162 mg once daily thereafter.
- Low-dose aspirin is associated with a reduced risk of major bleeding, particularly GI bleeding. Other GI disturbances (e.g., dyspepsia, nausea) are infrequent with low-dose aspirin. Ibuprofen should not be administered on a regular basis concurrently with aspirin because it may block aspirin's antiplatelet effects.

### Thienopyridines

- **Clopidogrel** is recommended for patients with an aspirin allergy. A 300- to 600-mg loading dose is given on the first hospital day, followed by a maintenance dose of 75 mg daily. It should be continued indefinitely.
- For patients treated with fibrinolytics and in those receiving no revascularization therapy, clopidogrel either 75 mg or 300 mg on day 1 followed by 75 mg once daily should be given for at least 14 to 28 days in addition to aspirin.
- For patients undergoing primary PCI, clopidogrel is administered as a 300- to 600-mg loading dose followed by a 75 mg/day maintenance dose, in combination with aspirin 325 mg once daily, to prevent subacute stent thrombosis and long-term cardiovascular events.
- The most frequent side effects of clopidogrel are nausea, vomiting, and diarrhea (5% of patients). Thrombotic thrombocytopenia purpura has been reported rarely. The most serious side effect of clopidogrel is hemorrhage.
- **Ticlopidine** is associated with neutropenia that requires frequent monitoring of the complete blood cell count during the first 3 months of use. For this reason, clopidogrel is the preferred thienopyridine for ACS and PCI patients.

### Glycoprotein IIb/IIIa Receptor Inhibitors

- **Abciximab** is a first-line GP IIb/IIIa inhibitor for patients undergoing primary PCI who have not received fibrinolytics. It should not be administered to STE ACS patients who will not be undergoing PCI.
- Abciximab is preferred over **eptifibatide** and **tirofiban** in this setting because it is the most widely studied agent in primary PCI trials.
- Abciximab, in combination with aspirin, a thienopyridine, and UFH (administered as an infusion for the duration of the procedure), reduces mortality and reinfarction without increasing the risk of major bleeding.
- The dose of abciximab is 0.25 mg/kg IV bolus given 10 to 60 minutes before the start of PCI, followed by 0.125 mcg/kg/min (maximum 10 mcg/min) for 12 hours.

- GP IIb/IIIa inhibitors may increase the risk of bleeding, especially if given in the setting of recent (<4 hours) administration of fibrinolytic therapy. An immune-mediated thrombocytopenia occurs in about 5% of patients.

### Anticoagulants

- **UFH** is a first-line anticoagulant for STE ACS, both for medical therapy and PCI.
- UFH should be initiated in the emergency department and continued for at least 48 hours in patients who will receive chronic warfarin after acute MI. If a patient undergoes PCI, UFH is discontinued immediately after the procedure.
- If a fibrinolytic agent is administered, UFH is given concomitantly with alteplase, reteplase, and tenecteplase, but UFH is not administered with streptokinase because no benefit of combined therapy has been demonstrated. Rates of reinfarction are higher if UFH is not given with the fibrin-selective agents.
- For STE ACS, the dose of UFH is 60 units/kg IV bolus (maximum 4,000 units) followed by a continuous IV infusion of 12 units/kg/hour (maximum 1,000 units/hour).
- The dose is titrated to maintain the activated partial thromboplastin time (aPTT) between 50 and 70 seconds. The first aPTT should be measured at 3 hours in patients with STE ACS who are treated with fibrinolytics and at 4 to 6 hours in patients not receiving thrombolytics.
- Besides bleeding, the most frequent adverse effect of UFH is immune-mediated thrombocytopenia, which occurs in up to 5% of patients.
- **Low-molecular-weight heparins** (LMWHs) may be an alternative to UFH in STE ACS. **Enoxaparin** may produce a modest benefit over UFH in reducing the risk of death or nonfatal MI. Enoxaparin has not been studied in the setting of primary PCI.

### Nitrates

- Immediately upon presentation, one SL NTG tablet should be administered every 5 minutes for up to three doses to relieve chest pain and myocardial ischemia.
- Intravenous NTG should be initiated in all patients with an ACS who do not have a contraindication and who have persistent ischemic symptoms, heart failure, or uncontrolled high BP. The usual dose is 5 to 10 mcg/min by continuous infusion, titrated up to 200 mcg/min until relief of symptoms or limiting side effects (e.g., headache or hypotension). Treatment should be continued for approximately 24 hours after ischemia is relieved.
- NTG causes venodilation, which lowers preload and myocardial oxygen demand. In addition, arterial vasodilation may lower BP, thereby reducing myocardial oxygen demand. Arterial dilation also relieves coronary artery vasospasm and improves myocardial blood flow and oxygenation.
- Oral nitrates play a limited role in ACS because clinical trials have failed to show a mortality benefit for IV followed by oral nitrate therapy in acute MI. Therefore, other life-saving therapy, such as ACE inhibitors and  $\beta$ -blockers, should not be withheld.
- The most significant adverse effects of nitrates are tachycardia, flushing, headache, and hypotension. Nitrates are contraindicated in patients who

have taken the oral phosphodiesterase-5 inhibitors sildenafil or vardenafil within the prior 24 hours or tadalafil within the prior 48 hours.

### $\beta$ -Adrenergic Blockers

- If there are no contraindications, a  $\beta$ -blocker should be administered early in the care of patients with STE ACS (within the first 24 hours) and continued indefinitely.
- The benefits result from blockade of  $\beta_1$  receptors in the myocardium, which reduces heart rate, myocardial contractility, and BP, thereby decreasing myocardial oxygen demand. The reduced heart rate increases diastolic time, thus improving ventricular filling and coronary artery perfusion.
- Because of these effects,  $\beta$ -blockers reduce the risk for recurrent ischemia, infarct size, risk of reinfarction, and occurrence of ventricular arrhythmias.
- The usual doses of  $\beta$ -blockers are as follows:
  - ✓ **Metoprolol:** 5 mg by slow (over 1 to 2 minutes) IV bolus, repeated every 5 minutes for a total initial dose of 15 mg. If a conservative regimen is desired, initial doses can be reduced to 1 to 2 mg. This is followed in 15 to 30 minutes by 25 to 50 mg orally every 6 hours. If appropriate, initial IV therapy may be omitted.
  - ✓ **Propranolol:** 0.5 to 1 mg slow IV push, followed in 1 to 2 hours by 40 to 80 mg orally every 6 to 8 hours. If appropriate, the initial IV therapy may be omitted.
  - ✓ **Atenolol:** 5 mg IV dose, followed 5 minutes later by a second 5-mg IV dose; then 50 to 100 mg orally every day beginning 1 to 2 hours after the IV dose. The initial IV therapy may be omitted.
  - ✓ **Esmolol:** Starting maintenance dose of 0.1 mg/kg/min IV, with titration in increments of 0.05 mg/kg/min every 10 to 15 minutes as tolerated by BP until the desired therapeutic response is obtained, limiting symptoms develop, or a dose of 0.2 mg/kg/min is reached. An optional loading dose of 0.5 mg/kg may be given by slow IV administration (2 to 5 minutes) for more rapid onset of action. Alternatively, the initial IV therapy may be omitted.
- The most serious side effects early in ACS are hypotension, bradycardia, and heart block. Initial acute administration of  $\beta$ -blockers is not appropriate for patients presenting with decompensated heart failure. However, therapy may be attempted in most patients before hospital discharge after treatment of acute heart failure. Diabetes mellitus is not a contraindication to  $\beta$ -blocker use. If possible intolerance to  $\beta$ -blockers is a concern (e.g., due to chronic obstructive pulmonary disease), a short-acting drug such as metoprolol or esmolol should be administered IV initially.

### Calcium Channel Blockers

- In the setting of STE ACS, calcium channel blockers are reserved for patients who have contraindications to  $\beta$ -blockers. They are used for relief of ischemic symptoms only.
- Patients who had been prescribed calcium channel blockers for hypertension who are not receiving  $\beta$ -blockers and who do not have a contraindication should have the calcium channel blocker discontinued and a  $\beta$ -blocker initiated.

- Dihydropyridine channel blockers (e.g., **nifedipine**) have little benefit on clinical outcomes beyond symptom relief. The role of **verapamil** and **diltiazem** appears to be limited to symptom relief or control of heart rate in patients with supraventricular arrhythmias in whom  $\beta$ -blockers are contraindicated or ineffective.
- Patients with variant (Prinzmetal's) angina or cocaine-induced ACS may benefit from calcium channel blockers as initial therapy because they can reverse coronary vasospasm.  $\beta$ -Blockers generally should be avoided in these situations because they may worsen vasospasm through an unopposed  $\beta_2$ -blocking effect on smooth muscle.

## EARLY PHARMACOTHERAPY FOR NON-ST-SEGMENT-ELEVATION ACUTE CORONARY SYNDROME

(Fig. 5-4)

- Early pharmacotherapy for NSTEMI ACS is similar to that for STE ACS except that: (1) fibrinolytic therapy is not administered; (2) GP IIb/IIIa receptor blockers are administered to high-risk patients; and (3) there are no standard quality performance measures for patients with NSTEMI ACS with UA.
- According to ACC/AHA practice guidelines, early pharmacotherapy should include: (1) **intranasal oxygen** (if oxygen saturation is  $<90\%$ ); (2) SL **NTG** (IV therapy for selected patients); (3) **aspirin**; (4) an oral  **$\beta$ -blocker** (IV therapy optional); and (5) an **anticoagulant** (**UFH, LMWH [enoxaparin], fondaparinux, or bivalirudin**). **Morphine** is also administered to patients with refractory angina, as described previously. These agents should be administered early, while the patient is still in the emergency department.

### Fibrinolytic Therapy

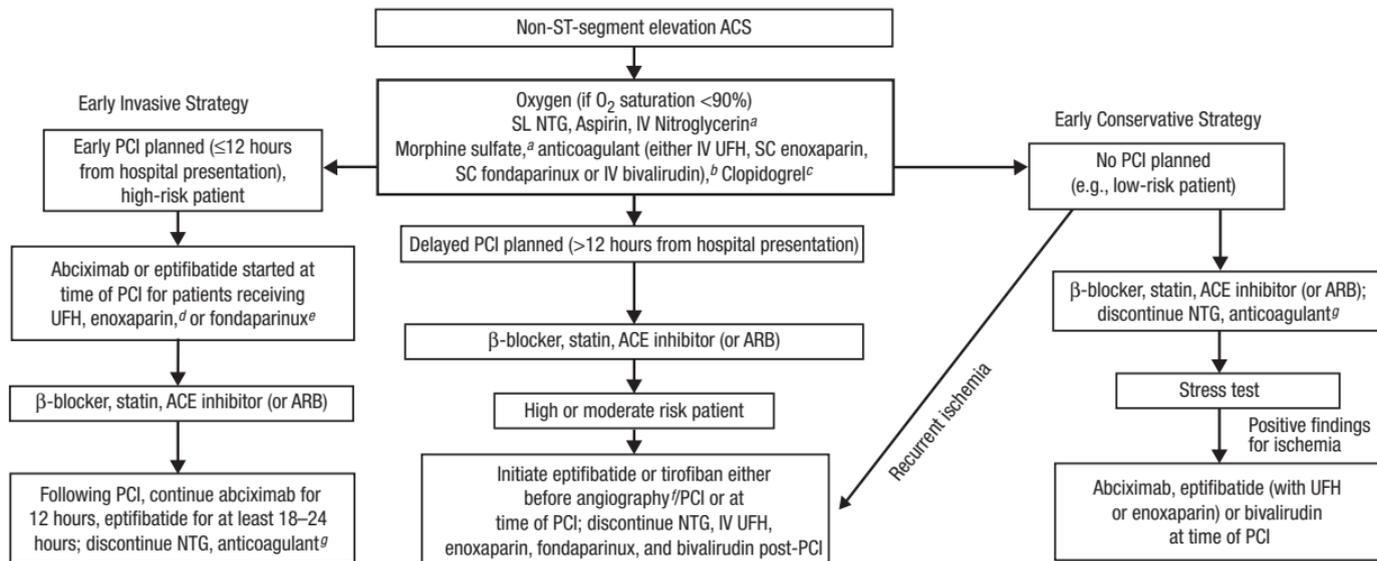
- Fibrinolytics are not indicated in any patient with NSTEMI ACS, even those who have positive biochemical markers that indicate infarction. The risk of death from MI is lower in these patients, and the hemorrhagic risks of fibrinolytic therapy outweigh the benefit.

### Aspirin

- **Aspirin** reduces the risk of death or developing MI by about 50% compared with no antiplatelet therapy in patients with NSTEMI ACS. Dosing of aspirin is the same as for STE ACS, and aspirin is continued indefinitely.

### Thienopyridines

- The addition of **clopidogrel** started on the first day of hospitalization as a 300- to 600-mg loading dose followed the next day by 75 mg/day orally is recommended for most patients. Although aspirin is the mainstay of antiplatelet therapy in ACS, addition of clopidogrel may further reduce morbidity and mortality.
- According to ACC/AHA 2007 guidelines, clopidogrel is indicated for up to 12 months in NSTEMI ACS patients, with a minimum treatment duration of 1 month after placement of a bare-metal stent and 12 months after placement of a sirolimus- or paclitaxel-coated stent.



**FIGURE 5-4.** Initial pharmacotherapy for non–ST-segment elevation acute coronary syndrome (ACS). (ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft surgery; NTG, nitroglycerin; PCI, percutaneous coronary intervention; UFH, unfractionated heparin.) <sup>a</sup>For selected patients. <sup>b</sup>Enoxaparin, UFH, fondaparinux, or bivalirudin for early invasive strategy; enoxaparin or fondaparinux preferred if no angiography/PCI planned but UFH acceptable; fondaparinux preferred if high risk for bleeding; UFH preferred anticoagulant for patients undergoing CABG. <sup>c</sup>In patients unlikely to undergo CABG. <sup>d</sup>May require an IV supplemental dose. <sup>e</sup>Requires supplemental UFH bolus for PCI. <sup>f</sup>For signs and symptoms of recurrent ischemia. <sup>g</sup>SC enoxaparin or UFH can be continued at a lower dose for venous thromboembolism prophylaxis. (Adapted with permission from the American College of Clinical Pharmacy. Spinler SA. Acute coronary syndromes. In: Dunsworth TS, Richardson MM, Cheng JWM, et al., eds. *Pharmacotherapy Self-Assessment Program, 6th ed. Cardiology II module. Kansas City: American College of Clinical Pharmacy, 2007:69–70.*)

- Because of the potential increased risk for bleeding with combination antiplatelet therapy, a low dose of aspirin (75 to 100 mg/day) is recommended for maintenance therapy with clopidogrel.
- In patients undergoing coronary artery bypass grafting, clopidogrel (but not aspirin) should be withheld at least 5 days and preferably 7 days before the procedure.

### Glycoprotein IIb/IIIa Receptor Inhibitors

- Administration of **tirofiban** or **eptifibatide** is recommended for high-risk NSTEMI ACS patients as medical therapy without planned revascularization.
- Administration of either abciximab or eptifibatide is recommended for NSTEMI ACS patients undergoing PCI.
- Tirofiban and eptifibatide are also indicated in patients with continued or recurrent ischemia despite treatment with aspirin, clopidogrel, and an anticoagulant.

### Anticoagulants

- For patients with NSTEMI ACS undergoing planned early angiography and revascularization with PCI, **UFH**, **LMWH (enoxaparin)**, **fondaparinux**, or **bivalirudin** should be administered. Therapy should be continued for up to 48 hours for UFH, until the patient is discharged, or a maximum of 8 days for either enoxaparin or fondaparinux, and until the end of the PCI or angiography procedure (or up to 42 hours after PCI) for bivalirudin.
- In patients initiating warfarin therapy, UFH or LMWHs should be continued until the international normalized ratio with warfarin is in the therapeutic range.
- For NSTEMI ACS, the dose of UFH is 60 to 70 units/kg IV bolus (maximum 5,000 units) followed by a continuous IV infusion of 12 to 15 units/kg/hour (maximum 1,000 units/hour). The dose is titrated to maintain the aPTT between 1.5 and 2.5 times control.
- LMWHs are administered by a fixed, weight-based dose:
  - ✓ **Enoxaparin:** 1 mg/kg subcutaneously every 12 hours (extend the interval to 24 hours if creatinine clearance is less than 30 mL/min)
  - ✓ **Dalteparin:** 120 international units/kg subcutaneously every 12 hours (maximum single bolus dose of 10,000 units)

### Nitrates

- In the absence of contraindications, SL followed by IV **NTG** should be administered to all patients with NSTEMI ACS. IV **NTG** is continued for approximately 24 hours after ischemia relief.

### $\beta$ -Blockers

- In the absence of contraindications, oral  $\beta$ -blockers should be administered to all patients with NSTEMI ACS. IV  $\beta$ -blockers should be considered in hemodynamically stable patients who present with persistent ischemia, hypertension, or tachycardia. The drugs are continued indefinitely.

### Calcium Channel Blockers

- As described previously for STE ACS (page 53), calcium channel blockers should not be administered to most patients with ACS.

## SECONDARY PREVENTION AFTER MYOCARDIAL INFARCTION

### DESIRED OUTCOME

- The long-term goals after MI are to: (1) control modifiable coronary heart disease (CHD) risk factors; (2) prevent development of systolic heart failure; (3) prevent recurrent MI and stroke; and (4) prevent death, including sudden cardiac death.

### PHARMACOTHERAPY

#### General Approach

- Pharmacotherapy that has been proven to decrease mortality, heart failure, reinfarction, or stroke should be started before hospital discharge for secondary prevention.
- The ACC/AHA guidelines suggest that after MI from either STE or NSTEMI ACS, patients should receive indefinite treatment with **aspirin**, a  $\beta$ -**blocker**, and an **ACE inhibitor**.
- All patients should receive **SL NTG** or **lingual spray** and instructions for use in case of recurrent ischemic chest discomfort.
- **Clopidogrel** should be considered for most patients, but the duration of therapy is individualized according to the type of ACS and whether the patient is treated medically or undergoes stent implantation.
- All patients should receive annual **influenza vaccination**.
- Selected patients also should be treated with long-term **warfarin** anticoagulation.
- For all ACS patients, treatment and control of modifiable risk factors such as hypertension, dyslipidemia, and diabetes mellitus are essential.

#### Aspirin

- **Aspirin** decreases the risk of death, recurrent MI, and stroke after MI. All patients should receive aspirin indefinitely (or clopidogrel if there are aspirin contraindications).
- The risk of major bleeding from chronic aspirin therapy is approximately 2% and is dose related. Therefore, after an initial dose of 325 mg, chronic low doses of 75 to 81 mg are recommended unless a stent is placed.

#### Thienopyridines

- For patients with NSTEMI ACS, **clopidogrel** decreases the risk of death, MI, or stroke. Most patients with NSTEMI ACS should receive clopidogrel, in addition to aspirin, for up to 12 months.
- For patients with STEMI treated medically without revascularization, clopidogrel can be given for 14 to 28 days. If a stent has been implanted, clopidogrel can be continued for up to 12 months in patients at low risk for bleeding.

#### Anticoagulation

- **Warfarin** should be considered in selected patients after an ACS, including those with an LV thrombus, extensive ventricular wall motion abnormality,

ties on cardiac echocardiogram, and a history of thromboembolic disease or chronic atrial fibrillation.

### ***Blockers, Nitrates, and Calcium Channel Blockers***

- After an ACS, patients should receive a  $\beta$ -blocker indefinitely, regardless of whether they have residual symptoms of angina. Therapy should continue indefinitely in the absence of contraindications or intolerance.
- A calcium channel blocker can be used to prevent anginal symptoms in patients who cannot tolerate or have a contraindication to a  $\beta$ -blocker but should not be used routinely in the absence of such symptoms.
- All patients should be prescribed a short-acting SL NTG or lingual NTG spray to relieve anginal symptoms when necessary. Chronic long-acting nitrates have not been shown to reduce CHD event after MI. Therefore, chronic long-acting oral nitrates are not used in ACS patients who have undergone revascularization unless the patient has chronic stable angina or significant coronary stenosis that was not revascularized.

### ***ACE Inhibitors and Angiotensin Receptor Blockers***

- ACE inhibitors should be initiated in all patients after MI to reduce mortality, decrease reinfarction, and prevent the development of heart failure. Data suggest that most patients with CAD (not just those with ACS or heart failure) benefit from an ACE inhibitor.
- The dose should be low initially and titrated to the dose used in clinical trials if tolerated. Example doses include the following:
  - ✓ **Captopril:** 6.25 to 12.5 mg initially; target dose 50 mg two or three times daily.
  - ✓ **Enalapril:** 2.5 to 5 mg initially; target dose 10 mg twice daily.
  - ✓ **Lisinopril:** 2.5 to 5 mg initially; target dose 10 to 20 mg once daily.
  - ✓ **Ramipril:** 1.25 to 2.5 mg initially; target dose 5 mg twice daily or 10 mg once daily.
  - ✓ **Trandolapril:** 1 mg initially; target dose 4 mg once daily.
- An angiotensin receptor blocker may be prescribed for patients with ACE inhibitor cough and a low LVEF and heart failure after MI. Example doses include the following:
  - ✓ **Candesartan:** 4 to 8 mg initially; target dose 32 mg once daily.
  - ✓ **Valsartan:** 40 mg initially; target dose 160 mg twice daily.

### ***Aldosterone Antagonists***

- Either **eplerenone** or **spironolactone** should be considered within the first 2 weeks after MI to reduce mortality in all patients already receiving an ACE inhibitor who have LVEF  $\leq 40\%$  and either heart failure symptoms or a diagnosis of diabetes mellitus. The drugs are continued indefinitely. Example oral doses include the following:
  - ✓ **Eplerenone:** 25 mg initially; target dose 50 mg once daily.
  - ✓ **Spironolactone:** 12.5 mg initially; target dose 25 to 50 mg once daily.

### ***Lipid-Lowering Agents***

- All patients with CAD should receive dietary counseling and pharmacotherapy in order to reach a low-density lipoprotein (LDL) cholesterol

concentration <100 mg/dL. Newer recommendations from the National Cholesterol Education Program give an optional LDL goal of <70 mg/dL in selected patients.

- **Statins** are the preferred agents for lowering LDL cholesterol and should be prescribed at or near discharge in most patients.
- A **fibrate derivative** or **niacin** should be considered in selected patients with a low high-density lipoprotein (HDL) cholesterol (<40 mg/dL) and/or a high triglyceride level (>200 mg/dL).

### *Fish Oils (Marine-Derived Omega-3 Fatty Acids)*

- Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are omega-3 polyunsaturated fatty acids that are most abundant in fatty fish such as sardines, salmon, and mackerel. A diet high in EPA plus DHA or supplementation with these fish oils reduces the risk of cardiovascular mortality, reinfarction, and stroke in patients who have experienced an MI.
- The AHA recommends that CHD patients consume approximately 1 g EPA plus DHA per day, preferably from oily fish. Because of variable fish oil content, one would need to consume from four to more than 14 6-oz servings of fish per week to provide 7 g of the fish oils. Because the average diet provides only 10% to 20% of that amount, supplements may be considered in selected patients. Approximately three 1-g fish oil capsules per day should be consumed to provide 1 g of EPA/DHA, depending on the brand. Alternatively, the prescription drug LOVAZA (omega-3-acid ethyl esters) can be used at a dose of 1 g/day. Higher doses of EPA/DHA (2 to 4 g/day) may be considered for managing hypertriglyceridemia.
- Adverse effects of fish oils include fishy aftertaste, nausea, and diarrhea.

## EVALUATION OF THERAPEUTIC OUTCOMES

- Monitoring parameters for efficacy of therapy for both STE and NSTEMI ACS include: (1) relief of ischemic discomfort; (2) return of ECG changes to baseline; and (3) absence or resolution of heart failure signs.
- Monitoring parameters for adverse effects are dependent upon the individual drugs used. In general, the most common adverse reactions from ACS therapies are hypotension and bleeding.

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*See Chap. 18, Acute Coronary Syndromes, authored by Sarah A. Spinler and Simon de Denus, for a more detailed discussion of this topic.*

**DEFINITION**

- Arrhythmia is defined as loss of cardiac rhythm, especially irregularity of heartbeat. This chapter covers the group of conditions caused by an abnormality in the rate, regularity, or sequence of cardiac activation.

**PATHOPHYSIOLOGY****SUPRAVENTRICULAR ARRHYTHMIAS**

- Common supraventricular tachycardias requiring drug treatment are atrial fibrillation (AF) or atrial flutter, paroxysmal supraventricular tachycardia (PSVT), and automatic atrial tachycardias. Other common supraventricular arrhythmias that usually do not require drug therapy are not discussed in this chapter (e.g., premature atrial complexes, wandering atrial pacemaker, sinus arrhythmia, sinus tachycardia).

**Atrial Fibrillation and Atrial Flutter**

- AF is characterized as an extremely rapid (400 to 600 atrial beats/min) and disorganized atrial activation. There is a loss of atrial contraction (atrial kick), and supraventricular impulses penetrate the atrioventricular (AV) conduction system in variable degrees, resulting in irregular ventricular activation and irregularly irregular pulse (120 to 180 beats/min).
- Atrial flutter is characterized by rapid (270 to 330 atrial beats/min) but regular atrial activation. The ventricular response usually has a regular pattern and a pulse of 300 beats/min. This arrhythmia occurs less frequently than AF but has similar precipitating factors, consequences, and drug therapy.
- The predominant mechanism of AF and atrial flutter is reentry, which is usually associated with organic heart disease that causes atrial distention (e.g., ischemia or infarction, hypertensive heart disease, valvular disorders). Additional associated disorders include acute pulmonary embolus and chronic lung disease, resulting in pulmonary hypertension and cor pulmonale; and states of high adrenergic tone such as thyrotoxicosis, alcohol withdrawal, sepsis, or excessive physical exertion.

**Paroxysmal Supraventricular Tachycardia Caused by Reentry**

- PSVT arising by reentrant mechanisms includes arrhythmias caused by AV nodal reentry, AV reentry incorporating an anomalous AV pathway, sinoatrial (SA) nodal reentry, and intraatrial reentry.

**Automatic Atrial Tachycardias**

- Automatic atrial tachycardias such as multifocal atrial tachycardia appear to arise from supraventricular foci with enhanced automatic properties. Severe pulmonary disease is the underlying precipitating disorder in 60% to 80% of patients.

## VENTRICULAR ARRHYTHMIAS

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### Premature Ventricular Complexes

- Premature ventricular complexes (PVCs) are common ventricular rhythm disturbances that occur in patients with or without heart disease and may be elicited experimentally by abnormal automaticity, triggered activity, or reentrant mechanisms.

### Ventricular Tachycardia

- Ventricular tachycardia (VT) is defined by three or more repetitive PVCs occurring at a rate greater than 100 beats/min. It occurs most commonly in acute myocardial infarction (MI); other causes are severe electrolyte abnormalities (e.g., hypokalemia), hypoxemia, and digitalis toxicity. The chronic recurrent form is almost always associated with underlying organic heart disease (e.g., idiopathic dilated cardiomyopathy or remote MI with left ventricular [LV] aneurysm).
- Sustained VT is that which requires therapeutic intervention to restore a stable rhythm or that lasts a relatively long time (usually longer than 30 seconds). Nonsustained VT self-terminates after a brief duration (usually less than 30 seconds). *Incessant VT* refers to VT occurring more frequently than sinus rhythm, so that VT becomes the dominant rhythm. Monomorphic VT has a consistent QRS configuration, whereas polymorphic VT has varying QRS complexes. Torsade de pointes (TdP) is a polymorphic VT in which the QRS complexes appear to undulate around a central axis.

### Ventricular Proarrhythmia

- *Proarrhythmia* refers to development of a significant new arrhythmia (such as VT, ventricular fibrillation [VF], or TdP) or worsening of an existing arrhythmia. Proarrhythmia results from the same mechanisms that cause other arrhythmias or from an alteration in the underlying substrate due to the antiarrhythmic agent. TdP is a rapid form of polymorphic VT associated with evidence of delayed ventricular repolarization due to blockade of potassium conductance. TdP may be hereditary or acquired. Acquired forms are associated with many clinical conditions and drugs, especially type Ia and type III  $I_{Kr}$  blockers.

### Ventricular Fibrillation

- VF is electrical anarchy of the ventricle resulting in no cardiac output and cardiovascular collapse. Sudden cardiac death occurs most commonly in patients with ischemic heart disease and primary myocardial disease associated with LV dysfunction. VF associated with acute MI may be classified as either (1) primary (an uncomplicated MI not associated with heart failure [HF]) or (2) secondary or complicated (an MI complicated by HF).

## BRADYARRHYTHMIAS

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- Asymptomatic sinus bradyarrhythmias (heart rate less than 60 beats/min) are common especially in young, athletically active individuals. However, some patients have sinus node dysfunction (sick sinus syndrome) because of underlying organic heart disease and the normal aging process, which

attenuates SA nodal function. Sinus node dysfunction is usually representative of diffuse conduction disease, which may be accompanied by AV block and by paroxysmal tachycardias such as AF. Alternating bradyarrhythmias and tachyarrhythmias are referred to as the tachy-brady syndrome.

- AV block or conduction delay may occur in any area of the AV conduction system. AV block may be found in patients without underlying heart disease (e.g., trained athletes) or during sleep when vagal tone is high. It may be transient when the underlying etiology is reversible (e.g., myocarditis, myocardial ischemia, after cardiovascular surgery, during drug therapy).  $\beta$ -Blockers, digoxin, or nondihydropyridine calcium antagonists may cause AV block, primarily in the AV nodal area. Type I antiarrhythmics may exacerbate conduction delays below the level of the AV node. AV block may be irreversible if the cause is acute MI, rare degenerative disease, primary myocardial disease, or a congenital condition.

## CLINICAL PRESENTATION

- Supraventricular tachycardias may cause a variety of clinical manifestations ranging from no symptoms to minor palpitations and/or irregular pulse to severe and even life-threatening symptoms. Patients may experience dizziness or acute syncopal episodes; symptoms of HF; anginal chest pain; or, more often, a choking or pressure sensation during the tachycardia episode.
- AF or atrial flutter may be manifested by the entire range of symptoms associated with other supraventricular tachycardias, but syncope is not a common presenting symptom. An additional complication of AF is arterial embolization resulting from atrial stasis and poorly adherent mural thrombi, which accounts for the most devastating complication: embolic stroke. Patients with AF and concurrent mitral stenosis or severe systolic HF are at particularly high risk for cerebral embolism.
- PVCs often cause no symptoms or only mild palpitations. The presentation of VT may vary from totally asymptomatic to pulseless hemodynamic collapse. Consequences of proarrhythmia range from no symptoms to worsening of symptoms to sudden death. VF results in hemodynamic collapse, syncope, and cardiac arrest.
- Patients with bradyarrhythmias experience symptoms associated with hypotension such as dizziness, syncope, fatigue, and confusion. If LV dysfunction exists, symptoms of congestive HF may be exacerbated.

## DIAGNOSIS

- The surface electrocardiogram (ECG) is the cornerstone of diagnosis for cardiac rhythm disturbances.
- Less sophisticated methods are often the initial tools for detecting qualitative and quantitative alterations of heartbeat. For example, direct auscultation can reveal the irregularly irregular pulse that is characteristic of AF.
- Proarrhythmia can be difficult to diagnose because of the variable nature of underlying arrhythmias.

- TdP is characterized by long QT intervals or prominent U waves on the surface ECG.
- Specific maneuvers may be required to delineate the etiology of syncope associated with bradyarrhythmias. Diagnosis of carotid sinus hypersensitivity can be confirmed by performing carotid sinus massage with ECG and blood pressure monitoring. Vasovagal syncope can be diagnosed using the upright body-tilt test.
- On the basis of ECG findings, AV block is usually categorized into three different types (first-, second-, or third-degree AV block).

## DESIRED OUTCOME

- The desired outcome depends on the underlying arrhythmia. For example, the ultimate treatment goals of treating AF or atrial flutter are restoring sinus rhythm, preventing thromboembolic complications, and preventing further recurrences.

## TREATMENT

### GENERAL APPROACH

- The use of antiarrhythmic drugs in the United States is declining because of major trials that showed increased mortality with their use in several clinical situations, the realization of proarrhythmia as a significant side effect, and the advancing technology of nondrug therapies such as ablation and the implantable cardioverter-defibrillator (ICD).

### CLASSIFICATION OF ANTIARRHYTHMIC DRUGS

- Drugs may have antiarrhythmic activity by directly altering conduction in several ways. Drugs may depress the automatic properties of abnormal pacemaker cells by decreasing the slope of phase 4 depolarization and/or by elevating threshold potential. Drugs may alter the conduction characteristics of the pathways of a reentrant loop.
- The most frequently used classification system is that proposed by Vaughan Williams (Table 6-1). Type Ia drugs slow conduction velocity, prolong refractoriness, and decrease the automatic properties of sodium-dependent (normal and diseased) conduction tissue. Type Ia drugs are broad-spectrum antiarrhythmics, being effective for both supraventricular and ventricular arrhythmias.
- Although categorized separately, type Ib drugs probably act similarly to type Ia drugs, except that type Ib agents are considerably more effective in ventricular than supraventricular arrhythmias.
- Type Ic drugs profoundly slow conduction velocity while leaving refractoriness relatively unaltered. Although effective for both ventricular and supraventricular arrhythmias, their use for ventricular arrhythmias has been limited by the risk of proarrhythmia.
- Collectively, type I drugs can be referred to as sodium channel blockers. Antiarrhythmic sodium channel receptor principles account for drug com-

**TABLE 6-1** Classification of Antiarrhythmic Drugs

Type	Drug	Conduction Velocity <sup>d</sup>	Refractory Period	Automat-icity	Ion Block
Ia	Quinidine Procainamide Disopyramide	↓	↑	↓	Sodium (intermediate) Potassium
Ib	Lidocaine Mexiletine	0/↓	↓	↓	Sodium (fast on/off)
Ic	Flecainide Propafenone <sup>b</sup> Morizine <sup>c</sup>	↓↓	0	↓	Sodium (slow on/off) Potassium <sup>d</sup>
II <sup>e</sup>	β-Blockers	↓	↑	↓	Calcium (indirect)
III	Amiodarone <sup>f</sup> Dofetilide Sotalol <sup>b</sup> Ibutilide	0	↑↑	0	Potassium
IV <sup>e</sup>	Verapamil Diltiazem	↓	↑	↓	Calcium

0, no change; ↑, increased; ↓, decreased.

<sup>a</sup>Variables for normal tissue models in ventricular tissue.

<sup>b</sup>Also has type II, β-blocking actions.

<sup>c</sup>Classification controversial.

<sup>d</sup>Not clinically manifest.

<sup>e</sup>Variables for sinoatrial and atrioventricular nodal tissue only.

<sup>f</sup>Also has sodium, calcium, and β-blocking actions.

binations that are additive (e.g., **quinidine** and **mexiletine**) and antagonistic (e.g., **flecainide** and **lidocaine**), as well as potential antidotes to excess sodium channel blockade (e.g., sodium bicarbonate, propranolol).

- Type II drugs include **β-adrenergic antagonists**; clinically relevant mechanisms result from their antiadrenergic actions. β-Blockers are most useful in tachycardias in which nodal tissues are abnormally automatic or are a portion of a reentrant loop. These agents are also helpful in slowing ventricular response in atrial tachycardias (e.g., AF) by their effects on the AV node.
- Type III drugs specifically prolong refractoriness in atrial and ventricular fibers and include very different drugs that share the common effect of delaying repolarization by blocking potassium channels.
- **Bretylium** (rarely used) has additional actions in that it first releases and then depletes catecholamines. It increases the VF threshold and seems to have selective antifibrillatory but not antitachycardic effects. Bretylium can be effective in VF but is often ineffective in VT.
- In contrast, **amiodarone** and **sotalol** are effective in most supraventricular and ventricular tachycardias. Amiodarone displays electrophysiologic characteristics consistent with each type of antiarrhythmic drug. It is a sodium channel blocker with relatively fast on-off kinetics, has nonselective β-blocking actions, blocks potassium channels, and has slight calcium antagonist activity. The impressive effectiveness and low proarrhythmic potential of amiodarone have challenged the notion that selective ion channel blockade is preferable. Sotalol is a potent inhibitor of outward

potassium movement during repolarization and also possesses nonselective  $\beta$ -blocking actions. Ibutilide and dofetilide block the rapid component of the delayed potassium rectifier current.

- Type IV drugs inhibit calcium entry into the cell, which slows conduction, prolongs refractoriness, and decreases SA and AV nodal automaticity. **Calcium channel antagonists** are effective for automatic or reentrant tachycardias that arise from or use the SA or AV nodes.
- Recommended doses of the oral antiarrhythmic dosage forms are given in Table 6-2; usual IV antiarrhythmic doses are shown in Table 6-3; common side effects are listed in Table 6-4.

## ATRIAL FIBRILLATION OR ATRIAL FLUTTER

- Many methods are available for restoring sinus rhythm, preventing thromboembolic complications, and preventing further recurrences (Fig. 6-1); however, treatment selection depends in part on onset and severity of symptoms.
- If symptoms are severe and of recent onset, patients may require direct-current cardioversion (DCC) to restore sinus rhythm immediately.
- If patients are hemodynamically stable, the focus should be directed toward control of ventricular rate. Drugs that slow conduction and increase refractoriness in the AV node should be used as initial therapy. In patients with normal LV function (left ventricular ejection fraction  $>40\%$ ), IV  $\beta$ -blockers (**propranolol**, **metoprolol**, **esmolol**), **diltiazem**, or **verapamil** is recommended. If a high adrenergic state is the precipitating factor, IV  $\beta$ -blockers can be highly effective and should be considered first. In patients with left ventricular ejection fraction  $\leq 40\%$ , IV diltiazem and verapamil

**TABLE 6-2** Typical Maintenance Doses of Oral Antiarrhythmic Drugs

Drug	Dose	Dose Adjusted
Quinidine	200–300 mg sulfate salt q 6 h 324–648 mg gluconate salt q 8–12 h	HEP, age $>60$ years
Procainamide	500–1,000 mg q 6 h (Pronestyl SR) 1,000–2,000 mg q 12 h (Procanbid)	HEP, REN <sup>a</sup>
Disopyramide	100–150 mg q 6 h 200–300 mg q 12 h (SR form)	HEP, REN
Mexiletine	200–300 mg q 8 h	HEP
Flecainide	50–150 mg q 8 h	HEP, REN
Propafenone	150–300 mg q 8 h	HEP
Moricizine	200 mg q 8 h	HEP, REN
Sotalol	80–160 mg q 12 h	REN <sup>b</sup>
Dofetilide	500 mcg q 12 h	REN <sup>c</sup>
Amiodarone	400 mg two to three times daily until 10 g total, then 200–400 mg daily <sup>d</sup>	

HEP, hepatic disease; REN, renal dysfunction; SR, sustained-release.

<sup>a</sup>Accumulation of parent compound or metabolite (e.g., NAPA) may occur.

<sup>b</sup>Should not be used for atrial fibrillation when creatinine clearance  $<40$  mL/min.

<sup>c</sup>Dose should be based upon creatinine clearance; should not be used when creatinine clearance  $<20$  mL/min.

<sup>d</sup>Usual maintenance dose for atrial fibrillation is 200 mg/day (may further decrease dose to 100 mg/day with long-term use if patient clinically stable in order to decrease risk of toxicity); usual maintenance dose for ventricular arrhythmias is 300–400 mg/day.

**TABLE 6-3** Intravenous Antiarrhythmic Dosing

Drug	Clinical Situation	Dose
Amiodarone	Pulseless VT/VF	300 mg IV/IO push (can give additional 150 mg IV/IO push if persistent VT/VF), followed by infusion of 1 mg/min for 6 hours, then 0.5 mg/min
	Stable VT (with a pulse)	150 mg IV over 10 minutes, followed by infusion of 1 mg/min for 6 hours, then 0.5 mg/min
	AF (termination)	5 mg/kg IV over 30 minutes, followed by infusion of 1 mg/min for 6 hours, then 0.5 mg/min
Diltiazem	PSVT; AF (rate control)	0.25 mg/kg IV over 2 minutes (may repeat with 0.35 mg/kg IV over 2 minutes), followed by infusion of 5–15 mg/hour
Ibutilide	AF (termination)	1 mg IV over 10 minutes (may repeat if needed)
Lidocaine	Pulseless VT/VF	1–1.5 mg/kg IV/IO push (can give additional 0.5–0.75 mg/kg IV/IO push every 5–10 minutes if persistent VT/VF [maximum cumulative dose = 3 mg/kg]), followed by infusion of 1–4 mg/min (1–2 mg/min if liver disease or HF)
	Stable VT (with a pulse)	1–1.5 mg/kg IV push (can give additional 0.5–0.75 mg/kg IV push every 5–10 minutes if persistent VT [maximum cumulative dose = 3 mg/kg]), followed by infusion of 1–4 mg/min (1–2 mg/min if liver disease or HF)
Procainamide	AF (termination); stable VT (with a pulse)	15–18 mg/kg IV over 60 minutes, followed by infusion of 1–4 mg/min
Verapamil	PSVT; AF (rate control)	2.5–5 mg IV over 2 minutes (may repeat up to maximum cumulative dose of 20 mg); can follow with infusion of 2.5–15 mg/hour

AF, atrial fibrillation; HF, heart failure; IO, intraosseous; PSVT, paroxysmal supraventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia.

should be avoided and IV  $\beta$ -blockers should be used with caution. In patients having an exacerbation of HF symptoms, IV **digoxin** or **amiodarone** should be used as first-line therapy for ventricular rate control. IV amiodarone can also be used in patients who are refractory or have contraindications to  $\beta$ -blockers, nondihydropyridine calcium channel blockers, and digoxin.

- After treatment with AV nodal blocking agents and a subsequent decrease in ventricular response, the patient should be evaluated for the possibility of restoring sinus rhythm if AF persists.
- If sinus rhythm is to be restored, anticoagulation should be initiated prior to cardioversion because return of atrial contraction increases risk of thromboembolism. Patients with AF for longer than 48 hours or an unknown duration should receive warfarin (target international normalized ratio [INR] 2 to 3) for at least 3 weeks prior to cardioversion and continuing for at least 4 weeks after effective cardioversion and return of normal sinus rhythm. Patients with AF less than 48 hours in duration do not require warfarin, but it is recommended that these patients receive either IV unfractionated heparin or a low-molecular-weight heparin (subcutaneously at treatment doses) at presentation prior to cardioversion.
- After prior anticoagulation (or after transesophageal echocardiography demonstrated the absence of a thrombus, thereby obviating the need for warfarin) methods for restoring sinus rhythm in patients with AF or atrial

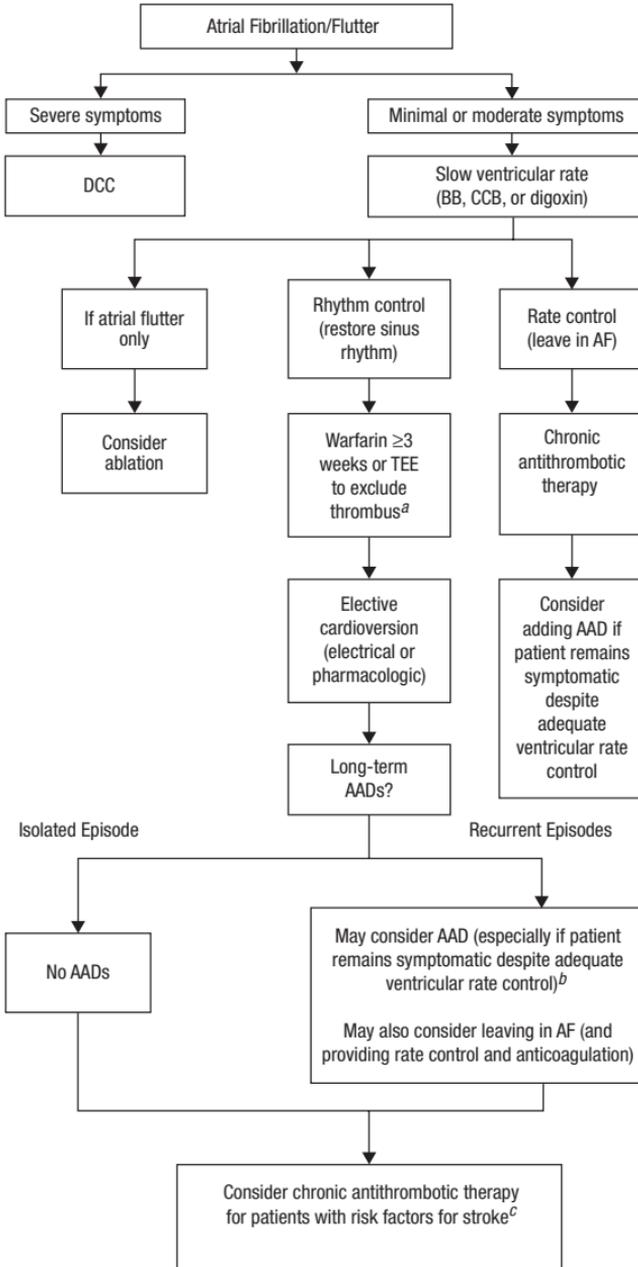
**TABLE 6-4** Side Effects of Antiarrhythmic Drugs

Quinidine	Cinchonism, diarrhea, abdominal cramps, nausea, vomiting, hypotension, TdP, aggravation of underlying HF, conduction disturbances or ventricular arrhythmias, fever, hepatitis, thrombocytopenia, hemolytic anemia
Procainamide	Systemic lupus erythematosus, diarrhea, nausea, vomiting, TdP, aggravation of underlying HF, conduction disturbances or ventricular arrhythmias, agranulocytosis
Disopyramide	Anticholinergic symptoms (dry mouth, urinary retention, constipation, blurred vision), nausea, anorexia, TdP, HF, aggravation of underlying conduction disturbances and/or ventricular arrhythmias, hypoglycemia
Lidocaine	Dizziness, sedation, slurred speech, blurred vision, paresthesia, muscle twitching, confusion, nausea, vomiting, seizures, psychosis, sinus arrest, aggravation of underlying conduction disturbances
Mexiletine	Dizziness, sedation, anxiety, confusion, paresthesia, tremor, ataxia, blurred vision, nausea, vomiting, anorexia, aggravation of underlying conduction disturbances or ventricular arrhythmias
Moricizine	Dizziness, headache, fatigue, insomnia, nausea, diarrhea, blurred vision, aggravation of underlying conduction disturbances or ventricular arrhythmias
Flecainide	Blurred vision, dizziness, dyspnea, headache, tremor, nausea, aggravation of underlying HF, conduction disturbances, or ventricular arrhythmias
Propafenone	Dizziness, fatigue, bronchospasm, headache, taste disturbances, nausea, vomiting, bradycardia or AV block, aggravation of underlying HF, conduction disturbances, or ventricular arrhythmias
Amiodarone	Tremor, ataxia, paresthesia, insomnia, corneal microdeposits, optic neuropathy/neuritis, nausea, vomiting, anorexia, constipation, TdP (<1%), bradycardia or AV block (IV and oral use), pulmonary fibrosis, liver function test abnormalities, hepatitis, hypothyroidism, hyperthyroidism, photosensitivity, blue-gray skin discoloration, hypotension (IV use), phlebitis (IV use)
Dofetilide	Headache, dizziness, TdP
Ibutilide	Headache, TdP, hypotension
Sotalol	Dizziness, weakness, fatigue, nausea, vomiting, diarrhea, bradycardia, TdP, bronchospasm, aggravation of underlying heart failure

AV, atrioventricular; HF, heart failure; TdP, torsade de pointes.

flutter are pharmacologic cardioversion and DCC. DCC is quick and more often successful, but it requires prior sedation or anesthesia and has a small risk of serious complications such as sinus arrest or ventricular arrhythmias. Advantages of initial drug therapy are that an effective agent may be determined in case long-term therapy is required. Disadvantages are significant side effects such as drug-induced TdP, drug–drug interactions, and lower cardioversion rate for drugs compared with DCC. There is relatively strong evidence for efficacy of type III pure  $I_k$  blockers (**ibutilide**, **dofetilide**), type Ic drugs (e.g., **flecainide**, **propafenone**), and amiodarone (oral or IV). With the “pill in the pocket” approach, outpatient, patient-controlled self-administration of a single, oral loading dose of either flecainide or propafenone can be relatively safe and effective for termination of recent-onset AF in selected patients without sinus or AV node dysfunction, bundle-branch block, QT interval prolongation, Brugada’s syndrome, or structural heart disease. It should only be considered in patients who have been successfully cardioverted with these drugs on an inpatient basis.

- The American College of Chest Physicians Consensus Conference on anti-thrombotic therapy recommends chronic **warfarin** treatment (target INR



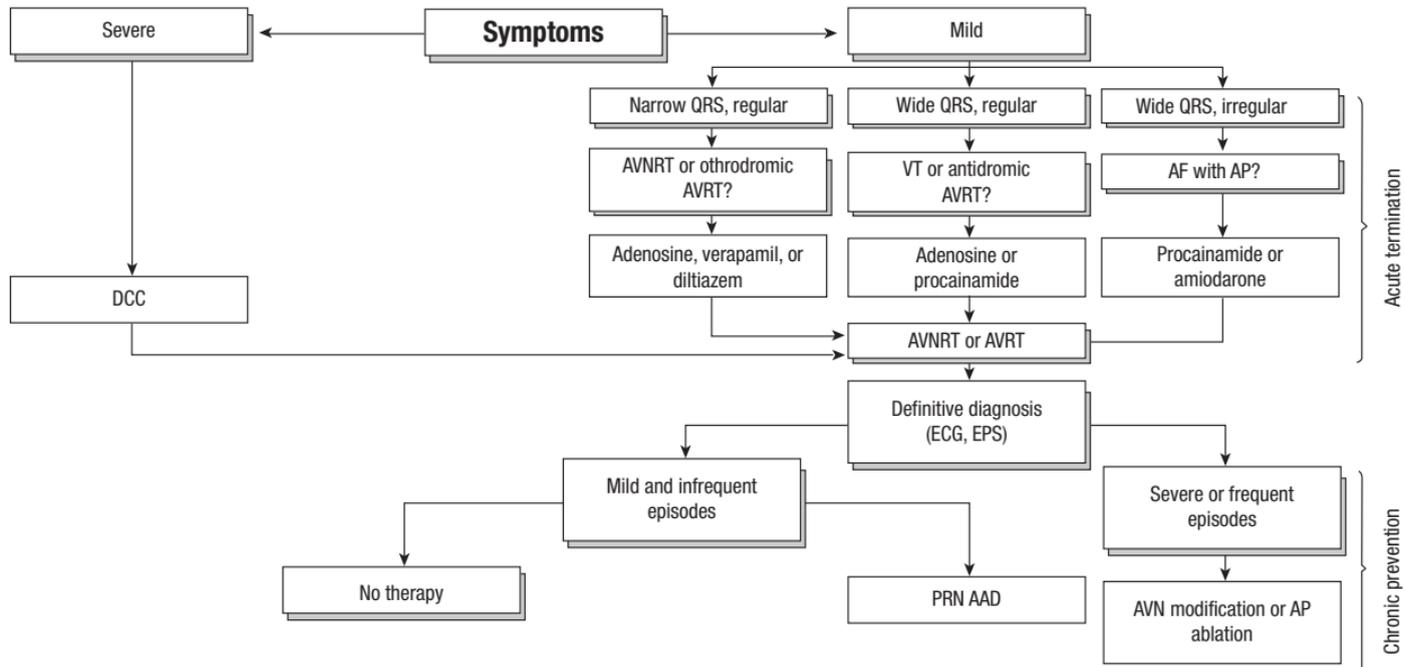
**FIGURE 6-1.** Algorithm for the treatment of atrial fibrillation (AF) and atrial flutter. <sup>a</sup>If AF <48 hours, anticoagulation prior to cardioversion is unnecessary; may consider transesophageal echocardiogram (TEE) if patient has risk factors for stroke. <sup>b</sup>Ablation may be considered for patients who fail or do not tolerate one antiarrhythmic drug (AAD). <sup>c</sup>Chronic antithrombotic therapy should be considered in all patients with AF and risk factors for stroke regardless of whether or not they remain in sinus rhythm. (BB,  $\beta$ -blocker; CCB, calcium channel blocker [i.e., verapamil or diltiazem]; DCC, direct-current cardioversion.)

2.5; range 2 to 3) for all patients with AF who are at high risk for stroke (rheumatic mitral valve disease; previous ischemic stroke, transient ischemic attack, or other systemic embolic event; age >75 years; moderate or severe LV systolic dysfunction and/or congestive HF; hypertension; or prosthetic heart valve). Those at intermediate risk (age 65 to 75 years with none of the high-risk factors) should receive either warfarin (target INR 2.5; range 2 to 3) or **aspirin** 325 mg/day. Those at low risk (age <65 years with none of the high-risk factors) should receive aspirin 325 mg/day. Chronic antithrombotic therapy should be considered for all patients with AF and risk factors for stroke regardless of whether or not they remain in sinus rhythm.

- AF often recurs after initial cardioversion because most patients have irreversible underlying heart or lung disease. A metaanalysis confirmed that **quinidine** maintained sinus rhythm better than placebo; however, 50% of patients had recurrent AF within 1 year, and more importantly, quinidine increased mortality, presumably due in part to proarrhythmia. Type Ic (e.g., **flecainide, propafenone**) and type III (e.g., **amiodarone, sotalol, dofetilide**) antiarrhythmic agents may be alternatives to quinidine; however, these agents are also associated with proarrhythmia. Consequently, chronic antiarrhythmic drugs should be reserved for patients with recurrent paroxysmal AF associated with intolerable symptoms during episodes of AF.

## PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA

- The choice between pharmacologic and nonpharmacologic methods for treating PSVT depends on symptom severity (Fig. 6-2). Synchronized DCC is the treatment of choice if symptoms are severe (e.g., syncope, near syncope, anginal chest pain, severe HF). Nondrug measures that increase vagal tone to the AV node (e.g., unilateral carotid sinus massage, Valsalva maneuver) can be used for mild to moderate symptoms. If these methods fail, drug therapy is the next option.
- The choice among drugs is based on the QRS complex (see Fig. 6-2). Drugs can be divided into three broad categories: (1) those that directly or indirectly increase vagal tone to the AV node (e.g., **digoxin**); (2) those that depress conduction through slow, calcium-dependent tissue (e.g., **adenosine,  $\beta$ -blockers, calcium channel blockers**); and (3) those that depress conduction through fast, sodium-dependent tissue (e.g., **quinidine, procainamide, disopyramide, flecainide**).
- **Adenosine** has been recommended as the drug of first choice in patients with PSVT because its short duration of action will not cause prolonged hemodynamic compromise in patients with wide QRS complexes who actually have VT rather than PSVT.
- After acute PSVT is terminated, long-term preventive treatment is indicated if frequent episodes necessitate therapeutic intervention or if episodes are infrequent but severely symptomatic. Serial testing of antiarrhythmic agents can be evaluated in the ambulatory setting via ambulatory ECG recordings (Holter monitors) or telephonic transmissions of cardiac rhythm (event monitors) or by invasive electrophysiologic techniques in the laboratory.
- Transcutaneous catheter ablation using radiofrequency current on the PSVT substrate should be considered in any patient who would have



**FIGURE 6-2.** Algorithm for the treatment of acute (*top portion*) paroxysmal supraventricular tachycardia and chronic prevention of recurrences (*bottom portion*). *Note:* For empiric bridge therapy prior to radiofrequency ablation procedures, calcium channel blockers (or other atrioventricular [AV] nodal blockers) should not be used if the patient has AV reentry with an accessory pathway. (AAD, antiarrhythmic drugs; AF, atrial fibrillation; AP, accessory pathway; AVN, atrioventricular nodal; AVNRT, atrioventricular nodal reentrant tachycardia; AVRT, atrioventricular reentrant tachycardia; DCC, direct-current cardioversion; ECG, electrocardiographic monitoring; EPS, electrophysiologic studies; PRN, as needed; VT, ventricular tachycardia.)

previously been considered for chronic antiarrhythmic drug treatment. It is highly effective and curative, rarely results in complications, obviates the need for chronic antiarrhythmic drug therapy, and is cost-effective.

## AUTOMATIC ATRIAL TACHYCARDIAS

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- Underlying precipitating factors should be corrected by ensuring proper oxygenation and ventilation and by correcting acid–base or electrolyte disturbances.
- If tachycardia persists, the need for additional treatment is determined by symptoms. Patients with asymptomatic atrial tachycardia and relatively slow ventricular response usually require no drug therapy.
- In symptomatic patients, medical therapy can be tailored either to control ventricular response or to restore sinus rhythm. Nondihydropyridine calcium antagonists (e.g., **verapamil**) are considered first-line drug therapy for decreasing ventricular response. Type I agents (e.g., **procainamide**, **quinidine**) are only occasionally effective in restoring sinus rhythm. DCC is ineffective, and  $\beta$ -blockers are usually contraindicated because of coexisting severe pulmonary disease or uncompensated HF.

## PREMATURE VENTRICULAR COMPLEXES

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- In apparently healthy individuals, drug therapy is unnecessary because PVCs without associated heart disease carry little or no risk. In patients with risk factors for arrhythmic death (recent MI, LV dysfunction, complex PVCs), chronic drug therapy should be restricted to  **$\beta$ -blockers** because only they have been conclusively proven to prevent mortality in these patients.

## VENTRICULAR TACHYCARDIA

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### Acute Ventricular Tachycardia

- If severe symptoms are present, synchronized DCC should be instituted immediately to restore sinus rhythm. Precipitating factors should be corrected if possible. If VT is an isolated electrical event associated with a transient initiating factor (e.g., acute myocardial ischemia, digitalis toxicity), there is no need for long-term antiarrhythmic therapy after precipitating factors are corrected.
- Patients with mild or no symptoms can be treated initially with antiarrhythmic drugs. IV **amiodarone** is now recommended as first-line therapy in this situation. **Procainamide** or lidocaine given IV is a suitable alternative. Synchronized DCC should be delivered if the patient's status deteriorates, VT degenerates to VF, or drug therapy fails.

### Sustained Ventricular Tachycardia

- Patients with chronic recurrent sustained VT are at extremely high risk for death; trial-and-error attempts to find effective therapy are unwarranted. Neither electrophysiologic studies nor serial Holter monitoring with drug testing is ideal. These findings and the side-effect profiles of antiarrhythmic agents have led to nondrug approaches.

- The automatic ICD is a highly effective method for preventing sudden death due to recurrent VT or VF.
- Patients with complex ventricular ectopy should not receive type I or III antiarrhythmic drugs.

### Ventricular Proarrhythmia

- The typical form of proarrhythmia caused by the type Ic antiarrhythmic drugs is a rapid, sustained, monomorphic VT with a characteristic sinusoidal QRS pattern that is often resistant to resuscitation with cardioversion or overdrive pacing. Some clinicians have had success with IV **lidocaine** (competes for the sodium channel receptor) or **sodium bicarbonate** (reverses the excessive sodium channel blockade).

### Torsade de Pointes

- For an acute episode of TdP, most patients require and respond to DCC. However, TdP tends to be paroxysmal and often recurs rapidly after DCC.
- IV **magnesium sulfate** is considered the drug of choice for preventing recurrences of TdP. If ineffective, strategies to increase heart rate and shorten ventricular repolarization should be instituted (i.e., temporary transvenous pacing at 105 to 120 beats/min or pharmacologic pacing with **isoproterenol** or **epinephrine** infusion). Agents that prolong the QT interval should be discontinued, and exacerbating factors (e.g., hypokalemia, hypomagnesemia) corrected. Drugs that further prolong repolarization (e.g., IV procainamide) are contraindicated. Lidocaine is usually ineffective.

### Ventricular Fibrillation

- Patients with pulseless VT or VF (with or without associated myocardial ischemia) should be managed according to the American Heart Association's guidelines for cardiopulmonary resuscitation and emergency cardiovascular care (see Chap. 7). After successful resuscitation, antiarrhythmics should be continued until the patient's rhythm and overall status are stable. Long-term antiarrhythmics or ICD implantation may or may not be required.

## BRADYARRHYTHMIAS

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- Treatment of sinus node dysfunction involves elimination of symptomatic bradycardia and possibly managing alternating tachycardias such as AF. Asymptomatic sinus bradyarrhythmias usually do not require therapeutic intervention.
- In general, long-term therapy of choice for patients with significant symptoms is a permanent ventricular pacemaker.
- Drugs commonly employed to treat supraventricular tachycardias should be used with caution, if at all, in the absence of a functioning pacemaker.
- Symptomatic carotid sinus hypersensitivity also should be treated with permanent pacemaker therapy. Patients who remain symptomatic may benefit from adding an  $\alpha$ -adrenergic stimulant such as **midodrine**.
- Vasovagal syncope has traditionally been treated successfully with oral  $\beta$ -blockers (e.g., **metoprolol**) to inhibit the sympathetic surge that causes

forceful ventricular contraction and precedes the onset of hypotension and bradycardia. Other drugs that have been used successfully (with or without  $\beta$ -blockers) include fludrocortisone, anticholinergics (**scopolamine patches, disopyramide**),  $\alpha$ -adrenergic agonists (**midodrine**), adenosine analogs (**theophylline, dipyridamole**), and selective serotonin reuptake inhibitors (**sertraline, fluoxetine**).

### Atrioventricular Block

- If patients with Mobitz II or third-degree AV block develop signs or symptoms of poor perfusion (e.g., altered mental status, chest pain, hypotension, shock) associated with bradycardia or AV block, transcutaneous pacing should be initiated immediately. **Atropine** (0.5 mg IV given every 3 to 5 minutes, up to 3 mg total dose) should be given as the pacing leads are being placed. Infusions of **epinephrine** (2 to 10 mcg/min) or **dopamine** (2 to 10 mcg/kg/min) can be used in the event of atropine failure. These agents will not help if AV block is below the AV node (Mobitz II or trifascicular AV block).
- Chronic symptomatic AV block warrants insertion of a permanent pacemaker. Patients without symptoms can sometimes be followed closely without the need for a pacemaker.

## EVALUATION OF THERAPEUTIC OUTCOMES

- The most important monitoring parameters include (1) mortality (total and due to arrhythmic death), (2) arrhythmia recurrence (duration, frequency, symptoms), (3) hemodynamic consequences (rate, blood pressure, symptoms), and (4) treatment complications (need for alternative or additional drugs, devices, or surgery).

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*See Chap. 19, The Arrhythmias, authored by Cynthia A. Sanoski, Marieke Dekker Schoen, and Jerry L. Bauman, for a more detailed discussion of this topic.*

## DEFINITION

- Cardiopulmonary arrest is the abrupt cessation of spontaneous and effective ventilation and circulation after a cardiac or respiratory event. Cardiopulmonary resuscitation (CPR) provides artificial ventilation and circulation until it is possible to provide advanced cardiac life support (ACLS) and reestablish spontaneous circulation.

## PATHOPHYSIOLOGY

- Cardiopulmonary arrest in adults usually results from arrhythmias. The most common arrhythmias are ventricular fibrillation (VF) and pulseless ventricular tachycardia (PVT), often in patients after myocardial infarction (MI) or pulmonary embolism (PE). In children, cardiopulmonary arrest is often the terminal event of progressive shock or respiratory failure.
- Two theories exist regarding the mechanism of blood flow in CPR.
  - ✓ The cardiac pump theory states that the active compression of the heart between the sternum and vertebrae creates an “artificial systole” in which intraventricular pressure increases, the atrioventricular valves close, the aortic valve opens, and blood is forced out of the ventricles. When ventricular compression ends, the decline in intraventricular pressure causes the mitral and tricuspid valves to open, and ventricular filling begins.
  - ✓ The more recent thoracic pump theory is based on the belief that blood flow during CPR results from intrathoracic pressure alterations induced by chest compressions. During compression (systole), a pressure gradient develops between the intrathoracic arteries and extrathoracic veins, causing forward blood flow from the lungs into the systemic circulation. After compression ends (diastole), intrathoracic pressure declines and blood flow returns to the lungs.
- Components of both theories may apply to the mechanism of blood flow during CPR.

## CLINICAL PRESENTATION

- The onset of cardiopulmonary arrest may be characterized by symptoms of anxiety, mental status changes, or unconsciousness; cold, clammy extremities; dyspnea, shortness of breath, or no respiration; chest pain; diaphoresis, and nausea or vomiting.
- Physical signs may include hypotension; tachycardia, bradycardia, irregular or no pulse; cyanosis; hypothermia; and distant or absent heart and lung sounds.

## DIAGNOSIS

- Rapid diagnosis of cardiopulmonary arrest is vital to the success of CPR. Patients must receive early intervention to prevent cardiac rhythms from degenerating into less treatable arrhythmias.
- Cardiopulmonary arrest is diagnosed initially by observation of clinical manifestations consistent with cardiac arrest. The diagnosis is confirmed by evaluating vital signs, especially heart rate and respirations.
- Electrocardiography (ECG) is useful for determining the cardiac rhythm, which in turn determines drug therapy.
  - ✓ VF is electrical anarchy of the ventricle resulting in no cardiac output and cardiovascular collapse.
  - ✓ Pulseless electrical activity (PEA) is the absence of a detectable pulse and the presence of some type of electrical activity other than VF or PVT.
  - ✓ Asystole is the presence of a “flat line” on the ECG monitor.

## DESIRED OUTCOME

- The goal of CPR is the return of spontaneous circulation (ROSC) with effective ventilation and perfusion as quickly as possible to minimize hypoxic damage to vital organs.
- After successful resuscitation, the primary goals include optimizing tissue oxygenation, identifying precipitating cause(s) of arrest, and preventing subsequent episodes.

## TREATMENT

### GENERAL APPROACH

- The philosophies for providing CPR and emergency cardiovascular care (ECC) have been organized and revised periodically by the American Heart Association. The latest evidence-based guidelines for CPR and ECC resulted from the Guidelines 2005 Conference (Table 7-1).
- The likelihood of a successful resuscitation outcome is enhanced if each of four critical elements in the “chain of survival” is implemented promptly: (1) early recognition of the emergency and activation of emergency medical services; (2) early bystander basic life support and CPR; (3) early delivery of a shock with a defibrillator; and (4) early ACLS followed by resuscitation care delivered by healthcare professionals.
- In basic life support, the following actions are performed in this order:
  - ✓ First, determine patient responsiveness. If there is no response, immediately activate the emergency medical response team and obtain an automated external defibrillator (AED) if one is available.
  - ✓ Next, open the victim’s airway and assess the effectiveness of breathing. If the victim is breathing, assist as needed. If the victim is not breathing, administer two rescue breaths.
  - ✓ Determine if there is an effective pulse. If an effective pulse is present, continue rescue breathing with frequent assessments of effective circu-

**TABLE 7-1** Evidence-Based Treatment Recommendations for Cardiopulmonary Resuscitation

Recommendations	Recommendation Grades <sup>a</sup>
<b>Immediate bystander CPR</b> High-quality CPR should be performed with minimal interruption in chest compressions and defibrillation as soon as it can be accomplished.	Class I
<b>Epinephrine</b> 1 mg IV/IO should be administered every 3–5 minutes in patients with VF, PVT, PEA, or asystole.	Class IIb
<b>Vasopressin</b> 40 units IV/IO can replace either the first or second dose of epinephrine in patients with VF, PVT, or asystole. There is insufficient evidence to recommend either for or against its use in PEA.	Class indeterminate
<b>Amiodarone</b> 300 mg IV/IO can be followed by 150 mg IV/IO in patients with VF/PVT unresponsive to CPR, shock, and a vasopressor.	Class IIb
<b>Lidocaine</b> Lidocaine can be considered an alternative to amiodarone in patients with VF/PVT. The initial dose is 1–1.5 mg/kg IV. Additional doses of 0.5–0.75 mg/kg can be administered at 5- to 10-minute intervals to a maximum dose of 3 mg/kg if VF/PVT persists.	Class indeterminate
<b>Magnesium</b> Magnesium is recommended for VF/PVT that is caused by torsade de pointes. 1–2 g diluted in 10 mL D5W should be administered IV/IO push over 5–20 minutes. Clinical studies have not demonstrated a benefit when magnesium was routinely administered during CPR when torsade de pointes was not present.	Class IIa
<b>Fibrinolysis</b> Thrombolytics should be considered on a case-by-case basis when pulmonary embolism is suspected.	Class IIa
<b>Hypothermia</b> Hypothermia should be implemented in unconscious adult patients with ROSC after out-of-hospital cardiac arrest when the initial rhythm was VF. These patients should be cooled to 32°C (89.6°F) to 34°C (93.2°F) for 12–24 hours.	Class IIa
Hypothermia may be beneficial for patients with non-VF arrest out-of-hospital or for in-hospital cardiac arrest.	Class IIb
<b>Atropine</b> Atropine 1 mg IV/IO every 3–5 minutes (maximum total of 3 doses or 3 mg) can be considered for patients with asystole or PEA.	Class indeterminate

CPR, cardiopulmonary resuscitation; D5W, 5% dextrose in water; PEA, pulseless electrical activity; PVT, pulseless ventricular tachycardia; ROSC, return of spontaneous circulation; VF, ventricular fibrillation.

<sup>a</sup>American College of Cardiology and American Heart Association evidence grading system.

**Key for evidence-based classifications:**

Class I: High-level prospective studies support the action or therapy and the benefit substantially outweighs the potential for harm. The treatment should be administered.

Class IIa: The weight of evidence supports the action or therapy, and the therapy is considered acceptable and useful. It is reasonable to administer the treatment.

Class IIb: The evidence documented only short-term benefits, or positive results were documented with lower levels of evidence. Class IIb recommendations can be considered either optional or recommended by experts despite the absence of high-level supporting evidence.

Class III: The risk outweighs the benefit for a particular treatment. The treatment should not be administered and can be harmful.

Class indeterminate: This is either a continuing area of research or an area where research is just beginning. No recommendation (either for or against) can be made.

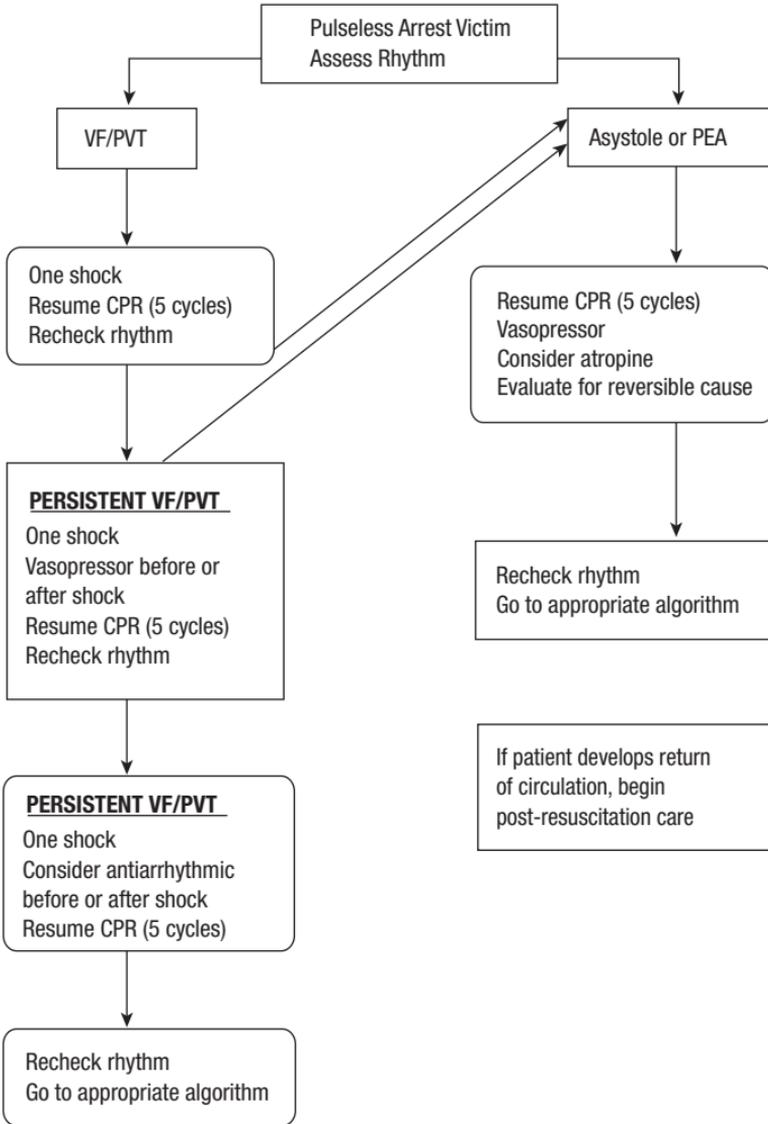
lation until help arrives. If there is no pulse, immediately institute chest compressions. The recommended rate is 100 beats/min, with cycles of 30 compressions followed by two rescue breaths.

- ✓ If there is no AED available, continue cycles of compressions/breaths, with pulse checks every 2 minutes (five cycles) until help arrives or the patient regains spontaneous circulation.
- ✓ If an AED is available, check the rhythm to determine if defibrillation is advised. If so, then deliver one shock with the immediate resumption of chest compressions/rescue breaths. After five cycles, reevaluate the rhythm to determine the need for further defibrillation. Repeat this sequence of actions until help arrives or the rhythm is no longer “shockable.”
- ✓ If the rhythm is not shockable, then continue chest compressions/rescue breath cycles until help arrives or the victim recovers spontaneous circulation.
- Once ACLS providers arrive, further definitive therapy is given (Fig. 7-1). If the rhythm is not shockable, it is likely to be either asystole or PEA.
- Central venous catheter access results in faster and higher peak drug concentrations than peripheral venous administration, but central line access is not needed in most resuscitation attempts. However, if a central line is already present, it should be the access site of choice. If IV access (either central or peripheral) has not been established, a large peripheral venous catheter should be inserted. Intraosseous (IO) administration is the preferred alternative if IV administration cannot be achieved.
- If neither IV nor IO access can be established, atropine, lidocaine, epinephrine, naloxone, and vasopressin may be administered endotracheally. The endotracheal dose should generally be two to two and one-half times larger than the IV/IO dose.

## TREATMENT OF VENTRICULAR FIBRILLATION AND VENTRICULAR TACHYCARDIA

### Nonpharmacologic Therapy

- Persons in VF or PVT should receive electrical defibrillation with one shock using 360 joules (monophasic defibrillator) or 150 to 200 joules (biphasic defibrillator). After defibrillation is attempted, CPR should be immediately restarted and continued for 2 minutes (five cycles) before checking a pulse. If there is still evidence of VF/PVT after 2 minutes, repeat attempts at single-discharge defibrillation should be attempted along with pharmacologic therapy. After the first unsuccessful shock, vasopressors are the initial recommended therapy (before or after the second shock). After the second unsuccessful shock, antiarrhythmics can be considered (before or after the third shock). Five cycles of chest compressions should be performed between attempts at defibrillation. This algorithm is repeated until either a pulse is obtained with effective circulation, the rhythm changes, or the patient expires.
- Endotracheal intubation and IV access should be obtained when feasible, but not at the expense of stopping chest compressions. Once an airway is achieved, patients should be ventilated with 100% oxygen.



**FIGURE 7-1.** Advanced cardiac life support (ACLS) treatment algorithm for adult cardiopulmonary arrest. (CPR, cardiopulmonary resuscitation; PEA, pulseless electrical activity; PVT, pulseless ventricular tachycardia; VF, ventricular fibrillation.)

- Hypothermia can protect from cerebral injury by suppressing chemical reactions that occur after restoration of blood flow following cardiac arrest. Based on the results of two clinical trials, unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32°C (89.6°F) to 34°C (93.2°F) for 12 to 24 hours when the initial rhythm is VF. Cooling may also benefit other rhythms or in-hospital cardiac arrest in adults; there is insufficient evidence to recommend therapeutic hypothermia in children.

## Pharmacologic Therapy

(See Table 7-1)

### *Sympathomimetics*

- The goal of sympathomimetic therapy is to augment both coronary and cerebral perfusion pressures during the low-flow state associated with CPR. These agents increase systemic arteriolar vasoconstriction, thereby improving coronary and cerebral perfusion pressure. They also maintain vascular tone, decrease arteriolar collapse, and shunt blood to the heart and brain.
- **Epinephrine** is a drug of first choice for treating VF, PVT, asystole, and PEA. It is an agonist of  $\alpha_1$ ,  $\alpha_2$ ,  $\beta_1$ , and  $\beta_2$  receptors. Its effectiveness is thought to be primarily due to its  $\alpha$  effects.
- The standard adult dose of epinephrine is 1 mg administered by IV or IO injection every 3 to 5 minutes. Although some studies have shown that higher doses (e.g., up to 5 mg) may increase the initial resuscitation rate, overall survival is not significantly improved.
- **Norepinephrine** (an  $\alpha_1$ ,  $\alpha_2$ , and  $\beta_1$  agonist) demonstrated higher resuscitation rates compared to epinephrine in one study (64% vs. 32%) but no significant difference in survival to hospital discharge. Consequently, epinephrine remains the first-line sympathomimetic for CPR.

### *Vasopressin*

- **Vasopressin** is a potent vasoconstrictor that increases blood pressure and systemic vascular resistance. It may have several advantages over epinephrine. First, the metabolic acidosis that frequently accompanies cardiopulmonary arrest can blunt the vasoconstrictive effect of epinephrine; this does not occur with vasopressin. Second, stimulation of  $\beta$  receptors by epinephrine can increase myocardial oxygen demand and complicate the postresuscitative phase of CPR. Vasopressin can also have a beneficial effect on renal blood flow in the kidney, causing vasodilation and increased water reabsorption.
- Despite these potential advantages, clinical experience with vasopressin is limited and comparative trials with epinephrine have produced mixed results. Overall, these studies suggest that vasopressin is effective as part of ACLS after cardiac arrest, but its superiority to epinephrine remains questionable.

### *Antiarrhythmics*

- The purpose of antiarrhythmic drug therapy after unsuccessful defibrillation and vasopressor administration is to prevent the development or recurrence of VF and PVT by raising the fibrillation threshold. However, the role of antiarrhythmics is limited because clinical evidence demonstrating improved survival to hospital discharge is lacking. Only amiodarone and lidocaine are recommended in the 2005 guidelines for CPR and ECC.
- **Amiodarone** is the preferred antiarrhythmic during cardiac arrest according to the 2005 guidelines. Hypotension occurs frequently but can generally be reversed by decreasing the infusion rate. Other acute effects include fever, elevated liver function tests, confusion, nausea, and thrombocytopenia.
- **Lidocaine** is recommended as an alternative to amiodarone in the 2005 guidelines.

### *Thrombolytics*

- The role of thrombolytics during CPR has been investigated because most cardiac arrests are related to either MI or PE. Although several studies demonstrated successful thrombolytic use, few have shown improvements to hospital discharge, and an increase in bleeding was noted. Therefore, thrombolytics should be considered on a case-by-case basis when PE is suspected.

### *Magnesium*

- Although severe hypomagnesemia has been associated with VF/PVT, clinical trials have not demonstrated any benefit with routine administration of magnesium during a cardiac arrest. Because two observation trials showed improvement in ROSC in patients with arrests associated with torsade de pointes, magnesium administration should be limited to these patients.

## TREATMENT OF PULSELESS ELECTRICAL ACTIVITY AND ASYSTOLE

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### **Nonpharmacologic Therapy**

- Successful treatment of PEA and asystole depends almost entirely on diagnosis of the underlying cause. Potentially reversible causes include (1) hypovolemia, (2) hypoxia, (3) preexisting acidosis, (4) hyperkalemia, (5) hypothermia, (6) hypoglycemia, (7) drug overdose, (8) cardiac tamponade, (9) tension pneumothorax, (10) coronary thrombosis, (11) pulmonary thrombosis, and (12) trauma.
- Treatment of PEA is similar to treatment of asystole. Both conditions require CPR, airway control, and IV access. Defibrillation should be avoided in asystole because the resulting parasympathetic discharge can reduce the chance of ROSC and worsen the chance of survival. If available, transcutaneous pacing can be attempted.

### **Pharmacologic Therapy**

(See Table 7-1)

- **Epinephrine** may be given in doses identical to those used for the treatment of VF or PVT.
- **Vasopressin** can be substituted for the first or second dose of epinephrine in patients with asystole. There is insufficient evidence to make a treatment recommendation for PEA.
- **Atropine** is an antimuscarinic agent that blocks the depressant effect of acetylcholine on the sinus and atrioventricular nodes, thereby decreasing parasympathetic tone. During asystole, parasympathetic tone may increase because of vagal stimulation from intubation, hypoxia and acidosis, or alterations in the balance of parasympathetic and sympathetic control. There are no prospective controlled trials showing benefit from atropine for treatment of asystole or PEA. Overall, the results show that although atropine may achieve ROSC in some instances, asystolic arrest is almost always fatal. Atropine should be considered for asystole or PEA because of its relative safety, ease of administration, low cost, and theoretical advantages.

## ACID–BASE MANAGEMENT DURING CARDIOPULMONARY RESUSCITATION

- Acidosis occurs during cardiac arrest because of decreased blood flow and inadequate ventilation. Chest compressions generate only about 20% to 30% of normal cardiac output, leading to inadequate organ perfusion, tissue hypoxia, and metabolic acidosis. Furthermore, the lack of ventilation causes retention of carbon dioxide, leading to respiratory acidosis. The combined acidosis reduces myocardial contractility and may cause arrhythmias because of a lower fibrillation threshold.
- In early cardiac arrest, adequate alveolar ventilation is the primary means of limiting carbon dioxide accumulation and controlling the acid–base imbalance. With arrests of long duration, buffer therapy is often necessary.
- Sodium bicarbonate administration for cardiac arrest is controversial because there are few clinical data supporting its use, and it may have some detrimental effects. Sodium bicarbonate can be used in special circumstances (i.e., underlying metabolic acidosis, hyperkalemia, salicylate overdose, or tricyclic antidepressant overdose). The dosage should be guided by laboratory analysis if possible.

## EVALUATION OF THERAPEUTIC OUTCOMES

- To measure the success of CPR, therapeutic outcome monitoring should occur both during the resuscitation attempt and in the postresuscitation phase. The optimal outcome following CPR is an awake, responsive, spontaneously breathing patient. Ideally, patients must remain neurologically intact with minimal morbidity after the resuscitation.
- Heart rate, cardiac rhythm, and blood pressure should be assessed and documented throughout the resuscitation attempt and after each intervention. Determination of the presence or absence of a pulse is paramount to deciding which interventions are appropriate.
- Coronary perfusion pressure should be assessed in patients for whom intraarterial monitoring is in place.
- End-tidal carbon dioxide monitoring is a safe and effective method to assess cardiac output during CPR and has been associated with ROSC.
- Clinicians should consider the precipitating cause of the cardiac arrest, such as MI, electrolyte imbalance, or primary arrhythmia. Prearrest status should be carefully reviewed, particularly if the patient was receiving drug therapy.
- Altered cardiac, hepatic, and renal function resulting from ischemic damage during the arrest warrant special attention.
- Neurologic function should be assessed by the Cerebral Performance Category and the Glasgow Coma Scale.

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*See Chap. 14, Cardiopulmonary Resuscitation, authored by Jeffrey F. Barletta and Jeffrey L. Wilt, for a more detailed discussion of this topic.*

## DEFINITION

- Heart failure (HF) is a clinical syndrome caused by the inability of the heart to pump sufficient blood to meet the metabolic needs of the body. HF can result from any disorder that reduces ventricular filling (diastolic dysfunction) and/or myocardial contractility (systolic dysfunction).

## PATHOPHYSIOLOGY

- Causes of systolic dysfunction (decreased contractility) are reduction in muscle mass (e.g., myocardial infarction [MI]), dilated cardiomyopathies, and ventricular hypertrophy. Ventricular hypertrophy can be caused by pressure overload (e.g., systemic or pulmonary hypertension, aortic or pulmonic valve stenosis) or volume overload (e.g., valvular regurgitation, shunts, high-output states).
- Causes of diastolic dysfunction (restriction in ventricular filling) are increased ventricular stiffness, ventricular hypertrophy, infiltrative myocardial diseases, myocardial ischemia and infarction, mitral or tricuspid valve stenosis, and pericardial disease (e.g., pericarditis, pericardial tamponade).
- The leading causes of HF are coronary artery disease and hypertension.
- As cardiac function decreases after myocardial injury, the heart relies on the following compensatory mechanisms: (1) tachycardia and increased contractility through sympathetic nervous system activation; (2) the Frank-Starling mechanism, whereby increased preload increases stroke volume; (3) vasoconstriction; and (4) ventricular hypertrophy and remodeling. Although these compensatory mechanisms initially maintain cardiac function, they are responsible for the symptoms of HF and contribute to disease progression.
- The neurohormonal model of HF recognizes that an initiating event (e.g., acute MI) leads to decreased cardiac output but that the HF state then becomes a systemic disease whose progression is mediated largely by neurohormones and autocrine/paracrine factors. These substances include angiotensin II, norepinephrine, aldosterone, natriuretic peptides, arginine vasopressin, proinflammatory cytokines (e.g., tumor necrosis factor  $\alpha$ , interleukin-6 and interleukin-1 $\beta$ ), and endothelin-1.
- Common precipitating factors that may cause a previously compensated patient to decompensate include noncompliance with diet or drug therapy, coronary ischemia, inappropriate medication use, cardiac events (e.g., MI, atrial fibrillation), pulmonary infections, and anemia.
- Drugs may precipitate or exacerbate HF because of their negative inotropic, cardiotoxic, or sodium- and water-retaining properties.

## CLINICAL PRESENTATION

- The patient presentation may range from asymptomatic to cardiogenic shock.

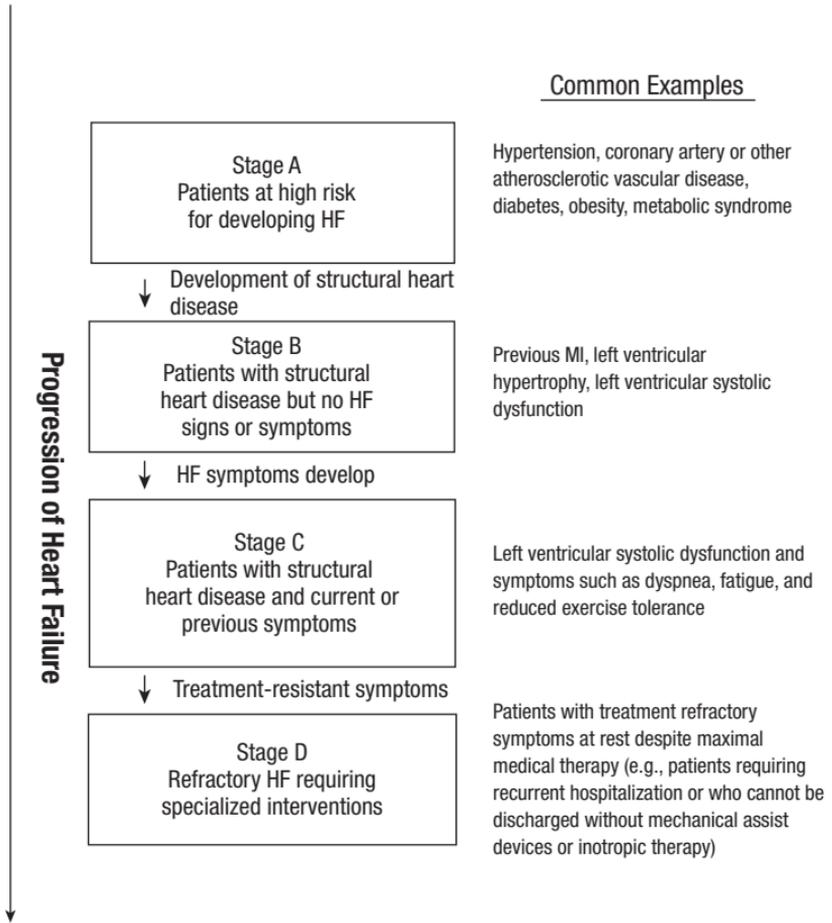
- The primary symptoms are dyspnea (particularly on exertion) and fatigue, which lead to exercise intolerance. Other pulmonary symptoms include orthopnea, paroxysmal nocturnal dyspnea, tachypnea, and cough.
- Fluid overload can result in pulmonary congestion and peripheral edema.
- Nonspecific symptoms may include fatigue, nocturia, hemoptysis, abdominal pain, anorexia, nausea, bloating, ascites, poor appetite, ascites, mental status changes, and weight gain.
- Physical examination findings may include pulmonary crackles, an  $S_3$  gallop, cool extremities, Cheyne-Stokes respiration, tachycardia, narrow pulse pressure, cardiomegaly, symptoms of pulmonary edema (extreme breathlessness, anxiety, sometimes with coughing pink, frothy sputum), peripheral edema, jugular venous distention, hepatojugular reflux, and hepatomegaly.

## DIAGNOSIS

- A diagnosis of HF should be considered in patients exhibiting characteristic signs and symptoms. A complete history and physical examination with appropriate laboratory testing are essential in the initial evaluation of patients suspected of having HF.
- Laboratory tests for identifying disorders that may cause or worsen HF include complete blood count; serum electrolytes (including calcium and magnesium); renal, hepatic, and thyroid function tests; urinalysis; lipid profile; and hemoglobin A1C.
- Ventricular hypertrophy can be demonstrated on chest x-ray or ECG. Chest x-ray may also show pleural effusions or pulmonary edema.
- The echocardiogram is the single most useful evaluation procedure because it can identify abnormalities of the pericardium, myocardium, or heart valves and quantify the left ventricular ejection fraction (LVEF) to determine if systolic or diastolic dysfunction is present.
- The New York Heart Association Functional Classification System is intended primarily to classify *symptomatic* HF patients according to the physician's subjective evaluation. Functional class (FC)-I patients have no limitation of physical activity, FC-II patients have slight limitation, FC-III patients have marked limitation, and FC-IV patients are unable to carry on physical activity without discomfort.
- The recent American College of Cardiology/American Heart Association (ACC/AHA) staging system provides a more comprehensive framework for evaluating, preventing, and treating HF (Fig. 8-1).

## DESIRED OUTCOME

- The therapeutic goals for chronic HF are to improve quality of life, relieve or reduce symptoms, prevent or minimize hospitalizations, slow disease progression, and prolong survival.



**FIGURE 8-1.** The American College of Cardiology/American Heart Association heart failure (HF) staging system. (MI, myocardial infarction.)

## TREATMENT OF CHRONIC HEART FAILURE

### GENERAL APPROACH

- The first step in managing chronic HF is to determine the etiology or precipitating factors. Treatment of underlying disorders (e.g., anemia, hyperthyroidism) may obviate the need for treating HF.
- Nonpharmacologic interventions include cardiac rehabilitation and restriction of fluid intake (maximum 2 L/day from all sources) and dietary sodium (approximately 2 to 3 g of sodium per day).
- **Stage A:** The emphasis is on identifying and modifying risk factors to prevent development of structural heart disease and subsequent HF. Strategies include smoking cessation and control of hypertension, diabetes mellitus, and dyslipidemia according to current treatment guidelines. **Angiotensin-converting enzyme (ACE) inhibitors (or angiotensin recep-**

**tor blockers [ARBs])** should be strongly considered for antihypertensive therapy in patients with multiple vascular risk factors.

- **Stage B:** In these patients with structural heart disease but no symptoms, treatment is targeted at minimizing additional injury and preventing or slowing the remodeling process. In addition to treatment measures outlined for stage A, patients with a previous MI should receive both **ACE inhibitors** (or **ARBs** in patients intolerant of ACE inhibitors) and  **$\beta$ -blockers** regardless of the ejection fraction. Patients with reduced ejection fractions (less than 40%) should also receive both agents, regardless of whether they have had an MI.
- **Stage C:** Most patients with structural heart disease and previous or current HF symptoms should receive the treatments for Stages A and B as well as initiation and titration of a **diuretic** (if clinical evidence of fluid retention), **ACE inhibitor**, and  **$\beta$ -blocker** (if not already receiving a  **$\beta$ -blocker** for previous MI, left ventricular [LV] dysfunction, or other indication). If diuresis is initiated and symptoms improve once the patient is euvolemic, long-term monitoring can begin. If symptoms do not improve, an **aldosterone receptor antagonist**, **ARB** (in ACE inhibitor-intolerant patients), **digoxin**, and/or **hydralazine/isosorbide dinitrate (ISDN)** may be useful in carefully selected patients. Other general measures include moderate sodium restriction, daily weight measurement, immunization against influenza and pneumococcus, modest physical activity, and avoidance of medications that can exacerbate HF.
- **Stage D:** Patients with symptoms at rest despite maximal medical therapy should be considered for specialized therapies, including mechanical circulatory support, continuous intravenous positive inotropic therapy, cardiac transplantation, or hospice care.

## PHARMACOLOGIC THERAPY

### Drug Therapies for Routine Use

#### *Diuretics*

- Compensatory mechanisms in HF stimulate excessive sodium and water retention, often leading to systemic and pulmonary congestion. Consequently, diuretic therapy (in addition to sodium restriction) is recommended in all patients with clinical evidence of fluid retention. However, because they do not alter disease progression or prolong survival, they are not considered mandatory therapy for patients without fluid retention.
- Thiazide diuretics (e.g., **hydrochlorothiazide**) are relatively weak diuretics and are used alone infrequently in HF. However, thiazides or the thiazide-like diuretic **metolazone** can be used in combination with a loop diuretic to promote effective diuresis. Thiazides may be preferred over loop diuretics in patients with only mild fluid retention and elevated blood pressure because of their more persistent antihypertensive effects.
- Loop diuretics (**furosemide**, **bumetanide**, **torsemide**) are usually necessary to restore and maintain euvolemia in HF. In addition to acting in the thick ascending limb of the loop of Henle, they induce a prostaglandin-mediated increase in renal blood flow that contributes to their natriuretic effect.

**TABLE 8-1** Loop Diuretic Use in Heart Failure

	<b>Furosemide</b>	<b>Bumetanide</b>	<b>Torsemide</b>
Usual daily dose (oral)	20–160 mg/day	0.5–4 mg/day	10–80 mg/day
Ceiling dose <sup>d</sup>			
Normal renal function	80–160 mg	1–2 mg	20–40 mg
CL <sub>CR</sub> : 20–50 mL/min	160 mg	2 mg	40 mg
CL <sub>CR</sub> : <20 mL/min	400 mg	8–10 mg	100 mg
Bioavailability	10–100%	80–90%	80–100%
	Average: 50%		
Affected by food	Yes	Yes	No
Half-life	0.3–3.4 hours	0.3–1.5 hours	3–4 hours

CL<sub>CR</sub>, creatinine clearance.

<sup>d</sup>Ceiling dose: single dose above which additional response is unlikely to be observed.

Unlike thiazides, loop diuretics maintain their effectiveness in the presence of impaired renal function, although higher doses may be necessary.

- Doses of loop diuretics above the recommended ceiling doses produce no additional diuresis in HF. Thus, once those doses are reached, more frequent dosing should be used for additional effect, rather than giving progressively higher doses. Ranges of doses and ceiling doses for loop diuretics in patients with varying degrees of renal function are listed in Table 8-1.

### Angiotensin-Converting Enzyme Inhibitors

- ACE inhibitors (Table 8-2) decrease angiotensin II and aldosterone, attenuating many of their deleterious effects, including reducing ventricular remodeling, myocardial fibrosis, myocyte apoptosis, cardiac hypertrophy, norepinephrine release, vasoconstriction, and sodium and water retention.

**TABLE 8-2** ACE Inhibitors Routinely Used for Treatment of Heart Failure

<b>Generic Name</b>	<b>Brand Name</b>	<b>Initial Dose</b>	<b>Target Dosing–Survival Benefit<sup>a</sup></b>	<b>Prodrug</b>	<b>Elimination<sup>b</sup></b>
Captopril	Capoten	6.25 mg three times daily	50 mg three times daily	No	Renal
Enalapril	Vasotec	2.5–5 mg twice daily	10 mg twice daily	Yes	Renal
Lisinopril	Zestril, Prinivil	2.5–5 mg daily	20–40 mg daily <sup>c</sup>	No	Renal
Quinapril	Accupril	10 mg twice daily	20–40 mg twice daily <sup>d</sup>	Yes	Renal
Ramipril	Altace	1.25–2.5 mg twice daily	5 mg twice daily	Yes	Renal
Fosinopril	Monopril	5–10 mg daily	40 mg daily <sup>d</sup>	Yes	Renal/hepatic
Trandolapril	Mavik	0.5–1 mg daily	4 mg daily	Yes	Renal/hepatic
Perindopril	Aceon	2 mg daily	8–16 mg daily	Yes	Renal/hepatic

<sup>a</sup>Target doses associated with survival benefits in clinical trials.

<sup>b</sup>Primary route of elimination.

<sup>c</sup>Note that in the ATLAS trial no significant difference in mortality was found between low-dose (~5 mg/day) and high-dose (~35 mg/day) lisinopril therapy.

<sup>d</sup>Effects on mortality have not been evaluated.

- Clinical trials have produced unequivocal evidence that ACE inhibitors improve symptoms, slow disease progression, and decrease mortality in patients with HF and reduced LVEF (stage C). These patients should receive ACE inhibitors unless contraindications are present. ACE inhibitors should also be used to prevent the development of HF in at-risk patients (i.e., stages A and B).

### *$\beta$ -Blockers*

- There is overwhelming clinical trial evidence that certain  $\beta$ -blockers slow disease progression, decrease hospitalizations, and reduce mortality in patients with HF.
- Beneficial effects of  $\beta$ -blockers may result from antiarrhythmic effects, slowing or reversing ventricular remodeling, decreasing myocyte death from catecholamine-induced necrosis or apoptosis, preventing fetal gene expression, improving LV systolic function, decreasing heart rate and ventricular wall stress and thereby reducing myocardial oxygen demand, and inhibiting plasma renin release.
- The ACC/AHA guidelines recommend use of  $\beta$ -blockers in all stable patients with HF and a reduced LVEF in the absence of contraindications or a clear history of  $\beta$ -blocker intolerance. Patients should receive a  $\beta$ -blocker even if symptoms are mild or well controlled with ACE inhibitor and diuretic therapy. It is not essential that ACE inhibitor doses be optimized before a  $\beta$ -blocker is started because the addition of a  $\beta$ -blocker is likely to be of greater benefit than an increase in ACE inhibitor dose.
- $\beta$ -Blockers are also recommended for asymptomatic patients with a reduced LVEF (stage B) to decrease the risk of progression to HF.
- Because of their negative inotropic effects,  $\beta$ -blockers should be started in very low doses with slow upward dose titration to avoid symptomatic worsening or acute decompensation. Patients should be titrated to target doses when possible to provide maximal survival benefits. However, even lower doses have benefits over placebo, so any dose is likely to provide some benefit.
- Metoprolol CR/XL, carvedilol, and bisoprolol are the only  $\beta$ -blockers shown to reduce mortality in large HF trials. It cannot be assumed that immediate-release metoprolol will provide benefits equivalent to metoprolol CR/XL. Because bisoprolol is not available in the necessary starting dose of 1.25 mg, the choice is typically limited to either carvedilol or metoprolol CR/XL. On the basis of regimens proven in large clinical trials to reduce mortality, initial and target oral doses are as follows:
  - ✓ **Carvedilol**, 3.125 mg twice daily initially; target dose, 25 mg twice daily (the target dose for patients weighing more than 85 kg is 50 mg twice daily). Carvedilol CR should be considered in patients with difficulty maintaining adherence to the immediate-release formulation.
  - ✓ **Metoprolol succinate CR/XL**, 12.5 to 25 mg once daily initially; target dose, 200 mg once daily.
  - ✓ **Bisoprolol**, 1.25 mg once daily initially; target dose, 10 mg once daily.
- Doses should be doubled no more often than every 2 weeks, as tolerated, until the target dose or the maximally tolerated dose is reached. Patients

should understand that dose up-titration is a long, gradual process and that achieving the target dose is important to maximize benefits. Further, the response to therapy may be delayed, and HF symptoms may actually worsen during the initiation period.

## Drug Therapies to Consider for Selected Patients

### *Angiotensin II Receptor Blockers*

- The angiotensin II receptor antagonists block the angiotensin II receptor subtype AT<sub>1</sub>, preventing the deleterious effects of angiotensin II, regardless of its origin. They do not appear to affect bradykinin and are not associated with the side effect of cough that sometimes results from ACE inhibitor–induced accumulation of bradykinin. Also, direct blockade of AT<sub>1</sub> receptors allows unopposed stimulation of AT<sub>2</sub> receptors, causing vasodilation and inhibition of ventricular remodeling.
- Although some data suggest that ARBs produce equivalent mortality benefits when compared to ACE inhibitors, the ACC/AHA guidelines recommend use of ARBs only in patients with stage A, B, or C HF who are intolerant of ACE inhibitors. Although there are seven ARBs on the market in the United States, only candesartan and valsartan are FDA-approved for the treatment of HF and are the preferred agents.
- Therapy should be initiated at low doses and then titrated to target doses:
  - ✓ **Candesartan**, 4 to 8 mg once daily initially; target dose, 32 mg once daily.
  - ✓ **Valsartan**, 20 to 40 mg twice daily initially; target dose, 160 mg twice daily.
- Blood pressure, renal function, and serum potassium should be evaluated within 1 to 2 weeks after therapy initiation and dose increases, with these endpoints used to guide subsequent dose changes. It is not necessary to reach target ARB doses before adding a  $\beta$ -blocker.
- Cough and angioedema are the most common causes of ACE inhibitor intolerance. Caution should be exercised when ARBs are used in patients with angioedema from ACE inhibitors because cross-reactivity has been reported. ARBs are not alternatives in patients with hypotension, hyperkalemia, or renal insufficiency due to ACE inhibitors because they are just as likely to cause these adverse effects.
- Combination therapy with an ARB and ACE inhibitor offers a theoretical advantage over either agent alone through more complete blockade of the deleterious effects of angiotensin II. However, clinical trial results indicate that the addition of an ARB to optimal HF therapy (e.g., ACE inhibitors,  $\beta$ -blockers, diuretics) offers marginal benefits at best with increased risk of adverse effects. Addition of an ARB may be considered in patients who remain symptomatic despite receiving optimal conventional therapy.

### *Aldosterone Antagonists*

- **Spironolactone** and **eplerenone** block the mineralocorticoid receptor, the target site for aldosterone. In the kidney, aldosterone antagonists inhibit sodium reabsorption and potassium excretion. However, diuretic effects are minimal, suggesting that their therapeutic benefits result from other

actions. Effects in the heart attenuate cardiac fibrosis and ventricular remodeling. Recent evidence also suggests an important role in attenuating the systemic proinflammatory state and oxidative stress caused by aldosterone. Spironolactone also interacts with androgen and progesterone receptors, which may lead to gynecomastia and other sexual side effects; these effects are less frequent with eplerenone because of its low affinity for androgen and progesterone receptors.

- Based on clinical trial results demonstrating reduced mortality, low-dose aldosterone antagonists may be appropriate for: (1) patients with moderately severe to severe HF who are receiving standard therapy; and (2) those with LV dysfunction early after MI.
- Data from clinical practice suggest that the risks of serious hyperkalemia and worsening renal function are much higher than observed in clinical trials. This may be due in part to failure of clinicians to consider renal impairment, reduce or stop potassium supplementation, or monitor renal function and potassium closely once the aldosterone antagonist is initiated. Thus, aldosterone antagonists must be used cautiously and with careful monitoring of renal function and potassium concentration. They should be avoided in patients with renal impairment, recent worsening of renal function, high-normal potassium levels, or a history of severe hyperkalemia.
- Initial doses should be low (spironolactone 12.5 mg/day; eplerenone 25 mg/day), especially in the elderly and those with diabetes or creatinine clearance <50 mL/min. A spironolactone dose of 25 mg/day was used in one major clinical trial. The eplerenone dose should be titrated to the target dose of 50 mg once daily, preferably within 4 weeks as tolerated by the patient.

### *Digoxin*

- Although digoxin has positive inotropic effects, its benefits in HF are related to its neurohormonal effects. Digoxin attenuates the excessive sympathetic nervous system activation present in HF patients, perhaps by reducing central sympathetic outflow and improving impaired baroreceptor function. It also increases parasympathetic activity in HF patients and decreases heart rate, thus enhancing diastolic filling. Digoxin does not improve survival in patients with HF but does provide symptomatic benefits.
- In patients with HF and supraventricular tachyarrhythmias such as atrial fibrillation, digoxin should be considered early in therapy to help control ventricular response rate.
- For patients in normal sinus rhythm, effects on symptom reduction and quality-of-life improvement are evident in patients with mild to severe HF. Therefore, it should be used together with standard HF therapies (ACE inhibitors,  $\beta$ -blockers, and diuretics) in patients with symptomatic HF to reduce hospitalizations.
- Doses should be adjusted to achieve plasma digoxin concentration of 0.5 to 1 ng/mL. Higher plasma levels are not associated with additional benefits but may increase the risk of toxicity. Most patients with normal renal function can achieve this level with a dose of 0.125 mg/day. Patients

with decreased renal function, the elderly, or those receiving interacting drugs (e.g., amiodarone) should receive 0.125 mg every other day. In the absence of supraventricular tachyarrhythmias, a loading dose is not indicated because digoxin is a mild inotropic agent that produces gradual effects over several hours, even after loading. Blood samples for measuring plasma digoxin concentrations should be collected at least 6 hours, and preferably 12 hours or more, after the last dose.

### Nitrates and Hydralazine

- Nitrates (e.g., **ISDN**) and **hydralazine** were combined originally in the treatment of HF because of their complementary hemodynamic actions. Nitrates are primarily venodilators, producing reductions in preload. Hydralazine is a direct vasodilator that acts predominantly on arterial smooth muscle to reduce systemic vascular resistance (SVR) and increase stroke volume and cardiac output. Evidence also suggests that the combination may provide additional benefits by interfering with the biochemical processes associated with HF progression.
- The combination of nitrates and hydralazine improves the composite endpoint of mortality, hospitalizations for HF, and quality of life in African Americans who receive standard therapy. A fixed-dose combination product is available that contains ISDN 20 mg and hydralazine 37.5 mg (BiDil). Practice guidelines recommend adding ISDN and hydralazine as part of standard therapy in African Americans with moderately severe to severe HF. The combination may also be reasonable for patients of other ethnicities with persistent symptoms despite optimized therapy with an ACE inhibitor (or ARB) and  $\beta$ -blocker. The combination is also appropriate as first-line therapy in patients unable to tolerate ACE inhibitors or ARBs because of renal insufficiency, hyperkalemia, or possibly hypotension.
- Obstacles to successful therapy with this drug combination include the need for frequent dosing (i.e., three times daily with the fixed-dose combination product), a high frequency of adverse effects (e.g., headache, dizziness, GI distress), and increased cost for the fixed-dose combination product.

## TREATMENT OF ACUTE DECOMPENSATED HEART FAILURE

### GENERAL APPROACH

- The term *decompensated HF* refers to patients with new or worsening signs or symptoms that are usually caused by volume overload and/or hypoperfusion and lead to the need for additional medical care, such as emergency department visits and hospitalizations.
- The goals of therapy are to relieve congestive symptoms, optimize volume status, treat symptoms of low cardiac output, and minimize the risks of drug therapy so the patient can be discharged in a compensated state on oral drug therapy.
- Hospitalization should occur or be considered depending on each patient's symptoms and physical findings. Admission to an intensive care unit may

be required if the patient experiences hemodynamic instability requiring frequent monitoring, invasive hemodynamic monitoring, or rapid titration of IV medications with close monitoring.

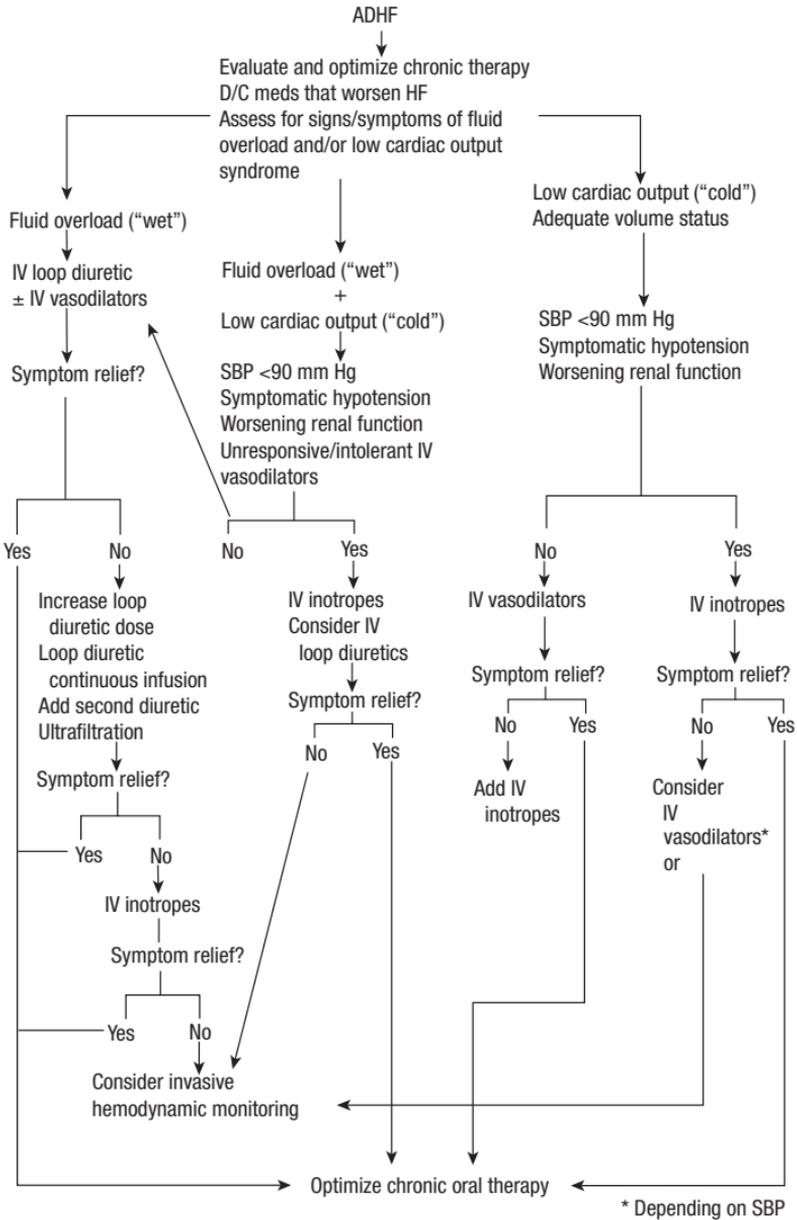
- Cardiopulmonary support must be instituted and adjusted rapidly. Electrocardiogram (ECG) monitoring, continuous pulse oximetry, urine flow monitoring, and automated blood pressure recording are necessary. Peripheral or femoral arterial catheters may be used for continuous assessment of arterial pressure.
- Reversible or treatable causes of decompensation should be addressed and corrected. Drugs that may aggravate HF should be evaluated carefully and discontinued when possible.
- The first step in managing decompensated HF is to ascertain that optimal treatment with oral medications has been achieved. If there is evidence of fluid retention, aggressive diuresis, often with IV diuretics, should be accomplished. Optimal treatment with an ACE inhibitor should be a priority. Although  $\beta$ -blockers should not be started during this period of instability, they should be continued, if possible, in patients who are already receiving them on a chronic basis. Most patients should be receiving digoxin at a low dose prescribed to achieve a trough serum concentration of 0.5 to 1 ng/mL.
- Appropriate management of decompensated HF is aided by determination of whether the patient has signs and symptoms of fluid overload (“wet” HF) or low cardiac output (“dry” HF) (Fig. 8-2).
- Invasive hemodynamic monitoring should be considered in patients who are refractory to initial therapy, whose volume status is unclear, or who have clinically significant hypotension such as systolic BP <80 mm Hg. Such monitoring helps guide treatment and classify patients into four specific hemodynamic subsets based on cardiac index and pulmonary artery occlusion pressure (PAOP). Refer to textbook Chap. 16 (Heart Failure) for more information.

## PHARMACOTHERAPY OF ACUTE DECOMPENSATED HEART FAILURE

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### Diuretics

- IV loop diuretics, including **furosemide**, **bumetanide**, and **torsemide**, are used for acute decompensated HF, with furosemide being the most widely studied and used agent.
- Bolus diuretic administration decreases preload by functional venodilation within 5 to 15 minutes and later (>20 min) via sodium and water excretion, thereby improving pulmonary congestion. However, acute reductions in venous return may severely compromise effective preload in patients with significant diastolic dysfunction or intravascular depletion.
- Because diuretics can cause excessive preload reduction, they must be used judiciously to obtain the desired improvement in congestive symptoms while avoiding a reduction in cardiac output, symptomatic hypotension, or worsening renal function.
- Diuresis may be improved by adding a second diuretic with a different mechanism of action (e.g., combining a loop diuretic with a distal tubule



**FIGURE 8-2.** General treatment algorithm for acute decompensated heart failure (ADHF) based on clinical presentation. IV vasodilators that may be used include nitroglycerin, nesiritide, or nitroprusside. Metolazone or spironolactone may be added if the patient fails to respond to loop diuretics and a second diuretic is required. IV inotropes that may be used include dobutamine or milrinone. (D/C, discontinue; HF, heart failure; SBP, systolic blood pressure.) (Reprinted and adapted from *J Cardiac Fail*, Vol 12, pages e1–e122, copyright 2006, with permission from Elsevier.)

blocker such as **metolazone** or **hydrochlorothiazide**). The loop diuretic-thiazide combination should generally be reserved for inpatients who can be monitored closely for the development of severe sodium, potassium, and volume depletion. Very low doses of the thiazide-type diuretic should be used in the outpatient setting to avoid serious adverse events.

## Positive Inotropic Agents

### *Dobutamine*

- **Dobutamine** is a  $\beta_1$ - and  $\beta_2$ -receptor agonist with some  $\alpha_1$ -agonist effects. The net vascular effect is usually vasodilation. It has a potent inotropic effect without producing a significant change in heart rate. Initial doses of 2.5 to 5 mcg/kg/min can be increased progressively to 20 mcg/kg/min on the basis of clinical and hemodynamic responses.
- Dobutamine increases cardiac index because of inotropic stimulation, arterial vasodilation, and a variable increase in heart rate. It causes relatively little change in mean arterial pressure compared with the more consistent increases observed with dopamine.
- Although concern over attenuation of dobutamine's hemodynamic effects with prolonged administration has been raised, some effect is likely retained. Consequently, the dobutamine dose should be tapered rather than abruptly discontinued.

### *Milrinone*

- **Milrinone** is a bipyridine derivative that inhibits phosphodiesterase III and produces positive inotropic and arterial and venous vasodilating effects; hence, milrinone has been referred to as an inodilator. It has supplanted use of amrinone, which has a higher rate of thrombocytopenia.
- During IV administration, milrinone increases stroke volume (and cardiac output) with little change in heart rate. It also decreases PAOP by venodilation and thus is particularly useful in patients with a low cardiac index and an elevated LV filling pressure. However, this decrease in preload can be hazardous for patients without excessive filling pressure, leading to a decrease in cardiac index.
- Milrinone should be used cautiously as a single agent in severely hypotensive HF patients because it will not increase, and may even decrease, arterial blood pressure.
- The usual loading dose of milrinone is 50 mcg/kg over 10 minutes. If rapid hemodynamic changes are unnecessary, the loading dose should be eliminated because of the risk of hypotension. Most patients are simply started on the maintenance continuous infusion of 0.25 mcg/kg/min (up to 0.75 mcg/kg/min).
- The most notable adverse events are arrhythmia, hypotension, and, rarely, thrombocytopenia. Patients should have platelet counts determined before and during therapy.
- Routine use of milrinone (and perhaps other inotropes) should be discouraged because recent studies suggest a higher in-hospital mortality rate than with some other drugs. However, inotropes may be needed in selected patients such as those with low cardiac output states with organ hypoperfusion and cardiogenic shock. It may be considered for patients receiving

chronic  $\beta$ -blocker therapy because its positive inotropic effect does not involve stimulation of  $\beta$ -receptors.

### **Dopamine**

- **Dopamine** should generally be avoided in decompensated HF, but its pharmacologic actions may be preferable to dobutamine or milrinone in patients with marked systemic hypotension or cardiogenic shock in the face of elevated ventricular filling pressures, where dopamine in doses greater than 5 mcg/kg/min may be necessary to raise central aortic pressure.
- Dopamine produces dose-dependent hemodynamic effects because of its relative affinity for  $\alpha_1$ -,  $\beta_1$ -,  $\beta_2$ -, and D<sub>1</sub>- (vascular dopaminergic) receptors. Positive inotropic effects mediated primarily by  $\beta_1$ -receptors become more prominent with doses of 2 to 5 mcg/kg/min. At doses between 5 to 10 mcg/kg/min, chronotropic and  $\alpha_1$ -mediated vasoconstricting effects become more prominent. Especially at higher doses, dopamine alters several parameters that increase myocardial oxygen demand and potentially decrease myocardial blood flow, worsening ischemia in some patients with coronary artery disease.

### **Vasodilators**

- Arterial vasodilators act as impedance-reducing agents, reducing afterload and causing a reflex increase in cardiac output. Venodilators act as preload reducers by increasing venous capacitance, reducing symptoms of pulmonary congestion in patients with high cardiac filling pressures. Mixed vasodilators act on both arterial resistance and venous capacitance vessels, reducing congestive symptoms while increasing cardiac output.

### **Nitroprusside**

- **Sodium nitroprusside** is a mixed arterial-venous vasodilator that acts directly on vascular smooth muscle to increase cardiac index and decrease venous pressure. Despite its lack of direct inotropic activity, nitroprusside exerts hemodynamic effects that are qualitatively similar to those of dobutamine and milrinone. However, nitroprusside generally decreases PAOP, SVR, and blood pressure more than those agents do.
- Hypotension is an important dose-limiting adverse effect of nitroprusside and other vasodilators. Therefore, nitroprusside is primarily used in patients who have a significantly elevated SVR and often requires invasive hemodynamic monitoring.
- Nitroprusside is effective in the short-term management of severe HF in a variety of settings (e.g., acute MI, valvular regurgitation, after coronary bypass surgery, decompensated HF). Generally, it will not worsen, and may improve, the balance between myocardial oxygen demand and supply. However, an excessive decrease in systemic arterial pressure can decrease coronary perfusion and worsen ischemia.
- Nitroprusside has a rapid onset and a duration of action of less than 10 minutes, which necessitates use of continuous IV infusions. It should be initiated at a low dose (0.1 to 0.2 mcg/kg/min) to avoid excessive hypotension, and then increased by small increments (0.1 to 0.2 mcg/kg/min)

every 5 to 10 minutes as needed and tolerated. Usual effective doses range from 0.5 to 3 mcg/kg/min. Because of a rebound phenomenon after abrupt withdrawal of nitroprusside in patients with HF, doses should be tapered slowly when stopping therapy. Nitroprusside-induced cyanide and thiocyanate toxicity are unlikely when doses less than 3 mcg/kg/min are administered for less than 3 days, except in patients with serum creatinine levels above 3 mg/dL.

### *Nitroglycerin*

- The major hemodynamic effects of IV **nitroglycerin** are decreased preload and PAOP because of functional venodilation and mild arterial vasodilation. It is used primarily as a preload reducer for patients with pulmonary congestion. In higher doses, nitroglycerin displays potent coronary vasodilating properties and beneficial effects on myocardial oxygen demand and supply, making it the vasodilator of choice for patients with severe HF and ischemic heart disease.
- Nitroglycerin should be initiated at 5 to 10 mcg/min (0.1 mcg/kg/min) and increased every 5 to 10 minutes as necessary and tolerated. Maintenance doses usually range from 35 to 200 mcg/min (0.5 to 3 mcg/kg/min). Hypotension and an excessive decrease in PAOP are important dose-limiting side effects. Some tolerance develops in most patients over 12 to 72 hours of continuous administration.

### *Nesiritide*

- **Nesiritide** is manufactured using recombinant techniques and is identical to the endogenous B-type natriuretic peptide secreted by the ventricular myocardium in response to volume overload. Consequently, nesiritide mimics the vasodilatory and natriuretic actions of the endogenous peptide, resulting in venous and arterial vasodilation; increases in cardiac output; natriuresis and diuresis; and decreased cardiac filling pressures, sympathetic nervous system activity, and renin-angiotensin-aldosterone system activity.
- The precise role of nesiritide in the pharmacotherapy of decompensated HF remains controversial. Compared to nitroglycerin, it appears to produce little improvement in clinical outcomes and is substantially more expensive. Two recent metaanalyses suggest an increased risk of worsening renal function as well as an increase in mortality with nesiritide. A prospective randomized trial is being conducted to clarify the safety and efficacy of nesiritide.

## **MECHANICAL CIRCULATORY SUPPORT**

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### **Intraaortic Balloon Pump**

- The intraaortic balloon pump (IABP) is typically employed in patients with advanced HF who do not respond adequately to drug therapy, such as those with intractable myocardial ischemia or patients in cardiogenic shock.
- IABP support increases cardiac index, coronary artery perfusion, and myocardial oxygen supply accompanied by decreased myocardial oxygen demand.
- IV vasodilators and inotropic agents are generally used in conjunction with the IABP to maximize hemodynamic and clinical benefits.

### Ventricular Assist Devices

- Ventricular assist devices are surgically implanted and assist, or in some cases replace, the pumping functions of the right and/or left ventricles.
- Ventricular assist devices can be used in the short-term (days to several weeks) for temporary stabilization of patients awaiting an intervention to correct the underlying cardiac dysfunction. They can also be used long term (several months to years) as a bridge to heart transplantation. Permanent device implantation has recently become an option for patients who are not candidates for heart transplantation.

## SURGICAL THERAPY

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- Orthotopic cardiac transplantation is the best therapeutic option for patients with chronic irreversible New York Heart Association Class IV HF, with a 10-year survival of approximately 50% in well-selected patients.
- The shortage of donor hearts has prompted development of new surgical techniques, including ventricular aneurysm resection, mitral valve repair, and myocardial cell transplantation, which have resulted in variable degrees of symptomatic improvement.

## EVALUATION OF THERAPEUTIC OUTCOMES

### CHRONIC HEART FAILURE

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- Patients should be asked about the presence and severity of symptoms and how the symptoms affect their daily activities.
- The efficacy of diuretic treatment is evaluated by disappearance of the signs and symptoms of excess fluid retention. Physical examination should focus on body weight, extent of jugular venous distension, presence of hepatojugular reflux, and presence and severity of pulmonary congestion (rales, dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea) and peripheral edema.
- Other outcomes include improvement in exercise tolerance and fatigue, decreased nocturia, and a decrease in heart rate.
- Blood pressure should be monitored to ensure that symptomatic hypotension does not develop as a result of drug therapy.
- Body weight is a sensitive marker of fluid loss or retention, and patients should weigh themselves daily and report changes to their healthcare provider so that adjustments can be made in diuretic doses.
- Symptoms may worsen initially on  $\beta$ -blocker therapy, and it may take weeks to months before patients notice symptomatic improvement.
- Routine monitoring of serum electrolytes and renal function is mandatory in patients with HF.

### ACUTE DECOMPENSATED HEART FAILURE

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- Initial stabilization requires achievement of adequate arterial oxygen saturation and content.

- Cardiac index and blood pressure must be sufficient to ensure adequate organ perfusion, as assessed by alert mental status, creatinine clearance sufficient to prevent metabolic azotemic complications, hepatic function adequate to maintain synthetic and excretory functions, a stable heart rate and rhythm, absence of ongoing myocardial ischemia or infarction, skeletal muscle and skin blood flow sufficient to prevent ischemic injury, and normal arterial pH (7.34 to 7.47) with a normal serum lactate concentration. These goals are most often achieved with a cardiac index greater than 2.2 L/min/m<sup>2</sup>, a mean arterial blood pressure greater than 60 mm Hg, and PAOP of 25 mm Hg or greater.
- Discharge from the intensive care unit requires maintenance of the preceding parameters in the absence of ongoing IV infusion therapy, mechanical circulatory support, or positive-pressure ventilation.

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*See Chap. 16, Heart Failure, authored by Robert B. Parker, Jo E. Rodgers, and Larisa H. Cavallari, for a more detailed discussion of this topic.*

## DEFINITION

- Dyslipidemia is defined as elevated total cholesterol, low-density lipoprotein (LDL) cholesterol, or triglycerides; a low high-density lipoprotein (HDL) cholesterol; or a combination of these abnormalities. Hyperlipoproteinemia describes an increased concentration of the lipoprotein macromolecules that transport lipids in the plasma. Abnormalities of plasma lipids can result in a predisposition to coronary, cerebrovascular, and peripheral vascular arterial disease.

## PATHOPHYSIOLOGY

- Cholesterol, triglycerides, and phospholipids are transported in the bloodstream as complexes of lipid and proteins known as lipoproteins. Elevated total and LDL cholesterol and reduced HDL cholesterol are associated with the development of coronary heart disease (CHD).
- The response-to-injury hypothesis states that risk factors such as oxidized LDL, mechanical injury to the endothelium, excessive homocysteine, immunologic attack, or infection-induced changes in endothelial and intimal function lead to endothelial dysfunction and a series of cellular interactions that culminate in atherosclerosis. The eventual clinical outcomes may include angina, myocardial infarction, arrhythmias, stroke, peripheral arterial disease, abdominal aortic aneurysm, and sudden death.
- Atherosclerotic lesions are thought to arise from transport and retention of plasma LDL through the endothelial cell layer into the extracellular matrix of the subendothelial space. Once in the artery wall, LDL is chemically modified through oxidation and nonenzymatic glycation. Mildly oxidized LDL then recruits monocytes into the artery wall. These monocytes then become transformed into macrophages that accelerate LDL oxidation.
- Oxidized LDL provokes an inflammatory response mediated by a number of chemoattractants and cytokines (e.g., monocyte colony-stimulating factor, intercellular adhesion molecule, platelet-derived growth factor, transforming growth factors, interleukin-1, interleukin-6).
- Repeated injury and repair within an atherosclerotic plaque eventually lead to a fibrous cap protecting the underlying core of lipids, collagen, calcium, and inflammatory cells such as T lymphocytes. Maintenance of the fibrous plaque is critical to prevent plaque rupture and subsequent coronary thrombosis.
- Primary or genetic lipoprotein disorders are classified into six categories for the phenotypic description of dyslipidemia. The types and corresponding lipoprotein elevations include the following: I (chylomicrons), IIa (LDL), IIb (LDL + very low density lipoprotein, or VLDL), III (intermediate-density lipoprotein), IV (VLDL), and V (VLDL + chylomicrons). Secondary forms of hyperlipidemia also exist, and several drug classes may elevate lipid levels

(e.g., progestins, thiazide diuretics, glucocorticoids,  $\beta$ -blockers, isotretinoin, protease inhibitors, cyclosporine, mirtazapine, sirolimus).

- The primary defect in familial hypercholesterolemia is the inability to bind LDL to the LDL receptor (LDL-R) or, rarely, a defect of internalizing the LDL-R complex into the cell after normal binding. This leads to lack of LDL degradation by cells and unregulated biosynthesis of cholesterol, with total cholesterol and LDL cholesterol (LDL-C) being inversely proportional to the deficit in LDL-Rs.

## CLINICAL PRESENTATION

- Familial hypercholesterolemia is characterized by a selective elevation in plasma LDL and deposition of LDL-derived cholesterol in tendons (xanthomas) and arteries (atheromas).
- Familial lipoprotein lipase deficiency is characterized by a massive accumulation of chylomicrons and a corresponding increase in plasma triglycerides or a type I lipoprotein pattern. Presenting manifestations include repeated attacks of pancreatitis and abdominal pain, eruptive cutaneous xanthomatosis, and hepatosplenomegaly beginning in childhood. Symptom severity is proportional to dietary fat intake, and consequently to the elevation of chylomicrons. Accelerated atherosclerosis is not associated with this disease.
- Patients with familial type III hyperlipoproteinemia develop the following clinical features after age 20: xanthoma striata palmaris (yellow discolorations of the palmar and digital creases); tuberous or tuberoeruptive xanthomas (bulbous cutaneous xanthomas); and severe atherosclerosis involving the coronary arteries, internal carotids, and abdominal aorta.
- Type IV hyperlipoproteinemia is common and occurs in adults, primarily in patients who are obese, diabetic, and hyperuricemic and do not have xanthomas. It may be secondary to alcohol ingestion and can be aggravated by stress, progestins, oral contraceptives, thiazides, or  $\beta$ -blockers.
- Type V is characterized by abdominal pain, pancreatitis, eruptive xanthomas, and peripheral polyneuropathy. These patients are commonly obese, hyperuricemic, and diabetic; alcohol intake, exogenous estrogens, and renal insufficiency tend to be exacerbating factors. The risk of atherosclerosis is increased with this disorder.

## DIAGNOSIS

- A fasting lipoprotein profile including total cholesterol, LDL, HDL, and triglycerides should be measured in all adults 20 years of age or older at least once every 5 years.
- Measurement of plasma cholesterol (which is about 3% lower than serum determinations), triglyceride, and HDL levels after a 12-hour or longer fast is important, because triglycerides may be elevated in nonfasted individuals; total cholesterol is only modestly affected by fasting.
- Two determinations, 1 to 8 weeks apart, with the patient on a stable diet and weight, and in the absence of acute illness, are recommended to minimize

variability and to obtain a reliable baseline. If the total cholesterol is  $>200$  mg/dL, a second determination is recommended, and if the values are more than 30 mg/dL apart, the average of three values should be used.

- After a lipid abnormality is confirmed, major components of the evaluation are the history (including age, gender, and, if female, menstrual and estrogen replacement status), physical examination, and laboratory investigations.
- A complete history and physical examination should assess (1) presence or absence of cardiovascular risk factors or definite cardiovascular disease in the individual; (2) family history of premature cardiovascular disease or lipid disorders; (3) presence or absence of secondary causes of hyperlipidemia, including concurrent medications; and (4) presence or absence of xanthomas, abdominal pain, or history of pancreatitis, renal or liver disease, peripheral vascular disease, abdominal aortic aneurysm, or cerebral vascular disease (carotid bruits, stroke, or transient ischemic attack).
- Diabetes mellitus is regarded as a CHD risk equivalent. That is, the presence of diabetes in patients without known CHD is associated with the same level of risk as patients without diabetes but having confirmed CHD.
- If the physical examination and history are insufficient to diagnose a familial disorder, then agarose-gel lipoprotein electrophoresis is useful to determine which class of lipoproteins is affected. If the triglyceride levels are  $<400$  mg/dL and neither type III hyperlipidemia nor chylomicrons are detected by electrophoresis, then one can calculate VLDL and LDL concentrations:  $VLDL = \text{triglycerides} \div 5$ ;  $LDL = \text{total cholesterol} - (VLDL + HDL)$ . Initial testing uses total cholesterol for case finding, but subsequent management decisions should be based on LDL.
- Because total cholesterol is composed of cholesterol derived from LDL, VLDL, and HDL, determination of HDL is useful when total plasma cholesterol is elevated. HDL may be elevated by moderate alcohol ingestion (fewer than two drinks per day), physical exercise, smoking cessation, weight loss, oral contraceptives, phenytoin, and terbutaline. HDL may be lowered by smoking, obesity, a sedentary lifestyle, and drugs such as  $\beta$ -blockers.
- Diagnosis of lipoprotein lipase deficiency is based on low or absent enzyme activity with normal human plasma or apolipoprotein C-II, a cofactor of the enzyme.

## DESIRED OUTCOME

- The goals of treatment are to lower total and LDL cholesterol in order to reduce the risk of first or recurrent events such as myocardial infarction, angina, heart failure, ischemic stroke, or other forms of peripheral arterial disease such as carotid stenosis or abdominal aortic aneurysm.

## TREATMENT

### GENERAL APPROACH

- The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) recommends that a fasting lipoprotein profile and risk factor assessment be used in the initial classification of adults.

**TABLE 9-1** Classification of Total, LDL, and HDL Cholesterol and Triglycerides

Total cholesterol	
<200 mg/dL	Desirable
200–239 mg/dL	Borderline high
≥240 mg/dL	High
LDL cholesterol	
<100 mg/dL	Optimal
100–129 mg/dL	Near or above optimal
130–159 mg/dL	Borderline high
160–189 mg/dL	High
≥190 mg/dL	Very high
HDL cholesterol	
<40 mg/dL	Low
≥60 mg/dL	High
Triglycerides	
<150 mg/dL	Normal
150–199 mg/dL	Borderline high
200–499 mg/dL	High
≥500 mg/dL	Very high

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

- If the total cholesterol is <200 mg/dL, then the patient has a desirable blood cholesterol level (Table 9-1). If the HDL is also >40 mg/dL, no further follow-up is recommended for patients without known CHD and who have fewer than two risk factors (Table 9-2).
- In patients with borderline-high blood cholesterol (200 to 239 mg/dL), assessment of risk factors is needed to more clearly define disease risk.
- Decisions regarding classification and management are based on the LDL cholesterol levels listed in Table 9-3.
- There are four categories of risk that modify the goals and modalities of LDL-lowering therapy. The highest risk category is having known CHD or CHD risk equivalents; the risk for major coronary events is equal to or greater than that for established CHD (i.e., >20% per 10 years, or 2% per year). The next category is moderately high risk, consisting of patients with

**TABLE 9-2** Major Risk Factors (Exclusive of LDL Cholesterol) That Modify LDL Goals<sup>a</sup>

Age
Men: ≥45 years
Women: ≥55 years or premature menopause without estrogen-replacement therapy
Family history of premature CHD (definite myocardial infarction or sudden death before 55 years of age in father or other male first-degree relative or before 65 years of age in mother or other female first-degree relative)
Cigarette smoking
Hypertension (≥140/90 mm Hg or on antihypertensive medication)
Low HDL cholesterol (<40 mg/dL) <sup>b</sup>

CHD, coronary heart disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

<sup>a</sup>Diabetes is regarded as a CHD risk equivalent.

<sup>b</sup>HDL cholesterol (≥60 mg/dL) counts as a “negative” risk factor; its presence removes one risk factor from the total count.

**TABLE 9-3** LDL Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes (TLCs) and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate TLCs (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
High risk: CHD or CHD risk equivalents (10-year risk >20%)	<100 (optional goal: <70)	≥100	≥100 (<100: consider drug options) <sup>d</sup>
Moderately high risk: 2+ risk factors (10-year risk 10–20%)	<130	≥130	≥130 (100–129: consider drug options)
Moderate risk: 2+ risk factors (10-year risk <10%)	<130	≥130	≥160
Lower risk: 0–1 risk factor <sup>b</sup>	<160	≥160	≥190 (160–189: LDL-lowering drug optional)

CHD, coronary heart disease; LDL, low-density lipoprotein.

<sup>d</sup>Some authorities recommend use of LDL-lowering drugs in this category if LDL cholesterol <100 mg/dL cannot be achieved by TLCs. Others prefer to use drugs that primarily modify triglycerides and HDL (e.g., nicotinic acid or fibrates). Clinical judgment also may call for deferring drug therapy in this subcategory.

<sup>b</sup>Almost all people with 0–1 risk factor have a 10-year risk <10%; thus 10-year risk assessment in people with 0–1 risk factor is not necessary.

two or more risk factors in which 10-year risk for CHD is 10% to 20%. Moderate risk is defined as two or more risk factors and a 10-year risk of ≥10%. The lowest risk category is persons with zero to one risk factor, which is usually associated with a 10-year CHD risk of <10%.

- ATP III recognizes the metabolic syndrome as a secondary target of risk reduction after LDL-C has been addressed. This syndrome is characterized by abdominal obesity, atherogenic dyslipidemia (elevated triglycerides, small LDL particles, low HDL cholesterol), increased blood pressure, insulin resistance (with or without glucose intolerance), and prothrombotic and proinflammatory states. If the metabolic syndrome is present, the patient is considered to have a CHD risk equivalent.
- Other targets include non-HDL goals for patients with triglycerides >200 mg/dL. Non-HDL cholesterol is calculated by subtracting HDL from total cholesterol, and the targets are 30 mg/dL greater than for LDL at each risk stratum.

## NONPHARMACOLOGIC THERAPY

- Therapeutic lifestyle changes are begun on the first visit and include dietary therapy, weight reduction, and increased physical activity. Inducing a weight loss of 10% should be discussed with patients who are overweight. In general, physical activity of moderate intensity 30 minutes a day for most days of the week should be encouraged. All patients should be counseled to stop smoking and to meet the Seventh Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure guidelines for control of hypertension.
- The objectives of dietary therapy are to progressively decrease the intake of total fat, saturated fat, and cholesterol and to achieve a desirable body weight (Table 9-4).

**TABLE 9-4** Macronutrient Recommendations for the Therapeutic Lifestyle Change Diet

Component <sup>a</sup>	Recommended Intake
Total fat	25–35% of total calories
Saturated fat	<7% of total calories
Polyunsaturated fat	Up to 10% of total calories
Monounsaturated fat	Up to 20% of total calories
Carbohydrates <sup>b</sup>	50–60% of total calories
Cholesterol	<200 mg/day
Dietary fiber	20–30 g/day
Plant sterols	2 g/day
Protein	Approximately 15% of total calories
Total calories	To achieve and maintain desirable body weight

<sup>a</sup>Calories from alcohol not included.

<sup>b</sup>Carbohydrates should derive from foods rich in complex carbohydrates, such as whole grains, fruits, and vegetables.

- Excessive dietary intake of cholesterol and saturated fatty acids leads to decreased hepatic clearance of LDL and deposition of LDL and oxidized LDL in peripheral tissues.
- Increased intake of soluble fiber in the form of oat bran, pectins, certain gums, and psyllium products can result in useful adjunctive reductions in total and LDL cholesterol (5% to 20%), but these dietary alterations or supplements should not be substituted for more active forms of treatment. They have little or no effect on HDL-C or triglyceride concentrations. These products may also be useful in managing constipation associated with the bile acid resins (BARs).
- Ingestion of 2 to 3 g/day of plant sterols and stanols will reduce LDL by 6% to 15%. They are usually available in commercial margarines.
- In epidemiologic studies, ingestion of large amounts of cold-water oily fish was associated with a reduction in CHD risk. Fish oil supplementation has a fairly large effect in reducing triglycerides and VLDL cholesterol, but it either has no effect on total and LDL cholesterol or may cause elevations in these fractions. Other actions of fish oil may account for any cardioprotective effects.
- If all recommended dietary changes from the NCEP were instituted, the estimated average reduction in LDL would range from 20% to 30%.

## PHARMACOLOGIC THERAPY

- The effect of drug therapy on lipids and lipoproteins is shown in Table 9-5.
- Recommended drugs of choice for each lipoprotein phenotype are given in Table 9-6.
- Available products and their doses are provided in Table 9-7.

### Bile Acid Resins (Cholestyramine, Colestipol, Colesevelam)

- The primary action of BARs is to bind bile acids in the intestinal lumen, with a concurrent interruption of enterohepatic circulation of bile acids, which decreases the bile acid pool size and stimulates hepatic synthesis of bile acids from cholesterol. Depletion of the hepatic pool of cholesterol results in an increase in cholesterol biosynthesis and an increase in the

**TABLE 9-5** Effects of Drug Therapy on Lipids and Lipoproteins

Drug	Mechanism of Action	Effects on Lipids	Effects on Lipoproteins
Cholestyramine, colestipol, colesvelam	↑ LDL catabolism ↓ Cholesterol absorption	↓ Cholesterol	↓ LDL ↑ VLDL
Niacin	↓ LDL and VLDL synthesis	↓ Triglyceride ↓ Cholesterol	↓ VLDL, ↓ LDL, ↑ HDL
Gemfibrozil, fenofibrate, clofibrate	↑ VLDL clearance ↓ VLDL synthesis	↓ Triglyceride ↓ Cholesterol	↓ VLDL, ↓ LDL, ↑ HDL
Lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, rosuvastatin	↑ LDL catabolism ↓ LDL synthesis	↓ Cholesterol	↓ LDL
Ezetimibe	Blocks cholesterol absorption across the intestinal border	↓ Cholesterol	↓ LDL

↑, increased; ↓, decreased.

number of LDL-Rs on the hepatocyte membrane, which stimulates an enhanced rate of catabolism from plasma and lowers LDL levels. The increase in hepatic cholesterol biosynthesis may be paralleled by increased hepatic VLDL production, and, consequently, BARs may aggravate hypertriglyceridemia in patients with combined hyperlipidemia.

- BARs are useful in treating primary hypercholesterolemia (familial hypercholesterolemia, familial combined hyperlipidemia, type IIa hyperlipoproteinemia).
- GI complaints of constipation, bloating, epigastric fullness, nausea, and flatulence are most commonly reported. These adverse effects can be

**TABLE 9-6** Lipoprotein Phenotype and Recommended Drug Treatment

Lipoprotein Type	Drug of Choice	Combination Therapy
I	Not indicated	—
IIa	Statins	Niacin or BARs
	Cholestyramine or colestipol	Statins or niacin
	Niacin	Statins or BARs Ezetimibe
IIb	Statins	BARs, fibrates, or niacin
	Fibrates	Statins or niacin or BARs <sup>a</sup>
	Niacin	Statins or fibrates Ezetimibe
III	Fibrates	Statins or niacin
	Niacin	Statins or fibrates Ezetimibe
IV	Fibrates	Niacin
	Niacin	Fibrates
V	Fibrates	Niacin
	Niacin	Fish oils

BARs, bile acid resins; fibrates include gemfibrozil or fenofibrate.

<sup>a</sup>BARs are not used as first-line therapy if triglycerides are elevated at baseline because hypertriglyceridemia may worsen with a BAR alone.

**TABLE 9-7** Comparison of Drugs Used in the Treatment of Hyperlipidemia

Drug	Dosage Forms	Usual Daily Dose	Maximum Daily Dose
Cholestyramine (Questran)	Bulk powder/4-g packets	8 g three times daily	32 g
Cholestyramine (Cholybar)	4 g resin per bar	8 g three times daily	32 g
Colestipol hydrochloride (Colestid)	Bulk powder/5-g packets	10 g twice daily	30 g
Colesevelam (Welchol)	625-mg tablets	1,875 mg twice daily	4,375 mg
Niacin	50-, 100-, 250-, and 500-mg tablets; 125-, 250-, and 500-mg capsules	2 g twice daily	9 g
Extended-release niacin (Niaspan)	500-, 750-, and 1,000-mg tablets	500 mg	2,000 mg
Extended-release niacin + lovastatin (Advicor)	Niacin/lovastatin 500-mg/20-mg tablets	500 mg/20 mg	1,000 mg/20 mg
	Niacin/lovastatin 750-mg/20-mg tablets	—	—
	Niacin/lovastatin 1,000-mg/20-mg tablets	—	—
Fenofibrate (Tricor)	67-, 134-, and 200-mg capsules (micronized); 54- and 160-mg tablets	54 mg or 67 mg	201 mg
Gemfibrozil (Lopid)	300-mg capsules	600 mg twice daily	1.5 g
Lovastatin (Mevacor)	20- and 40-mg tablets	20–40 mg	80 mg
Pravastatin (Pravachol)	10-, 20-, 40-, and 80-mg tablets	10–20 mg	40 mg
Simvastatin (Zocor)	5-, 10-, 20-, 40-, and 80-mg tablets	10–20 mg	80 mg
Atorvastatin (Lipitor)	10-, 20-, 40-, and 80-mg tablets	10 mg	80 mg
Rosuvastatin (Crestor)	5-, 10-, 20-, and 40-mg tablets	5 mg	40 mg
Ezetimibe (Zetia)	10-mg tablet	10 mg	10 mg
Simvastatin/ezetimibe (Vytorin)	Simvastatin/ezetimibe 10 mg/10 mg, 20 mg/10 mg, 40 mg/10 mg, and 80 mg/10 mg	Simvastatin/ezetimibe	Simvastatin/ezetimibe
		20 mg/10 mg	80 mg/10 mg
		—	—

Gemfibrozil, fenofibrate, and lovastatin are available as generic products. This table does not include all drugs used for treating dyslipidemia.

managed by increasing fluid intake, modifying the diet to increase bulk, and using stool softeners.

- The gritty texture and bulk may be minimized by mixing the powder with orange drink or juice. Colestipol may have better palatability than cholestyramine because it is odorless and tasteless. Tablet forms should help improve adherence with this form of therapy.
- Other potential adverse effects include impaired absorption of fat-soluble vitamins A, D, E, and K; hypernatremia and hyperchloremia; GI obstruction; and reduced bioavailability of acidic drugs such as warfarin, nicotinic acid, thyroxine, acetaminophen, hydrocortisone, hydrochlorothiazide, loperamide, and possibly iron. Drug interactions may be avoided by alternating administration times with an interval of 6 hours or greater between the BAR and other drugs.

**Niacin**

- **Niacin** (nicotinic acid) reduces the hepatic synthesis of VLDL, which in turn leads to a reduction in the synthesis of LDL. Niacin also increases HDL by reducing its catabolism.
- The principal use of niacin is for mixed hyperlipidemia or as a second-line agent in combination therapy for hypercholesterolemia. It is a first-line agent or alternative for the treatment of hypertriglyceridemia and diabetic dyslipidemia.
- Niacin has many common adverse drug reactions; most of the symptoms and biochemical abnormalities seen do not require discontinuation of therapy.
- Cutaneous flushing and itching appear to be prostaglandin mediated and can be reduced by taking aspirin 325 mg shortly before niacin ingestion. Taking the niacin dose with meals and slowly titrating the dose upward may minimize these effects. Concomitant alcohol and hot drinks may magnify the flushing and pruritus from niacin, and they should be avoided at the time of ingestion. GI intolerance is also a common problem.
- Potentially important laboratory abnormalities occurring with niacin therapy include elevated liver function tests, hyperuricemia, and hyperglycemia. Niacin-associated hepatitis is more common with sustained-release preparations, and their use should be restricted to patients intolerant of regular-release products. Niacin is contraindicated in patients with active liver disease, and it may exacerbate preexisting gout and diabetes.
- Nicotinamide should not be used in the treatment of hyperlipidemia because it does not effectively lower cholesterol or triglyceride levels.

**HMG-CoA Reductase Inhibitors (Atorvastatin, Fluvastatin, Lovastatin, Pravastatin, Rosuvastatin, Simvastatin)**

- Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, interrupting the conversion of HMG-CoA to mevalonate, the rate-limiting step in de novo cholesterol biosynthesis. Reduced synthesis of LDL and enhanced catabolism of LDL mediated through LDL-Rs appear to be the principal mechanisms for lipid-lowering effects.
- When used as monotherapy, statins are the most potent total and LDL cholesterol-lowering agents and among the best tolerated. Total and LDL cholesterol are reduced in a dose-related fashion by 30% or more when added to dietary therapy.
- Combination therapy with a statin and BAR is rational because numbers of LDL-Rs are increased, leading to greater degradation of LDL cholesterol; intracellular synthesis of cholesterol is inhibited; and enterohepatic recycling of bile acids is interrupted.
- Combination therapy with a statin and ezetimibe is also rational because ezetimibe inhibits cholesterol absorption across the gut border and adds 12% to 20% further reduction when combined with a statin or other drugs.
- Constipation occurs in fewer than 10% of patients taking statins. Other adverse effects include elevated serum aminotransferase levels (primarily alanine aminotransferase), elevated creatine kinase levels, myopathy, and rarely rhabdomyolysis.

### Fibric Acids (Gemfibrozil, Fenofibrate, Clofibrate)

- Fibrate monotherapy is effective in reducing VLDL, but a reciprocal rise in LDL may occur and total cholesterol values may remain relatively unchanged. Plasma HDL concentrations may rise 10% to 15% or more with fibrates.
- Gemfibrozil reduces the synthesis of VLDL and, to a lesser extent, apolipoprotein B with a concurrent increase in the rate of removal of triglyceride-rich lipoproteins from plasma. Clofibrate is less effective than gemfibrozil or niacin in reducing VLDL production.
- GI complaints occur in 3% to 5% of patients, rash in 2%, dizziness in 2.4%, and transient elevations in transaminase levels and alkaline phosphatase in 4.5% and 1.3%, respectively. Clofibrate and, less commonly, gemfibrozil may enhance the formation of gallstones.
- A myositis syndrome of myalgia, weakness, stiffness, malaise, and elevations in creatine kinase and aspartate aminotransferase may occur and seems to be more common in patients with renal insufficiency.
- Fibrates may potentiate the effects of oral anticoagulants, and the international normalized ratio should be monitored very closely with this combination.

### Ezetimibe

- **Ezetimibe** interferes with the absorption of cholesterol from the brush border of the intestine, a novel mechanism that makes it a good choice for adjunctive therapy. It is approved as both monotherapy and for use with a statin. The dose is 10 mg once daily, given with or without food. When used alone, it results in an approximate 18% reduction in LDL cholesterol. When added to a statin, ezetimibe lowers LDL by about an additional 12% to 20%. A combination product (Vytorin) containing ezetimibe 10 mg and simvastatin 10, 20, 40, or 80 mg is available. Ezetimibe is well tolerated; approximately 4% of patients experience GI upset. Because cardiovascular outcomes with ezetimibe have not been evaluated, it should be reserved for patients unable to tolerate statin therapy or those who do not achieve satisfactory lipid lowering with a statin alone.

### Fish Oil Supplementation

- Diets high in omega-3 polyunsaturated fatty acids (from fish oil), most commonly eicosapentaenoic acid (EPA), reduce cholesterol, triglycerides, LDL, and VLDL and may elevate HDL cholesterol.
- Fish oil supplementation may be most useful in patients with hypertriglyceridemia, but its role in treatment is not well defined.
- **Lovaza (omega-3-acid ethyl esters)** is a prescription form of concentrated fish oil EPA 465 mg and docosahexaenoic acid 375 mg. The daily dose is 4 g/day, which can be taken as four 1-g capsules once daily or two 1-g capsules twice daily. This product lowers triglycerides by 14% to 30% and raises HDL by about 10%.
- Complications of fish oil supplementation such as thrombocytopenia and bleeding disorders have been noted, especially with high doses (EPA, 15 to 30 g/day).

## TREATMENT RECOMMENDATIONS

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- Treatment of type I hyperlipoproteinemia is directed toward reduction of chylomicrons derived from dietary fat with the subsequent reduction in plasma triglycerides. Total daily fat intake should be no more than 10 to 25 g/day, or approximately 15% of total calories. Secondary causes of hypertriglyceridemia should be excluded, and, if present, the underlying disorder should be treated appropriately.
- Primary hypercholesterolemia (familial hypercholesterolemia, familial combined hyperlipidemia, type IIa hyperlipoproteinemia) is treated with **BARs, statins, niacin, or ezetimibe**.
- Combined hyperlipoproteinemia (type IIb) may be treated with **statins, niacin, or gemfibrozil** to lower LDL-C without elevating VLDL and triglycerides. Niacin is the most effective agent and may be combined with a BAR. A BAR alone in this disorder may elevate VLDL and triglycerides, and their use as single agents for treating combined hyperlipoproteinemia should be avoided.
- Type III hyperlipoproteinemia may be treated with **fibrates or niacin**. Although fibrates have been suggested as the drugs of choice, niacin is a reasonable alternative because of the lack of data supporting a cardiovascular mortality benefit from fibrates and because of their potentially serious adverse effects. Fish oil supplementation may be an alternative therapy.
- Type V hyperlipoproteinemia requires stringent restriction of dietary fat intake. Drug therapy with **fibrates or niacin** is indicated if the response to diet alone is inadequate. **Medium-chain triglycerides**, which are absorbed without chylomicron formation, may be used as a dietary supplement for caloric intake if needed for both types I and V.

### Combination Drug Therapy

- Combination therapy may be considered after adequate trials of monotherapy and for patients documented to be adherent to the prescribed regimen. Two or three lipoprotein profiles at 6-week intervals should confirm lack of response prior to initiation of combination therapy.
- Contraindications to and drug interactions with combined therapy should be screened carefully, and the extra cost of drug product and monitoring should be considered.
- In general, a **statin** plus a **BAR** or **niacin** plus a **BAR** provide the greatest reduction in total and LDL cholesterol.
- Regimens intended to increase HDL levels should include either **gemfibrozil** or **niacin**, bearing in mind that **statins** combined with either of these drugs may result in a greater incidence of hepatotoxicity or myositis.
- Familial combined hyperlipidemia may respond better to a fibrate and a statin than to a fibrate and a BAR.

## TREATMENT OF HYPERTRIGLYCERIDEMIA

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- Lipoprotein pattern types I, III, IV, and V are associated with hypertriglyceridemia, and these primary lipoprotein disorders should be excluded prior to implementing therapy.

- A family history positive for CHD is important in identifying patients at risk for premature atherosclerosis. If a patient with CHD has elevated triglycerides, the associated abnormality is probably a contributing factor to CHD and should be treated.
- High serum triglycerides (see Table 9-1) should be treated by achieving desirable body weight, consumption of a low saturated fat and cholesterol diet, regular exercise, smoking cessation, and restriction of alcohol (in selected patients).
- ATP III identifies the sum of LDL and VLDL (termed *non-HDL* [total cholesterol – HDL]) as a secondary therapeutic target in persons with high triglycerides ( $\geq 200$  mg/dL). The goal for non-HDL with high serum triglycerides is set at 30 mg/dL higher than that for LDL on the premise that a VLDL level of 30 mg/dL or less is normal.
- Drug therapy with **niacin** should be considered in patients with borderline-high triglycerides but with accompanying risk factors of established CHD, family history of premature CHD, concomitant LDL elevation or low HDL, and genetic forms of hypertriglyceridemia associated with CHD. Niacin may be used cautiously in persons with diabetes because a clinical trial found only a slight increase in glucose and no change in hemoglobin A1C. Alternative therapies include **gemfibrozil**, **statins**, and **fish oil**. The goal of therapy is to lower triglycerides and VLDL particles that may be atherogenic, increase HDL, and reduce LDL.
- Very high triglycerides are associated with pancreatitis and other adverse consequences. Management includes dietary fat restriction (10% to 20% of calories as fat), weight loss, alcohol restriction, and treatment of coexisting disorders (e.g., diabetes). Drug therapy includes **gemfibrozil**, **niacin**, and higher-potency statins (**atorvastatin**, **rosuvastatin**, and **simvastatin**).

### TREATMENT OF LOW HIGH-DENSITY LIPOPROTEIN CHOLESTEROL

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- Low HDL cholesterol is a strong independent risk predictor of CHD. ATP III redefined low HDL cholesterol as  $< 40$  mg/dL but specified no goal for HDL cholesterol raising. In low HDL, the primary target remains LDL, but treatment emphasis shifts to weight reduction, increased physical activity, smoking cessation, and to **fibrates** and **niacin** if drug therapy is required.

### TREATMENT OF DIABETIC DYSLIPIDEMIA

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- Diabetic dyslipidemia is characterized by hypertriglyceridemia, low HDL, and minimally elevated LDL. Small, dense LDL (pattern B) in diabetes is more atherogenic than larger, more buoyant forms of LDL (pattern A).
- ATP III considers diabetes to be a CHD risk equivalent, and the primary target is to lower the LDL to  $< 100$  mg/dL. When LDL is  $> 130$  mg/dL, most patients require simultaneous therapeutic lifestyle changes and drug therapy. When LDL is between 100 and 129 mg/dL, intensifying glycemic control, adding drugs for atherogenic dyslipidemia (**fibrates**, **niacin**), and intensifying LDL-lowering therapy are options. **Statins** are considered by many to be the drugs of choice because the primary target is LDL.

## EVALUATION OF THERAPEUTIC OUTCOMES

- Short-term evaluation of therapy for hyperlipidemia is based on response to diet and drug treatment as measured in the clinical laboratory by total cholesterol, LDL-C, HDL cholesterol, and triglycerides.
- Many patients treated for primary hyperlipidemia have no symptoms or clinical manifestations of a genetic lipid disorder (e.g., xanthomas), so monitoring is solely laboratory based.
- In patients treated for secondary intervention, symptoms of atherosclerotic cardiovascular disease, such as angina or intermittent claudication, may improve over months to years. Xanthomas or other external manifestations of hyperlipidemia should regress with therapy.
- Lipid measurements should be obtained in the fasted state to minimize interference from chylomicrons. Monitoring is needed every few months during dosage titration. Once the patient is stable, monitoring at intervals of 6 months to 1 year is sufficient.
- Patients on BAR therapy should have a fasting panel checked every 4 to 8 weeks until a stable dose is reached; triglycerides should be checked at a stable dose to ensure they have not increased.
- Niacin requires baseline tests of liver function (alanine aminotransferase), uric acid, and glucose. Repeat tests are appropriate at doses of 1,000 to 1,500 mg/day. Symptoms of myopathy or diabetes should be investigated and may require creatine kinase or glucose determinations. Patients with diabetes may require more frequent monitoring.
- Patients receiving statins should have a fasting panel 4 to 8 weeks after the initial dose or dose changes. Liver function tests should be obtained at baseline and periodically thereafter based on package insert information. Some experts believe that monitoring for hepatotoxicity and myopathy should be triggered by symptoms.
- Patients with multiple risk factors and established CHD should also be monitored and evaluated for progress in managing their other risk factors such as blood pressure control, smoking cessation, exercise and weight control, and glycemic control (if diabetic).
- Evaluation of dietary therapy with diet diaries and recall survey instruments allows information about diet to be collected in a systematic fashion and may improve patient adherence to dietary recommendations.

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*See Chap. 23, Hyperlipidemia, authored by Robert L. Talbert, for a more detailed discussion of this topic.*

## DEFINITION

- Hypertension is defined by persistent elevation of arterial blood pressure (BP). The Seventh Report of the Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) classifies adult BP as shown in Table 10-1.
- Patients with diastolic blood pressure (DBP) values  $<90$  mm Hg and systolic blood pressure (SBP) values  $\geq 140$  mm Hg have isolated systolic hypertension.
- A hypertensive crisis (BP  $>180/120$  mm Hg) may be categorized as either a hypertensive emergency (extreme BP elevation with acute or progressing target organ damage) or a hypertensive urgency (severe BP elevation without acute or progressing target organ injury).

## PATHOPHYSIOLOGY

- Hypertension is a heterogeneous disorder that may result either from a specific cause (secondary hypertension) or from an underlying pathophysiologic mechanism of unknown etiology (primary or essential hypertension). Secondary hypertension accounts for fewer than 10% of cases, and most of these are caused by chronic kidney disease or renovascular disease. Other conditions causing secondary hypertension include pheochromocytoma, Cushing's syndrome, hyperthyroidism, hyperparathyroidism, primary aldosteronism, pregnancy, obstructive sleep apnea, and coarctation of the aorta. Some drugs that may increase BP include corticosteroids, estrogens, nonsteroidal antiinflammatory drugs (NSAIDs), amphetamines, sibutramine, cyclosporine, tacrolimus, erythropoietin, and venlafaxine.
- Multiple factors may contribute to the development of primary hypertension, including:
  - ✓ Humoral abnormalities involving the renin-angiotensin-aldosterone system, natriuretic hormone, or hyperinsulinemia;
  - ✓ A pathologic disturbance in the CNS, autonomic nerve fibers, adrenergic receptors, or baroreceptors;
  - ✓ Abnormalities in either the renal or tissue autoregulatory processes for sodium excretion, plasma volume, and arteriolar constriction;
  - ✓ A deficiency in the local synthesis of vasodilating substances in the vascular endothelium, such as prostacyclin, bradykinin, and nitric oxide, or an increase in production of vasoconstricting substances such as angiotensin II and endothelin I;
  - ✓ A high sodium intake and increased circulating natriuretic hormone inhibition of intracellular sodium transport, resulting in increased vascular reactivity and a rise in BP; and
  - ✓ Increased intracellular concentration of calcium, leading to altered vascular smooth muscle function and increased peripheral vascular resistance.

**TABLE 10-1** Classification of Blood Pressure in Adults

Classification	Systolic (mm Hg)		Diastolic (mm Hg)
Normal	<120	and	<80
Prehypertension	120–139	or	80–89
Stage 1 hypertension	140–159	or	90–99
Stage 2 hypertension	≥160	or	≥100

- The main causes of death in hypertensive subjects are cerebrovascular accidents, cardiovascular (CV) events, and renal failure. The probability of premature death correlates with the severity of BP elevation.

## CLINICAL PRESENTATION

- Patients with uncomplicated primary hypertension are usually asymptomatic initially.
- Patients with secondary hypertension may complain of symptoms suggestive of the underlying disorder. Patients with pheochromocytoma may have a history of paroxysmal headaches, sweating, tachycardia, palpitations, and orthostatic hypotension. In primary aldosteronism, hypokalemic symptoms of muscle cramps and weakness may be present. Patients with hypertension secondary to Cushing's syndrome may complain of weight gain, polyuria, edema, menstrual irregularities, recurrent acne, or muscular weakness.

## DIAGNOSIS

- Frequently, the only sign of primary hypertension on physical examination is elevated BP. The diagnosis of hypertension should be based on the average of two or more readings taken at each of two or more clinical encounters.
- As hypertension progresses, signs of end-organ damage begin to appear, chiefly related to pathologic changes in the eye, brain, heart, kidneys, and peripheral blood vessels.
- The fundoscopic examination may reveal arteriolar narrowing, focal arteriolar narrowing, arteriovenous nicking, and retinal hemorrhages, exudates, and infarcts. The presence of papilledema indicates hypertensive emergency requiring rapid treatment.
- Cardiopulmonary examination may reveal an abnormal heart rate or rhythm, left ventricular (LV) hypertrophy, precordial heave, third and fourth heart sounds, and rales.
- Peripheral vascular examination can detect evidence of atherosclerosis, which may present as aortic or abdominal bruits, distended veins, diminished or absent peripheral pulses, or lower extremity edema.
- Patients with renal artery stenosis may have an abdominal systolic-diastolic bruit.
- Patients with Cushing's syndrome may have the classic physical features of moon face, buffalo hump, hirsutism, and abdominal striae.

- Baseline hypokalemia may suggest mineralocorticoid-induced hypertension. The presence of protein, blood cells, and casts in the urine may indicate renovascular disease.
- Laboratory tests that should be obtained in all patients prior to initiating drug therapy include urinalysis, complete blood cell count, serum chemistries (sodium, potassium, creatinine, fasting glucose, fasting lipid panel), and a 12-lead electrocardiogram (ECG). These tests are used to assess other risk factors and to develop baseline data for monitoring drug-induced metabolic changes.
- More specific laboratory tests are used to diagnose secondary hypertension. These include plasma norepinephrine and urinary metanephrine levels for pheochromocytoma, plasma and urinary aldosterone levels for primary aldosteronism, and plasma renin activity, captopril stimulation test, renal vein renins, and renal artery angiography for renovascular disease.

## DESIRED OUTCOME

- The overall goal of treating hypertension is to reduce morbidity and mortality by the least intrusive means possible.
- Goal BP values are <140/90 for most patients, but <130/80 for patients with diabetes mellitus, significant chronic kidney disease, known coronary artery disease (myocardial infarction [MI], angina), noncoronary atherosclerotic vascular disease (ischemic stroke, transient ischemic attack, peripheral arterial disease [PAD], abdominal aortic aneurysm), or a 10% or greater Framingham 10-year risk of fatal coronary heart disease or nonfatal MI. Patients with LV dysfunction have a BP goal of <120/80 mm Hg.
- SBP is a better predictor of CV risk than DBP and must be used as the primary clinical marker of disease control in hypertension.

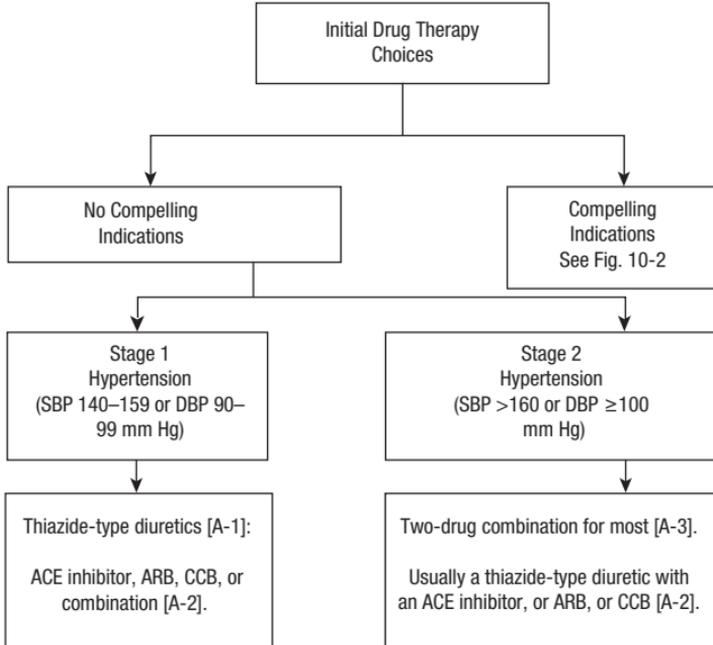
## TREATMENT

### NONPHARMACOLOGIC THERAPY

- All patients with prehypertension and hypertension should be prescribed lifestyle modifications, including (1) weight reduction if overweight, (2) adoption of the Dietary Approaches to Stop Hypertension eating plan, (3) dietary sodium restriction ideally to 1.5 g/day (3.8 g/day sodium chloride), (4) regular aerobic physical activity, (5) moderate alcohol consumption (two or fewer drinks per day), and (6) smoking cessation.
- Lifestyle modification alone is appropriate therapy for patients with prehypertension. Patients diagnosed with stage 1 or 2 hypertension should be placed on lifestyle modifications and drug therapy concurrently.

### PHARMACOLOGIC THERAPY

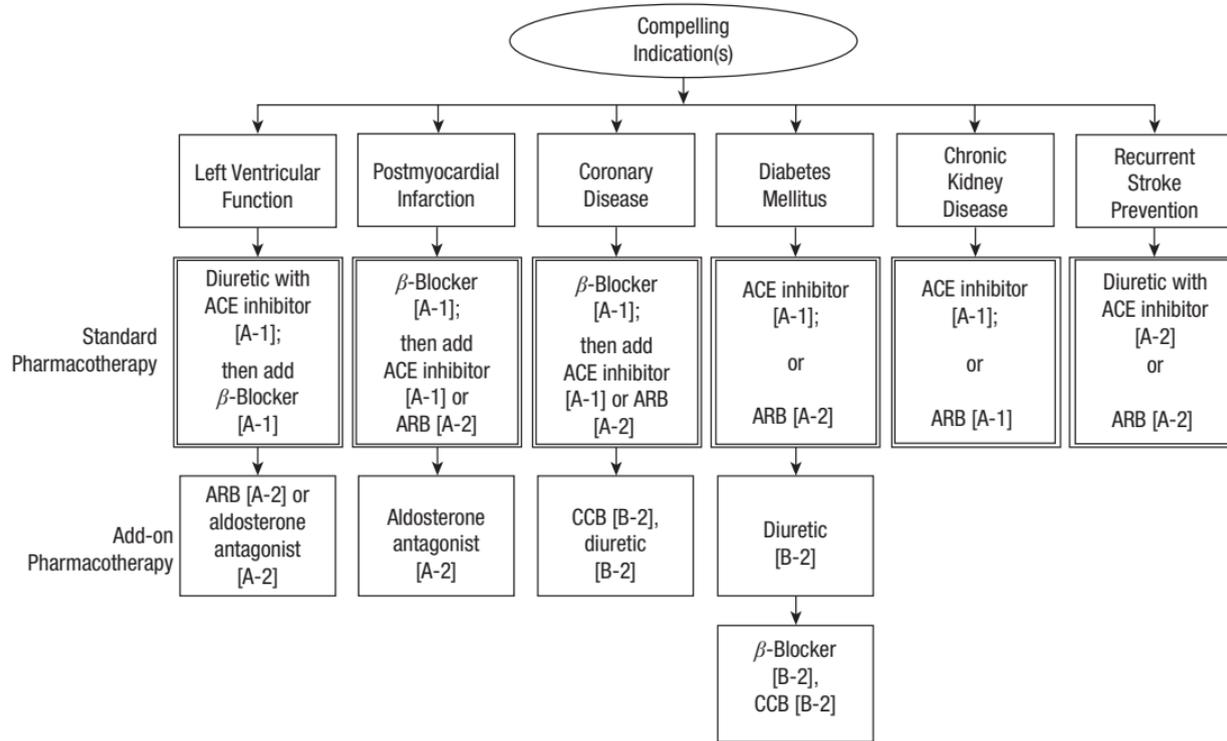
- Initial drug selection depends on the degree of BP elevation and the presence of compelling indications for selected drugs.
- Most patients with stage 1 hypertension should be treated initially with a **thiazide diuretic, angiotensin-converting enzyme (ACE) inhibitor, angio-**



**FIGURE 10-1.** Algorithm for treatment of hypertension. Drug therapy recommendations are graded with strength of recommendation and quality of evidence in brackets. Strength of recommendations: A, B, C = good, moderate, and poor evidence to support recommendation, respectively. Quality of evidence: 1 = Evidence from more than one properly randomized, controlled trial. 2 = Evidence from at least one well-designed clinical trial with randomization; from cohort or case-controlled analytic studies; or dramatic results from uncontrolled experiments or subgroup analyses. 3 = Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert communities. (ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; DBP, diastolic blood pressure; SBP, systolic blood pressure.)

**tensin II receptor blocker (ARB), or calcium channel blocker (CCB)** (Fig. 10-1). Combination therapy is recommended for patients with stage 2 disease, with one of the agents being a thiazide-type diuretic unless contraindications exist.

- There are six compelling indications where specific antihypertensive drug classes have shown evidence of unique benefits (Fig. 10-2).
- **Diuretics, ACE inhibitors, ARBs, and CCBs** are primary agents acceptable as first-line options based on outcome data demonstrating CV risk reduction benefits (Table 10-2).  **$\beta$ -Blockers** may be used either to treat a specific compelling indication or as combination therapy with a primary antihypertensive agent for patients without a compelling indication.
- **$\alpha_1$ -Blockers, direct renin inhibitors, central  $\alpha_2$ -agonists, peripheral adrenergic antagonists, and direct arterial vasodilators** are alternatives that may be used in select patients after primary agents (Table 10-3).



**FIGURE 10-2.** Compelling indications for individual drug classes. Compelling indications for specific drugs are evidence-based recommendations from outcome studies or existing clinical guidelines. (ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.)

**TABLE 10-2** Primary Antihypertensive Agents

<b>Class/Subclass/Drug (brand name)</b>	<b>Usual Dose Range, mg/day</b>	<b>Daily Frequency</b>
<b>Diuretics</b>		
<b>Thiazides</b>		
Chlorthalidone (Hygroton)	12.5–25	1
Hydrochlorothiazide (Microzide)	12.5–25	1
Indapamide (Lozol)	1.25–2.5	1
Metolazone (Zaroxolyn)	2.5–5	1
<b>Loops</b>		
Bumetanide (Bumex)	0.5–4	2
Furosemide (Lasix)	20–80	2
Torsemide (Demadex)	5–10	1
<b>Potassium sparing</b>		
Amiloride (Midamor)	5–10	1 or 2
Amiloride/hydrochlorothiazide (Moduretic)	5–10/50–100	1
Triamterene (Dyrenium)	50–100	1 or 2
Triamterene/hydrochlorothiazide (Dyazide)	37.5–75/25–50	1
<b>Aldosterone antagonists</b>		
Eplerenone (Inspra)	50–100	1 or 2
Spironolactone (Aldactone)	25–50	1 or 2
Spironolactone/hydrochlorothiazide (Aldactazide)	25–50/25–50	1
<b>Angiotensin-converting enzyme inhibitors</b>		
Benazepril (Lotensin)	10–40	1 or 2
Captopril (Capoten)	12.5–150	2 or 3
Enalapril (Vasotec)	5–40	1 or 2
Fosinopril (Monopril)	10–40	1
Lisinopril (Prinivil, Zestril)	10–40	1
Moexipril (Univasc)	7.5–30	1 or 2
Perindopril (Aceon)	4–16	1
Quinapril (Accupril)	10–80	1 or 2
Ramipril (Altace)	2.5–10	1 or 2
Trandolapril (Mavik)	1–4	1
<b>Angiotensin II receptor blockers</b>		
Candesartan (Atacand)	8–32	1 or 2
Eprosartan (Teveten)	600–800	1 or 2
Irbesartan (Avapro)	150–300	1
Losartan (Cozaar)	50–100	1 or 2
Olmесartan (Benicar)	20–40	1
Telmisartan (Micardis)	20–80	1
Valsartan (Diovan)	80–320	1
<b>Calcium channel blockers</b>		
<b>Dihydropyridines</b>		
Amlodipine (Norvasc)	2.5–10	1
Felodipine (Plendil)	5–20	1
Isradipine (DynaCirc)	5–10	2
Isradipine SR (DynaCirc SR)	5–20	1
Nicardipine sustained release (Cardene SR)	60–120	2
Nifedipine long-acting (Adalat CC, Procardia XL)	30–90	1
Nisoldipine (Sular)	10–40	1

*(continued)*

**TABLE 10-2** Primary Antihypertensive Agents (Continued)

Class/Subclass/Drug (brand name)	Usual Dose Range, mg/day	Daily Frequency
Calcium channel blockers ( <i>cont'd</i> )		
Nondihydropyridines		
Diltiazem sustained-release (Cardizem SR)	180–360	2
Diltiazem sustained-release (Cardizem CD, Cartia XT, Dilacor XR, Diltia XT, Tiazac, Taztia XT)	120–480	1
Diltiazem extended-release (Cardizem LA)	120–540	1 (morning or evening)
Verapamil sustained-release (Calan SR, Isoptin SR, Verelan)	180–480	1 or 2
Verapamil controlled-onset extended-release (Covera HS)	180–420	1 (in the evening)
Verapamil oral drug absorption system (Verelan PM)	100–400	1 (in the evening)
$\beta$ -Blockers		
Cardioselective		
Atenolol (Tenormin)	25–100	1
Betaxolol (Kerlone)	5–20	1
Bisoprolol (Zebeta)	2.5–10	1
Metoprolol tartrate (Lopressor)	100–400	2
Metoprolol succinate extended release (Toprol XL)	50–200	1
Nonselective		
Nadolol (Corgard)	40–120	1
Propranolol (Inderal)	160–480	2
Propranolol long-acting (Inderal LA, InnoPran XL)	80–320	1
Timolol (Blocadren)	10–40	1
Intrinsic sympathomimetic activity		
Acebutolol (Sectral)	200–800	2
Carteolol (Cartrol)	2.5–10	1
Penbutolol (Levatol)	10–40	1
Pindolol (Visken)	10–60	2
Mixed $\alpha$ - and $\beta$ -blockers		
Carvedilol (Coreg)	12.5–50	2
Carvedilol phosphate (Coreg CR)	20–80	1
Labetalol (Normodyne, Trandate)	200–800	2

**TABLE 10-3** Alternative Antihypertensive Agents

Class Drug (Brand Name)	Usual Dose Range, mg/day	Daily Frequency
$\alpha_1$ -Blockers		
Doxazosin (Cardura)	1–8	1
Prazosin (Minipress)	2–20	2 or 3
Terazosin (Hytrin)	1–20	1 or 2
Direct renin inhibitor		
Aliskiren (Tekturna)	150–300	1
Central $\alpha_2$ -agonists		
Clonidine (Catapres)	0.1–0.8	2
Clonidine patch (Catapres-TTS)	0.1–0.3	1 weekly
Methyldopa (Aldomet)	250–1,000	2
Peripheral adrenergic antagonist		
Reserpine (generic only)	0.05–0.25	1
Direct arterial vasodilators		
Minoxidil (Loniten)	10–40	1 or 2
Hydralazine (Apresoline)	20–100	2 to 4

## Diuretics

- **Thiazides** are the preferred type of diuretic for treating hypertension, and all are equally effective in lowering BP.
- **Potassium-sparing diuretics** are weak antihypertensives when used alone but provide an additive hypotensive effect when combined with thiazide or loop diuretics. Moreover, they counteract the potassium- and magnesium-losing properties and perhaps glucose intolerance caused by other diuretics.
- **Aldosterone antagonists (spironolactone, eplerenone)** are also potassium-sparing diuretics but are more potent antihypertensives with a slow onset of action (up to 6 weeks with spironolactone).
- Acutely, diuretics lower BP by causing diuresis. The reduction in plasma volume and stroke volume associated with diuresis decreases cardiac output and, consequently, BP. The initial drop in cardiac output causes a compensatory increase in peripheral vascular resistance. With chronic diuretic therapy, the extracellular fluid volume and plasma volume return almost to pretreatment levels, and peripheral vascular resistance falls below its pretreatment baseline. The reduction in peripheral vascular resistance is responsible for the long-term hypotensive effects. Thiazides lower BP by mobilizing sodium and water from arteriolar walls, which may contribute to decreased peripheral vascular resistance.
- When diuretics are combined with other antihypertensive agents, an additive hypotensive effect is usually observed because of independent mechanisms of action. Furthermore, many nondiuretic antihypertensive agents induce salt and water retention, which is counteracted by concurrent diuretic use.
- Side effects of thiazides include hypokalemia, hypomagnesemia, hypercalcemia, hyperuricemia, hyperglycemia, hyperlipidemia, and sexual dysfunction. Loop diuretics have less effect on serum lipids and glucose, but hypocalcemia may occur.
- Hypokalemia and hypomagnesemia may cause muscle fatigue or cramps. Serious cardiac arrhythmias may occur, especially in patients receiving digitalis therapy, patients with LV hypertrophy, and those with ischemic heart disease. Low-dose therapy (e.g., 25 mg **hydrochlorothiazide** or 12.5 mg **chlorthalidone** daily) rarely causes significant electrolyte disturbances.
- Potassium-sparing diuretics may cause hyperkalemia, especially in patients with chronic kidney disease or diabetes, and in patients receiving concurrent treatment with an ACE inhibitor, ARB, NSAID, or potassium supplement. **Eplerenone** has an increased risk for hyperkalemia and is contraindicated in patients with impaired renal function or type 2 diabetes with proteinuria. **Spironolactone** may cause gynecomastia in up to 10% of patients, but this effect occurs rarely with eplerenone.

## Angiotensin-Converting Enzyme Inhibitors

- ACE facilitates production of angiotensin II, which has a major role in regulating arterial BP. ACE is distributed in many tissues and is present in several different cell types, but its principal location is in endothelial cells. Therefore, the major site for angiotensin II production is in the blood vessels, not the kidney. ACE inhibitors block the conversion of angiotensin

I to angiotensin II, a potent vasoconstrictor and stimulator of aldosterone secretion. ACE inhibitors also block the degradation of bradykinin and stimulate the synthesis of other vasodilating substances including prostaglandin E<sub>2</sub> and prostacyclin. The fact that ACE inhibitors lower BP in patients with normal plasma renin activity suggests that bradykinin and perhaps tissue production of ACE are important in hypertension.

- Starting doses of ACE inhibitors should be low with slow dose titration. Acute hypotension may occur at the onset of ACE inhibitor therapy, especially in patients who are sodium- or volume-depleted, in heart failure exacerbation, very elderly, or on concurrent vasodilators or diuretics. Patients with these risk factors should start with half the normal dose followed by slow dose titration (e.g., 6-week intervals).
- All 10 ACE inhibitors available in the United States can be dosed once daily for hypertension except captopril, which is usually dosed two or three times daily. The absorption of captopril (but not enalapril or lisinopril) is reduced by 30% to 40% when given with food.
- ACE inhibitors decrease aldosterone and can increase serum potassium concentrations. Hyperkalemia occurs primarily in patients with chronic kidney disease or diabetes and in those also taking ARBs, NSAIDs, potassium supplements, or potassium-sparing diuretics.
- Acute renal failure is a rare but serious side effect of ACE inhibitors; preexisting kidney disease increases the risk. Bilateral renal artery stenosis or unilateral stenosis of a solitary functioning kidney renders patients dependent on the vasoconstrictive effect of angiotensin II on efferent arterioles, making these patients particularly susceptible to acute renal failure.
- The GFR decreases in patients receiving ACE inhibitors because of inhibition of angiotensin II vasoconstriction on efferent arterioles. Serum creatinine concentrations often increase, but modest elevations (e.g., absolute increases of less than 1 mg/dL) do not warrant changes. Therapy should be stopped or the dose reduced if larger increases occur.
- Angioedema is a serious potential complication that occurs in less than 1% of patients. It may be manifested as lip and tongue swelling and possibly difficulty breathing. Drug withdrawal is necessary for all patients with angioedema, and some patients may also require drug treatment and/or emergent intubation. Cross-reactivity between ACE inhibitors and ARBs has been reported.
- A persistent dry cough occurs in up to 20% of patients and is thought to be due to inhibition of bradykinin breakdown.
- ACE inhibitors are absolutely contraindicated in pregnancy because of possible major congenital malformations associated with exposure in the first trimester and serious neonatal problems, including renal failure and death in the infant, from exposure during the second and third trimesters.

### Angiotensin II Receptor Blockers

- Angiotensin II is generated by the renin-angiotensin pathway (which involves ACE) and an alternative pathway that uses other enzymes such as chymases. ACE inhibitors block only the renin-angiotensin pathway, whereas ARBs antagonize angiotensin II generated by either pathway. The ARBs directly block the angiotensin type 1 receptor that mediates the

known effects of angiotensin II (vasoconstriction, aldosterone release, sympathetic activation, antidiuretic hormone release, and constriction of the efferent arterioles of the glomerulus).

- Unlike ACE inhibitors, ARBs do not block the breakdown of bradykinin. While this accounts for the lack of cough as a side effect, there may be negative consequences because some of the antihypertensive effect of ACE inhibitors may be due to increased levels of bradykinin. Bradykinin may also be important for regression of myocyte hypertrophy and fibrosis, and increased levels of tissue plasminogen activator.
- All drugs in this class have similar antihypertensive efficacy and fairly flat dose-response curves. The addition of low doses of a thiazide diuretic can increase efficacy significantly.
- In patients with type 2 diabetes and nephropathy, ARB therapy has been shown to significantly reduce progression of nephropathy. For patients with LV dysfunction, ARB therapy has also been shown to reduce the risk of CV events when added to a stable regimen of a diuretic, ACE inhibitor, and  $\beta$ -blocker or as alternative therapy in ACE inhibitor-intolerant patients.
- ARBs appear to have the lowest incidence of side effects compared with other antihypertensive agents. Because they do not affect bradykinin, they do not cause a dry cough like ACE inhibitors. Like ACE inhibitors, they may cause renal insufficiency, hyperkalemia, and orthostatic hypotension. Angioedema is less likely to occur than with ACE inhibitors, but cross-reactivity has been reported. ARBs should not be used in pregnancy.

### Calcium Channel Blockers

- CCBs cause relaxation of cardiac and smooth muscle by blocking voltage-sensitive calcium channels, thereby reducing the entry of extracellular calcium into cells. Vascular smooth muscle relaxation leads to vasodilation and a corresponding reduction in BP. Dihydropyridine calcium channel antagonists may cause reflex sympathetic activation, and all agents (except amlodipine and felodipine) may demonstrate negative inotropic effects.
- **Verapamil** decreases heart rate, slows atrioventricular (AV) nodal conduction, and produces a negative inotropic effect that may precipitate heart failure in patients with borderline cardiac reserve. **Diltiazem** decreases AV conduction and heart rate to a lesser extent than verapamil.
- Diltiazem and verapamil can cause cardiac conduction abnormalities such as bradycardia, AV block, and heart failure. Both can cause anorexia, nausea, peripheral edema, and hypotension. Verapamil causes constipation in about 7% of patients.
- Dihydropyridines cause a baroreceptor-mediated reflex increase in heart rate because of their potent peripheral vasodilating effects. Dihydropyridines do not decrease AV node conduction and are not effective for treating supraventricular tachyarrhythmias.
- Short-acting nifedipine may rarely cause an increase in the frequency, intensity, and duration of angina in association with acute hypotension. This effect may be obviated by using sustained-released formulations of nifedipine or other dihydropyridines. Other side effects of dihydropyridines include dizziness, flushing, headache, gingival hyperplasia, and peripheral edema. Side effects due to vasodilation such as dizziness, flushing, head-

ache, and peripheral edema occur more frequently with dihydropyridines than with verapamil or diltiazem.

### **$\beta$ -Blockers**

- The exact hypotensive mechanism of  $\beta$ -blockers is not known but may involve decreased cardiac output through negative chronotropic and inotropic effects on the heart and inhibition of renin release from the kidney.
- Even though there are important pharmacodynamic and pharmacokinetic differences among the various  $\beta$ -blockers, there is no difference in clinical antihypertensive efficacy.
- **Atenolol, betaxolol, bisoprolol, and metoprolol** are cardioselective at low doses and bind more avidly to  $\beta_1$ -receptors than to  $\beta_2$ -receptors. As a result, they are less likely to provoke bronchospasm and vasoconstriction and may be safer than nonselective  $\beta$ -blockers in patients with asthma, chronic obstructive pulmonary disease, diabetes, and PAD. Cardioselectivity is a dose-dependent phenomenon, and the effect is lost at higher doses.
- **Acebutolol, carteolol, penbutolol, and pindolol** possess intrinsic sympathomimetic activity (ISA) or partial  $\beta$ -receptor agonist activity. When sympathetic tone is low, as in resting states,  $\beta$ -receptors are partially stimulated, so resting heart rate, cardiac output, and peripheral blood flow are not reduced when receptors are blocked. Theoretically, these drugs may have advantages in patients with heart failure or sinus bradycardia. Unfortunately, they do not reduce CV events as well as other  $\beta$ -blockers and may increase risk after MI or in those with high coronary disease risk. Thus, agents with ISA are rarely needed.
- There are pharmacokinetic differences among  $\beta$ -blockers in first-pass metabolism, serum half-lives, degree of lipophilicity, and route of elimination. **Propranolol** and **metoprolol** undergo extensive first-pass metabolism. **Atenolol** and **nadolol** have relatively long half-lives and are excreted renally; the dosage may need to be reduced in patients with moderate to severe renal insufficiency. Even though the half-lives of the other  $\beta$ -blockers are much shorter, once-daily administration still may be effective.  $\beta$ -Blockers vary in their lipophilic properties and thus CNS penetration.
- Side effects from  $\beta$ -blockade in the myocardium include bradycardia, AV conduction abnormalities, and acute heart failure. Blocking  $\beta_2$ -receptors in arteriolar smooth muscle may cause cold extremities and aggravate PAD or Raynaud's phenomenon because of decreased peripheral blood flow.
- Abrupt cessation of  $\beta$ -blocker therapy may produce unstable angina, MI, or even death in patients with coronary disease. In patients without heart disease, abrupt discontinuation of  $\beta$ -blockers may be associated with tachycardia, sweating, and generalized malaise in addition to increased BP. For these reasons, it is always prudent to taper the dose gradually over 1 to 2 weeks before discontinuation.
- Increases in serum lipids and glucose appear to be transient and of little clinical importance.  $\beta$ -Blockers increase serum triglyceride levels and decrease high-density lipoprotein cholesterol levels slightly.  $\beta$ -Blockers with  $\alpha$ -blocking properties (carvedilol and labetalol) do not affect serum lipid concentrations.

### $\alpha_1$ -Receptor Blockers

- **Prazosin, terazosin, and doxazosin** are selective  $\alpha_1$ -receptor blockers that inhibit catecholamine uptake in smooth muscle cells of the peripheral vasculature, resulting in vasodilation.
- A potentially severe side effect is a first-dose phenomenon characterized by orthostatic hypotension accompanied by transient dizziness or faintness, palpitations, and even syncope within 1 to 3 hours of the first dose or after later dosage increases. These episodes can be obviated by having the patient take the first dose, and subsequent first increased doses, at bedtime. Occasionally, orthostatic dizziness persists with chronic administration.
- Sodium and water retention can occur with chronic administration. These agents are most effective when given with a diuretic to maintain antihypertensive efficacy and minimize potential edema.
- Because data suggest that doxazosin (and probably other  $\alpha_1$ -receptor blockers) are not as protective against CV events as other therapies, they should be reserved as alternative agents for unique situations, such as men with benign prostatic hyperplasia. If used to lower BP in this situation, they should only be used in combination with primary antihypertensive agents.

### Direct Renin Inhibitor

- **Aliskiren** blocks the renin-angiotensin-aldosterone system at its point of a activation, which results in reduced plasma renin activity and BP. It provides BP reductions comparable to an ACE inhibitor, ARB, or CCB. It also has additive antihypertensive effects when used in combination with thiazides, ACE inhibitors, ARBs, or CCBs. It is approved for monotherapy or in combination with other agents.
- Many of the cautions and adverse effects seen with ACE inhibitors and ARBs apply to aliskiren. It is contraindicated in pregnancy.
- At this time, aliskiren should be used only as an alternative therapy because of the lack of long-term studies evaluating CV event reduction and its significant cost compared to generic agents with outcomes data.

### Central $\alpha_2$ -Agonists

- **Clonidine, guanabenz, guanfacine, and methyldopa** lower BP primarily by stimulating  $\alpha_2$ -adrenergic receptors in the brain, which reduces sympathetic outflow from the vasomotor center and increases vagal tone. Stimulation of presynaptic  $\alpha_2$ -receptors peripherally may contribute to the reduction in sympathetic tone. Consequently, there may be decreases in heart rate, cardiac output, total peripheral resistance, plasma renin activity, and baroreceptor reflexes.
- Chronic use results in sodium and fluid retention. Other side effects may include depression, orthostatic hypotension, dizziness, and anticholinergic effects.
- Abrupt cessation may lead to rebound hypertension, which is thought to result from a compensatory increase in norepinephrine release that follows discontinuation of presynaptic  $\alpha$ -receptor stimulation.
- Methyldopa rarely may cause hepatitis or hemolytic anemia. A transient elevation in hepatic transaminases occasionally occurs and is clinically unimportant. However, the drug should be quickly discontinued if persis-

tent increases in serum hepatic transaminases or alkaline phosphatase are detected, as this may herald the onset of a fulminant, life-threatening hepatitis. A Coombs-positive hemolytic anemia occurs in less than 1% of patients receiving methyl dopa, although 20% exhibit a positive direct Coombs test without anemia. For these reasons, methyl dopa has limited usefulness in the management of hypertension except in pregnancy.

### Reserpine

- **Reserpine** depletes norepinephrine from sympathetic nerve endings and blocks the transport of norepinephrine into its storage granules. When the nerve is stimulated, less than the usual amount of norepinephrine is released into the synapse. This reduces sympathetic tone, decreasing peripheral vascular resistance and BP.
- Reserpine has a long half-life that allows for once-daily dosing, but it may take 2 to 6 weeks before the maximal antihypertensive effect is seen.
- Reserpine can cause significant sodium and fluid retention, and it should be given with a diuretic (preferably a thiazide).
- Reserpine's strong inhibition of sympathetic activity allows increased parasympathetic activity to occur, which is responsible for side effects of nasal stuffiness, increased gastric acid secretion, diarrhea, and bradycardia.
- The most serious side effect is dose-related mental depression resulting from CNS depletion of catecholamines and serotonin. This can be minimized by not exceeding 0.25 mg daily.

### Direct Arterial Vasodilators

- **Hydralazine** and **minoxidil** cause direct arteriolar smooth muscle relaxation. Compensatory activation of baroreceptor reflexes results in increased sympathetic outflow from the vasomotor center, producing an increase in heart rate, cardiac output, and renin release. Consequently, the hypotensive effectiveness of direct vasodilators diminishes over time unless the patient is also taking a sympathetic inhibitor and a diuretic.
- All patients taking these drugs for long-term hypertension therapy should first receive both a diuretic and a  $\beta$ -blocker. The diuretic minimizes the side effect of sodium and water retention. Direct vasodilators can precipitate angina in patients with underlying coronary artery disease unless the baroreceptor reflex mechanism is completely blocked with a  $\beta$ -blocker. Nondihydropyridine CCBs can be used as an alternative to  $\beta$ -blockers in patients with contraindications to  $\beta$ -blockers.
- Hydralazine may cause a dose-related, reversible lupus-like syndrome, which is more common in slow acetylators. Lupus-like reactions can usually be avoided by using total daily doses of less than 200 mg. Other hydralazine side effects include dermatitis, drug fever, peripheral neuropathy, hepatitis, and vascular headaches. For these reasons, hydralazine has limited usefulness in the treatment of hypertension. However, it may be useful in patients with severe chronic kidney disease and in kidney failure.
- Minoxidil is a more potent vasodilator than hydralazine, and the compensatory increases in heart rate, cardiac output, renin release, and sodium retention are more dramatic. Severe sodium and water retention may precipitate congestive heart failure. Minoxidil also causes reversible hyper-

trichosis on the face, arms, back, and chest. Minoxidil is reserved for very difficult to control hypertension and in patients requiring hydralazine who experience drug-induced lupus.

### Postganglionic Sympathetic Inhibitors

- **Guanethidine** and **guanadrel** deplete norepinephrine from postganglionic sympathetic nerve terminals and inhibit the release of norepinephrine in response to sympathetic nerve stimulation. This reduces cardiac output and peripheral vascular resistance.
- Orthostatic hypotension is common due to blockade of reflex-mediated vasoconstriction. Other side effects include erectile dysfunction, diarrhea, and weight gain. Because of these complications, postganglionic sympathetic inhibitors have little or no role in the management of hypertension.

## COMPELLING INDICATIONS

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- The six compelling indications identified by JNC 7 represent specific comorbid conditions for which clinical trial data support using specific antihypertensive drug classes to treat both hypertension and the compelling indication (see Fig. 10-2).

### Left Ventricular Dysfunction (Systolic Heart Failure)

- ACE inhibitor with diuretic therapy is recommended as the first-line regimen of choice. ACE inhibitors have numerous outcome data showing reduced CV morbidity and mortality. Diuretics provide symptomatic relief of edema by inducing diuresis. Loop diuretics are often needed, especially in patients with more advanced disease.
- Because of the high renin status of patients with heart failure, ACE inhibitors should be initiated at low doses to avoid orthostatic hypotension.
- $\beta$ -Blocker therapy is appropriate to further modify disease in LV dysfunction and is a component of this first-line regimen (standard therapy) for these patients. Because of the risk of exacerbating heart failure, they must be started in very low doses and titrated slowly to high doses based on tolerability. Bisoprolol, carvedilol, and metoprolol succinate are the only  $\beta$ -blockers proven to be beneficial in LV dysfunction.
- ARBs are acceptable as alternative therapy for patients who cannot tolerate ACE inhibitors and possibly as add-on therapy for those already receiving a standard three-drug regimen.
- An aldosterone antagonist may be considered in addition to a diuretic, ACE inhibitor or ARB, and  $\beta$ -blocker. Regimens employing both an aldosterone antagonist and ARB are not recommended because of the potential risk of severe hyperkalemia.

### Postmyocardial Infarction

- $\beta$ -Blocker (without ISA) and ACE inhibitor therapy is recommended.  $\beta$ -Blockers decrease cardiac adrenergic stimulation and reduce the risk of a subsequent MI or sudden cardiac death. ACE inhibitors improve cardiac function and reduce CV events after MI. ARBs are alternatives to ACE inhibitors in postmyocardial patients with LV dysfunction.
- The aldosterone antagonist eplerenone reduces CV morbidity and mortality in patients soon after an acute MI (within 3 to 14 days) in patients with

symptoms of acute LV dysfunction. Its use should be limited to selected patients, and then with diligent monitoring of serum potassium.

### Coronary Artery Disease

- $\beta$ -Blockers (without ISA) are first-line therapy in chronic stable angina and have the ability to reduce BP, improve myocardial consumption, and decrease demand. Long-acting CCBs are either alternatives (the nondihydropyridines verapamil and diltiazem) or add-on therapy (dihydropyridines) to  $\beta$ -blockers in chronic stable angina. Once ischemic symptoms are controlled with  $\beta$ -blocker and/or CCB therapy, other antihypertensive drugs (e.g., ACE inhibitor, ARB) can be added to provide additional CV risk reduction. Thiazide diuretics may be added thereafter to provide additional BP lowering and further reduce CV risk.
- For acute coronary syndromes, first-line therapy should consist of a  $\beta$ -blocker and ACE inhibitor; the combination lowers BP, controls acute ischemia, and reduces CV risk.

### Diabetes Mellitus

- The BP goal in diabetes is less than 130/80 mm Hg.
- All patients with diabetes and hypertension should be treated with either an ACE inhibitor or an ARB. Both classes provide nephroprotection and reduced CV risk.
- A thiazide-type diuretic is recommended as the second agent to lower BP and provide additional CV risk reduction.
- CCBs are useful add-on agents for BP control in hypertensive patients with diabetes. Limited data suggest that nondihydropyridines may have more renal protective effects than dihydropyridines.
- $\beta$ -Blockers reduce CV risk in patients with diabetes and should be used when needed as add-on therapy with other standard agents or to treat another compelling indication (e.g., postmyocardial infarction). However, they may mask most of the symptoms of hypoglycemia (tremor, tachycardia, and palpitations but not sweating) in tightly controlled patients, delay recovery from hypoglycemia, and produce elevations in BP due to vasoconstriction caused by unopposed  $\alpha$ -receptor stimulation during the hypoglycemic recovery phase. Despite these potential problems,  $\beta$ -blockers can be used safely in patients with diabetes.

### Chronic Kidney Disease

- Either an ACE inhibitor or ARB is recommended as first-line therapy to control BP and preserve kidney function in chronic kidney disease. Some data indicate that the combination of an ACE inhibitor and ARB may be more effective than either agent alone. However, routine use of the combination is controversial.
- Because these patients usually require multiple-drug therapy, diuretics and a third antihypertensive drug class (e.g.,  $\beta$ -blocker, CCB) are often needed.

### Recurrent Stroke Prevention

- One clinical trial showed that the combination of an ACE inhibitor and thiazide diuretic reduces the incidence of recurrent stroke in patients with a history of ischemic stroke or transient ischemic attacks.

- Reductions in risk of recurrent ischemic stroke have also been seen with ARB-based therapy.

## SPECIAL POPULATIONS

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- Selection of drug therapy should follow the JNC 7 guidelines, but the treatment approach in some patient populations may be slightly different. In these situations, alternative agents may have unique properties that benefit a coexisting condition, but the data may not be based on evidence from outcome studies in hypertension.

### Older People

- Elderly patients may present with either isolated systolic hypertension or an elevation in both SBP and DBP. Epidemiologic data indicate that CV morbidity and mortality are more closely related to SBP than to DBP in patients 50 years of age and older.
- Diuretics and ACE inhibitors provide significant benefits and can be used safely in the elderly, but smaller-than-usual initial doses might be needed, and dosage titrations should occur over a longer period to minimize the risk of hypotension.
- Centrally acting agents and  $\beta$ -blockers should generally be avoided or used with caution because they are frequently associated with dizziness and postural hypotension.

### Children and Adolescents

- Secondary hypertension is much more common in children than in adults. Kidney disease (e.g., pyelonephritis, glomerulonephritis) is the most common cause of secondary hypertension in children. Coarctation of the aorta can also produce secondary hypertension. Medical or surgical management of the underlying disorder usually restores normal BP.
- Nonpharmacologic treatment (particularly weight loss in obese children) is the cornerstone of therapy of primary hypertension.
- ACE inhibitors, ARBs,  $\beta$ -blockers, CCBs, and thiazide-type diuretics are all acceptable drug therapy choices.
- ACE inhibitors, ARBs, and direct renin inhibitors are contraindicated in sexually active girls because of potential teratogenic effect and in those who might have bilateral renal artery stenosis or unilateral stenosis in a solitary kidney.

### Pregnant Women

- Preeclampsia, defined as BP  $\geq$ 140/90 mm Hg that appears after 20 weeks' gestation accompanied by new-onset proteinuria ( $\geq$ 300 mg/24 hours), can lead to life-threatening complications for both the mother and fetus.
- Definitive treatment of preeclampsia is delivery, and this is indicated if pending or frank eclampsia (preeclampsia and convulsions) is present. Otherwise, management consists of restricting activity, bedrest, and close monitoring. Salt restriction or other measures that contract blood volume should be avoided. Antihypertensives are used prior to induction of labor if the DBP is  $>$ 105–110 mm Hg, with a target DBP of 95–105 mm Hg. IV hydralazine is most commonly used; IV labetalol is also effective.

- Chronic hypertension is defined as elevated BP that was noted before pregnancy began. Methyldopa is considered the drug of choice because of experience with its use.  $\beta$ -Blockers, labetalol, and CCBs are also reasonable alternatives. ACE inhibitors and ARBs are known teratogens and are absolutely contraindicated. The direct renin inhibitor aliskiren also should not be used in pregnancy.

### **African Americans**

- Hypertension is more common and more severe in African Americans than in those of other races. Differences in electrolyte homeostasis, glomerular filtration rate, sodium excretion and transport mechanisms, plasma renin activity, and BP response to plasma volume expansion have been noted.
- Lifestyle modifications are recommended to augment drug therapy. Thiazide diuretics are first-line drug therapy for most patients, but recent guidelines aggressively promote combination therapy. Two drugs are recommended in patients with SBP values  $\geq 15$  mm Hg from goal.
- Thiazides and CCBs are particularly effective in African Americans. Anti-hypertensive response is significantly increased when either class is combined with a  $\beta$ -blocker, ACE inhibitor, or ARB.

### **Pulmonary Disease and Peripheral Arterial Disease**

- Although  $\beta$ -blockers (especially nonselective agents) have generally been avoided in hypertensive patients with asthma and chronic obstructive pulmonary disease because of fear of inducing bronchospasm, data suggest that cardioselective  $\beta$ -blockers can be used safely. Consequently, cardioselective agents should be used to treat a compelling indication (i.e., postmyocardial infarction, coronary disease, or heart failure) in patients with reactive airway disease.
- PAD is a coronary artery disease risk equivalent, and a BP goal of  $< 130/80$  mm Hg is recommended. ACE inhibitors may be ideal in patients with symptomatic lower-extremity PAD; CCBs may also be beneficial.  $\beta$ -Blockers have traditionally been considered problematic because of possible decreased peripheral blood flow secondary to unopposed stimulation of  $\alpha$ -receptors that results in vasoconstriction. However,  $\beta$ -blockers are not contraindicated in PAD and have not been shown to adversely affect walking capability.

### **Dyslipidemia**

- Dyslipidemia is a major CV risk factor, and it should be controlled in hypertensive patients.
- Thiazide diuretics and  $\beta$ -blockers without ISA may affect serum lipids adversely, but these effects generally are transient and of no clinical consequence.
- The  $\alpha$ -blockers have favorable effects (decreased low-density lipoprotein cholesterol and increased high-density lipoprotein cholesterol levels). However, because they do not reduce CV risk as effectively as thiazide diuretics, this benefit is not clinically applicable.
- ACE inhibitors and CCBs have no effect on serum cholesterol.

## HYPERTENSIVE URGENCIES AND EMERGENCIES

- **Hypertensive urgencies** are ideally managed by adjusting maintenance therapy by adding a new antihypertensive and/or increasing the dose of a present medication.
  - ✓ Acute administration of a short-acting oral drug (captopril, clonidine, or labetalol) followed by careful observation for several hours to ensure a gradual BP reduction is an option.
  - ✓ Oral captopril doses of 25 to 50 mg may be given at 1- to 2-hour intervals. The onset of action is 15 to 30 minutes.
  - ✓ For treatment of hypertensive rebound after withdrawal of clonidine, 0.2 mg is given initially, followed by 0.2 mg hourly until the DBP falls below 110 mm Hg or a total of 0.7 mg has been administered; a single dose may be sufficient.
  - ✓ Labetalol can be given in a dose of 200 to 400 mg, followed by additional doses every 2 to 3 hours.
- **Hypertensive emergencies** require immediate BP reduction to limit new or progressing target-organ damage. The goal is not to lower BP to normal; instead, the initial target is a reduction in mean arterial pressure of up to 25% within minutes to hours. If BP is then stable, it can be reduced toward 160/100–110 mm Hg within the next 2 to 6 hours. Precipitous drops in BP may cause end-organ ischemia or infarction. If BP reduction is well tolerated, additional gradual decrease toward the goal BP can be attempted after 24 to 48 hours.
  - ✓ Nitroprusside is the agent of choice for minute-to-minute control in most cases. It is usually given as a continuous IV infusion at a rate of 0.25 to 10 mcg/kg/min. Its onset of hypotensive action is immediate and disappears within 1 to 2 minutes of discontinuation. When the infusion must be continued longer than 72 hours, serum thiocyanate levels should be measured, and the infusion should be discontinued if the level exceeds 12 mg/dL. The risk of thiocyanate toxicity is increased in patients with impaired kidney function. Other adverse effects include nausea, vomiting, muscle twitching, and sweating.
  - ✓ Dosing guidelines and adverse effects of parenteral agents for treating hypertensive emergency are listed in Table 10-4.

## EVALUATION OF THERAPEUTIC OUTCOMES

- Clinic-based BP monitoring is the standard for managing hypertension. BP response should be evaluated 2 to 4 weeks after initiating or making changes in therapy. Once goal BP values are obtained, BP monitoring can be done every 3 to 6 months, assuming no signs or symptoms of acute target-organ disease. More frequent evaluations are required in patients with a history of poor control, nonadherence, progressive target-organ damage, or symptoms of adverse drug effects.
- Self-measurements of BP or automatic ambulatory BP monitoring can be useful to establish effective 24-hour control. These techniques are currently recommended only for select situations such as suspected white coat hypertension.
- Patients should be monitored for signs and symptoms of progressive target-organ disease. A careful history should be taken for chest pain (or

**TABLE 10-4** Parenteral Antihypertensive Agents for Hypertensive Emergency

Drug	Dose	Onset (minutes)	Duration (minutes)	Adverse Effects
Sodium nitroprusside	0.25–10 mcg/kg/min IV infusion (requires special delivery system)	Immediate	1–2	Nausea, vomiting, muscle twitching, sweating, thiocyanate and cyanide intoxication
Nicardipine hydrochloride	5–15 mg/hour IV	5–10	15–30; may exceed 240	Tachycardia, headache, flushing, local phlebitis
Fenoldopam mesylate	0.1–0.3 mcg/kg/min IV infusion	<5	30	Tachycardia, headache, nausea, flushing
Nitroglycerin	5–100 mcg/min IV infusion	2–5	5–10	Headache, vomiting, methemoglobinemia, tolerance with prolonged use
Hydralazine hydrochloride	12–20 mg IV 10–50 mg intramuscular	10–20 20–30	60–240 240–360	Tachycardia, flushing, headache, vomiting, aggravation of angina
Labetalol hydrochloride	20–80 mg IV bolus every 10 minutes; 0.5–2.0 mg/min IV infusion	5–10	180–360	Vomiting, scalp tingling, bronchoconstriction, dizziness, nausea, heart block, orthostatic hypotension
Esmolol hydrochloride	250–500 mcg/kg/min IV bolus, then 50–100 mcg/kg/min IV infusion; may repeat bolus after 5 minutes or increase infusion to 300 mcg/min	1–2	10–20	Hypotension, nausea, asthma, first-degree heart block, heart failure

pressure), palpitations, dizziness, dyspnea, orthopnea, headache, sudden change in vision, one-sided weakness, slurred speech, and loss of balance to assess for the presence of complications.

- Other clinical parameters that should be monitored periodically include fundoscopic changes on eye examination, LV hypertrophy on ECG, proteinuria, and changes in kidney function.
- Monitoring for adverse drug effects should typically occur 2 to 4 weeks after starting a new agent or dose increases, and then every 6 to 12 months in stable patients. Additional monitoring may be needed for other concomitant diseases. Patients taking aldosterone antagonists should have potassium concentration and kidney function assessed within 3 days and again at 1 week after initiation to detect potential hyperkalemia.
- Patient adherence with the therapeutic regimen should be assessed regularly. Patients should be questioned periodically about changes in their general health perception, energy level, physical functioning, and overall satisfaction with treatment.

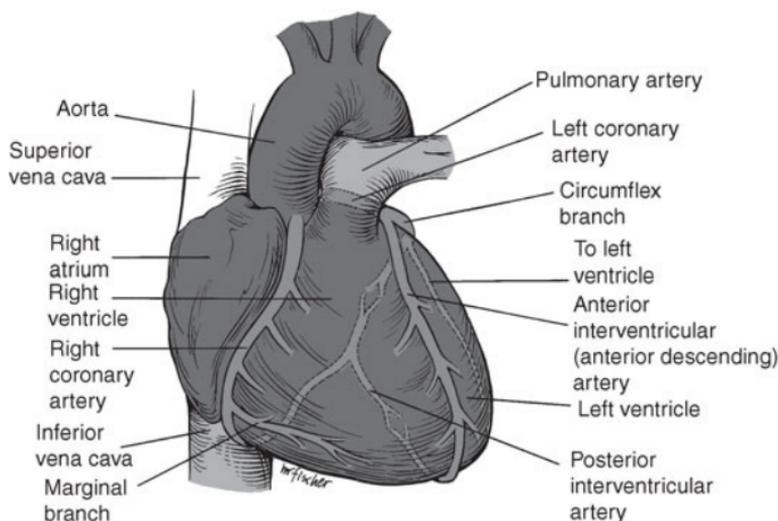
See Chap. 15, *Hypertension*, authored by Joseph J. Saseen and Eric J. MacLaughlin, for a more detailed discussion of this topic.

## DEFINITION

- Ischemic heart disease (IHD) is defined as a lack of oxygen and decreased or no blood flow to the myocardium resulting from coronary artery narrowing or obstruction. IHD may present as an acute coronary syndrome (ACS, which includes unstable angina and non-ST-segment elevation or ST-segment elevation myocardial infarction [MI]), chronic stable exertional angina, ischemia without symptoms, or ischemia due to coronary artery vasospasm (variant or Prinzmetal angina).

## PATHOPHYSIOLOGY

- The major determinants of myocardial oxygen demand ( $MVO_2$ ) are heart rate (HR), contractility, and intramyocardial wall tension during systole. Wall tension is thought to be the most important factor. Because the consequences of IHD usually result from increased demand in the face of a fixed oxygen supply, alterations in  $MVO_2$  are important in producing ischemia and for interventions intended to alleviate it.
- A clinically useful indirect estimate of  $MVO_2$  is the double product (DP), which is HR multiplied by systolic blood pressure (SBP) ( $DP = HR \times SBP$ ). The DP does not consider changes in contractility (an independent variable), and because only changes in pressure are considered, volume loading of the left ventricle and increased  $MVO_2$  related to ventricular dilation are underestimated.
- The caliber of the resistance vessels delivering blood to the myocardium and  $MVO_2$  are the prime determinants in the occurrence of ischemia.
- The normal coronary system consists of large epicardial or surface vessels ( $R_1$ ) that offer little resistance to myocardial flow and intramyocardial arteries and arterioles ( $R_2$ ), which branch into a dense capillary network to supply basal blood flow (Fig. 11-1). Under normal circumstances, the resistance in  $R_2$  is much greater than that in  $R_1$ . Myocardial blood flow is inversely related to arteriolar resistance and directly related to the coronary driving pressure.
- Atherosclerotic lesions occluding  $R_1$  increase arteriolar resistance, and  $R_2$  can vasodilate to maintain coronary blood flow. With greater degrees of obstruction, this response is inadequate, and the coronary flow reserve afforded by  $R_2$  vasodilation is insufficient to meet oxygen demand. Relatively severe stenosis (greater than 70%) may provoke ischemia and symptoms at rest, whereas less severe stenosis may allow a reserve of coronary blood flow for exertion.
- The diameter and length of obstructing lesions and the influence of pressure drop across an area of stenosis also affect coronary blood flow and function of the collateral circulation. Dynamic coronary obstruction can occur in normal vessels and vessels with stenosis in which vasomotion or



**FIGURE 11-1.** Coronary artery anatomy. (From Tintinalli JE, Kelen GD, Stapczynski JR, eds. *Tintinalli's Emergency Medicine: A Comprehensive Study Guide*, 6th ed. New York: McGraw-Hill, 2004:344.)

spasm may be superimposed on a fixed stenosis. Persisting ischemia may promote growth of developed collateral blood flow.

- Critical stenosis occurs when the obstructing lesion encroaches on the luminal diameter and exceeds 70%. Lesions creating obstruction of 50% to 70% may reduce blood flow, but these obstructions are not consistent, and vasospasm and thrombosis superimposed on a “noncritical” lesion may lead to clinical events such as MI. If the lesion enlarges from 80% to 90%, resistance in that vessel is tripled. Coronary reserve is diminished at about 85% obstruction due to vasoconstriction.
- Abnormalities of ventricular contraction can occur, and regional loss of contractility may impose a burden on the remaining myocardial tissue, resulting in heart failure, increased  $MVO_2$ , and rapid depletion of blood flow reserve. Zones of tissue with marginal blood flow may develop that are at risk for more severe damage if the ischemic episode persists or becomes more severe. Nonischemic areas of myocardium may compensate for the severely ischemic and border zones of ischemia by developing more tension than usual in an attempt to maintain cardiac output. The left or right ventricular dysfunction that ensues may be associated with clinical findings of an  $S_3$  gallop, dyspnea, orthopnea, tachycardia, fluctuating blood pressure, transient murmurs, and mitral or tricuspid regurgitation. Impaired diastolic and systolic function leads to elevation of the filling pressure of the left ventricle.

## CLINICAL PRESENTATION

- Many episodes of ischemia do not cause symptoms of angina (silent ischemia). Patients often have a reproducible pattern of pain or other

symptoms that appear after a specific amount of exertion. Increased symptom frequency, severity, or duration, and symptoms at rest suggest an unstable pattern that requires immediate medical evaluation.

- Symptoms may include a sensation of pressure or burning over the sternum or near it, which often radiates to the left jaw, shoulder, and arm. Chest tightness and shortness of breath may also occur. The sensation usually lasts from 30 seconds to 30 minutes.
- Precipitating factors include exercise, cold environment, walking after a meal, emotional upset, fright, anger, and coitus. Relief occurs with rest and within 45 seconds to 5 minutes of taking nitroglycerin.
- Patients with variant or Prinzmetal angina secondary to coronary spasm are more likely to experience pain at rest and in the early morning hours. Pain is not usually brought on by exertion or emotional stress nor is it relieved by rest; the electrocardiogram (ECG) pattern is that of current injury with ST-segment elevation rather than depression.
- Unstable angina is stratified into categories of low, intermediate, or high risk for short-term death or nonfatal MI. Features of high-risk unstable angina include (but are not limited to): (1) accelerating tempo of ischemic symptoms in the preceding 48 hours; (2) pain at rest lasting more than 20 minutes; (3) age greater than 75 years; (4) ST-segment changes; and (5) clinical findings of pulmonary edema, mitral regurgitation,  $S_3$ , rales, hypotension, bradycardia, or tachycardia.
- Episodes of ischemia may also be painless, or “silent,” in at least 60% of patients, perhaps due to a higher threshold and tolerance for pain than in patients who have pain more frequently.

## DIAGNOSIS

- Important aspects of the clinical history include the nature or quality of the chest pain, precipitating factors, duration, pain radiation, and the response to nitroglycerin or rest. There appears to be little relationship between the historical features of angina and the severity or extent of coronary artery vessel involvement. Ischemic chest pain may resemble pain arising from a variety of noncardiac sources, and the differential diagnosis of anginal pain from other etiologies may be difficult based on history alone.
- The patient should be asked about existing personal risk factors for coronary heart disease (CHD) including smoking, hypertension, and diabetes mellitus.
- A detailed family history should be obtained that includes information about premature CHD, hypertension, familial lipid disorders, and diabetes mellitus.
- There are few signs on physical examination to indicate the presence of coronary artery disease (CAD). Findings on the cardiac examination may include abnormal precordial systolic bulge, decreased intensity of  $S_1$ , paradoxical splitting of  $S_2$ ,  $S_3$ ,  $S_4$ , apical systolic murmur, and diastolic murmur. Elevated HR or blood pressure can yield an increased DP and may be associated with angina. Noncardiac physical findings suggesting significant cardiovascular disease include abdominal aortic aneurysms or peripheral vascular disease.

- Recommended laboratory tests include hemoglobin (to ensure adequate oxygen-carrying capacity), fasting glucose (to exclude diabetes), and fasting lipoprotein panel. Important risk factors in some patients may include C-reactive protein; homocysteine level; evidence of *Chlamydia* infection; and elevations in lipoprotein (a), fibrinogen, and plasminogen activator inhibitor. Cardiac enzymes should all be normal in stable angina. Troponin T or I, myoglobin, and creatinine kinase MB may be elevated in unstable angina.
- The resting ECG is normal in about one-half of patients with angina who are not experiencing an acute attack. Typical ST-T-wave changes include depression, T-wave inversion, and ST-segment elevation. Variant angina is associated with ST-segment elevation, whereas silent ischemia may produce elevation or depression. Significant ischemia is associated with ST-segment depression of greater than 2 mm, exertional hypotension, and reduced exercise tolerance.
- Exercise tolerance (stress) testing (ETT) is recommended for patients with an intermediate probability of CAD. Results correlate well with the likelihood of progressing to angina, occurrence of acute MI, and cardiovascular death. Ischemic ST-segment depression during ETT is an independent risk factor for cardiovascular events and mortality. Thallium myocardial perfusion scintigraphy may be used in conjunction with ETT to detect reversible and irreversible defects in blood flow to the myocardium.
- Radionuclide angiocardigraphy is used to measure ejection fraction (EF), regional ventricular performance, cardiac output, ventricular volumes, valvular regurgitation, asynchrony or wall motion abnormalities, and intracardiac shunts.
- Ultrarapid computed tomography may minimize artifact from heart motion during contraction and relaxation and provides a semiquantitative assessment of calcium content in coronary arteries.
- Echocardiography is useful if the history or physical findings suggest valvular pericardial disease or ventricular dysfunction. In patients unable to exercise, pharmacologic stress echocardiography (e.g., dobutamine, dipyridamole, or adenosine) may identify abnormalities that would occur during stress.
- Cardiac catheterization and coronary angiography are used in patients with suspected CAD to document the presence and severity of disease as well as for prognostic purposes. Interventional catheterization is used for thrombolytic therapy in patients with acute MI and for managing patients with significant CAD to relieve obstruction through percutaneous transluminal coronary angioplasty, atherectomy, laser treatment, or stent placement.
- A chest radiograph should be done if the patient has heart failure symptoms.

## DESIRED OUTCOME

- The short-term goals of therapy for IHD are to reduce or prevent anginal symptoms that limit exercise capability and impair quality of life. Long-term goals are to prevent CHD events such as MI, arrhythmias, and heart failure and to extend the patient's life.

## TREATMENT

### RISK-FACTOR MODIFICATION

- Primary prevention through the modification of risk factors should significantly reduce the prevalence of IHD. Secondary intervention is effective in reducing subsequent morbidity and mortality.
- Risk factors for IHD are additive and can be classified as alterable or unalterable. Unalterable risk factors include gender, age, family history or genetic composition, environmental influences, and, to some extent, diabetes mellitus. Alterable risk factors include smoking, hypertension, hyperlipidemia, obesity, sedentary lifestyle, hyperuricemia, psychosocial factors such as stress and type A behavior patterns, and the use of drugs that may be detrimental (e.g., progestins, corticosteroids, and cyclosporine). Although thiazide diuretics and  $\beta$ -blockers (nonselective without intrinsic sympathomimetic activity) may elevate both cholesterol and triglycerides by 10% to 20%, and these effects may be detrimental, no objective evidence exists from prospective well-controlled studies to support avoiding these drugs.

### PHARMACOLOGIC THERAPY

#### $\beta$ -Adrenergic Blocking Agents

- Decreased HR, contractility, and blood pressure reduce  $MVO_2$  and oxygen demand in patients with effort-induced angina.  $\beta$ -Blockers do not improve oxygen supply and, in certain instances, unopposed  $\alpha$ -adrenergic stimulation may lead to coronary vasoconstriction.
- $\beta$ -Blockers improve symptoms in about 80% of patients with chronic exertional stable angina, and objective measures of efficacy demonstrate improved exercise duration and delay in the time at which ST-segment changes and initial or limiting symptoms occur.  $\beta$ -Blockade may allow angina patients previously limited by symptoms to perform more exercise and ultimately improve overall cardiovascular performance through a training effect.
- Ideal candidates for  $\beta$ -blockers include patients in whom physical activity is a prominent cause of attacks; those with coexisting hypertension, supraventricular arrhythmias, or postmyocardial infarction angina; and those with anxiety associated with anginal episodes.  $\beta$ -Blockers may be used safely in angina and heart failure.
- $\beta$ -Blockade is effective in chronic exertional angina as monotherapy and in combination with nitrates and/or calcium channel antagonists.  $\beta$ -Blockers are the first-line drugs in chronic angina requiring daily maintenance therapy because they are more effective in reducing episodes of silent ischemia and early morning peak of ischemic activity and improving mortality after Q-wave MI than nitrates or calcium channel antagonists.
- If  $\beta$ -blockers are ineffective or not tolerated, then monotherapy with a calcium channel antagonist or combination therapy may be instituted. Reflex tachycardia from nitrates can be blunted with  $\beta$ -blocker therapy, making this a useful combination. Patients with severe angina, rest angina,

or variant angina may be better treated with calcium channel antagonists or long-acting nitrates.

- Initial doses of  $\beta$ -blockers should be at the lower end of the usual dosing range and titrated to response. Treatment objectives include lowering the resting HR to 50 to 60 beats/min and limiting maximal exercise HR to about 100 beats/min or less. HR with modest exercise should be no more than about 20 beats/min above resting HR (or a 10% increment over resting HR).
- There is little evidence to suggest superiority of any particular  $\beta$ -blocker. Those with longer half-lives may be administered less frequently, but even **propranolol** may be given twice a day in most patients. Membrane stabilizing activity is irrelevant in the treatment of angina. Intrinsic sympathomimetic activity appears to be detrimental in patients with rest or severe angina because the reduction in HR would be minimized, therefore limiting a reduction in  $MVO_2$ . Cardioselective  $\beta$ -blockers may be used in some patients to minimize adverse effects such as bronchospasm, intermittent claudication, and sexual dysfunction. Combined nonselective  $\beta$ - and  $\alpha$ -blockade with **labetalol** may be useful in some patients with marginal left ventricular (LV) reserve.
- Adverse effects of  $\beta$ -blockade include hypotension, heart failure, bradycardia, heart block, bronchospasm, altered glucose metabolism, fatigue, malaise, and depression. Abrupt withdrawal in patients with angina has been associated with increased severity and number of pain episodes and MI. Tapering of therapy over about 2 days should minimize the risk of withdrawal reactions if therapy is to be discontinued.

## Nitrates

- The action of nitrates appears to be mediated indirectly through reduction of  $MVO_2$  secondary to venodilation and arterial-arteriolar dilation, leading to a reduction in wall stress from reduced ventricular volume and pressure. Direct actions on the coronary circulation include dilation of large and small intramural coronary arteries, collateral dilation, coronary artery stenosis dilation, abolition of normal tone in narrowed vessels, and relief of spasm.
- Pharmacokinetic characteristics common to nitrates include a large first-pass effect of hepatic metabolism, short to very short half-lives (except for **isosorbide mononitrate** [ISMN]), large volumes of distribution, high clearance rates, and large interindividual variations in plasma or blood concentrations. The half-life of **nitroglycerin** is 1 to 5 minutes regardless of the route, hence the potential advantage of sustained-release and transdermal products. **Isosorbide dinitrate** (ISDN) is metabolized to ISMN. ISMN has a half-life of about 5 hours and may be given once or twice daily, depending on the product chosen.
- Nitrate therapy may be used to terminate an acute anginal attack, to prevent effort- or stress-induced attacks, or for long-term prophylaxis, usually in combination with  $\beta$ -blockers or calcium channel antagonists. Sublingual, buccal, or spray nitroglycerin products are preferred for alleviation of anginal attacks because of rapid absorption (Table 11-1). Symptoms may be prevented by prophylactic oral or transdermal products (usually in combination with  $\beta$ -blockers or calcium channel antagonists), but development of tolerance may be problematic.

**TABLE 11-1** Nitrate Products

Product	Onset (minutes)	Duration	Initial Dose
Nitroglycerin			
IV	1–2	3–5 minutes	5 mcg/min
Sublingual/lingual	1–3	30–60 minutes	0.3 mg
Oral	40	3–6 hours	2.5–9 mg three times daily
Ointment	20–60	2–8 hours	1/2–1 inch
Patch	40–60	>8 hours	1 patch
Erythritol tetranitrate	5–30	4–6 hours	5–10 mg three times daily
Pentaerythritol tetranitrate	30	4–8 hours	10–20 mg three times daily
Isosorbide dinitrate			
Sublingual/chewable	2–5	1–2 hours	2.5–5 mg three times daily
Oral	20–40	4–6 hours	5–20 mg three times daily
Isosorbide mononitrate	30–60	6–8 hours	20 mg daily, twice daily <sup>a</sup>

<sup>a</sup>Product-dependent.

- **Sublingual nitroglycerin**, 0.3 to 0.4 mg, relieves pain in about 75% of patients within 3 minutes, with another 15% becoming pain-free in 5 to 15 minutes. Pain persisting beyond 20 to 30 minutes after use of two to three nitroglycerin tablets suggests ACS, and the patient should be instructed to seek emergency aid.
- Chewable, oral, and transdermal products are acceptable for long-term prophylaxis of angina. Dosing of long-acting preparations should be adjusted to provide a hemodynamic response. This may require doses of oral ISDN ranging from 10 to 60 mg as often as every 3 to 4 hours due to tolerance or first-pass metabolism. Intermittent (10 to 12 hours on, 12 to 14 hours off) transdermal nitroglycerin therapy may produce modest but significant improvement in exercise time in chronic stable angina.
- Adverse effects include postural hypotension with associated CNS symptoms, reflex tachycardia, headaches and flushing, and occasional nausea. Excessive hypotension may result in MI or stroke. Noncardiovascular adverse effects include rash (especially with transdermal nitroglycerin) and methemoglobinemia with high doses given for extended periods.
- Because both the onset and offset of tolerance to nitrates occur quickly, one strategy to circumvent it is to provide a daily nitrate-free interval of 8 to 12 hours. For example, ISDN should not be used more often than three times a day to avoid tolerance.
- Nitrates may be combined with other drugs with complementary mechanisms of action for chronic prophylactic therapy. Combination therapy is generally used in patients with more frequent symptoms or symptoms that do not respond to  $\beta$ -blockers alone (nitrates plus  $\beta$ -blockers or calcium channel antagonists), in patients intolerant of  $\beta$ -blockers or calcium channel antagonists, and in patients having an element of vasospasm leading to decreased supply (nitrates plus calcium channel antagonists).

### Calcium Channel Antagonists

- Direct actions include vasodilation of systemic arterioles and coronary arteries, leading to a reduction of arterial pressure and coronary vascular resistance as well as depression of myocardial contractility and the conduc-

tion velocity of the sinoatrial and atrioventricular (AV) nodes. Reflex  $\beta$ -adrenergic stimulation overcomes much of the negative inotropic effect, and depression of contractility becomes clinically apparent only in the presence of LV dysfunction and when other negative inotropic drugs are used concurrently.

- **Verapamil** and **diltiazem** cause less peripheral vasodilation than dihydropyridines such as **nifedipine** but greater decreases in AV node conduction. They must be used with caution in patients with preexisting conduction abnormalities or in patients taking other drugs with negative chronotropic properties.
- $MVO_2$  is reduced with all calcium channel antagonists primarily because of reduced wall tension secondary to reduced arterial pressure. Overall, the benefit provided by calcium channel antagonists is related to reduced  $MVO_2$  rather than improved oxygen supply.
- In contrast to the  $\beta$ -blockers, calcium channel antagonists have the potential to improve coronary blood flow through areas of fixed coronary obstruction by inhibiting coronary artery vasomotion and vasospasm.
- Good candidates for calcium channel antagonists include patients with contraindications or intolerance to  $\beta$ -blockers, coexisting conduction system disease (excluding the use of verapamil and possibly diltiazem), Prinzmetal angina, peripheral vascular disease, severe ventricular dysfunction, and concurrent hypertension. **Amlodipine** is probably the agent of choice in severe ventricular dysfunction, and the other dihydropyridines should be used with caution if the EF is less than 40%.

### Ranolazine

- The mechanism of action of ranolazine has not been determined, but it may be related to reduction in calcium overload in ischemic myocytes through inhibition of the late sodium current. Its antianginal effects do not depend on reductions in HR or blood pressure.
- Ranolazine is indicated for the treatment of chronic angina. Based on controlled trials, the improvement in exercise time is a modest increase of 15 to about 45 seconds compared with placebo. In a large ACS trial, ranolazine reduced recurrent ischemia but did not improve the primary efficacy composite end point of cardiovascular death, MI, or recurrent ischemia.
- Because it prolongs the QT interval, ranolazine should be reserved for patients who have not achieved an adequate response to other antianginal drugs. It should be used in combination with amlodipine,  $\beta$ -blockers, or nitrates.
- The most common adverse effects are dizziness, headache, constipation, and nausea. Ranolazine should be started at 500 mg twice daily and increased to 1,000 mg twice daily if needed based on symptoms. Baseline and followup ECGs should be obtained to evaluate effects on the QT interval.

## TREATMENT OF STABLE EXERTIONAL ANGINA PECTORIS

- Table 11-2 lists the evidence-based drug therapy recommendations of the American College of Cardiology and American Heart Association. A treatment algorithm is shown in Fig. 11-2.

**TABLE 11-2** Evidence-Based Recommendations for Treatment of Stable Exertional Angina Pectoris

Recommendations	Recommendation Grades <sup>a</sup>
All patients should be given the following unless contraindications exist:	
• Aspirin	Class I, Level A
• $\beta$ -Blockers with prior MI	Class I, Level A
• Angiotensin-converting enzyme inhibitor (ACEI) to patients with CAD and diabetes or LV dysfunction	Class I, Level A
• LDL-lowering therapy with CAD and LDL >130 mg/dL	Class I, Level A
• Sublingual nitroglycerin for immediate relief of angina	Class I, Level B
• Calcium antagonists or long-acting nitrates for reduction of symptoms when $\beta$ -blockers are contraindicated	Class I, Level B
• Calcium antagonists or long-acting nitrates in combination with $\beta$ -blockers when initial treatment with $\beta$ -blockers is unsuccessful	Class I, Level C
• Calcium antagonists or long-acting nitrates as a substitute for $\beta$ -blockers if initial treatment with $\beta$ -blockers leads to unacceptable side effects	Class I, Level A
Clopidogrel may be substituted for aspirin when aspirin is absolutely contraindicated	Class IIa, Level B
Long-acting nondihydropyridine calcium antagonists instead of $\beta$ -blockers as initial therapy	Class IIa, Level B
ACEIs are recommended in patients with CAD or other vascular disease	Class IIa, Level B
Low-intensity anticoagulation with warfarin, in addition to aspirin, is recommended but bleeding would be increased	Class IIb, Level B
Therapies to be avoided include:	
• Dipyridamole	Class III, Level B
• Chelation therapy	Class III, Level B

CAD, coronary artery disease; LDL, low-density lipoprotein; LV, left ventricular; MI, myocardial infarction.

<sup>a</sup>American College of Cardiology and American Heart Association Evidence Grading System. Recommendation Class:

I = Conditions for which there is evidence or general agreement that a given procedure or treatment is useful and effective.

II = Conditions for which there is conflicting evidence or a divergence of opinion about the usefulness/efficacy of a given procedure or treatment.

IIa = Weight of evidence/opinion is in favor of usefulness or efficacy.

IIb = Usefulness/efficacy is less well established by evidence/opinion.

III = Conditions for which there is evidence or general agreement that a given procedure or treatment is not useful/effective and in some cases may be harmful.

Level of Evidence:

A = Data derived from multiple randomized clinical trials with large numbers of patients.

B = Data derived from a limited number of randomized trials with small numbers of patients, careful analyses of nonrandomized studies, or observational registries.

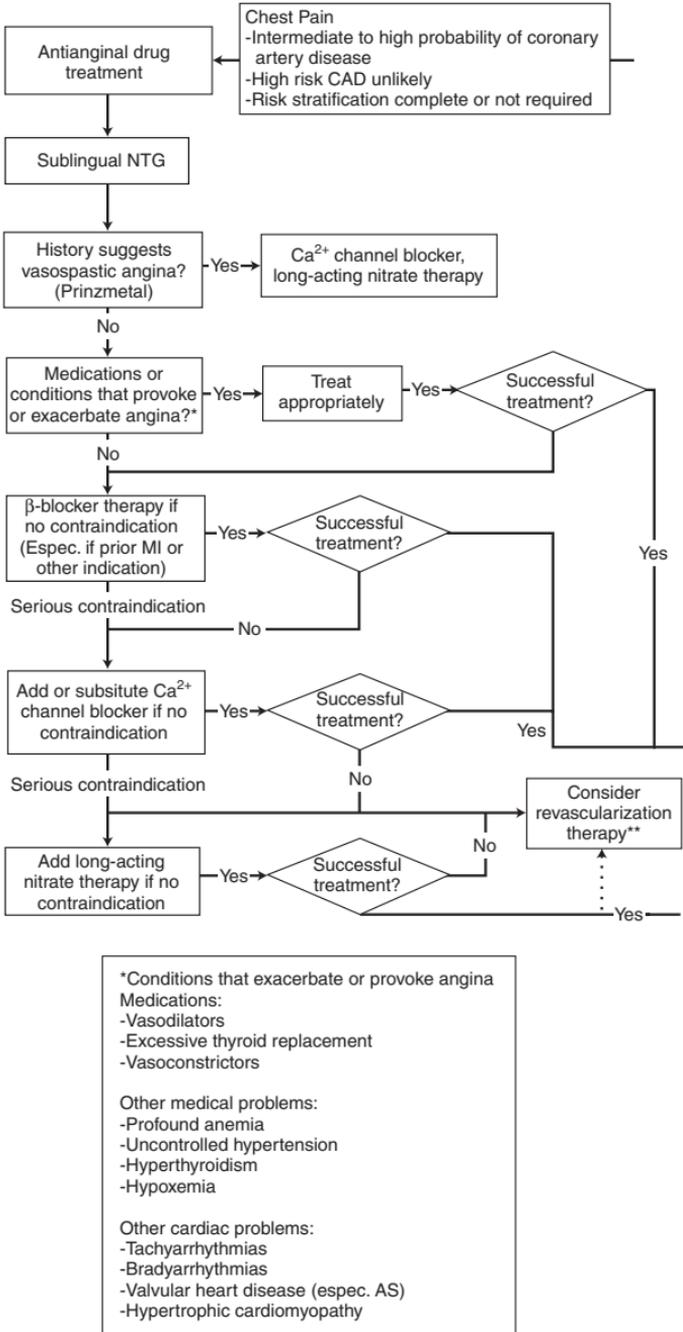
C = Expert consensus was the primary basis for the recommendation.

- After assessing and manipulating alterable risk factors, a regular exercise program should be undertaken with caution in a graduated fashion and with adequate supervision to improve cardiovascular and muscular fitness.
- Nitrate therapy should be the first step in managing acute attacks of chronic stable angina if the episodes are infrequent (e.g., a few times per month). If angina occurs no more often than once every few days, then sublingual nitroglycerin tablets or spray or buccal products may be sufficient.
- For prophylaxis when undertaking activities that predictably precipitate attacks, nitroglycerin 0.3 to 0.4 mg sublingually may be used about 5 minutes prior to the time of the activity. Nitroglycerin spray may be useful when inadequate saliva is produced to rapidly dissolve sublingual **nitroglycerin** or if a patient has difficulty opening the tablet container. The response usually lasts about 30 minutes.

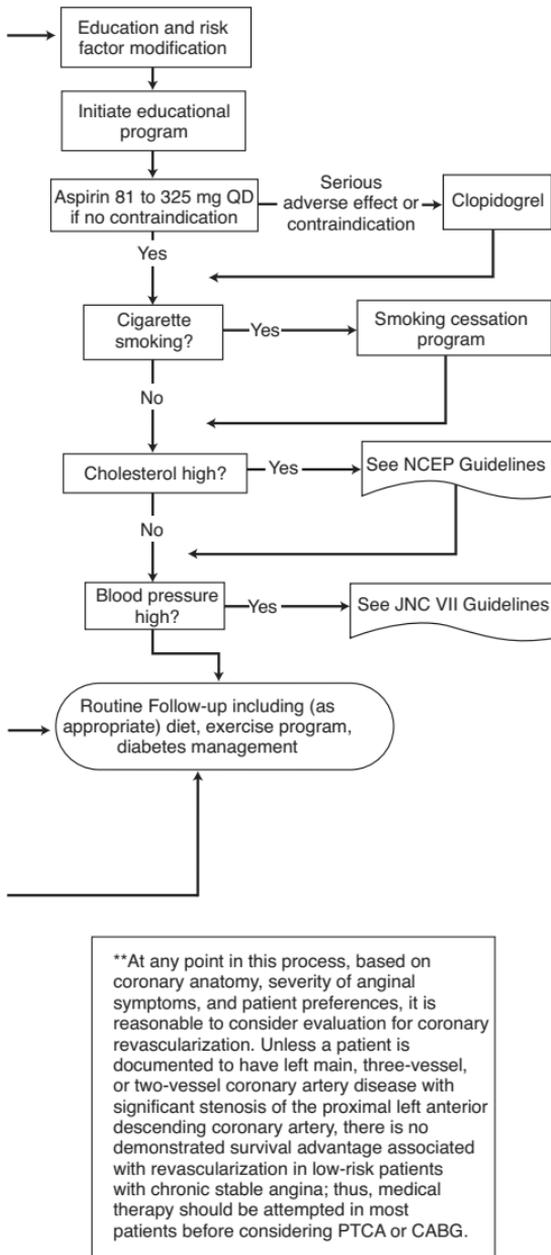
- When angina occurs more frequently than once a day, chronic prophylactic therapy should be instituted.  **$\beta$ -Blockers** may be preferable because of less frequent dosing and other desirable properties (e.g., potential cardioprotective effects, antiarrhythmic effects, lack of tolerance, antihypertensive efficacy). The appropriate dose should be determined by the goals outlined for HR and DP. An agent should be selected that is well tolerated by individual patients at a reasonable cost. Patients most likely to respond well to  $\beta$ -blockade are those with a high resting HR and those with a relatively fixed anginal threshold (i.e., their symptoms appear at the same level of exercise or workload on a consistent basis).
- **Calcium channel antagonists** have the potential advantage of improving coronary blood flow through coronary artery vasodilation as well as decreasing  $MVO_2$  and may be used instead of  $\beta$ -blockers for chronic prophylactic therapy. They are as effective as  $\beta$ -blockers and are most useful in patients who have a variable threshold for exertional angina. Calcium antagonists may provide better skeletal muscle oxygenation, resulting in decreased fatigue and better exercise tolerance. They can be used safely in many patients with contraindications to  $\beta$ -blocker therapy. The available drugs have similar efficacy in the management of chronic stable angina. Patients with conduction abnormalities and moderate to severe LV dysfunction (EF <35%) should not be treated with **verapamil**, whereas **amlodipine** may be used safely in many of these patients. **Diltiazem** has significant effects on the AV node and can produce heart block in patients with preexisting conduction disease or when other drugs with effects on conduction (e.g., digoxin,  $\beta$ -blockers) are used concurrently. **Nifedipine** may cause excessive HR elevation, especially if the patient is not receiving a  $\beta$ -blocker, and this may offset its beneficial effect on  $MVO_2$ . The combination of calcium channel antagonists and  $\beta$ -blockers is rational because the hemodynamic effect of calcium antagonists is complementary to  $\beta$ -blockade. However, combination therapy may not always be more effective than single-agent therapy.
- Chronic prophylactic therapy with long-acting forms of **nitroglycerin** (oral or transdermal), **ISDN**, **ISMN**, and **pentaerythritol trinitrate** may also be effective when angina occurs more than once a day, but development of tolerance is a limitation. Monotherapy with nitrates should not be first-line therapy unless  $\beta$ -blockers and calcium channel antagonists are contraindicated or not tolerated. A nitrate-free interval of 8 hours per day or longer should be provided to maintain efficacy. Dose titration should be based on changes in the DP. The choice among nitrate products should be based on experience, cost, and patient acceptance.

## TREATMENT OF CORONARY ARTERY SPASM AND VARIANT ANGINA PECTORIS

- All patients should be treated for acute attacks and maintained on prophylactic treatment for 6 to 12 months after the initial episode. Aggravating factors such as alcohol or cocaine use and cigarette smoking should be stopped.
- **Nitrates** are the mainstay of therapy, and most patients respond rapidly to sublingual **nitroglycerin** or **ISDN**. IV and intracoronary nitroglycerin may be useful for patients not responding to sublingual preparations.



**FIGURE 11-2.** Treatment of stable angina pectoris. (AS, aortic stenosis; CABG, coronary artery bypass grafting; CAD, coronary artery disease; JNC VII, Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; MI, myocardial infarction, NCEP, National Cholesterol Education Program; NTG, nitroglycerin; PTCA, percutaneous transluminal coronary angioplasty; QD, every day.) (continued)



**FIGURE 11-2.** (Continued)

- Because calcium channel antagonists may be more effective, have few serious adverse effects, and can be given less frequently than nitrates, some authorities consider them the agents of choice for variant angina. **Nifedipine**, **verapamil**, and **diltiazem** are all equally effective as single agents for

initial management. Patients unresponsive to calcium channel antagonists alone may have nitrates added. Combination therapy with nifedipine plus diltiazem or nifedipine plus verapamil is reported to be useful in patients unresponsive to single-drug regimens.

- $\beta$ -Blockers have little or no role in the management of variant angina as they may induce coronary vasoconstriction and prolong ischemia.

## EVALUATION OF THERAPEUTIC OUTCOMES

- Subjective measures of drug response include the number of painful episodes, amount of rapid-acting nitroglycerin consumed, and patient-reported alterations in activities of daily living (e.g., time to walk two blocks, number of stairs climbed without pain).
- Objective clinical measures of response include HR, blood pressure, and the DP as a measure of  $MVO_2$ .
- Objective assessment also includes the resolution of ECG changes at rest, during exercise, or with ambulatory ECG monitoring.
- Monitoring for major adverse effects should be undertaken; they include headache and dizziness with nitrates; fatigue and lassitude with  $\beta$ -blockers; and peripheral edema, constipation, and dizziness with calcium channel antagonists.
- The ECG is very useful, particularly if the patient is experiencing chest pain or other symptoms thought to be of ischemic origin. ST-segment deviations are very important, and the extent of their deviation is related to the severity of ischemia.
- ETT may also be used to evaluate the response to therapy, but the expense and time needed to perform this test preclude its routine use.
- A comprehensive plan includes ancillary monitoring of lipid profiles, fasting plasma glucose, thyroid function tests, hemoglobin/hematocrit, and electrolytes.
- For variant angina, reduction in symptoms and nitroglycerin consumption as documented by a patient diary can assist the interpretation of objective data obtained from ambulatory ECG recordings. Evidence of efficacy includes the reduction of ischemic events, both ST-segment depression and elevation. Additional evidence is a reduced number of attacks of angina requiring hospitalization, and the absence of MI and sudden death.

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*See Chap. 17, Ischemic Heart Disease, authored by Robert L. Talbert, for a more detailed discussion of this topic.*

## DEFINITION

- *Shock* refers to conditions manifested by hemodynamic alterations (e.g., hypotension, tachycardia, low cardiac output [CO], and oliguria) caused by intravascular volume deficit (hypovolemic shock), myocardial pump failure (cardiogenic shock), or peripheral vasodilation (septic, anaphylactic, or neurogenic shock). The underlying problem in these situations is inadequate tissue perfusion resulting from circulatory failure.

## PATHOPHYSIOLOGY

- Shock results in failure of the circulatory system to deliver sufficient oxygen (O<sub>2</sub>) to body tissues despite normal or reduced O<sub>2</sub> consumption. General pathophysiologic mechanisms of different forms of shock are similar except for initiating events.
- Hypovolemic shock is characterized by acute intravascular volume deficiency due to external losses or internal redistribution of extracellular water. This type of shock can be precipitated by hemorrhage, burns, trauma, surgery, intestinal obstruction, and dehydration from considerable insensible fluid loss, overaggressive loop-diuretic administration, and severe vomiting or diarrhea. Relative hypovolemia leading to hypovolemic shock occurs during significant vasodilation, which accompanies anaphylaxis, sepsis, and neurogenic shock.
- Regardless of the etiology, fall in blood pressure (BP) is compensated by an increase in sympathetic outflow, activation of the renin-angiotensin system, and other humoral factors that stimulate peripheral vasoconstriction. Compensatory vasoconstriction redistributes blood away from the skin, skeletal muscles, kidneys, and GI tract toward vital organs (e.g., heart, brain) in an attempt to maintain oxygenation, nutrition, and organ function.
- Severe metabolic lactic acidosis often develops secondary to tissue ischemia and causes localized vasodilation, which further exacerbates the impaired cardiovascular state.

## CLINICAL PRESENTATION

- Shock presents with a diversity of signs and symptoms. Patients with hypovolemic shock may present with thirst, anxiousness, weakness, lightheadedness, and dizziness. Patients may also report scanty urine output and dark-yellow-colored urine.
- Hypotension, tachycardia, tachypnea, confusion, and oliguria are common symptoms. Myocardial and cerebral ischemia, pulmonary edema (cardiogenic shock), and multisystem organ failure often follow.
- Significant hypotension (systolic blood pressure [SBP] less than 90 mm Hg) with reflex sinus tachycardia (greater than 120 beats/min) and increased

respiratory rate (more than 30 breaths/min) are often observed in hypovolemic patients. Clinically, the patient presents with extremities cool to the touch and a “thready” pulse. The patient may be cyanotic due to hypoxemia. Sweating results in a moist, clammy feel. Digits will have severely slowed capillary refill.

- Mental status changes associated with volume depletion may range from subtle fluctuations in mood to agitation to unconsciousness.
- Respiratory alkalosis secondary to hyperventilation is usually observed secondary to CNS stimulation of ventilatory centers as a result of trauma, sepsis, or shock. Lung auscultation may reveal crackles (pulmonary edema) or absence of breath sounds (pneumothorax, hemothorax). Chest roentgenogram can confirm early suspicions or disclose an undetected abnormality such as pneumonia (pulmonary infiltrates). Continued insult to the lungs may result in adult respiratory distress syndrome.
- Kidneys are exquisitely sensitive to changes in perfusion pressures. Moderate alterations can lead to significant changes in glomerular filtration rate. Oliguria, progressing to anuria, occurs because of vasoconstriction of afferent arterioles.
- Redistribution of blood flow away from the GI tract may cause stress gastritis, gut ischemia, and, in some cases, infarction, resulting in GI bleeding.
- Progressive liver damage (shock liver) manifests as elevated serum hepatic transaminases and unconjugated bilirubin. Impaired synthesis of clotting factors may increase prothrombin time (PT), international normalized ratio, and activated partial thromboplastin time (aPTT).

## DIAGNOSIS AND MONITORING

- Information from noninvasive and invasive monitoring (Table 12-1) and evaluation of past medical history, clinical presentation, and laboratory findings are key components in establishing the diagnosis as well as in assessing general mechanisms responsible for shock. Regardless of the etiology, consistent findings include hypotension (SBP less than 90 mm Hg), depressed cardiac index (CI less than 2.2 L/min/m<sup>2</sup>), tachycardia (heart rate greater than 100 beats/min), and low urine output (less than 20 mL/hour).
- Noninvasive assessment of BP using the sphygmomanometer and stethoscope may be inaccurate in the shock state.
- A pulmonary artery (Swan-Ganz) catheter can be used to determine central venous pressure (CVP); pulmonary artery pressure; CO; and pulmonary artery occlusive pressure (PAOP), an approximate measure of the left ventricular end-diastolic volume and a major determinant of left ventricular preload.
- CO (2.5 to 3 L/min) and mixed venous oxygen saturation (70% to 75%) may be very low in a patient with extensive myocardial damage.
- Respiratory alkalosis is associated with low partial pressure of O<sub>2</sub> (25 to 35 mm Hg) and alkaline pH, but normal bicarbonate. The first two values are measured by arterial blood gas, which also yields partial pressure of carbon dioxide and arterial oxygen saturation. Circulating arterial oxygen saturation can also be measured by an oximeter, which is a noninvasive method that is fairly accurate and useful at the patient’s bedside.

**TABLE 12-1** Hemodynamic and Oxygen-Transport Monitoring Parameters

Parameter	Normal Value <sup>a</sup>
Blood pressure (systolic/diastolic)	100–130/70–85 mm Hg
Mean arterial pressure	80–100 mm Hg
Pulmonary artery pressure	25/10 mm Hg
Mean pulmonary artery pressure	12–15 mm Hg
Central venous pressure	8–12 mm Hg
Pulmonary artery occlusive pressure	12–15 mm Hg
Heart rate	60–80 beats/min
Cardiac output	4–7 L/min
Cardiac index	2.8–3.6 L/min/m <sup>2</sup>
Stroke volume index	30–50 mL/m <sup>2</sup>
Systemic vascular resistance index	1,300–2,100 dyne • sec/m <sup>2</sup> • cm <sup>5</sup>
Pulmonary vascular resistance index	45–225 dyne • sec/m <sup>2</sup> • cm <sup>5</sup>
Arterial oxygen saturation	97% (range 95–100%)
Mixed venous oxygen saturation	70–75%
Arterial oxygen content	20.1 vol% (range 19–21%)
Venous oxygen content	15.5 vol% (range 11.5–16.5%)
Oxygen content difference	5 vol% (range, 4–6%)
Oxygen consumption index	131 mL/min/m <sup>2</sup> (range, 100–180)
Oxygen delivery index	578 mL/min/m <sup>2</sup> (range, 370–730)
Oxygen extraction ratio	25% (range, 22–30%)
Intramucosal pH	7.40 (range, 7.35–7.45)
Index	Parameter indexed to body surface area

<sup>a</sup>Normal values may not be the same as values needed to optimize management of a critically ill patient.

- Renal function can be grossly assessed by hourly measurements of urine output, but estimation of creatinine clearance based on isolated serum creatinine values in critically ill patients may yield erroneous results. Decreased renal perfusion and aldosterone release result in sodium retention and, thus, low urinary sodium (<30 mEq/L).
- In normal individuals, oxygen consumption ( $VO_2$ ) is dependent on oxygen delivery ( $DO_2$ ) up to a certain critical level ( $VO_2$  flow dependency). At this point, tissue  $O_2$  requirements have apparently been satisfied and further increases in  $DO_2$  will not alter  $VO_2$  (flow independency). However, studies in critically ill patients show a continuous, pathologic dependence relationship of  $VO_2$  on  $DO_2$ . These indexed parameters are calculated as:  $DO_2 = CI \times (CaO_2)$  and  $VO_2 = CI \times (CaO_2 - CVO_2)$ , where  $CI$  = cardiac index,  $CaO_2$  = arterial oxygen content, and  $CVO_2$  = mixed venous oxygen content. Currently available data do not support the concept that patient outcome or survival is altered by treatment measures directed to achieve supranormal levels of  $DO_2$  and  $VO_2$ .
- The  $VO_2:DO_2$  ratio (oxygen extraction ratio) can be used to assess adequacy of perfusion and metabolic response. Patients who are able to increase  $VO_2$  when  $DO_2$  is increased are more likely to survive. However, low  $VO_2$  and  $O_2$  extraction ratio values are indicative of poor  $O_2$  utilization and lead to greater mortality.
- Blood lactate concentrations may be used as another measure of tissue oxygenation and may show better correlation with outcome than  $O_2$  transport parameters in some patients.

- Gastric tonometry measures gut luminal  $\text{PCO}_2$  at equilibrium by placing a saline-filled gas-permeable balloon in the gastric lumen. Increases in mucosal  $\text{PCO}_2$  and calculated decreases in gastric intramucosal pH (pHi) are associated with mucosal hypoperfusion and perhaps increased mortality. However, the presence of respiratory acid–base disorders, systemic bicarbonate administration, arterial blood gas measurement errors, enteral feeding products, and blood or stool in the gut may confound pHi determinations. Many clinicians believe that the change in gastric mucosal  $\text{PCO}_2$  may be more accurate than pHi.

## DESIRED OUTCOME

- The initial goal is to support  $\text{O}_2$  delivery through the circulatory system by assuring effective intravascular plasma volume, optimal  $\text{O}_2$ -carrying capacity, and adequate BP while definitive diagnostic and therapeutic strategies are being determined. The ultimate goals are to prevent further progression of the disease with subsequent organ damage and, if possible, to reverse organ dysfunction that has already occurred.

## TREATMENT

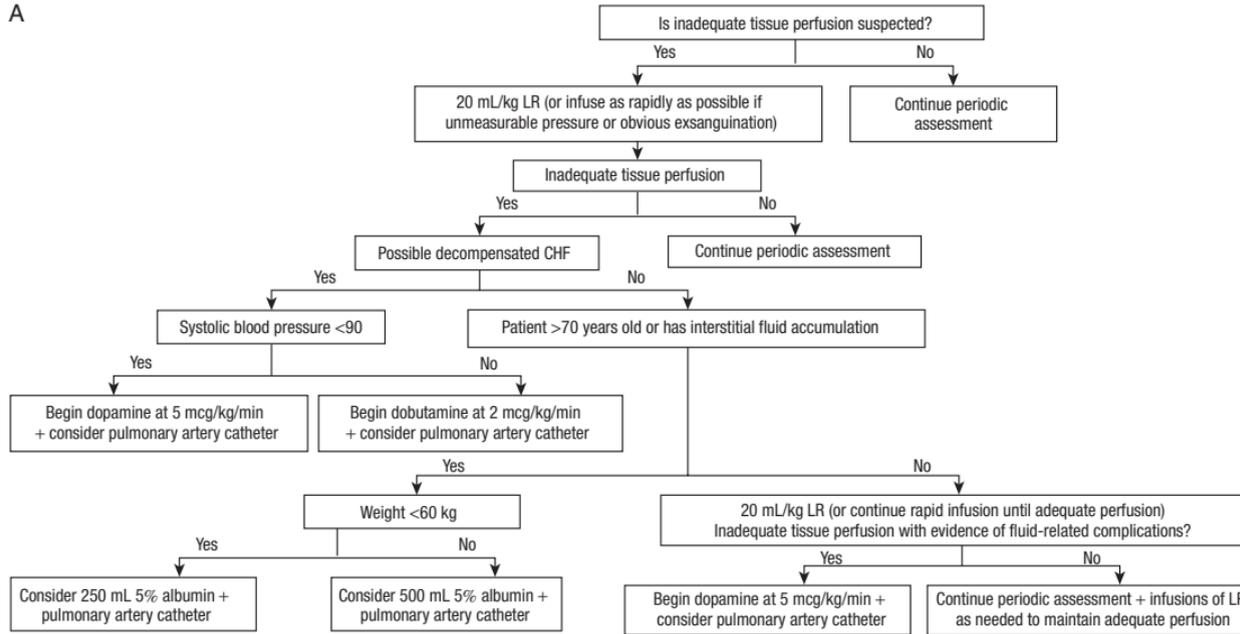
### GENERAL PRINCIPLES

- Fig. 12-1 contains an algorithm summarizing one approach to an adult patient presenting with hypovolemia.
- Supplemental  $\text{O}_2$  should be initiated at the earliest signs of shock, beginning with 4 to 6 L/min via nasal cannula or 6 to 10 L/min by face mask.
- Adequate fluid resuscitation to maintain circulating blood volume is essential in managing all forms of shock. Different therapeutic options are discussed in the next section.
- If fluid challenge does not achieve desired end points, pharmacologic support is necessary with inotropic and vasoactive drugs.

### FLUID RESUSCITATION FOR HYPOVOLEMIC SHOCK

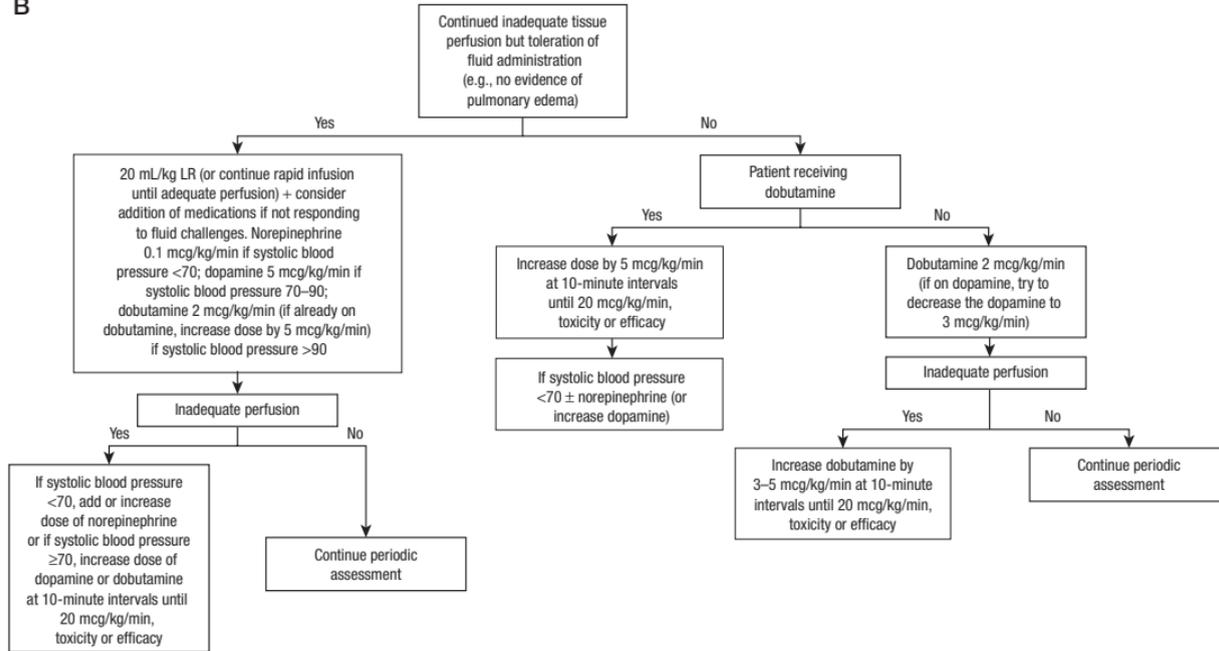
- Initial fluid resuscitation consists of isotonic crystalloid (**0.9% sodium chloride** or **lactated Ringer's solution**), colloid (**5% Plasmanate** or **albumin**, **6% hetastarch**), or **whole blood**. Choice of solution is based on  $\text{O}_2$ -carrying capacity (e.g., hemoglobin, hematocrit), cause of hypovolemic shock, accompanying disease states, degree of fluid loss, and required speed of fluid delivery.
- Most clinicians agree that crystalloids should be the initial therapy of circulatory insufficiency. Crystalloids are preferred over colloids as initial therapy for burn patients because they are less likely to cause interstitial fluid accumulation. If volume resuscitation is suboptimal following several liters of crystalloid, colloids should be considered. Some patients may require blood products to assure maintenance of  $\text{O}_2$ -carrying capacity, as well as clotting factors and platelets for blood hemostasis.

A



**FIGURE 12-1.** A. Hypovolemia protocol for adults. This protocol is not intended to replace or delay therapies such as surgical intervention or blood products for restoring oxygen-carrying capacity or hemostasis. If available, some measurements may be used in addition to those listed in the algorithm, such as mean arterial pressure or pulmonary artery catheter recordings. The latter may be used to assist in medication choices (e.g., agents with primary pressor effects may be desirable in patients with normal cardiac outputs, whereas dopamine or dobutamine may be indicated in patients with suboptimal cardiac outputs). Lower maximal doses of the medications in this algorithm should be considered when pulmonary artery catheterization is not available. Colloids that may be substituted for albumin are hetastarch 6% and dextran 40. (*continued*)

B



**FIGURE 12-1.** (Continued) *B.* Ongoing management of inadequate tissue perfusion. (CHF, congestive heart failure; LR, lactated Ringer's solution.)

## Crystalloids

- Crystalloids consist of electrolytes (e.g.,  $\text{Na}^+$ ,  $\text{Cl}^-$ ,  $\text{K}^+$ ) in water solutions, with or without dextrose. **Lactated Ringer's solution** may be preferred because it is unlikely to cause the hyperchloremic metabolic acidosis seen with infusion of large amounts of normal saline.
- Crystalloids are administered at a rate of 500 to 2,000 mL/hour, depending on the severity of the deficit, degree of ongoing fluid loss, and tolerance to infusion volume. Usually 2 to 4 L of crystalloid normalizes intravascular volume.
- Advantages of crystalloids include rapidity and ease of administration, compatibility with most drugs, absence of serum sickness, and low cost.
- The primary disadvantage is the large volume necessary to replace or augment intravascular volume. Approximately 4 L of normal saline must be infused to replace 1 L of blood loss. In addition, dilution of colloid oncotic pressure leading to pulmonary edema is more likely to follow crystalloid than colloid resuscitation.

## Colloids

- Colloids are larger molecular weight solutions (more than 30,000 daltons) that have been recommended for use in conjunction with or as replacements for crystalloid solutions. **Albumin** is a monodisperse colloid because all of its molecules are of the same molecular weight, whereas **hetastarch** and **dextran** solutions are polydisperse compounds with molecules of varying molecular weights.
- The theoretical advantage of colloids is their prolonged intravascular retention time compared to crystalloid solutions. Isotonic crystalloid solutions have substantial interstitial distribution within minutes of IV administration, but colloids remain in the intravascular space for hours or days, depending on factors such as capillary permeability. However, even with intact capillary permeability, the colloid molecules eventually leak through capillary membranes.
- **Albumin** 5% and 25% concentrations are available. It takes approximately three to four times as much lactated Ringer's or normal saline solution to yield the same volume expansion as 5% albumin solution. However, albumin is much more costly than crystalloid solutions. The 5% albumin solution is relatively iso-oncotic, whereas 25% albumin is hyperoncotic and tends to pull fluid into the compartment containing the albumin molecules. In general, 5% albumin is used for hypovolemic states. The 25% solution should not be used for acute circulatory insufficiency unless diluted with other fluids or unless it is being used in patients with excess total body water but intravascular depletion, as a means of pulling fluid into the intravascular space.
- **Hetastarch** 6% has comparable plasma expansion to 5% albumin solution but is usually less expensive, which accounts for much of its use. Hetastarch should be avoided in situations in which short-term impairments in hemostasis could have adverse consequences (e.g., cardiopulmonary bypass surgery, intracranial hemorrhage), because it may aggravate bleeding due to mechanisms such as decreased factor VIII activity.

Hetastarch may cause elevations in serum amylase concentrations but does not cause pancreatitis.

- **Dextran-40, dextran-70, and dextran-75** are available for use as plasma expanders (the number indicates the average molecular weight  $\times 1,000$ ). These solutions are not used as often as albumin or hetastarch for plasma expansion, possibly due to concerns related to aggravation of bleeding (i.e., anticoagulant actions related to inhibiting stasis of microcirculation) and anaphylaxis, which is more likely to occur with the higher molecular weight solutions.
- Colloids (especially albumin) are expensive solutions, and a large study involving almost 7,000 critically ill patients found no significant difference in 28-day mortality between patients resuscitated with either normal saline or 4% albumin. For these reasons, crystalloids should be considered first-line therapy in patients with hypovolemic shock.
- Adverse effects of colloids are generally extensions of their pharmacologic activity (e.g., fluid overload, dilutional coagulopathy). **Albumin** and **dextran** may be associated with anaphylactoid reactions or anaphylaxis. Bleeding may occur in certain patients receiving **hetastarch** and **dextran**.

### Blood Products

- **Whole blood** could be used for large volume blood loss, but most institutions use component therapy, with crystalloids or colloids used for plasma expansion.
- **Packed red blood cells** contain hemoglobin that increases the  $O_2$ -carrying capacity of blood, thereby increasing  $O_2$  delivery to tissues. This is a function not performed by crystalloids or colloids. Packed red cells are usually indicated in patients with continued deterioration after volume replacement or obvious exsanguination. The product needs to be warmed before administration, especially when used in children.
- **Fresh frozen plasma** replaces clotting factors. Although it is often overused, the product is indicated if there is ongoing hemorrhage in patients with a PT or aPTT greater than 1.5 times normal, severe hepatic disease, or other bleeding disorders.
- **Platelets** are used for bleeding due to severe thrombocytopenia (platelet counts less than  $10,000/\text{mm}^3$ ) or in patients with rapidly dropping platelet counts, as seen in massive bleeding.
- **Cryoprecipitate** and **factor VIII** are generally not indicated in acute hemorrhage but may be used once specific deficiencies have been identified.
- Risks associated with infusion of blood products include transfusion-related reactions, virus transmission (rare), hypocalcemia resulting from added citrate, elevations in serum potassium and phosphorus concentrations from use of stored blood that has hemolyzed, increased blood viscosity from supranormal hematocrit elevations, and hypothermia from failure to appropriately warm solutions before administration.

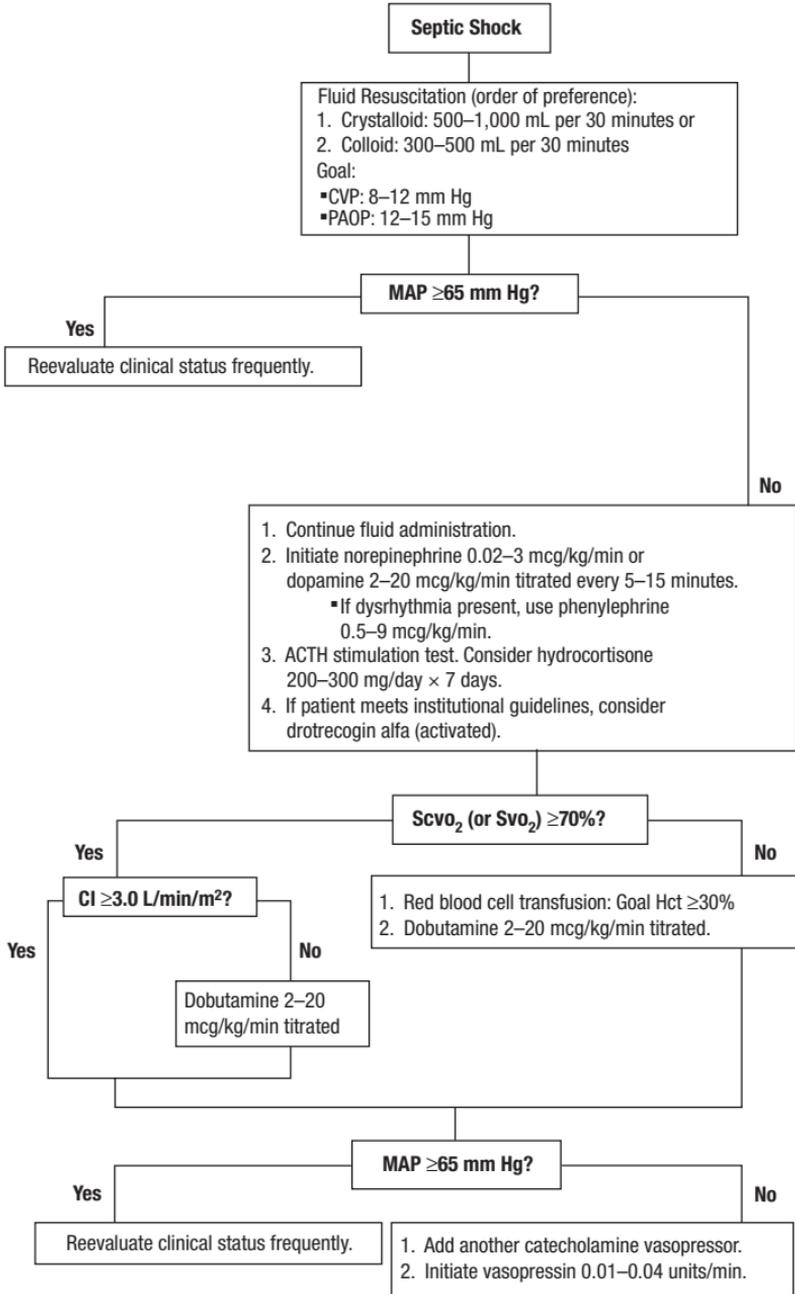
### PHARMACOLOGIC THERAPY FOR SHOCK

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- Inotropic agents and vasopressors are generally not indicated in the initial treatment of hypovolemic shock (assuming that fluid therapy is adequate),

as the body's normal response is to increase CO and constrict blood vessels to maintain BP. However, once the cause of circulatory insufficiency has been stopped or treated and fluids have been optimized, medications may be needed in patients who continue to have signs and symptoms of inadequate tissue perfusion. Pressor agents such as **norepinephrine** and **high-dose dopamine** should be avoided if possible because they may increase BP at the expense of peripheral tissue ischemia. In patients with unstable BP despite massive fluid replacement and increasing interstitial fluid accumulation, inotropic agents such as **dobutamine** are preferred if BP is adequate (SBP 90 mm Hg or greater) because they should not aggravate the existing vasoconstriction. When pressure cannot be maintained with inotropes, or when inotropes with vasodilatory properties cannot be used due to concerns about inadequate BP, pressors may be required as a last resort.

- The choice of vasopressor or inotropic agent in septic shock should be made according to the needs of the patient. An algorithm for the use of fluid resuscitation and these pharmacologic agents in septic shock is shown in Fig. 12-2. The traditional approach is to start with **dopamine**, then **norepinephrine**; **dobutamine** is added for low CO states, and occasionally **epinephrine** and **phenylephrine** are used when necessary. However, recent observations of improved outcomes with norepinephrine and decreased regional perfusion with dopamine are calling into question the use of dopamine as a first-line agent.
- The receptor selectivities of vasopressors and inotropes are listed in Table 12-2. In general, these drugs act rapidly with short durations of action and are given as continuous infusions. Potent vasoconstrictors such as norepinephrine and phenylephrine should be given through central veins due to the possibility of extravasation and tissue damage with peripheral administration. Careful monitoring and calculation of infusion rates are advised because dosing adjustments are made frequently and varying admixture concentrations are used in volume-restricted patients.
- **Dopamine** is often the initial vasopressor used in septic shock because it increases BP by increasing myocardial contractility and vasoconstriction. Although dopamine has been reported to have dose-related receptor activity at dopamine,  $\beta_1$ , and  $\alpha_1$  receptors, this dose-response relationship has not been confirmed in critically ill patients. In patients with septic shock, there is overlap of hemodynamic effects with doses as low as 3 mcg/kg/min. Doses of 5 to 10 mcg/kg/min are initiated to improve MAP. In septic shock, these doses increase CI by improving ventricular contractility, heart rate, MAP, and systemic vascular resistance (SVR). The clinical utility of dopamine in septic shock is limited because large doses are frequently necessary to maintain CO and MAP. At doses above 20 mcg/kg/min, there is limited further improvement in cardiac performance and regional hemodynamics. The use of dopamine is also hampered frequently by tachycardia and tachydysrhythmias. Other adverse effects limiting its use in septic shock include increases in PAOP, pulmonary shunting, and decreases in PaO<sub>2</sub>. Dopamine should be used with caution in patients with elevated preload, as it may worsen pulmonary edema. Low doses of dopamine (1 to 3 mcg/kg/min) once were advocated for use in patients with septic shock receiving vasopressors with or



**FIGURE 12-2.** Algorithmic approach to the use of vasopressors and inotropes in septic shock. Approach is intended to be used in conjunction with clinical judgment, hemodynamic monitoring parameters, and therapy end points. (ACTH, adrenocorticotropic hormone; CI, cardiac index; CVP, central venous pressure; Hct, hematocrit; MAP, mean arterial pressure; PAOP, pulmonary artery occlusive pressure; ScvO<sub>2</sub>, central venous oxygen saturation; SvO<sub>2</sub>, mixed venous oxygen saturation.)

**TABLE 12-2** Receptor Pharmacology of Selected Inotropic and Vasopressor Agents Used in Septic Shock<sup>a</sup>

Agent	$\alpha_1$	$\alpha_2$	$\beta_1$	$\beta_2$	D
Dobutamine (0.5–4 mg/mL D <sub>5</sub> W or NS)					
2–10 mcg/kg/min	+	0	++++	++	0
>10–20 mcg/kg/min	++	0	++++	+++	0
Dopamine (0.8–3.2 mg/mL D <sub>5</sub> W or NS)					
1–3 mcg/kg/min	0	0	+	0	++++
3–10 mcg/kg/min	0/+	0	++++	++	++++
>10–20 mcg/kg/min	+++	0	++++	+	0
Epinephrine (0.008–0.016 mg/mL D <sub>5</sub> W or NS)					
0.01–0.05 mcg/kg/min	++	++	++++	+++	0
>0.05–3 mcg/kg/min	++++	++++	+++	+	0
Norepinephrine (0.016–0.064 mg/mL D <sub>5</sub> W)					
0.02–3 mcg/kg/min	+++	+++	+++	+ / ++	0
Phenylephrine (0.1–0.4 mg/mL D <sub>5</sub> W or NS)					
0.5–9 mcg/kg/min	+++	+	+	0	0

<sup>a</sup>Activity ranges from no activity (0) to maximal (++++) activity.

D, dopamine; D<sub>5</sub>W, dextrose 5% in water; NS, normal saline.

without oliguria. The goal of therapy is to minimize or reverse renal vasoconstriction caused by other pressors, to prevent oliguric renal failure, or to convert it to nonoliguric renal failure. Based on recent clinical trial results, low-dose dopamine for treatment or prevention of acute renal failure cannot be justified and should be eliminated from routine clinical use.

- **Norepinephrine** is a combined  $\alpha$ - and  $\beta$ -agonist, but it primarily produces vasoconstriction, thereby increasing SVR. It generally produces either no change or a slight decrease in CO. Norepinephrine is initiated after vasopressor doses of dopamine (4 to 20 mcg/kg/min), alone or in combination with dobutamine (5 mcg/kg/min), fail to achieve the desired goals. Doses of dopamine and dobutamine are kept constant or stopped; in some instances, dopamine is kept at low doses for purported renal protection. Norepinephrine, 0.01 to 2 mcg/kg/min, reliably and predictably improves hemodynamic parameters to normal or supranormal values in most patients with septic shock. Recent data suggest that norepinephrine should potentially be repositioned as the vasopressor of choice in septic shock.
- **Dobutamine** is primarily a selective  $\beta_1$ -agonist with mild  $\beta_2$  and vascular  $\alpha_1$  activity, resulting in strong positive inotropic activity without concomitant vasoconstriction. Dobutamine produces a larger increase in CO and is less arrhythmogenic than dopamine. Clinically,  $\beta_2$ -induced vasodilation and the increased myocardial contractility with subsequent reflex reduction in sympathetic tone lead to a decrease in SVR. Even though dobutamine is optimally used for low CO states with high filling pressures or in cardiogenic shock, vasopressors may be needed to counteract arterial vasodilation. The addition of dobutamine (held constant at 5 mcg/kg/min) to epinephrine regimens can improve gastric mucosal perfusion as measured by improvements in pHi, arterial lactate concentrations, and PCO<sub>2</sub> gap. Dobutamine should be started with doses ranging from 2.5 to 5 mcg/kg/min. Doses above 5 mcg/kg/min provide limited beneficial effects on

O<sub>2</sub> transport values and hemodynamics and may increase adverse cardiac effects. Infusion rates should be guided by clinical end points and mixed venous oxygen saturation/central venous oxygen saturation. Decreases in partial pressure of O<sub>2</sub>, as well as myocardial adverse effects such as tachycardia, ischemic changes on ECG, tachydysrhythmias, and hypotension, are seen.

- **Phenylephrine** is a pure  $\alpha_1$ -agonist and is thought to increase BP through vasoconstriction. It may also increase contractility and CO. Phenylephrine may be beneficial in septic shock because of its selective  $\alpha$ -agonism, vascular effects, rapid onset, and short duration. Phenylephrine may be a useful alternative in patients who cannot tolerate the tachycardia or tachydysrhythmias with use of dopamine or norepinephrine, in patients with known underlying myocardial dysfunction, and in patients refractory to dopamine or norepinephrine (because of  $\beta$ -receptor desensitization). It is generally initiated at dosages of 0.5 mcg/kg/min and may be titrated every 5 to 15 minutes to desired effects. Adverse effects such as tachydysrhythmias are infrequent when it is used as a single agent or with higher doses.
- **Epinephrine** has combined  $\alpha$ - and  $\beta$ -agonist effects and has traditionally been reserved as the vasopressor of last resort because of reports of peripheral vasoconstriction, particularly in the splanchnic and renal beds. At the high infusion rates used in septic shock,  $\alpha$ -adrenergic effects are predominantly seen, and SVR and MAP are increased. It is an acceptable single agent in septic shock due to its combined vasoconstrictor and inotropic effects. Epinephrine may be particularly useful when used earlier in the course of septic shock in young patients and those without known cardiac abnormalities. Infusion rates of 0.04 to 1 mcg/kg/min alone increase hemodynamic and O<sub>2</sub> transport variables to supranormal levels without adverse effects in patients without coronary heart disease. Large doses (0.5 to 1 mcg/kg/min) may be required when epinephrine is added to other agents. Smaller doses (0.1 to 0.5 mcg/kg/min) are effective if dobutamine and dopamine infusions are kept constant. Although DO<sub>2</sub> increases mainly as a function of consistent increases in CI (and a more variable increase in SVR), VO<sub>2</sub> may not increase and the oxygen extraction ratio may fall. Lactate concentrations may rise during the first few hours of epinephrine therapy but normalize over the ensuing 24 hours in survivors. Caution must be used before considering epinephrine for managing hypoperfusion in hypodynamic patients with coronary artery disease to avoid ischemia, chest pain, and myocardial infarction.
- **Vasopressin** causes vasoconstrictive effects that, unlike adrenergic receptor agonists, are preserved during hypoxia and severe acidosis. It also causes vasodilation in the pulmonary, coronary, and selected renal vascular beds that may reduce pulmonary artery pressure and preserve cardiac and renal function. However, based on available evidence, vasopressin is not recommended as a replacement for norepinephrine or dopamine in patients with septic shock but may be considered in patients who are refractory to catecholamine vasopressors despite adequate fluid resuscitation. If used, the dose should not exceed 0.01 to 0.04 units/min.
- **Corticosteroids** were shown in a metaanalysis to improve hemodynamics and survival and reduce the duration of vasopressor support in septic shock.

Corticosteroids can be initiated in septic shock when adrenal insufficiency is present or when weaning of vasopressor therapy proves futile. A daily dose equivalent to 200 to 300 mg hydrocortisone should be continued for 7 days. Adverse events are few because of the short duration of therapy.

## EVALUATION OF THERAPEUTIC OUTCOMES

- The initial monitoring of a patient with suspected volume depletion should include vital signs, urine output, mental status, and physical examination.
- Placement of a CVP line provides a useful (although indirect and insensitive) estimate of the relationship between increased right atrial pressure and CO.
- The indications for pulmonary artery catheterization are controversial. Because there is a lack of a well-defined outcome of data associated with this procedure, its use is presently best reserved for complicated cases of shock not responding to conventional fluid and medication therapies. Complications related to catheter insertion, maintenance, and removal include damage to vessels and organs during insertion, arrhythmias, infections, and thromboembolic damage.
- Laboratory tests indicated for the ongoing monitoring of shock include electrolytes and renal function tests (blood urea nitrogen, serum creatinine); complete blood count to assess possible infection, O<sub>2</sub>-carrying capacity of the blood, and ongoing bleeding; PT and aPTT to assess clotting ability; and lactate concentration and base deficit to detect inadequate tissue perfusion.
- Cardiovascular and respiratory parameters should be monitored continuously (see Table 12-1). Trends, rather than specific CVP or PAOP numbers, should be monitored because of interpatient variability in response.
- Successful fluid resuscitation should increase SBP (greater than 90 mm Hg), CI (greater than 2.2 L/min/m<sup>2</sup>), and urine output (0.5 to 1 mL/kg/hour) while decreasing SVR to the normal range. MAP greater than 60 mm Hg should be achieved to ensure adequate cerebral and coronary perfusion pressure.
- Intravascular volume overload is characterized by high filling pressures (CVP greater than 12 to 15 mm Hg, PAOP greater than 20 to 24 mm Hg) and decreased CO (less than 3.5 L/min). If volume overload occurs, furosemide, 20 to 40 mg, should be administered by slow IV push to produce rapid diuresis of intravascular volume and “unload” the heart through venous dilation.
- Coagulation problems are primarily associated with low levels of clotting factors in stored blood as well as dilution of endogenous clotting factors and platelets following administration of the blood. As a result, a coagulation panel (PT, international normalized ratio, aPTT) should be checked in patients undergoing replacement of 50% to 100% of blood volume in 12 to 24 hours.

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See Chap. 25, *Use of Vasopressors and Inotropes in the Pharmacotherapy of Shock*, authored by Robert MacLaren, Maria I. Rudis, and Joseph F. Dasta, and Chap. 26, *Hypovolemic Shock*, authored by Brian L. Erstad, for a more detailed discussion of this topic.

**DEFINITION**

- *Stroke* is a term used to describe an abrupt onset of focal neurologic deficit that lasts at least 24 hours and is presumed to be of vascular origin. Stroke can be either ischemic or hemorrhagic in origin. Transient ischemic attacks (TIAs) are focal ischemic neurologic deficits lasting less than 24 hours and usually less than 30 minutes.

**PATHOPHYSIOLOGY****RISK FACTORS FOR STROKE**

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- Nonmodifiable risk factors for stroke include increased age, male gender, race (African American, Asian, Hispanic), family history of stroke, and low birth weight.
- The major modifiable risk factors include hypertension and cardiac disease (especially atrial fibrillation).
- Other major risk factors include diabetes mellitus, dyslipidemia, and cigarette smoking.

**ISCHEMIC STROKE**

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- Ischemic strokes account for 88% of all strokes and are due either to local thrombus formation or to emboli that occlude a cerebral artery. Cerebral atherosclerosis is a causative factor in most cases of ischemic stroke, although 30% are of unknown etiology. Emboli can arise either from intra- or extracranial arteries. Twenty percent of embolic strokes arise from the heart.
- In carotid atherosclerosis, plaques may rupture, resulting in collagen exposure, platelet aggregation, and thrombus formation. The clot may cause local occlusion or may dislodge and travel distally, eventually occluding a cerebral vessel.
- In the case of cardiogenic embolism, stasis of blood flow in the atria or ventricles leads to formation of local clots that can dislodge and travel through the aorta to the cerebral circulation.
- The final result of both thrombus formation and embolism is arterial occlusion, decreasing cerebral blood flow and causing ischemia and ultimately infarction distal to the occlusion.

**HEMORRHAGIC STROKE**

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- Hemorrhagic strokes account for 12% of strokes and include subarachnoid hemorrhage, intracerebral hemorrhage, and subdural hematomas. Subarachnoid hemorrhage may result from trauma or rupture of an intracranial aneurysm or arteriovenous malformation. Intracerebral hemorrhage occurs when a ruptured blood vessel within the brain parenchyma causes formation of a hematoma. Subdural hematomas are most often caused by trauma.

- The presence of blood in the brain parenchyma causes damage to surrounding tissue through a mass effect and the neurotoxicity of blood components and their degradation products. Compression of tissue surrounding hematomas may lead to secondary ischemia. Much of the early mortality of hemorrhagic stroke is due to an abrupt increase in intracranial pressure that can lead to herniation and death.

## CLINICAL PRESENTATION

- The patient may not be able to give a reliable history because of cognitive or language deficits. This information may need to be obtained from family members or other witnesses.
- The patient may experience weakness on one side of the body, inability to speak, loss of vision, vertigo, or falling. Ischemic stroke is not usually painful, but headache may occur and may be severe in hemorrhagic stroke.
- Patients usually have multiple signs of neurologic dysfunction on physical examination. The specific deficits observed depend upon the area of the brain involved. Hemi- or monoparesis and hemisensory deficits are common. Patients with posterior circulation involvement may present with vertigo and diplopia. Anterior circulation strokes commonly result in aphasia. Patients may also experience dysarthria, visual field defects, and altered levels of consciousness.

## DIAGNOSIS

- Laboratory tests for hypercoagulable states should be done only when the cause of the stroke cannot be determined based on the presence of well-known risk factors. Protein C, protein S, and antithrombin III are best measured in steady state rather than in the acute stage. Antiphospholipid antibodies are of higher yield but should be reserved for patients aged less than 50 years and those who have had multiple venous or arterial thrombotic events or livedo reticularis.
- Computed tomography (CT) head scan will reveal an area of hyperintensity (white) in an area of hemorrhage and will be normal or hypointense (dark) in an area of infarction. The area of infarction may not be visible on CT scan for 24 hours (and rarely longer).
- Magnetic resonance imaging of the head will reveal areas of ischemia with higher resolution and earlier than the CT scan. Diffusion-weighted imaging will reveal an evolving infarct within minutes.
- Carotid Doppler studies will determine whether there is a high degree of stenosis in the carotid arteries.
- The electrocardiogram will determine whether atrial fibrillation is present.
- A transthoracic echocardiogram can detect valve or wall motion abnormalities that are sources of emboli to the brain.
- A transesophageal echocardiogram is a more sensitive test for left atrial thrombus. It is also effective in examining the aortic arch for atheroma, another potential source of emboli.

- Transcranial Doppler can determine the presence of intracranial sclerosis (e.g., middle cerebral artery stenosis).

## DESIRED OUTCOME

- The goals of treatment for acute stroke are to: (1) reduce the ongoing neurologic injury and decrease mortality and long-term disability; (2) prevent complications secondary to immobility and neurologic dysfunction; and (3) prevent stroke recurrence.

## TREATMENT

### GENERAL APPROACH

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- The initial approach is to ensure adequate respiratory and cardiac support and to determine quickly whether the lesion is ischemic or hemorrhagic based on a CT scan.
- Ischemic stroke patients presenting within hours of symptom onset should be evaluated for reperfusion therapy.
- Elevated blood pressure should remain untreated in the acute period (first 7 days) after ischemic stroke because of the risk of decreasing cerebral blood flow and worsening symptoms. The pressure should be lowered if it exceeds 220/120 mm Hg or there is evidence of aortic dissection, acute myocardial infarction, pulmonary edema, or hypertensive encephalopathy. If blood pressure is treated in the acute phase, short-acting parenteral agents (e.g., labetalol, nicardipine, nitroprusside) are preferred.
- Patients with hemorrhagic stroke should be assessed to determine whether they are candidates for surgical intervention via an endovascular or craniotomy approach.
- After the hyperacute phase has passed, attention is focused on preventing progressive deficits, minimizing complications, and instituting appropriate secondary prevention strategies.

### NONPHARMACOLOGIC THERAPY

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- In acute ischemic stroke, surgical interventions are limited. However, surgical decompression can be lifesaving in cases of significant swelling associated with cerebral infarction. An interdisciplinary approach to stroke care that includes early rehabilitation is very effective in reducing long-term disability. In secondary prevention, carotid endarterectomy is effective in reducing stroke incidence and recurrence in appropriate patients. Carotid stenting may be effective in reducing recurrent stroke risk in patients at high risk of complications during endarterectomy.
- In subarachnoid hemorrhage due to a ruptured intracranial aneurysm or arteriovenous malformation, surgical intervention to clip or ablate the vascular abnormality substantially reduces mortality from rebleeding. The benefits of surgery are less well documented in cases of primary intracerebral hemorrhage. In patients with intracerebral hematomas, insertion of an intraventricular drain with monitoring of intracranial pressure is

commonly performed. Surgical decompression of a hematoma is controversial except when it is a last resort in a life-threatening situation.

## PHARMACOLOGIC THERAPY OF ISCHEMIC STROKE

- The American Heart Association/American Stroke Association (AHA/ASA) Stroke Council guidelines for the management of acute ischemic stroke give grade A recommendations (i.e., evidence supported by data from randomized trials) to only two pharmacologic therapies: (1) IV tissue plasminogen activator (alteplase) within 3 hours of onset; and (2) aspirin within 48 hours of onset. Evidence-based recommendations for pharmacotherapy of ischemic stroke are given in Table 13-1.
- **Alteplase** initiated within 3 hours of symptom onset has been shown to reduce the ultimate disability due to ischemic stroke. A head CT scan must be obtained to rule out hemorrhage before beginning therapy. The patient must also meet specific inclusion criteria and no exclusionary criteria (Table 13-2). The dose is 0.9 mg/kg (maximum 90 mg) infused IV over 1 hour after a bolus of 10% of the total dose given over 1 minute. Anticoagulant and

**TABLE 13-1** Recommendations for Pharmacotherapy of Ischemic Stroke

	<b>Recommendation</b>	<b>Recommendation Grades<sup>a</sup></b>
<b>Acute treatment</b>	Alteplase 0.9 mg/kg IV (maximum 90 mg) over 1 hour in selected patients within 3 hours of onset	Class I, Level A
	Aspirin 160–325 mg daily started within 48 hours of onset	Class I, Level A
<b>Secondary prevention</b>		
Noncardioembolic	Antiplatelet therapy	Class I, Level A
	Aspirin 50–325 mg daily	Class IIa, Level A
	Clopidogrel 75 mg daily	Class IIb, Level B
	Aspirin 25 mg + extended-release dipyridamole 200 mg twice daily	Class IIa, Level A
Cardioembolic (esp. atrial fibrillation)	Warfarin (INR = 2.5)	Class I, Level A
All patients	Antihypertensive treatment	Class I, Level A
Previously hypertensive	ACE inhibitor + diuretic	Class I, Level A
Previously normotensive	ACE inhibitor + diuretic	Class IIa, Level B
Dyslipidemic	Statin	Class I, Level A
Normal lipids	Statin	Class IIa, Level B

ACE, angiotensin-converting enzyme; INR, international normalized ratio.

<sup>a</sup>American Stroke Association Evidence Grading System.

Recommendation Class:

I = Conditions for which there is evidence or general agreement that a procedure or treatment is useful and effective.

II = Conditions for which there is conflicting evidence or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.

IIa = Weight of evidence/opinion is in favor of usefulness or efficacy.

IIb = Usefulness/efficacy is less well established by evidence/opinion.

III = Conditions for which there is evidence or general agreement that a procedure or treatment is not useful/effective and in some cases may be harmful.

Level of Evidence:

A = Data derived from multiple randomized clinical trials.

B = Data derived from a single randomized trial or nonrandomized studies.

C = Expert consensus or case studies.

**TABLE 13-2** Inclusion and Exclusion Criteria for Alteplase Use in Acute Ischemic Stroke**Inclusion Criteria (all YES boxes must be checked before treatment)****YES**

- Age 18 years or older
- Clinical diagnosis of ischemic stroke causing a measurable neurologic deficit
- Time of symptom onset well established to be less than 180 minutes before treatment would begin

**Exclusion Criteria (all NO boxes must be checked before treatment)****NO**

- Evidence of intracranial hemorrhage on noncontrast head CT
- Only minor or rapidly improving stroke symptoms
- High clinical suspicion of subarachnoid hemorrhage even with normal CT
- Active internal bleeding (e.g., GI/GU bleeding within 21 days)
- Known bleeding diathesis, including but not limited to platelet count  $<100,000/\text{mm}^3$
- Patient has received heparin within 48 hours and had an elevated aPTT
- Recent use of anticoagulant (e.g., warfarin) and elevated PT ( $>15$  seconds)/INR
- Intracranial surgery, serious head trauma, or previous stroke within 3 months
- Major surgery or serious trauma within 14 days
- Recent arterial puncture at noncompressible site
- Lumbar puncture within 7 days
- History of intracranial hemorrhage, arteriovenous malformation, or aneurysm
- Witnessed seizure at stroke onset
- Recent acute myocardial infarction
- SBP  $>185$  mm Hg or DBP  $>110$  mm Hg at time of treatment

aPTT, activated partial thromboplastin time; CT, computed tomography; DBP, diastolic blood pressure; GU, genitourinary; INR, international normalized ratio; PT, prothrombin time; SBP, systolic blood pressure.

antiplatelet therapy should be avoided for 24 hours, and the patient should be monitored closely for hemorrhage.

- **Aspirin** 50 to 325 mg/day started between 24 and 48 hours after completion of alteplase has also been shown to reduce long-term death and disability.
- The AHA/ASA guidelines recommend that antiplatelet therapy as the cornerstone of antithrombotic therapy for the secondary prevention of ischemic stroke and should be used in noncardioembolic strokes. **Aspirin, clopidogrel, and extended-release dipyridamole plus aspirin** are all considered first-line antiplatelet agents (see Table 13-1). The combination of aspirin and clopidogrel can only be recommended in patients with ischemic stroke and a recent history of myocardial infarction or coronary stent placement and then only with ultra-low-dose aspirin to minimize bleeding risk.
- **Warfarin** is the antithrombotic agent of first choice for secondary prevention in patients with atrial fibrillation and a presumed cardiac source of embolism.
- Elevated blood pressure is common after ischemic stroke, and its treatment is associated with a decreased risk of stroke recurrence. The Joint National Committee and AHA/ASA guidelines recommend an **angiotensin-converting enzyme inhibitor and a diuretic** for reduction of blood pressure in patients with stroke or TIA after the acute period (first 7 days). **Angiotensin II receptor blockers** have also been shown to reduce the risk of stroke and should be considered in patients unable to tolerate angiotensin-converting enzyme inhibitors after acute ischemic stroke.
- The National Cholesterol Education Program considers ischemic stroke or TIA to be a coronary risk equivalent and recommends the use of statins in

ischemic stroke patients to achieve a low-density lipoprotein cholesterol concentration of less than 100 mg/dL.

- **Low-molecular-weight heparin** or **low-dose subcutaneous unfractionated heparin** (5,000 units twice daily) is recommended for prevention of deep venous thrombosis in hospitalized patients with decreased mobility due to stroke and should be used in all but the most minor strokes.
- The use of **full-dose unfractionated heparin** in the acute stroke period has not been proven to positively affect stroke outcome, and it significantly increases the risk of intracerebral hemorrhage. Trials of low-molecular-weight heparins and heparinoids have been largely negative and do not support their routine use in stroke patients.

## PHARMACOLOGIC THERAPY OF HEMORRHAGIC STROKE

- There are currently no standard pharmacologic strategies for treating intracerebral hemorrhage. Medical guidelines for managing blood pressure, increased intracranial pressure, and other medical complications in acutely ill patients in neurointensive care units should be followed.
- Subarachnoid hemorrhage due to aneurysm rupture is associated with a high incidence of delayed cerebral ischemia in the 2 weeks after the bleeding episode. Vasospasm of the cerebral vasculature is thought to be responsible for the delayed ischemia and occurs between 4 and 21 days after the bleed. The calcium channel blocker **nimodipine** is recommended to reduce the incidence and severity of neurologic deficits resulting from delayed ischemia. Nimodipine 60 mg every 4 hours should be initiated on diagnosis and continued for 21 days in all subarachnoid hemorrhage patients. If hypotension occurs, it can be managed by reducing the dosing interval to 30 mg

**TABLE 13-3** Monitoring Hospitalized Acute Stroke Patients

	Treatment	Parameter(s)	Frequency
Ischemic stroke	Alteplase	BP, neurologic function, bleeding	Every 15 minutes $\times$ 1 hour; every 0.5 hour $\times$ 6 hours; every 1 hour $\times$ 17 hours; every shift after
	Aspirin	Bleeding	Daily
	Clopidogrel	Bleeding	Daily
	ERDP/ASA	Headache, bleeding	Daily
	Warfarin	Bleeding, INR, Hb/Hct	INR daily $\times$ 3 days; weekly until stable; monthly
Hemorrhagic stroke	Nimodipine (for SAH)	BP, neurologic function, ICP BP, neurologic function, fluid status	Every 2 hours in ICU Every 2 hours in ICU
All patients		Temperature, CBC	Temp. every 8 hours; CBC daily
		Pain (calf or chest)	Every 8 hours
		Electrolytes and ECG	Up to daily
	Heparins for DVT prophylaxis	Bleeding, platelets	Bleeding daily, platelets if suspected thrombocytopenia

BP, blood pressure; CBC, complete blood count; DVT, deep vein thrombosis; ECG, electrocardiogram; ERDP/ASA, extended-release dipyridamole plus aspirin; Hb, hemoglobin; Hct, hematocrit; ICP, intracranial pressure; ICU, intensive care unit; INR, international normalized ratio; SAH, subarachnoid hemorrhage.

every 2 hours (same daily dose), reducing the total daily dose (30 mg every 4 hours), and maintaining intravascular volume and pressor therapy.

## EVALUATION OF THERAPEUTIC OUTCOMES

- Patients with acute stroke should be monitored intensely for the development of neurologic worsening, complications, and adverse effects from treatments. The most common reasons for clinical deterioration in stroke patients are: (1) extension of the original lesion in the brain; (2) development of cerebral edema and raised intracranial pressure; (3) hypertensive emergency; (4) infection (e.g., urinary and respiratory tract); (5) venous thromboembolism; (6) electrolyte abnormalities and rhythm disturbances; and (7) recurrent stroke. The approach to monitoring stroke patients is summarized in Table 13-3.

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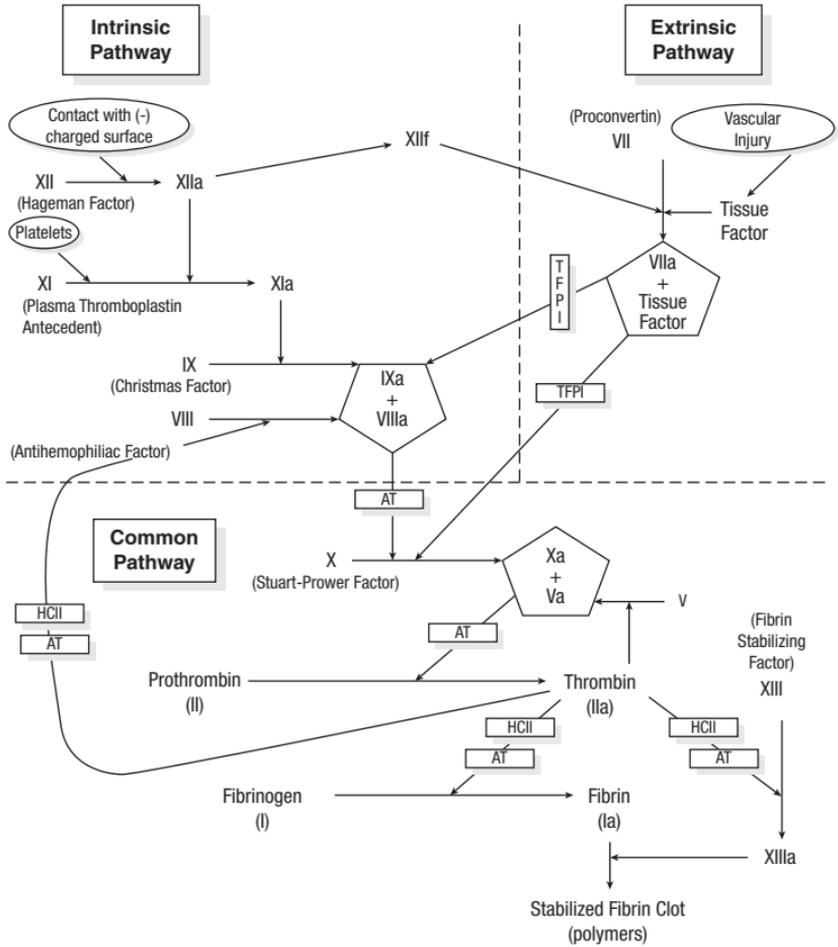
*See Chap. 22, Stroke, authored by Susan C. Fagan and David C. Hess, for a more detailed discussion of this topic.*

## DEFINITION

- Venous thromboembolism (VTE) results from clot formation in the venous circulation and is manifested as deep vein thrombosis (DVT) and pulmonary embolism (PE). A DVT is a thrombus composed of cellular material (red and white blood cells, platelets) bound together with fibrin strands. A PE is a thrombus that arises from the systemic circulation and lodges in the pulmonary artery or one of its branches, causing complete or partial obstruction of pulmonary blood flow.

## PATHOPHYSIOLOGY

- The coagulation cascade is a stepwise series of enzymatic reactions that results in the formation of a fibrin mesh (Fig. 14-1). It can be triggered through either the intrinsic or extrinsic pathways. The intrinsic pathway is activated when negatively charged surfaces in contact with the blood activate factor XII, and activated platelets convert factor XI. The extrinsic pathway is activated when damaged vascular tissue releases tissue thromboplastin. Vascular injury also exposes the subendothelium, causing adherence, activation, and aggregation of platelets. The intrinsic and extrinsic pathways meet at a common point with the activation of factor X. With its partner, factor Va, factor Xa converts prothrombin (II) to thrombin (IIa), which then cleaves fibrinogen-forming fibrin monomers. Factor XIII covalently bonds fibrin strands together. The fibrinolytic protein plasmin ultimately degrades the fibrin mesh into soluble end products known as fibrin split products or fibrin degradation products.
- Three primary components—venous stasis, vascular injury, and hypercoagulability (Virchow's triad)—play a role in the development of a pathogenic thrombus.
- Venous stasis is slowed blood flow in the deep veins of the legs resulting from damage to venous valves, vessel obstruction, prolonged periods of immobility, or increased blood viscosity. Conditions associated with venous stasis include major medical illness (e.g., heart failure, myocardial infarction), major surgery, paralysis (e.g., stroke, spinal cord injury), polycythemia vera, obesity, or varicose veins.
- Vascular injury may result from major orthopedic surgery (e.g., knee and hip replacement), trauma (especially fractures of the pelvis, hip, or leg), or indwelling venous catheters.
- Hypercoagulable states include malignancy; activated protein C resistance; deficiency of protein C, protein S, or antithrombin; factor VIII or XI excess; antiphospholipid antibodies; and other situations. Estrogens and selective estrogen receptor modulators have been linked to venous thrombosis, perhaps due in part to increased serum clotting factor concentrations.
- Although a thrombus can form in any part of the venous circulation, the majority of thrombi begin in the lower extremities. Once formed, a venous



**FIGURE 14-1.** Coagulation cascade. (AT, antithrombin; HCI, heparin cofactor II; TFPI, tissue factor pathway inhibitor.)

thrombus may: (1) remain asymptomatic; (2) lyse spontaneously; (3) obstruct the venous circulation; (4) propagate into more proximal veins; (5) embolize; or (6) act in any combination of these ways. Even asymptomatic patients may experience long-term consequences, such as the postthrombotic syndrome and recurrent VTE.

## CLINICAL PRESENTATION

- Most patients with VTE never develop symptoms from the acute event.
- Symptoms of DVT include unilateral leg swelling, pain, tenderness, erythema, and warmth. Physical signs may include a palpable cord and a positive Homans' sign.
- Postthrombotic syndrome (a long-term complication of DVT caused by damage to venous valves) may produce chronic lower extremity swelling, pain, tenderness, skin discoloration, and ulceration.

- Symptoms of PE include dyspnea, tachypnea, pleuritic chest pain, tachycardia, palpitations, cough, diaphoresis, and hemoptysis. Cardiovascular collapse, characterized by cyanosis, shock, and oliguria, is an ominous sign.

## DIAGNOSIS

- Assessment of the patient's status should focus on the search for risk factors (e.g., increased age, major surgery, previous VTE, trauma, malignancy, hypercoagulable states, and drug therapy). Signs and symptoms of DVT are nonspecific, and objective tests are required to confirm or exclude the diagnosis.
- Radiographic contrast studies are the most accurate and reliable method for diagnosis of VTE. Contrast venography allows visualization of the entire venous system in the lower extremity and abdomen. Pulmonary angiography allows visualization of the pulmonary arteries. The diagnosis of VTE can be made if there is a persistent intraluminal filling defect on multiple x-ray films.
- Because contrast studies are expensive, invasive, and technically difficult to perform and evaluate, noninvasive tests (e.g., ultrasonography, computed tomography scans, and the ventilation-perfusion scan) are used frequently for the initial evaluation of patients with suspected VTE.
- D-dimer is a degradation product of fibrin blood clots, and levels obtained by a simple blood test are substantially elevated in patients with acute thrombosis. Although the D-dimer test is a very sensitive marker of clot formation, elevated levels can result from a variety of other conditions (e.g., recent surgery or trauma, pregnancy, and cancer). Therefore, a negative test can help exclude the diagnosis of VTE, but a positive test cannot confirm the diagnosis.

## DESIRED OUTCOME

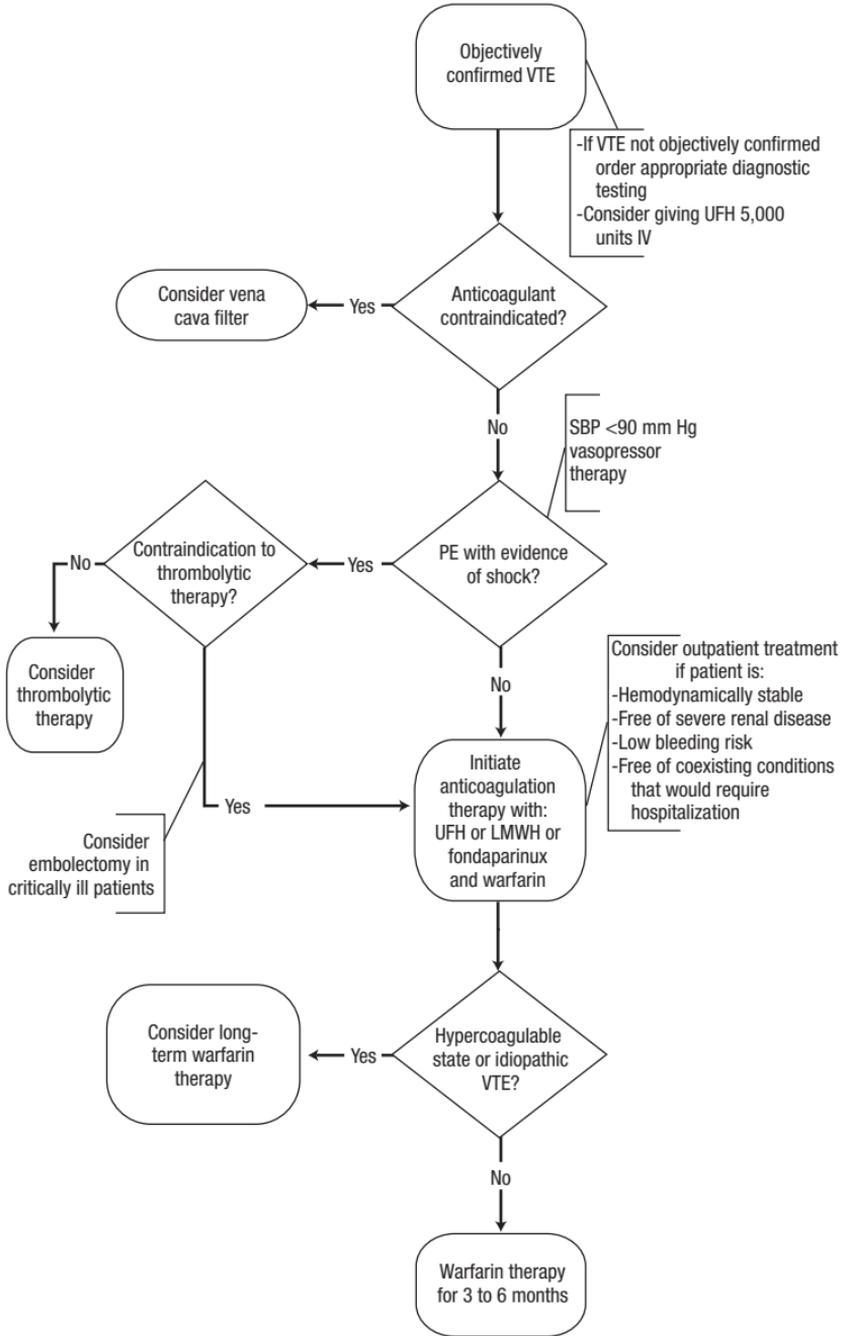
- The objectives of treating VTE are to prevent the development of PE and the postthrombotic syndrome, to reduce morbidity and mortality from the acute event, and to minimize adverse effects and cost of treatment.

## TREATMENT

(Fig. 14-2 and Table 14-1)

### UNFRACTIONATED HEPARIN

- **Unfractionated heparin (UFH)** is a heterogeneous mixture of sulfated glycosaminoglycans of variable lengths and pharmacologic properties. The molecular weight of these molecules ranges from 3,000 to 30,000 daltons (mean 15,000 daltons).
- The anticoagulant effect of UFH is mediated through a specific pentasaccharide sequence on the heparin molecule that binds to antithrombin, provoking a conformational change. The UFH-antithrombin complex is 100 to 1,000 times more potent as an anticoagulant than antithrombin alone.



**FIGURE 14-2.** Treatment of venous thromboembolism (VTE). (LMWH, low-molecular-weight heparin; PE, pulmonary embolism; SBP, systolic blood pressure; UFH, unfractionated heparin.)

**TABLE 14-1** Consensus Guidelines for Venous Thromboembolism Treatment

	<b>Recommendation</b>	<b>Grade<sup>a</sup></b>
Acute anticoagulation	Acute treatment of DVT or PE should be with LMWH, fondaparinux, intravenous UFH, or adjusted-dose subcutaneous UFH	1A
	The dose of UFH should be sufficient to prolong the aPTT to a range that corresponds to a plasma heparin level of 0.2 to 0.4 international units/mL by protamine titration or an anti-Xa level of 0.3 to 0.6 international units/mL	1C+
	LMWH and fondaparinux are preferred over UFH	2B
Duration of acute treatment	An LMWH is preferred in patients with cancer	1A
	Treatment with UFH, LMWH, or fondaparinux should be overlapped with warfarin for at least 5 days and can be stopped when the INR is >2.0; most patients should have warfarin started at the same time as UFH, LMWH, or fondaparinux	1A
	Patients with cancer should be treated with an LMWH for at least 6 months	1A
Long-term anticoagulation	A longer period of heparin therapy (approximately 10 days) is recommended for massive PE or severe iliofemoral thrombosis	1C
	Oral anticoagulation therapy (target INR 2.5, range: 2.0 to 3.0) should be continued for at least 3 months; if oral anticoagulation therapy is contraindicated (e.g., pregnancy), a treatment dose of LMWH or adjusted-dose UFH should be used	1A
	Patients with an idiopathic VTE, an inherited disorder of hypercoagulability, or antiphospholipid antibodies should be treated indefinitely (at least 2.5 years)	1A
	Patients with continuing risk factors (e.g., malignancy, immobility) should be treated for <i>at least</i> 12 months	1C

aPTT, activated partial thromboplastin time; DVT, deep vein thrombosis; INR, international normalized ratio; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; UFH, unfractionated heparin; VTE, venous thromboembolism.

<sup>a</sup>Refers to grade of recommendation (1A, strong recommendation applying to most patients without reservation; 1C, intermediate-strength recommendation that may change when stronger evidence becomes available; 1C+, strong recommendation that applies to most patients in most circumstances; 2B, weak recommendation where alternative approaches likely to be better for some patients under some circumstances).

Antithrombin inhibits the activity of factors IXa, Xa, XIIa, and thrombin (IIa). It also inhibits thrombin-induced activation of factors V and VIII.

- UFH prevents the growth and propagation of a formed thrombus and allows the patient's own thrombolytic system to degrade the clot.
- Contraindications to heparin therapy include hypersensitivity to the drug, active bleeding, hemophilia, severe liver disease with elevated prothrombin time (PT), severe thrombocytopenia, malignant hypertension, and inability to meticulously supervise and monitor treatment.
- UFH must be given parenterally, preferably by the IV or subcutaneous (SC) route. Intramuscular administration is discouraged because absorption is erratic and it may cause large hematomas.
- IV administration is needed when rapid anticoagulation is required. A weight-based IV bolus dose followed by a continuous IV infusion is preferred (Table 14-2).
- The activated partial thromboplastin time (aPTT) should be measured prior to initiation of therapy then no sooner than 6 hours after beginning the infusion or after a dose change. The traditional therapeutic range is 1.5 to 2.5

**TABLE 14-2** Weight-Based<sup>a</sup> Dosing for Unfractionated Heparin Administered by Continuous IV Infusion

Indication	Initial Loading Dose	Initial Infusion Rate
Deep venous thrombosis/pulmonary embolism	80–100 units/kg Maximum = 10,000 units	17–20 units/kg/hour Maximum = 2,300 units/hour
<b>Maintenance Infusion Rate</b>		
Activated Partial Thromboplastin Time (seconds)	Dose Adjustment	
<37 (or >12 seconds below institution-specific therapeutic range)	80 units/kg bolus then increase infusion by 4 units/kg/hour	
37–47 (or 1–12 seconds below institution-specific therapeutic range)	40 units/kg bolus then increase infusion by 2 units/kg/hour	
48–71 (within institution-specific therapeutic range)	No change	
72–93 (or 1–22 seconds above institution-specific therapeutic range)	Decrease infusion by 2 units/kg/hour	
>93 (or >22 seconds above institution-specific therapeutic range)	Hold infusion for 1 hour then decrease by 3 units/kg/hour	

<sup>a</sup>Use actual body weight for all calculations. Adjusted body weight may be used for obese patients (>130% of ideal body weight).

times the mean normal control value. Because of interlaboratory variability, an institution-specific aPTT therapeutic range that correlates with a plasma heparin concentration of 0.3 to 0.7 units/mL should be established. The dose of heparin should be adjusted promptly based on the patient's response and the institution-specific therapeutic range (see Table 14-1). Once the target aPTT is achieved, daily monitoring is indicated for minor dosing adjustments.

- Bleeding is the primary adverse effect associated with UFH. The most common bleeding sites are the GI tract, urinary tract, and soft tissues. Critical areas include intracranial, pericardial, and intraocular sites as well as the adrenal glands. Symptoms of bleeding may include severe headache, joint pain, chest pain, abdominal pain, swelling, tarry stools, hematuria, or the passing of bright red blood through the rectum.
- If major bleeding occurs, UFH should be discontinued immediately and IV **protamine sulfate** should be given by slow IV infusion over 10 minutes (1 mg/100 units of UFH infused during the previous 4 hours; maximum 50 mg).
- Thrombocytopenia (platelet count less than 150,000/mm<sup>3</sup>) is common and two distinct types can occur:
  - ✓ Heparin-associated thrombocytopenia is a benign, transient, and mild phenomenon that usually occurs within the first few days of treatment. Platelet counts rarely drop below 100,000/mm<sup>3</sup> and recover with continued therapy.
  - ✓ Heparin-induced thrombocytopenia (HIT) is a serious immune-mediated problem that requires immediate intervention. For patients receiving therapeutic UFH doses, a baseline platelet count should be obtained before therapy is initiated and then every-other-day for 14 days or until therapy is stopped, whichever occurs first. HIT should be suspected if a patient develops a thromboembolic event (e.g., DVT, PE, stroke, myocardial infarction, limb artery occlusion) during or soon after receiving UFH. The platelet

count invariably drops by more than 50% from baseline and is typically less than  $150,000/\text{mm}^3$ . Platelet counts typically begin to fall after 5 to 10 days of UFH therapy but may drop sooner if the patient has received UFH in the past 3 months. Laboratory testing to detect heparin antibodies must be performed to confirm the diagnosis of HIT. All sources of heparin (including heparin flushes) should be discontinued immediately, and an alternative anticoagulant should be initiated. Anticoagulants that rapidly inhibit thrombin activity and are devoid of significant cross-reactivity with heparin–PF-4 antibodies are the drugs of choice. The direct thrombin inhibitors **lepirudin** and **argatroban** are FDA approved for this use; **bivalirudin** is also commercially available (see section on direct thrombin inhibitors).

- Bruising, local irritation, mild pain, erythema, histamine-like reactions, and hematoma can occur at the site of injection. Hypersensitivity reactions involving chills, fever, urticaria, and rarely bronchospasm, nausea, vomiting, and shock have been reported in patients with HIT. Long-term UFH has been reported to cause alopecia, priapism, hyperkalemia, and osteoporosis.

## LOW-MOLECULAR-WEIGHT HEPARINS

- Low-molecular-weight heparins (LMWHs) are fragments of UFH that are heterogeneous mixtures of sulfated glycosaminoglycans with approximately one-third the molecular weight of UFH.
- Advantages of LMWHs over UFH include: (1) more predictable anticoagulation dose response; (2) improved SC bioavailability; (3) dose-independent clearance; (4) longer biologic half-life; (5) lower incidence of thrombocytopenia; and (6) less need for routine laboratory monitoring.
- Like UFH, the LMWHs enhance and accelerate the activity of antithrombin and prevent the growth and propagation of formed thrombi. The peak anticoagulant effect is seen in 3 to 5 hours after SC dosing.
- The usefulness of LMWHs has been evaluated extensively for many indications, including acute coronary syndromes, DVT, PE, and prevention of VTE in several high-risk populations.
- SC dosage regimens are based on body weight and vary depending upon the product and indication. The recommended doses (based on actual body weight) for treatment of DVT with or without PE are:
  - ✓ **Enoxaparin** (Lovenox) 1 mg/kg every 12 hours or 1.5 mg/kg every 24 hours
  - ✓ **Dalteparin** (Fragmin) 100 units/kg every 12 hours or 200 units/kg every 24 hours
  - ✓ **Tinzaparin** (Innohep) 175 units/kg every 24 hours
- Because the LMWHs achieve predictable anticoagulant response when given subcutaneously, routine laboratory monitoring is unnecessary to guide dosing. The PT and aPTT are minimally affected by LMWH. Prior to the initiation of therapy, a baseline PT/international normalized ratio (INR), aPTT, complete blood cell count (CBC) with platelet count, and serum creatinine should be obtained. Periodic monitoring of the CBC and platelet counts and occult fecal blood is recommended during therapy.
- Measuring antifactor Xa activity may be helpful in patients who have significant renal impairment, weigh less than 50 kg, are morbidly obese, require prolonged therapy (e.g., more than 14 days), are pregnant, or are

at a very high risk for bleeding or thrombotic recurrence. Samples for antifactor Xa activity should be drawn approximately 4 hours after the second or third SC injection. For the treatment of VTE, an acceptable target range is 0.5 to 1 unit/mL.

- As with UFH, bleeding is the most common adverse effect of the LMWHs, but major bleeding may be less common than with UFH. Minor bleeding occurs frequently, particularly at the site of injection. If major bleeding occurs, **protamine sulfate** should be administered IV, although it cannot neutralize the anticoagulant effect completely. The recommended dose of protamine sulfate is 1 mg per 1 mg of enoxaparin or 1 mg per 100 antifactor Xa units of dalteparin or tinzaparin administered in the previous 8 hours. If the LMWH dose was given in the previous 8 to 12 hours, the protamine sulfate dose is 0.5 mg per 100 antifactor Xa units. Protamine sulfate is not recommended if the LMWH was given more than 12 hours earlier.

## FONDAPARINUX

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- **Fondaparinux sodium** (Arixtra) is a selective inhibitor of factor Xa. Similar to UFH and the LMWHs, it binds to antithrombin, greatly accelerating its activity. However, it has no direct effect on thrombin activity at therapeutic plasma concentrations. It is approved for prevention of VTE in patients undergoing orthopedic (hip fracture, hip and knee replacement) surgery and for treatment of VTE and PE. For VTE prevention, the dose is 2.5 mg subcutaneously once daily starting 6 to 8 hours after surgery. For treatment of DVT and PE, the usual dose is 7.5 mg subcutaneously once daily. A CBC should be measured at baseline and periodically thereafter to detect occult bleeding. Signs and symptoms of bleeding should be monitored daily. Patients receiving fondaparinux do not require routine coagulation testing.

## DIRECT THROMBIN INHIBITORS

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- These agents interact directly with thrombin and do not require antithrombin to have antithrombotic activity. They are capable of inhibiting both circulating and clot-bound thrombin, which is a potential advantage over UFH and the LMWHs. They also do not induce immune-mediated thrombocytopenia and are widely used for the treatment of HIT.
- **Lepirudin** (Refludan) is indicated for anticoagulation in patients with HIT and associated thrombosis to prevent further thromboembolic complications. The recommended dose is 0.4 mg/kg as an IV bolus over 15 to 20 seconds, followed by a 0.15-mg/kg/hour continuous IV infusion for 2 to 10 days or longer if clinically needed. After obtaining a baseline aPTT, an aPTT should be obtained at least 4 hours after starting the infusion and then at least daily thereafter. The dose should be titrated to achieve an aPTT 1.5 to 2.5 times control. Dose adjustment is required in patients with impaired renal function. Many patients develop antibodies to lepirudin, which may increase its anticoagulant effect; close monitoring of aPTT is necessary during prolonged therapy. Because fatal anaphylaxis has been reported in patients who developed antibodies, patients should not be treated with lepirudin more than once.

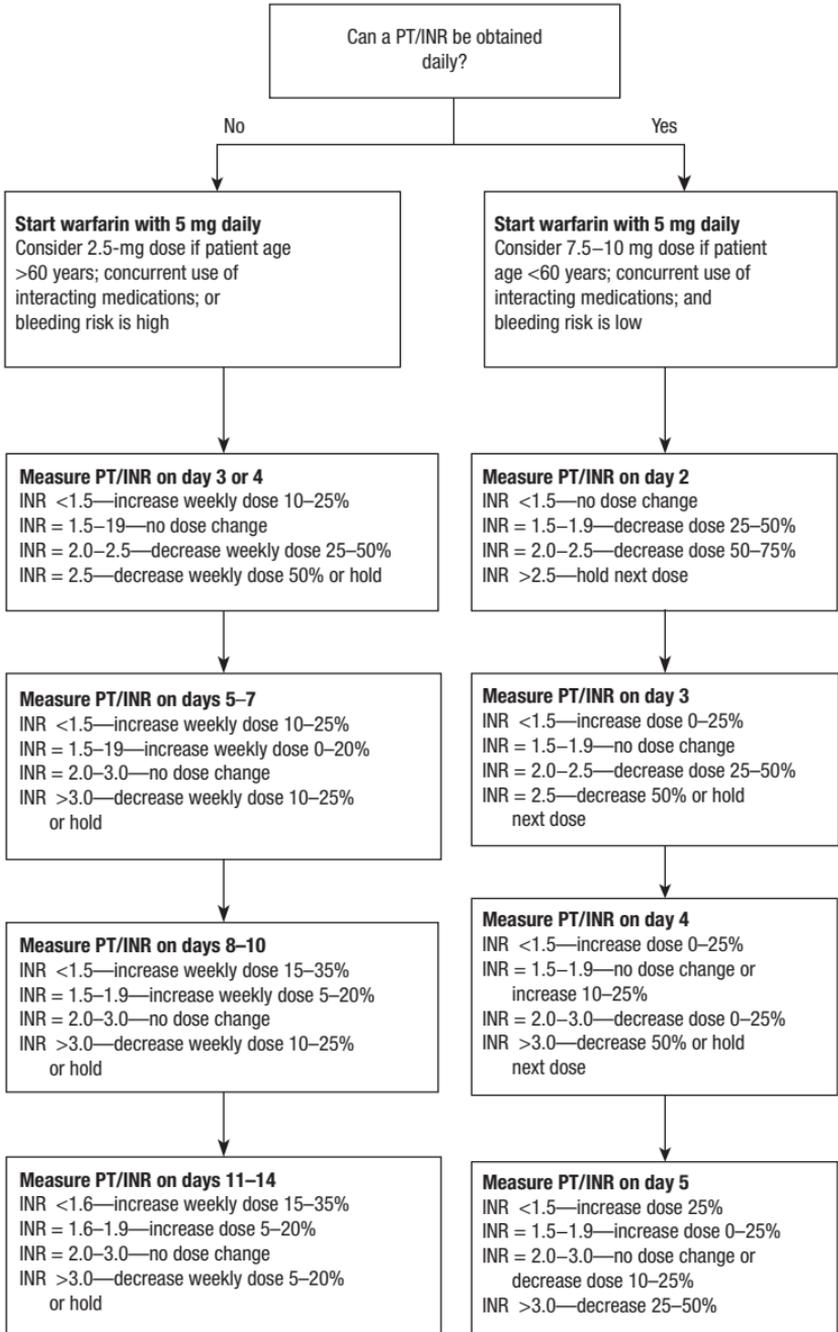
- **Bivalirudin** (Angiomax, formerly known as Hirulog) has several indications: (1) use as an anticoagulant in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty; (2) with provisional use of glycoprotein IIb/IIIa inhibitor for use as an anticoagulant in patients undergoing percutaneous coronary intervention; (3) for patients with (or at risk of) HIT undergoing PCI. For PCI, the recommended dose is an IV bolus of 0.75 mg/kg followed by a continuous infusion of 1.75 mg/kg/hour for the duration of the PCI procedure. Bivalirudin is intended for use with aspirin 300 to 325 mg/day. The activated clotting time is used to monitor the anticoagulant effect of bivalirudin.
- **Argatroban** has two indications: (1) prevention or treatment of thrombosis in patients with HIT; and (2) as an anticoagulant in patients with HIT, or at risk of HIT, who are undergoing PCI. The recommended dose for the treatment of HIT is 2 mcg/kg/min by continuous IV infusion. The first aPTT should be obtained 2 hours after initiation. The dose can be adjusted as clinically indicated (maximum 10 mcg/kg/min) until the aPTT is 1.5 to 3 times control.
- **Desirudin** (Iprivask) is approved for prevention of DVT in patients undergoing elective hip replacement surgery; it is expected to be available for sale in the United States in late 2008. The recommended dose is 15 mg subcutaneously every 12 hours beginning 5 to 15 minutes prior to surgery and for up to 12 days thereafter. Daily aPTT monitoring is recommended.
- Contraindications are similar to those of other antithrombotic drugs, and hemorrhage is the most common and serious adverse effect. For all agents in this class, a CBC should be obtained at baseline and periodically thereafter to detect potential bleeding. There are no known agents that reverse the activity of direct thrombin inhibitors.

## WARFARIN

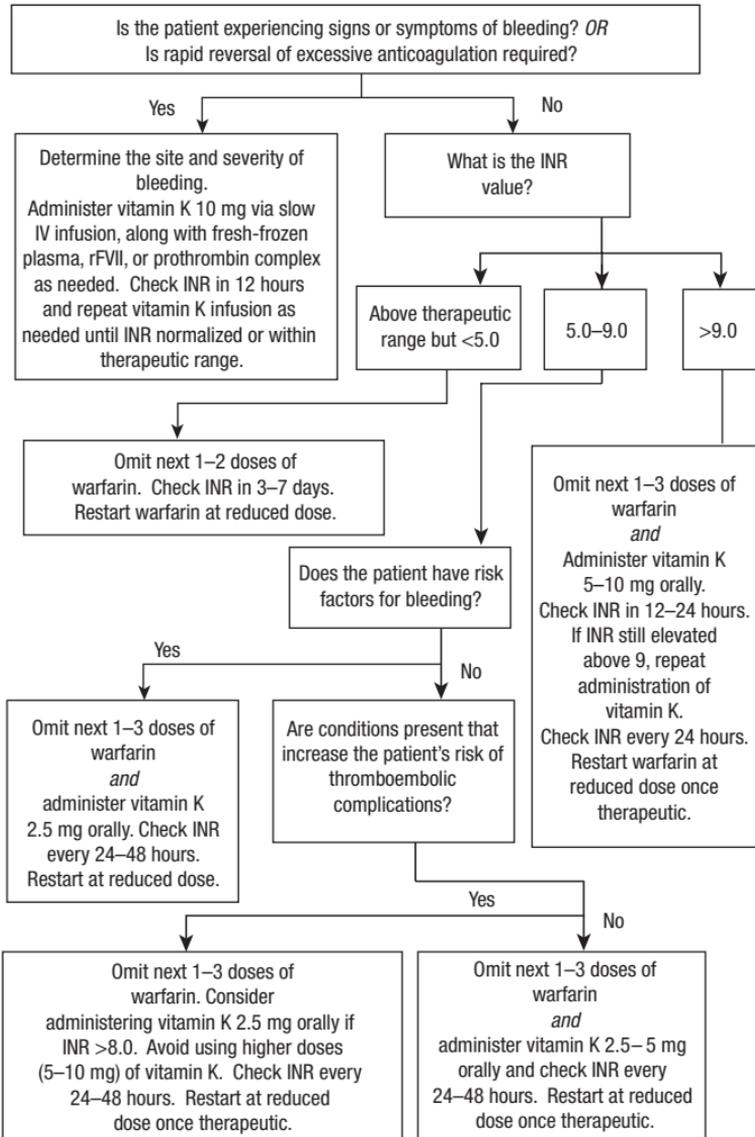
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- **Warfarin** inhibits the enzymes responsible for the cyclic interconversion of vitamin K in the liver. Reduced vitamin K is a cofactor required for the carboxylation of the vitamin K–dependent coagulation proteins prothrombin (II); factors VII, IX, and X; and the endogenous anticoagulant proteins C and S. By reducing the supply of vitamin K available to serve as a cofactor in the production of these proteins, warfarin indirectly slows their rate of synthesis. By suppressing the production of clotting factors, warfarin prevents the initial formation and propagation of thrombi. Warfarin has no direct effect on previously circulating clotting factors or previously formed thrombi. The time required to achieve its anticoagulant effect depends on the elimination half-lives of the coagulation proteins. Because prothrombin has a 2- to 3-day half-life, warfarin's full antithrombotic effect is not achieved for 8 to 15 days after initiation of therapy.
- Warfarin should begin concurrently with UFH or LMWH therapy. For patients with acute VTE, heparin and warfarin therapy should be overlapped for at least 4 to 5 days, regardless of whether the target INR has been achieved earlier. The UFH or LMWH can then be discontinued once the INR is within the desired range for 2 consecutive days.

- Guidelines for initiating warfarin therapy are given in Fig. 14-3. The usual initial dose is 5 to 10 mg. In older patients (age >60 years) and those taking potentially interacting medications, a starting dose of 2.5 mg should be considered.
- Warfarin therapy is monitored by the INR (target: 2 to 3 for DVT or PE). After an acute thromboembolic event, the INR should be measured minimally every 3 days during the first week of therapy. In general, dose changes should not be made more frequently than every 3 days. Doses should be adjusted by calculating the weekly dose and reducing or increasing it by 5% to 25%. The effect of a small dose change may not become evident for 5 to 7 days. Once the patient's dose response is established, an INR should be determined every 7 to 14 days until it stabilizes and then every 4 weeks thereafter.
- If the initial thrombotic event was associated with a major transient or reversible factor (e.g., hospitalization), only 3 months of oral anticoagulation is warranted. For VTE associated with a minor transient or reversible factor (e.g., within 6 weeks of starting estrogen therapy), 3 months is reasonable but some experts prefer 6 months of treatment. Patients with unprovoked (idiopathic) VTE have a high recurrence rate and should be considered for indefinite oral anticoagulation if possible, but should receive at least 6 to 12 months of therapy. Indefinite or lifelong anticoagulation should be considered for patients with recurrent VTE events or one of the thrombophilias known to impart a high lifetime risk of thrombosis.
- Hemorrhagic complications ranging from mild to severe and life-threatening can occur at any body site. The GI tract is the most frequent site of bleeding. Bruising on the arms and legs is common, but a painful hematoma may necessitate temporary discontinuation of therapy. Intracranial hemorrhage is the most serious complication and often results in permanent disability and death. Fig. 14-4 outlines guidelines for managing an elevated INR. Patients with a mildly elevated INR (3.5 to 5) and no signs or symptoms of bleeding can usually be managed by either reducing the dose or holding one or two warfarin doses. If rapid reduction of an elevated INR is required, oral or IV administration of vitamin K<sub>1</sub> (**phytonadione**) can be given. Oral administration is preferable in the absence of major bleeding. The IV route produces the most rapid reversal of anticoagulation, but it has been associated with anaphylactoid reactions. If the INR is 5 to 9, warfarin doses may be withheld or may be combined with oral phytonadione 1 to 5 mg. If the INR is greater than 9, a 5-mg oral dose is recommended. Low vitamin K doses reduce the INR consistently within 24 hours without making the patient refractory to warfarin. In the event of serious or life-threatening bleeding, IV vitamin K should be administered together with fresh-frozen plasma, clotting factor concentrates, or recombinant factor VII.
- Nonhemorrhagic adverse effects include the rare "purple toe syndrome" and skin necrosis.
- Absolute contraindications to warfarin include active bleeding, hemorrhagic tendencies, pregnancy, and a history of warfarin-induced skin necrosis. It should be used with great caution in patients with a history of GI bleeding, recent neurosurgery, alcoholic liver disease, severe renal



**FIGURE 14-3.** Initiation of warfarin therapy. (INR, international normalized ratio; PT, prothrombin time.)



**FIGURE 14-4.** Management of an elevated international normalized ratio (INR) in patients taking warfarin. Dose reductions should be made by determining the weekly warfarin dose and reducing the weekly dose by 10% to 25% based on the degree of INR elevation. Conditions that increase the risk of thromboembolic complications include history of hypercoagulability disorders (e.g., protein C or S deficiency, presence of antiphospholipid antibodies, antithrombin deficiency, activated protein C resistance), arterial or venous thrombosis within the previous month, thromboembolism associated with malignancy, and mechanical mitral valve in conjunction with atrial fibrillation, previous stroke, poor ventricular function, or coexisting mechanical aortic valve. (rFVII, recombinant factor VII.)

- impairment, or inability to keep follow-up appointments for monitoring.
- Because of the large number of food–drug and drug–drug interactions with warfarin, close monitoring and additional INR determinations may be indicated whenever other medications are initiated, or discontinued, or an alteration in consumption of vitamin K–containing foods is noted.

## THROMBOLYSIS AND THROMBECTOMY

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- Thrombolytic agents are proteolytic enzymes that enhance the conversion of plasminogen to plasmin, which subsequently degrades the fibrin matrix.
- In the management of PE, thrombolytics restore pulmonary artery patency more rapidly when compared to UFH alone, but this early benefit does not improve long-term patient outcomes. Thrombolytic therapy has not been shown to improve morbidity or mortality and is associated with a substantial risk of hemorrhage. For these reasons, thrombolytics should be reserved for patients with PE who are most likely to benefit (e.g., those who present with shock, hypotension, right ventricular strain, or massive DVT with limb gangrene).
- Three thrombolytic agents and regimens are available for treatment of DVT and/or PE:
  - ✓ **Streptokinase** (Streptase): 250,000 units IV over 30 minutes followed by a continuous IV infusion of 100,000 units/hour for 24 hours (PE) or 24 to 72 hours (DVT).
  - ✓ **Urokinase** (Abbokinase): For PE, 4,400 international units/kg IV over 10 minutes followed by 4,400 international units/kg/hour for 12 to 24 hours.
  - ✓ **Alteplase** (Activase): For PE, 100 mg by IV infusion over 2 hours.
- UFH should not be used during thrombolytic therapy. The aPTT should be measured after the completion of thrombolytic therapy. If the aPTT at that time is <2.5 times control, a UFH infusion should be started and adjusted to maintain the aPTT in the therapeutic range. If the posttreatment aPTT is >2.5 times control, it should be remeasured every 2 to 4 hours and a UFH infusion started when the aPTT is <2.5 times control.
- Venous thrombectomy may be performed to remove a massive obstructive thrombus in a patient with significant iliofemoral venous thrombosis, particularly if the patient is either not a candidate for or has not responded to thrombolysis. Full-dose anticoagulation therapy is essential during the entire operative and postoperative period. These patients need indefinite oral anticoagulation therapy targeted to an INR of 2.5 (range 2.0 to 3.0).

## PREVENTION OF VENOUS THROMBOEMBOLISM

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- Nonpharmacologic methods improve venous blood flow by mechanical means and include early ambulation, electrical stimulation of calf muscles during prolonged surgery, graduated compression stockings, intermittent pneumatic compression devices, and inferior vena cava filters.
- Pharmacologic techniques counteract the propensity for thrombosis formation by dampening the coagulation cascade. Appropriately selected therapy can dramatically reduce the incidence of VTE after hip or knee replacement, general surgery, myocardial infarction, and ischemic stroke.

**TABLE 14-3** Risk Classification and Consensus Guidelines for VTE Prevention

Level of Risk	Prevention Strategies
<b>Low</b> Minor surgery, age <40 years, and no clinical risk factors	Ambulation
<b>Moderate</b> Major or minor surgery, age 40–60 years, and no clinical risk factors Major surgery, age <40 years and no clinical risk factors Minor surgery, with clinical risk factor(s) Acutely ill (e.g., MI, ischemic stroke, CHF exacerbation), and no clinical risk factors	UFH 5,000 units SC q 12 h Dalteparin 2,500 units SC q 24 h Enoxaparin 40 mg SC q 24 h Tinzaparin 3,500 units SC q 24 h IPC Graduated compression stockings
<b>High</b> Major surgery, age >60 years, and no clinical risk factors Major surgery, age 40–60 years, with clinical risk factor(s) Acutely ill (e.g., MI, ischemic stroke, CHF exacerbation), with risk factor(s)	UFH 5,000 units SC q 8 h Dalteparin 5,000 units SC q 24 h Enoxaparin 40 mg SC q 24 h Fondaparinux 2.5 mg SC q 24 h Tinzaparin 75 units/kg SC q 24 h IPC
<b>Highest</b> Major lower extremity orthopedic surgery Hip fracture Multiple trauma Major surgery, age >40 years, and prior history of VTE Major surgery, age >40 years, and malignancy Major surgery, age >40 years, and hypercoagulable state Spinal cord injury or stroke with limb paralysis	Adjusted dose UFH SC q 8 h (aPTT >36 seconds) Dalteparin 5,000 units SC q 24 h Desirudin 15 mg SC q 12 h Enoxaparin 30 mg SC q 12 h Fondaparinux 2.5 mg SC q 24 h Tinzaparin 75 units/kg SC q 24 h Warfarin (INR = 2.0–3.0) IPC with UFH 5,000 units SC q 8 h

aPTT, activated partial thromboplastin time; CHF, congestive heart failure; INR, international normalized ratio; IPC, intermittent pneumatic compression; MI, myocardial infarction; UFH, unfractionated heparin; VTE, venous thromboembolism.

The LMWHs and **fondaparinux** provide superior protection against VTE compared with **low-dose UFH**. Even so, UFH is a highly effective, cost-conscious choice for many patients, provided that it is given in the appropriate dose (Table 14-3). Adjusted-dose SC UFH with doses adjusted to maintain the aPTT at high-normal is more effective than low-dose UFH in the highest risk patients (hip and knee replacement surgery). There is no evidence that one LMWH is superior to another for the prevention of VTE. **Warfarin** is commonly used for VTE prevention after orthopedic surgeries of the lower extremities, but evidence is equivocal regarding its relative effectiveness compared to LMWH for preventing clinically important VTE events in the highest risk populations.

- Prophylaxis should be continued throughout the period of risk. For general surgical procedures and medical conditions, prophylaxis can be discontinued once the patient is able to ambulate regularly and other risk factors are no longer present. Most clinical trials support the use of antithrombotic therapy for 21 to 35 days after total hip replacement and hip fracture repair surgeries.

**EVALUATION OF THERAPEUTIC OUTCOMES**

- Patients should be monitored for resolution of symptoms, the development of recurrent thrombosis, and symptoms of the postthrombotic syndrome, as well as for adverse effects from the treatments described in this chapter.
- Hemoglobin, hematocrit, and blood pressure should be monitored carefully to detect bleeding from anticoagulant therapy.
- Coagulation tests (aPTT, PT, INR) should be performed prior to initiating therapy to establish the patient's baseline values and guide later anticoagulation.
- Outpatients taking warfarin should be questioned about medication adherence and symptoms related to bleeding and thromboembolic complications. Any changes in concurrent medications should be carefully explored.

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*See Chap. 21, Venous Thromboembolism, authored by Stuart T. Haines, Daniel M. Witt, and Edith A. Nutescu, for a more detailed discussion of this topic.*

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## DEFINITION

- Acne vulgaris is a common, usually self-limiting, multifactorial disease involving inflammation of the sebaceous follicles of the face and upper trunk.

## PATHOPHYSIOLOGY

- The four primary factors involved in the formation of acne lesions are increased sebum production, sloughing of keratinocytes, bacterial growth, and inflammation.
- Increased androgen activity at puberty triggers growth of sebaceous glands and enhanced sebum production. Sebum consists of glycerides, wax esters, squalene, and cholesterol. Glyceride is converted to free fatty acids and glycerol by lipases, which are products of *Propionibacterium acnes*. Free fatty acids may irritate the follicular wall and cause increased cell turnover and inflammation.
- The primary lesion, the comedo, forms as a result of plugging of the pilosebaceous follicle. The follicular canal widens, and cell production increases. Sebum mixes with excess loose cells in the follicular canal to form a keratinous plug. This appears as an open comedo, or “blackhead” (because of melanin accumulation). Inflammation or trauma to the follicle may lead to formation of a closed comedo, or “whitehead.” Closed comedones can become larger, inflammatory lesions secondary to *P. acnes* activity. *P. acnes* is a resident anaerobic organism that proliferates in the environment created by the mixture of excessive sebum and keratinocytes. It can trigger inflammatory acne lesions by producing biologically active mediators and promoting proinflammatory cytokine release.
- If the follicular wall is damaged or ruptured, follicle contents may extrude into the dermis and present as a pustule.
- A primary factor in the development of acne is an alteration in the pattern of keratinization within the follicle. Increased production and sloughing of keratinocytes correlate with comedo formation.

## CLINICAL PRESENTATION

- Acne lesions typically occur on the face, back, upper chest, and shoulders. Severity varies from a mild comedonal form to severe inflammatory necrotic acne. The disease is categorized as mild, moderate, or severe, depending on the type and severity of lesions.
- Lesions may take months to heal completely, and fibrosis associated with healing may lead to permanent scarring.

## DIAGNOSIS

- Diagnosis is established by observation of acne lesions (e.g., comedones, pustules, papules, nodules, cysts) on the face, back, or chest. The presence of five to 10 comedones is usually considered to be diagnostic.

## DESIRED OUTCOME

- The goals of treatment are to prevent the formation of new acne lesions, heal existing lesions, and prevent or minimize scarring.

## TREATMENT

### GENERAL APPROACH

- Patient education about goals, realistic expectations, and dangers of overtreatment is important to optimize therapeutic outcomes. Treatment regimens are targeted to types of lesions and acne severity (Fig. 15-1):
  - ✓ Mild acne usually is managed with topical retinoids alone or with topical antimicrobials, salicylic acid, or azelaic acid.
  - ✓ Moderate acne can be managed with topical retinoids in combination with oral antibiotics and, if indicated, benzoyl peroxide.
  - ✓ Severe acne is often managed with oral isotretinoin.
- Initial treatment is aimed at reducing lesion count and may last from a few months to several years; chronic indefinite therapy may be required to maintain control in some cases.
- Topical treatment forms include creams, lotions, solutions, gels, and disposable wipes. Responses to different formulations may depend on skin type and individual preference.
- Antibiotics such as tetracyclines and macrolides are the agents of choice for papulopustular acne.
- Oral isotretinoin is the treatment of choice in severe papulopustular acne and nodulocystic/conglobate acne. Hormonal therapy may be an effective alternative in female patients.

### NONPHARMACOLOGIC THERAPY

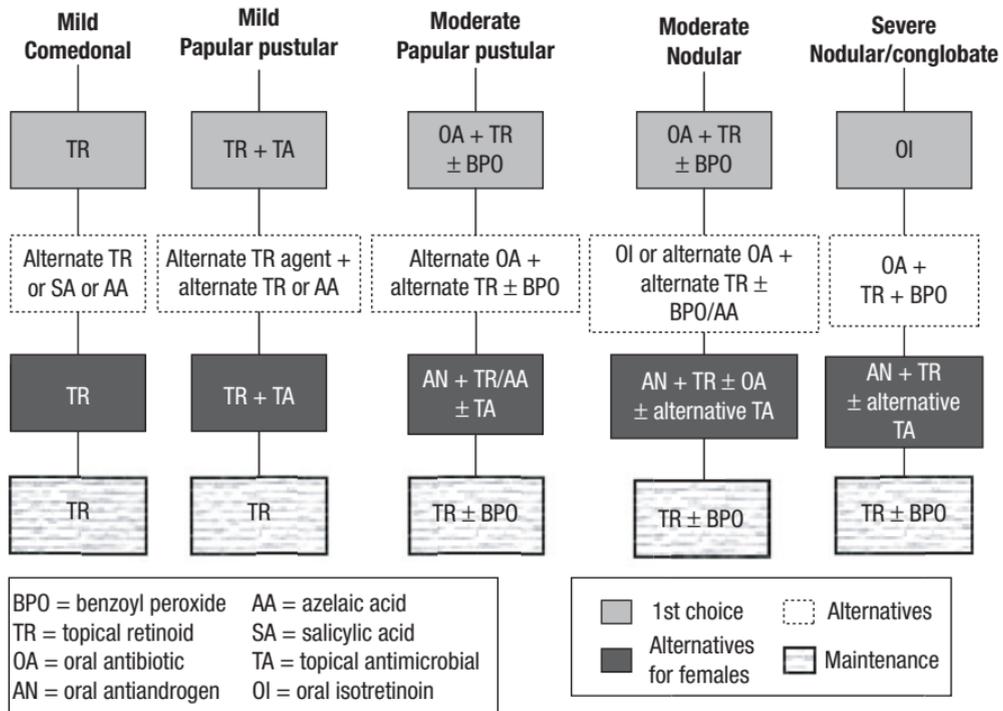
- Surface skin cleansing with soap and water has a relatively small effect on acne because it has minimal impact within follicles.
- Skin scrubbing or excessive face washing does not necessarily open or cleanse pores and may lead to skin irritation.
- Use of gentle, nondrying cleansing agents is important to avoid skin irritation and dryness during some acne therapies.

### TOPICAL PHARMACOTHERAPY

#### Benzoyl Peroxide

- **Benzoyl peroxide** may be used to treat superficial inflammatory acne. It is a nonantibiotic antibacterial that is bacteriostatic against *P. acnes*. It is decomposed on the skin by cysteine, liberating free oxygen radicals that oxidize

## Acne Treatment Algorithms



**FIGURE 15-1.** Algorithms for acne treatment.

bacterial proteins. It increases the sloughing rate of epithelial cells and loosens the follicular plug structure, resulting in some degree of comedolytic activity.

- Soaps, lotions, creams, washes, and gels are available in concentrations of 1% to 10%. The 10% concentration is not significantly more effective but may be more irritating. Gel formulations are usually most potent, whereas lotions, creams, and soaps have weaker potency. Alcohol-based gel preparations generally cause more dryness and irritation.
- To limit irritation and increase tolerability, begin with a low-potency formulation (2.5%) and increase either the strength (5% to 10%) or application frequency (every other day, each day, then twice daily).
- Patients should be advised to apply the formulation chosen to cool, clean, dry skin no more often than twice daily to minimize irritation. Fair or moist skin is more sensitive; patients should apply the medication to dry skin at least 30 minutes after washing.
- Side effects include dryness, irritation, and allergic contact dermatitis. It may bleach or discolor some fabrics (e.g., clothing, bed linen, towels).

### Tretinoin

- **Tretinoin** (a retinoid; topical vitamin A acid) is a comedolytic agent that increases cell turnover in the follicular wall and decreases cohesiveness of cells, leading to extrusion of comedones and inhibition of new comedo formation. It also decreases the number of cell layers in the stratum corneum from about 14 to about five.
- Tretinoin is available as 0.05% solution (most irritating), 0.01% and 0.025% gels, and 0.025%, 0.05%, and 0.1% creams (least irritating).
- Treatment initiation with 0.025% cream is recommended for mild acne in people with sensitive and nonoily skin, 0.01% gel for moderate acne on easily irritated skin in people with oily complexions, and 0.025% gel for moderate acne in those with nonsensitive and oily skin.
- Patients should be advised to apply the medication to dry skin approximately 30 minutes after washing to minimize erythema and irritation. Slowly increasing the application frequency from every other day to daily and then twice daily may also increase tolerability.
- A flare of acne may appear suddenly after initiation of treatment, followed by clinical clearing in 8 to 12 weeks. Once control is established, therapy should be continued at the lowest effective concentration and the longest effective interval that minimizes acne exacerbations.
- Side effects include skin irritation, erythema, peeling, allergic contact dermatitis (rare), and increased sensitivity to sun exposure, wind, cold, and other irritants.
- Concomitant use of an antibacterial agent with tretinoin can decrease keratinization, inhibit *P. acnes*, and decrease inflammation. A regimen of benzoyl peroxide each morning and tretinoin at bedtime may enhance efficacy and be less irritating than either agent used alone.

### Adapalene

- **Adapalene** (Differin) is a third-generation retinoid with comedolytic, keratolytic, and antiinflammatory activity. It is available as 0.1% gel, cream, alcoholic solution, and pledgets. A 0.3% gel formulation is also available.

- Adapalene is indicated for mild to moderate acne vulgaris. The 0.1% gel can be used as an alternative to tretinoin 0.025% gel to achieve better tolerability in some patients.
- Coadministration with a topical or oral antibiotic is reasonable for moderate forms of acne.

### Tazarotene

- **Tazarotene** (Tazorac) is a synthetic acetylenic retinoid that is converted to its active form, tazarotenic acid, after topical application.
- It is used in the treatment of mild to moderate acne vulgaris and has comedolytic, keratolytic, and antiinflammatory action.
- The product is available as a 0.05% and 0.1% gel or cream.
- Dose-related adverse effects include erythema, pruritus, stinging, and burning.

### Erythromycin

- **Erythromycin** in concentrations of 1% to 4% with or without zinc is effective against inflammatory acne. Zinc combination products may enhance penetration of erythromycin into the pilosebaceous unit.
- Topical erythromycin formulations include a gel, lotion, solution, and disposable pads that are usually applied twice daily.
- Development of *P. acnes* resistance to erythromycin may be reduced by combination therapy with benzoyl peroxide.

### Clindamycin

- **Clindamycin** inhibits *P. acnes* and provides comedolytic and antiinflammatory activity.
- It is available as 1% or 2% concentrations in gel, lotion, solution, foam, and disposable pad formulations and is usually applied twice daily. Combination with benzoyl peroxide increases efficacy.

### Azelaic Acid

- **Azelaic acid** (Azelex) has antibacterial, antiinflammatory, and comedolytic activity.
- Azelaic acid is useful for mild to moderate acne in patients who do not tolerate benzoyl peroxide. It is also useful for postinflammatory hyperpigmentation because it has skin-lightening properties.
- It is available in 20% cream and 15% gel formulations, which are usually applied twice daily on clean, dry skin.
- Although uncommon, mild transient burning, pruritus, stinging, and tingling may occur.

### Salicylic Acid, Sulfur, and Resorcinol

- **Salicylic acid, sulfur, and resorcinol** are second-line topical therapies. They are keratolytic and mildly antibacterial agents. Salicylic acid has comedolytic and antiinflammatory action.
- Each agent has been classified as safe and effective by an FDA advisory panel. Some combinations may be synergistic (e.g., sulfur and resorcinol).
- Keratolytics may be less irritating than benzoyl peroxide and tretinoin, but they are not as effective comedolytic agents.
- Disadvantages include the odor created by hydrogen sulfide on reaction of sulfur with skin, the brown scale from resorcinol, and (rarely) salicylism

from long-term use of high concentrations of salicylic acid on highly permeable (inflamed or abraded) skin.

## SYSTEMIC PHARMACOTHERAPY

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### Isotretinoin

- **Isotretinoin** (Accutane) decreases sebum production, changes sebum composition, inhibits *P. acnes* growth within follicles, inhibits inflammation, and alters patterns of keratinization within follicles.
- It is the treatment of choice for severe nodulocystic acne. It can be used in patients who have failed conventional treatment as well as those who have scarring acne, chronic relapsing acne, or acne associated with severe psychological distress.
- Dosing guidelines range from 0.5 to 1 mg/kg/day, but the cumulative dose taken during a treatment course may be the major factor influencing long-term outcome. Optimal results are usually attained with cumulative doses of 120 to 150 mg/kg.
- A 5-month course is sufficient for most patients. Alternatively, an initial dose of 1 mg/kg/day for 3 months, then reduced to 0.5 mg/kg/day and, if possible, to 0.2 mg/kg/day for 3 to 9 more months may optimize the therapeutic outcome.
- Adverse effects are frequent and often dose related. About 90% of patients experience mucocutaneous effects; drying of the mouth, nose, and eyes is most common. Cheilitis and skin desquamation occur in more than 80% of patients. The conjunctiva and nasal mucosa are affected less frequently. Systemic effects include transient increases in serum cholesterol and triglycerides, increased creatine kinase, hyperglycemia, photosensitivity, pseudotumor cerebri, excess granulation tissue, hepatomegaly with abnormal liver injury tests, bone abnormalities, arthralgias, muscle stiffness, headache, and a high incidence of teratogenicity. Patients should be counseled about and screened for depression during therapy, although a causal relationship to isotretinoin therapy is controversial.
- Because of teratogenicity, contraception is required in female patients beginning 1 month before therapy, continuing throughout treatment, and for up to 3 months after discontinuation of therapy. All patients receiving isotretinoin must participate in the iPLEDGE program, which requires pregnancy tests and assurances by prescribers and pharmacists that they will follow required procedures.

### Oral Antibacterial Agents

- **Erythromycin** has efficacy similar to tetracycline, but it induces higher rates of bacterial resistance. Resistance may be reduced by combination therapy with benzoyl peroxide. Erythromycin can be used for patients who require systemic antibiotics but cannot tolerate tetracyclines, or those who acquire bacterial resistance to tetracyclines. The usual dose is 1 g/day with meals to minimize GI intolerance.
- **Azithromycin** is a safe and effective alternative for moderate to severe inflammatory acne. Its long half-life permits intermittent dosing three times a week.

- **Tetracyclines** inhibit *P. acnes*, reduce the amount of keratin in sebaceous follicles, and have antiinflammatory properties (inhibiting chemotaxis, phagocytosis, complement activation, and cell-mediated immunity). Drawbacks to tetracyclines include hepatotoxicity and predisposition to infections (e.g., vaginal candidiasis). Other adverse effects include GI disturbances, photosensitivity, tooth discoloration in children, and inhibition of skeletal growth in the developing fetus. Tetracyclines must not be combined with systemic retinoids because of an increased risk of intracranial hypertension.
  - ✓ **Tetracycline** is the least expensive agent in this class and is often prescribed for initial therapy in moderate to severe acne vulgaris. A common initial dose is 500 mg twice daily given 1 hour before meals; after 1 or 2 months when marked improvement is observed, the dose may be reduced to 500 mg daily for another 1 or 2 months. Tetracycline administration must be separated from food and dairy products.
  - ✓ **Doxycycline** is commonly used for moderate to severe acne vulgaris. It is more effective and produces less resistance than tetracycline. The initial dose is 100 or 200 mg daily, followed by 50 mg daily as a maintenance dose after improvement is seen. Doxycycline may be given with food, but it is more effective when taken 30 minutes before meals.
  - ✓ **Minocycline** is also commonly used for moderate to severe acne vulgaris. It is more effective than tetracycline. It is dosed similar to doxycycline (100 mg/day or 50 mg twice daily) and on an indefinite basis in selected patients. Minocycline has the most reported adverse effects of the tetracyclines, some of which may be serious.
- **Trimethoprim-sulfamethoxazole** (or trimethoprim alone) is a second-line oral agent that may be used for patients who do not tolerate tetracyclines and erythromycin or in cases of resistance to these antibiotics. The adult dose is usually 800 mg sulfamethoxazole and 160 mg trimethoprim twice daily.
- **Clindamycin** use is limited by diarrhea and the risk of pseudomembranous colitis.

### Oral Contraceptives

- Oral contraceptives containing both an estrogen and progestin are used as an alternate treatment for moderate acne in women. Contraceptive agents currently FDA approved for this indication include **norgestimate with ethinyl estradiol** and **norethindrone acetate with ethinyl estradiol**.

## EVALUATION OF THERAPEUTIC OUTCOMES

- Information regarding pathogenic factors and the importance of medication compliance should be conveyed to patients.
- Patients should understand that effectiveness of any therapeutic regimen may require 6 to 8 weeks and that they may also notice an exacerbation of acne after initiation of topical comedolytic therapy.

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See Chap. 100, *Acne Vulgaris*, authored by Dennis P. West, Amy Lloyd, Kimberly A. Bauer, Lee E. West, Laura Scuderi, and Giuseppe Micali, for a more detailed discussion of this topic.

## DEFINITION

- Psoriasis is a common chronic inflammatory disease characterized by recurrent exacerbations and remissions of thickened, erythematous, and scaling plaques.

## PATHOPHYSIOLOGY

- Cell-mediated immune mechanisms play a central role in psoriasis. Cutaneous inflammatory T-cell-mediated immune activation requires two T-cell signals mediated via cell-cell interactions by surface proteins and antigen-presenting cells such as dendritic cells or macrophages. The first signal is the interaction of the T-cell receptor with antigen presented by antigen-presenting cells. The second signal (called costimulation) is mediated through various surface interactions.
- Once T cells are activated, they migrate from lymph nodes and the bloodstream into skin and secrete various cytokines (e.g., interferon  $\gamma$ , interleukin 2 [IL-2]) that induce the pathologic changes of psoriasis. Local keratinocytes and neutrophils are induced to produce other cytokines, such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), IL-8, and others.
- As a result of pathogenic T-cell production and activation, psoriatic epidermal cells proliferate at a rate sevenfold faster than normal epidermal cells. Epidermal proliferation is also elevated in apparently normal skin of psoriatic patients.
- There is a significant genetic component in psoriasis. Studies of histocompatibility antigens in psoriatic patients indicate a number of significant associations, especially with HLA-Cw6, where the relative likelihood for developing psoriasis is 9 to 15 times normal.
- Climate, stress, alcohol, smoking, infection, trauma, and drugs may aggravate psoriasis. Warm seasons and sunlight improve psoriasis in 80% of patients, whereas 90% of patients worsen in cold weather. Psoriatic lesions may develop at the site of injury (e.g., rubbing, venipuncture, bites, surgery) on normal-appearing skin (Koebner response). Lithium carbonate,  $\beta$ -adrenergic blockers, some antimalarials, nonsteroidal antiinflammatory drugs, and tetracyclines have been reported to exacerbate psoriasis.

## CLINICAL PRESENTATION

- Psoriatic lesions are relatively asymptomatic, but about 25% of patients complain of pruritus.
- Lesions are characterized by sharply demarcated, erythematous papules and plaques often covered with silver-white fine scales. Initial lesions are usually small papules that enlarge over time and coalesce into plaques. If the fine scale is removed, a salmon-pink lesion is exposed, perhaps with punctate bleeding from prominent dermal capillaries (Auspitz sign).

- Scalp psoriasis ranges from diffuse scaling on an erythematous scalp to thickened plaques with exudation, microabscesses, and fissures. Trunk, back, arm, and leg lesions may be generalized, scattered, discrete, droplike lesions or large plaques. Palms, soles, face, and genitalia may also be involved. Affected nails are often pitted and associated with subungual keratotic material. Yellowing under the nail plate may be seen.
- Psoriatic arthritis is a distinct clinical entity in which both psoriatic lesions and inflammatory arthritis-like symptoms occur. Distal interphalangeal joints and adjacent nails are most commonly involved, but knees, elbows, wrists, and ankles may also be affected.

## DIAGNOSIS

- The diagnosis is based on physical examination findings of the characteristic lesions of psoriasis.
- The medical history of a patient with psoriasis should include information about the onset and duration of lesions, family history of psoriasis, presence of exacerbating factors, previous history of antipsoriatic treatment (if any) along with efficacy and adverse effect data, exposure to chemicals and toxins, and allergies (food, drugs, and environmental).
- Skin biopsy of lesional skin is useful in confirming the diagnosis.

## DESIRED OUTCOME

- The goal of therapy is to achieve resolution of lesions, but partial clearing using regimens with decreased toxicity and increased patient acceptability is acceptable in some cases.

## TREATMENT

### NONPHARMACOLOGIC THERAPY

- **Emollients (moisturizers)** hydrate the stratum corneum and minimize water evaporation. They may enhance desquamation, eliminate scaling, and decrease pruritus. The lotions, creams, or ointments often need to be applied up to four times a day to achieve a beneficial response. Adverse effects include folliculitis and allergic or irritant contact dermatitis.
- **Balneotherapy** (and **climatotherapy**) involves bathing in waters containing certain salts, often combined with natural sun exposure. The salts in certain waters (e.g., the Dead Sea) reduce activated T cells in skin and may be remittive for psoriasis.

### FIRST-LINE TOPICAL PHARMACOTHERAPY

#### Keratolytics

- **Salicylic acid** is one of the most commonly used keratolytics. It causes a disruption in corneocyte-to-corneocyte cohesion in the abnormal horny layer of psoriatic skin. This serves to remove scales, smooth the skin, and decrease hyperkeratosis. The keratolytic effect enhances penetration and

efficacy of some other topical agents such as corticosteroids. It is applied as a 2% to 10% gel or lotion two or three times a day. Salicylic acid produces local irritation. Application to large, inflamed areas may induce salicylism with symptoms of nausea, vomiting, tinnitus, or hyperventilation.

### Corticosteroids

- **Topical corticosteroids** (Table 16-1) may halt synthesis and mitosis of DNA in epidermal cells and appear to inhibit phospholipase A, lowering the amounts of arachidonic acid, prostaglandins, and leukotrienes in the skin. These effects, coupled with local vasoconstriction, reduce erythema, pruritus, and scaling. As antipsoriatic agents, they are best used adjunctively with a product that specifically functions to normalize epidermal hyperproliferation.
- Low-potency products (e.g., hydrocortisone 1%) have a weak antiinflammatory effect and are safest for long-term application, for use on the face and intertriginous areas, for use with occlusion, and for use in infants and young children.
- Medium-potency products are used in moderate inflammatory dermatoses. They may be used on the face and intertriginous areas for a limited time.
- High-potency preparations are used primarily as alternatives to systemic corticosteroids when local therapy is feasible.
- Very high potency products may be used for thick, chronic psoriatic lesions but for only short periods of time and on relatively small surface areas.
- Ointments are the most effective formulations for psoriasis because they have an occlusive oily phase that conveys a hydrating effect and enhances penetration of the corticosteroid into the dermis. They are not suited for use in the axilla, groin, or other intertriginous areas where maceration and folliculitis may develop secondary to the occlusive effect.
- Creams are more cosmetically desirable for some patients. They may be used in intertriginous areas even though their lower oil content makes them more drying than ointments.
- Topical corticosteroids are applied two to four times daily during long-term therapy.
- Adverse effects include local tissue atrophy, skin degeneration, and striae. If detected early, these effects may be reversible with discontinuation. Thinning of the epidermis may result in visibly distended capillaries (telangiectasias) and purpura. Acneiform eruptions and masking of symptoms of bacterial or fungal skin infections have been reported. Systemic consequences include risk of suppression of the hypothalamic-pituitary-adrenal axis, hyperglycemia, and development of cushingoid features. Tachyphylaxis and rebound flare of psoriasis after abrupt cessation of therapy can also occur.

### Vitamin D Analogs

- Vitamin D and its analogs inhibit keratinocyte differentiation and proliferation and have antiinflammatory effects by reducing IL-8, IL-2, and other cytokines. Use of vitamin D itself is limited by its propensity to cause hypercalcemia.

**TABLE 16-1** Selected Topical Corticosteroids and Vasoconstricting Potency

<b>Corticosteroids</b>	<b>Dosage Forms/Strength (%)</b>	<b>USP Potency Ratings<sup>a</sup></b>	<b>Vasoconstrictive Potency Rating<sup>b</sup></b>
Aldometasone dipropionate	Cream 0.05	Low	VI
	Ointment 0.05	Low	V
Amcinonide	Lotion, ointment 0.1	High	II
	Cream 0.1	High	III
Bedomethasone dipropionate	Cream, lotion, ointment 0.025	Medium	—
Betamethasone benzoate	Cream, gel 0.025	Medium	III
	Ointment 0.025	Medium	IV
Betamethasone dipropionate	Cream AF (optimized vehicle) 0.05	Very high	I
	Cream 0.05	High	III
	Gel, lotion, ointment (optimized vehicle) 0.05	Very high	I
	Lotion 0.05	High	V
	Ointment 0.05	High	II
	Topical aerosol 0.1	High	—
Betamethasone valerate	Cream 0.01, 0.05, 0.1	Medium	V
	Lotion, ointment 0.05, 0.1	Medium	III
	Foam 0.12	Medium	IV
Clobetasol propionate	Cream, ointment, solution, foam 0.05	Very high	I
Clobetasol butyrate	Cream, ointment 0.05	Medium	—
Clocortolone pivalate	Cream 0.1	Low	—
Desonide	Cream, lotion, ointment 0.05	Low	VI
Desoximetasone	Cream 0.05	Medium	II
	Cream, ointment 0.25	High	II
	Gel 0.05	High	II
Dexamethasone	Gel 0.1	Low	VII
	Topical aerosol 0.01, 0.04	Low	VII
Dexamethasone sodium phosphate	Cream 0.1	Low	VII
Diflorasone diacetate	Cream 0.05	High	III
	Ointment 0.05	High	II
	Ointment (optimized vehicle) 0.05	Very high	II
Diflucortolone valerate	Cream, ointment 0.1	Medium	—
Flumethasone pivalate	Cream, ointment 0.03	Low	—
Fluocinolone acetonide	Cream 0.01	Medium	VI
	Cream 0.025	Medium	V
	Cream 0.2	High	—
	Ointment 0.025	Medium	IV
	Solution 0.01	Medium	VI
	Solution 0.05	High	II
Fluocinonide	Gel, cream, ointment 0.05	High	II
	Solution 0.05	High	II
Flurandrenolide	Cream, ointment 0.0125	Low	—
	Ointment 0.05	Medium	IV
	Cream, lotion 0.05	Medium	V
	Tape 4 mcg/cm <sup>2</sup>	Medium	I
Fluticasone propionate	Cream 0.05	Medium	IV
	Ointment 0.05	Medium	III
Halcinonide	Cream 0.025, 0.1	High	II
	Ointment 0.1	High	III
	Solution 0.1	High	—

*(continued)*

**TABLE 16-1** Selected Topical Corticosteroids and Vasoconstricting Potency (Continued)

Corticosteroids	Dosage Forms/Strength (%)	USP Potency Ratings <sup>a</sup>	Vasoconstrictive Potency Rating <sup>b</sup>
Halobetasol propionate	Cream, ointment 0.05	Very high	I
Hydrocortisone	Cream, lotion, ointment (all strengths)	Low	VII
Hydrocortisone acetate	Cream, lotion, ointment (all strengths)	Low	VII
Hydrocortisone butyrate	Cream 0.1	Medium	V
	Ointment 0.1	Medium	—
Hydrocortisone valerate	Cream 0.2	Medium	V
	Ointment 0.2	Medium	IV
Methylprednisolone acetate	Cream, ointment 0.25	Low	VII
	Ointment 1	Low	VII
Mometasone furoate	Cream 0.1	Medium	IV
	Lotion, ointment 0.1	Medium	II
Triamcinolone acetonide	Cream, ointment 0.1	Medium	IV
	Cream, lotion, ointment 0.025	Medium	—
	Cream (Aristocort) 0.1	Medium	VI
	Cream (Kenalog) 0.1	High	IV
	Lotion 0.1	Medium	V
	Ointment (Aristocort, Kenalog) 0.1	High	III
	Cream, ointment 0.5	High	III
Topical aerosol 0.015	Medium	—	

<sup>a</sup>USP ratings are low, medium, high, and very high.

<sup>b</sup>Vasoconstriction potency scale is I (highest) to VII (lowest); — denotes unknown vasoconstrictive properties.

- **Calcipotriene** (Dovonex) is a synthetic vitamin D analog used for mild to moderate plaque psoriasis. Improvement is usually seen within 2 weeks of treatment, and approximately 70% of patients demonstrate marked improvement after 8 weeks. Adverse effects occur in about 10% of patients and include lesional and perilesional burning and stinging. Calcipotriene 0.005% cream, ointment, or solution is applied one or two times a day (no more than 100 g/wk).
- Calcitriol and tacalcitol are other vitamin D derivatives that have been studied for treatment of psoriasis.

### Tazarotene

- **Tazarotene** (Tazorac) is a synthetic retinoid that is hydrolyzed to its active metabolite, tazarotenic acid, which modulates keratinocyte proliferation and differentiation. It is available as a 0.05% or 0.1% gel and cream and is applied once daily (usually in the evening) for mild to moderate plaque psoriasis. Adverse effects are dose- and frequency related and include mild to moderate pruritus, burning, stinging, and erythema. Application of the gel to eczematous skin or to more than 20% of body surface area is not recommended because this may lead to extensive systemic absorption. Tazarotene is often used with topical corticosteroids to decrease local adverse effects and increase efficacy.

## SECOND-LINE TOPICAL PHARMACOTHERAPY

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### Coal Tar

- **Coal tar** contains numerous hydrocarbon compounds formed from distillation of bituminous coal. Ultraviolet B (UVB) light-activated coal tar photoadducts with epidermal DNA and inhibits DNA synthesis. This normalized epidermal replication rate reduces plaque elevation.
- Coal tar preparations of 2% to 5% tar are available in lotions, creams, shampoos, ointments, gels, and solutions. It is usually applied directly to lesions in the evening and allowed to remain in skin contact through the night. It may also be used in bathwater.
- Coal tar is an effective treatment, but it is time-consuming, causes local irritation, has an unpleasant odor, stains skin and clothing, and increases sensitivity to UV light (including the sun).
- The risk of carcinogenicity is low, but there may be a higher rate of nonmyeloma skin cancers in patients chronically exposed to coal tar and UV light.

### Anthralin

- **Anthralin** possesses antiproliferative activity on keratinocytes, inhibiting DNA synthesis by intercalation between DNA strands.
- Because anthralin exerts its clinical effects at low cellular concentrations, therapy usually starts with low concentrations (0.1% to 0.25%) with gradual increases to higher concentrations (0.5% to 1%). Cream and ointment formulations are usually applied in the evening and allowed to remain overnight.
- Alternatively, short-contact anthralin therapy (SCAT) with application for 10 to 20 minutes of higher concentrations (1% to 5%) in water-soluble vehicles is effective with decreased local adverse effects.
- Anthralin products must be applied only to affected areas because contact with uninvolved skin may result in excessive irritation and staining, which usually disappear within 1 to 2 weeks of discontinuation. Staining of affected plaques indicates a positive response because cell turnover has been slowed enough to take up the stain.
- Inflammation, irritation, and staining of skin and clothing are often therapy-limiting effects.

## FIRST-LINE SYSTEMIC PHARMACOTHERAPY

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- Biologic therapies—primarily immunomodulating agents designed to alter immune responses—comprise first-line systemic therapy.
- **Infliximab** (Remicade) is a chimeric monoclonal antibody directed against TNF- $\alpha$ . Recently, its indications have been expanded to include psoriatic arthritis and treatment of adults with chronic severe plaque psoriasis. An advantage over other systemic psoriasis treatments is that infliximab does not adversely affect blood counts, hepatic enzyme levels, or kidney function. The recommended dose is 5 mg/kg as an IV infusion at weeks 0, 2, and 6, then every 8 weeks thereafter. For psoriatic arthritis, it may be used with or without methotrexate. Adverse effects include headaches, fever, chills, fatigue, diarrhea, pharyngitis, upper respiratory and urinary tract infec-

tions. Hypersensitivity reactions (urticaria, dyspnea, hypotension) and lymphoproliferative disorders have been reported.

- **Etanercept** (Enbrel) is a fusion protein that binds TNF- $\alpha$ , competitively interfering with its interaction with cell-bound receptors. Unlike the chimeric infliximab, etanercept is fully humanized, thereby minimizing the risk of immunogenicity. Etanercept is FDA approved for reducing signs and symptoms and inhibiting the progression of joint damage in patients with psoriatic arthritis. It can be used in combination with methotrexate in patients who do not respond adequately to methotrexate alone. It is also indicated for adult patients with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. The recommended dose for psoriatic arthritis is 50 mg subcutaneously once per week. For plaque psoriasis, the dose is 50 mg subcutaneously twice weekly (administered 3 or 4 days apart) for 3 months followed by a maintenance dose of 50 mg per week. Adverse effects include local reactions at the injection site (20% of patients), respiratory tract and GI infections, abdominal pain, nausea and vomiting, headaches, and rash. Serious infections (including tuberculosis) and malignancies are rare.
- **Adalimumab** (Humira) is a human immunoglobulin G<sub>1</sub> monoclonal TNF- $\alpha$  antibody. The binding of adalimumab results in inactivation of the proinflammatory cytokine TNF- $\alpha$ . It is indicated for psoriatic arthritis and treatment of adults with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy. The recommended dose for psoriatic arthritis is 40 mg subcutaneously every other week. The recommended dose for adults with plaque psoriasis is an initial dose of 80 mg, followed by 40 mg every other week starting 1 week after the initial dose. The most common adverse reactions are infections (e.g., upper respiratory, sinusitis), injection site reactions, headache, and rash.
- **Alefacept** (Amevive) is a dimeric fusion protein that binds to CD2 on T cells to inhibit cutaneous T-cell activation and proliferation. It also produces a dose-dependent decrease in circulating total lymphocytes. Alefacept is approved for treatment of moderate to severe plaque psoriasis and is also effective for treatment of psoriatic arthritis. Significant response is usually achieved after about 3 months of therapy. The recommended dose is 15 mg intramuscularly once weekly for 12 weeks. Adverse effects are mild and include pharyngitis, flu-like symptoms, chills, dizziness, nausea, headache, injection site pain and inflammation, and nonspecific infection.
- **Efalizumab** (Raptiva) is a humanized monoclonal antibody that inhibits CD11- $\alpha$  integrin, which is involved in T-cell activation, migration into skin, and cytotoxic function. It is approved for adults with chronic, moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. The recommended dose is a single 0.7 mg/kg subcutaneous conditioning dose followed by weekly subcutaneous doses of 1 mg/kg (200 mg maximum single dose). The most frequent adverse effects are mild to moderate flu-like complaints such as headache, nausea, chills, nonspecific infection, pain, fever, and asthenia. Cases of exacerbation of psoriasis on discontinuation have been reported, leading to the suggestion that continuous treatment may be required to maintain disease suppression.

## SECOND-LINE SYSTEMIC PHARMACOTHERAPY

- **Acitretin** (Soriatane) is a retinoic acid derivative and the active metabolite of etretinate. It is indicated for severe psoriasis, including erythrodermic and generalized pustular types. However, it is more useful as an adjunct in the treatment of plaque psoriasis. It has shown good results when combined with other therapies, including UVA combined with oral methoxsalen (PUVA) and UVB and topical calcipotriol. The initial recommended dose is 25 or 50 mg; therapy is continued until lesions have resolved. It is better tolerated when taken with meals. Adverse effects include hypervitaminosis A (dry lips/cheilitis, dry mouth, dry nose, dry eyes/conjunctivitis, dry skin, pruritus, scaling, and hair loss), hepatotoxicity, skeletal changes, hypercholesterolemia, and hypertriglyceridemia. Acitretin is a teratogen and is contraindicated in females who are pregnant or who plan pregnancy within 3 years after drug discontinuation.
- **Cyclosporine** demonstrates immunosuppressive activity by inhibiting the first phase of T-cell activation. It also inhibits release of inflammatory mediators from mast cells, basophils, and polymorphonuclear cells. It is used in the treatment of both cutaneous and arthritis manifestations of severe psoriasis. The usual dose is between 2.5 and 5 mg/kg/day given in two divided doses. Adverse effects include nephrotoxicity, hypertension, hypomagnesemia, hyperkalemia, alterations in liver function tests, elevations of serum lipids, GI intolerance, paresthesias, hypertrichosis, and gingival hyperplasia. Cumulative treatment for more than 2 years may increase the risk of malignancy, including skin cancers and lymphoproliferative disorders.
- **Tacrolimus**, an immunosuppressant that inhibits T-cell activation, is a useful alternative in severe recalcitrant psoriasis. Although it is not FDA approved for this indication, patients have received oral doses of 0.05 mg/kg daily, with increases up to 0.15 mg/kg daily, depending on results. Adverse effects include diarrhea, nausea, paresthesias, hypertension, tremor, and insomnia.
- **Methotrexate**, an antimetabolite, is indicated for moderate to severe psoriasis. It is particularly beneficial for psoriatic arthritis. It is also indicated for patients refractory to topical or UV therapy. Methotrexate can be administered orally, subcutaneously, or intramuscularly. The starting dose is 7.5 to 15 mg per week, increased incrementally by 2.5 mg every 2 to 4 weeks until response; maximal doses are approximately 25 mg/wk. Adverse effects include nausea, vomiting, mucosal ulceration, stomatitis, malaise, headache, macrocytic anemia, and hepatic and pulmonary toxicity. Nausea and macrocytic anemia can be ameliorated by giving oral folic acid 1 to 5 mg/day. Methotrexate should be avoided in patients with active infections and in those with liver disease. It is contraindicated in pregnancy because it is teratogenic.
- **Mycophenolate mofetil** (CellCept) inhibits DNA and RNA synthesis and has been shown to have a specific lymphocyte antiproliferative effect. Although not FDA approved for this indication, oral mycophenolate mofetil appears effective in the treatment of moderate to severe plaque psoriasis. The usual dose is 500 mg orally four times a day, up to a maximum of 4 g/day. Common adverse effects include GI toxicity (diarrhea, nausea, vomiting), hematologic effects (anemia, neutropenia, thrombocytopenia), and viral and bacterial infections. Lymphoproliferative disease or lymphoma has been reported.

- **Sulfasalazine** is an antiinflammatory agent that inhibits 5-lipoxygenase. It is used selectively as an alternative treatment, particularly in patients with concurrent psoriatic arthritis. When used alone, it is not as effective as methotrexate, PUVA, or acitretin. However, it has a relatively high margin of safety. The usual oral dose is 3 to 4 g/day for 8 weeks. Its adverse effects are similar to other sulfonamide antibiotics.
- **6-Thioguanine** is a purine analog that has been used as an alternative treatment for psoriasis when conventional therapies have failed. The typical dose is 80 mg twice weekly, increased by 20 mg every 2 to 4 weeks; the maximum dose is 160 mg three times a week. Adverse effects include bone marrow suppression, GI complications (e.g., nausea, diarrhea), and elevation of liver function tests. 6-Thioguanine may be less hepatotoxic and therefore more useful than methotrexate in hepatically compromised patients with severe psoriasis.
- **Hydroxyurea** inhibits cell synthesis in the S phase of the DNA cycle. It is used selectively in the treatment of psoriasis, especially in those with liver disease who would be at risk of adverse effects with other agents. However, it is less effective than methotrexate. The typical dose is 1 g/day, with a gradual increase to 2 g/day as needed and as tolerated. Adverse effects include bone marrow toxicity with leukopenia or thrombocytopenia, cutaneous reactions, leg ulcers, and megaloblastic anemia.

## PHOTOTHERAPY AND PHOTOCHEMOTHERAPY

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- **UVB light** (290 to 320 nm) therapy is an important phototherapeutic intervention for psoriasis. The most effective wavelength is 310 to 315 nm, which led to development of a UVB narrowband light source, in which 83% of the UVB emission is at 310 to 313 nm. Topical and systemic psoriatic therapies are used adjunctively to hasten and improve the response to UVB phototherapy. Emollients enhance efficacy of UVB and can be applied just before treatments. Combining short-contact anthralin, calcipotriene, or topical retinoids to UVB may also improve results. However, topical application should be done after or at least 2 hours before UVB therapy because phototherapy can inactivate the topical product. UVB phototherapy may also be more effective when added to systemic treatments such as methotrexate and oral retinoids.
- **PUVA** is a photochemotherapeutic approach for selected patients. Candidates for PUVA therapy usually have moderate to severe, incapacitating psoriasis unresponsive to conventional topical and systemic therapies. Systemic PUVA consists of oral ingestion of a potent photosensitizer such as methoxsalen (8-methoxypsoralen) at a constant dose (0.6 to 0.8 mg/kg) and variable doses of UVA depending on patient skin phototype and history of previous response to UV radiation. Two hours after ingesting psoralen, the patient is exposed to UVA light. Photochemotherapy is performed two or three times a week. Partial clearing occurs in most patients by the twenty-fifth treatment.
- Another method that may have less carcinogenic potential is to topically deliver the photosensitizer (methoxsalen) to the skin by adding it to bath water (**bath PUVA**) or as a topical cream (**PUVA cream**) instead of through systemic administration. Advantages of this approach include minimal risk of systemic effects, overall reduction of PUVA dose to one-

fourth of that required with conventional PUVA, and reduction in the risk of nonmelanoma skin cancer.

## COMBINATIONAL, ROTATIONAL, AND SEQUENTIAL THERAPY

- If monotherapy with a systemic agent does not provide optimal outcomes, combining systemic therapies with other modalities may enhance benefit. The dose of each agent may often be reduced, resulting in lower toxicity. Combinations include:
  - ✓ Acitretin + UVB light
  - ✓ Acitretin + photochemotherapy using UVA light (PUVA)
  - ✓ Methotrexate + UVB light
  - ✓ PUVA + UVB light
  - ✓ Methotrexate + cyclosporine
- Rotational therapy involves using a biologic regimen for a limited period and then switching to a nonbiologic regimen, continuing on a rotational basis. One objective of this approach is to minimize cumulative drug toxicity.
- Sequential therapy involves rapid clearing of psoriasis with aggressive therapy (e.g., cyclosporine), followed by a transitional period in which a safer drug such as acitretin is started at maximal dosing. Subsequently, a maintenance period using acitretin in lower doses or in combination with UVB or PUVA can be continued.

## EVALUATION OF THERAPEUTIC OUTCOMES

- Patients should understand the general concepts of therapy and the importance of adherence.
- Monitoring for disease resolution and side effects is critical to successful therapy. A positive response is noted with the normalization of involved areas of skin, as measured by reduced erythema and scaling, as well as reduction of plaque elevation.
- The psoriasis area and severity index is a uniform method to determine the extent of body surface area affected, along with the degree of erythema, induration, and scaling. Severity scores are rated as <12 (mild), 12 to 18 (moderate), and >18 (severe).
- The Physician Global Assessment can also be used to summarize erythema, induration, scaling, and extent of plaques relative to baseline assessment.
- The National Psoriasis Foundation Psoriasis Score incorporates quality of life and the patient's perception of well-being as well as induration, extent of involvement, the physician's static global assessment, and pruritus.
- Achievement of efficacy by any therapeutic regimen requires days to weeks. Initial dramatic response may be achieved with some agents such as corticosteroids. However, sustained benefit with pharmacologically specific antipsoriatic therapy may require 2 to 8 weeks or longer for clinically meaningful response.

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*See Chap. 101, Psoriasis, authored by Dennis P. West, Amy Lloyd, Lee E. West, Kimberly A. Bauer, Maria Letizia Musumeci, and Giuseppe Micali, for a more detailed discussion of this topic.*

## DEFINITION

- The word *dermatitis* denotes an inflammatory erythematous rash. The disorders discussed in this chapter include contact dermatitis, seborrheic dermatitis, diaper dermatitis, and atopic dermatitis. Drug-induced skin disorders have been associated with most commonly used medications and may present as maculopapular eruptions, fixed-drug eruptions, and photosensitivity reactions.

## PATHOPHYSIOLOGY

- *Contact dermatitis* is an acute or chronic inflammatory skin condition resulting from contact of an inciting factor with the skin. In *allergic contact dermatitis*, an antigenic substance triggers Langerhans cells, and their immunologic responses produce the allergic skin reaction, sometimes several days later. *Irritant contact dermatitis* is caused by an organic substance that usually results in a reaction within a few hours of exposure.
- *Diaper dermatitis* (diaper rash) is an acute, inflammatory dermatitis of the buttocks, genitalia, and perineal region. The reaction is a type of contact dermatitis, as it results from direct fecal and moisture contact with the skin in an occlusive environment.
- *Atopic dermatitis* is an inflammatory condition with genetic, environmental, and immunologic mechanisms. Many immune cells have demonstrated abnormalities, including Langerhans cells, monocytes, macrophages, lymphocytes, mast cells, and keratinocytes.
- *Drug-induced cutaneous reactions* tend to be immunologic in origin and relate to hypersensitivity, but some reactions are nonallergic. The pathogenesis of fixed-drug reactions is not well understood.
- Drug-induced photosensitivity reactions are divided into *phototoxicity* (a nonimmunologic reaction) and *photoallergic reactions* (an immunologic reaction). The latter form is far less common. Medications associated with photosensitivity reactions include fluoroquinolones, nonsteroidal anti-inflammatory drugs, phenothiazines, antihistamines, estrogens, progestins, sulfonamides, sulfonyleureas, thiazide diuretics, and tricyclic antidepressants.

## CLINICAL PRESENTATION

- The skin lesions of dermatitis may or may not be painful or pruritic. Typically, lesions are described as being less than or greater than 0.5 cm in diameter.
- *Macules* are circumscribed, flat lesions of any shape or size that differ from surrounding skin because of their color. They may result from hyperpigmentation, hypopigmentation, vascular abnormalities, capillary dilatation (erythema), or purpura.

- *Papules* are small, solid, elevated lesions that are usually less than 1 cm in diameter. They may result from metabolic deposits in the dermis, from localized dermal cellular infiltrates, or from localized hyperplasia of cellular elements in the dermis and epidermis.
- *Plaques* are mesa-like elevations that occupy a relatively large surface area in comparison with their height above the skin surface.
- *Seborrheic dermatitis* typically occurs around the areas of skin rich in sebaceous follicles (e.g., the face, ears, scalp, and upper trunk). In infants with involvement of the scalp, the condition is commonly referred to as cradle cap.
- *Diaper dermatitis* results in erythematous patches, skin erosions, vesicles, and ulcerations. Although commonly seen in infants, it can occur in adults who wear diapers for incontinence.
- *Atopic dermatitis* in its acute phase is associated with intensely pruritic, erythematous papules and vesicles over erythematous skin. Scratching may result in excoriations and exudates. Subacute lesions are thicker, paler, scaly, erythematous and excoriated plaques. Chronic lesions are characterized by thickened plaques, accentuated skin markings (lichenification), and fibrotic papules. In all phases, the atopic skin has a dry luster.
- *Drug-induced cutaneous reactions* are unpredictable, ranging from mild, self-limiting episodes to more severe, life-threatening conditions. Selected drugs implicated in various types of skin eruptions are included in Table 17-1. *Maculopapular eruptions* are most common and often involve the

**TABLE 17-1** Types of Drug-Induced Skin Eruptions

Clinical Presentation	Pattern and Distribution of Skin Lesions	Mucous Membrane Involvement	Implicated Drugs	Treatment
Erythema multiforme	Target lesions, limbs	Absent	Anticonvulsants (including lamotrigine), sulfonamide antibiotics, allopurinol, NSAIDs, dapsone	Supportive <sup>a</sup>
Stevens-Johnson's syndrome	Atypical targets, widespread	Present	As above	IV immunoglobulins, cyclosporine
Toxic epidermal necrolysis	Epidermal necrosis with skin detachment	Present	As above	Supportive <sup>a</sup>
Pseudoporphyria	Skin fragility, blister formation in photodistribution	Absent	Tetracycline, furosemide, naproxen	Supportive <sup>a</sup>
Linear IgA disease	Bullous dermatosis	Present or absent	Vancomycin, lithium, diclofenac, piroxicam, amiodarone	Supportive <sup>a</sup>
Pemphigus	Flaccid bullae, chest	Present or absent	Penicillamine, captopril, piroxicam, penicillin, rifampin	Supportive <sup>a</sup>
Bullous pemphigoid	Tense bullae, widespread	Present or absent	Furosemide, penicillamine, penicillins, sulfasalazine, captopril	Supportive <sup>a</sup>

IgA, immunoglobulin A; NSAIDs, nonsteroidal antiinflammatory drugs.

<sup>a</sup>Supportive care includes administration of systemic glucocorticoids until all symptoms of active disease disappear.

trunk or pressure areas in a symmetric fashion. Early eruptions appear within a few hours to 3 days after drug ingestion, whereas late eruptions occur up to 9 days after exposure.

- A *fixed-drug reaction* usually presents as an erythematous or hyperpigmented round or oval lesion usually between a few millimeters to 20 cm in diameter. The oral mucosa and genitalia are the most common sites involved, but lesions can appear anywhere on the body. If the patient takes the drug again, the reaction tends to recur within 30 minutes to 8 hours in the same location. Although this is highly indicative of a fixed-drug reaction, rechallenge should be avoided when possible.
- *Sun-induced drug eruptions* appear similar to a sunburn and present with erythema, papules, edema, and sometimes vesicles. They appear in areas exposed to sunlight (e.g., the ears, nose, cheeks, forearms, and hands).

## DIAGNOSIS

- Patient age and hormonal status in women should be considered in the initial evaluation of patients with skin disorders. Older patients are predisposed to developing psoriasis, seborrhea, and other skin conditions. Atopic dermatitis is most likely to occur in children. Menopausal women tend to develop brown hyperpigmentation, or melasma. Pregnant women may develop hyperpigmentation of the areola and genitalia as well as melasma.
- Patients presenting with a rash or skin lesion should be evaluated for potential anaphylaxis or angioedema (e.g., symptoms of difficulty in breathing, fever, nausea, vomiting).
- The area involved and the number of lesions present are important considerations. A rash involving only the arms and legs suggests a nonsystemic cause, whereas involvement of the trunk as well as the arms and legs indicates a systemic cause.
- Lesions should be inspected for color, texture, size, and temperature. Areas that are oozing, erythematous, and warm to the touch may be infected.
- The duration of the skin condition should be determined, and the temporal relationship with any new medications should be established.
- Assessment for potential drug-induced skin disorders begins with a comprehensive medication history, including episodes of previous drug allergies.
- Diagnostic criteria for atopic dermatitis include the presence of pruritus with three or more of the following: (1) history of flexural dermatitis of the face in children younger than 10 years of age; (2) history of asthma or allergic rhinitis in the child or a first-degree relative; (3) history of generalized xerosis (dry skin) within the past year; (4) visible flexural eczema; (5) onset of rash before 2 years of age.

## DESIRED OUTCOME

- The goals of treatment for contact dermatitis are to relieve the patient's symptoms, identify the underlying cause, identify and remove offending agents, and avoid future exposure to likely offending agents.

- Therapeutic goals for seborrheic dermatitis are to loosen and remove scales, prevent yeast colonization, control secondary infections, and reduce itching and erythema.
- General treatment goals for patients with skin disorders are to relieve bothersome symptoms, remove precipitating factors, prevent recurrences, avoid adverse treatment effects, and improve quality of life.

## TREATMENT

### CONTACT DERMATITIS

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- Initial treatment should focus on identification and removal of the offending agent.
- Products that relieve itching, rehydrate the skin, and decrease the weeping of lesions provide some immediate relief.
- In the acute inflammatory stage, wet dressings are preferred because ointments and creams further irritate the tissue.
- Astringents such as **aluminum acetate** or **witch hazel** decrease weeping from lesions, dry out the skin, and relieve itching. They are applied as a wet dressing for no longer than 7 days.
- For chronic dermatitis, lubricants, emollients, or moisturizers should be applied after bathing. Soap-free cleansers and colloidal oatmeal products also alleviate itching and soothe the skin.
- If the reaction does not subside within a few days, **topical** or **oral corticosteroids** may be needed.

### SEBORRHEIC DERMATITIS

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- Depending on the area of the body that is affected, topical solutions or scalp shampoos may be used.
- Scalp involvement can be treated with twice-daily **topical corticosteroids** in conjunction with a shampoo containing **selenium sulfide**, **coal tar**, or **salicylic acid** to help soften and remove scales.
- **Topical calcineurin inhibitors** (e.g., **tacrolimus ointment**, **pimecrolimus cream**) have fungicidal and antiinflammatory properties and can be used for the scalp or face.

### DIAPER DERMATITIS

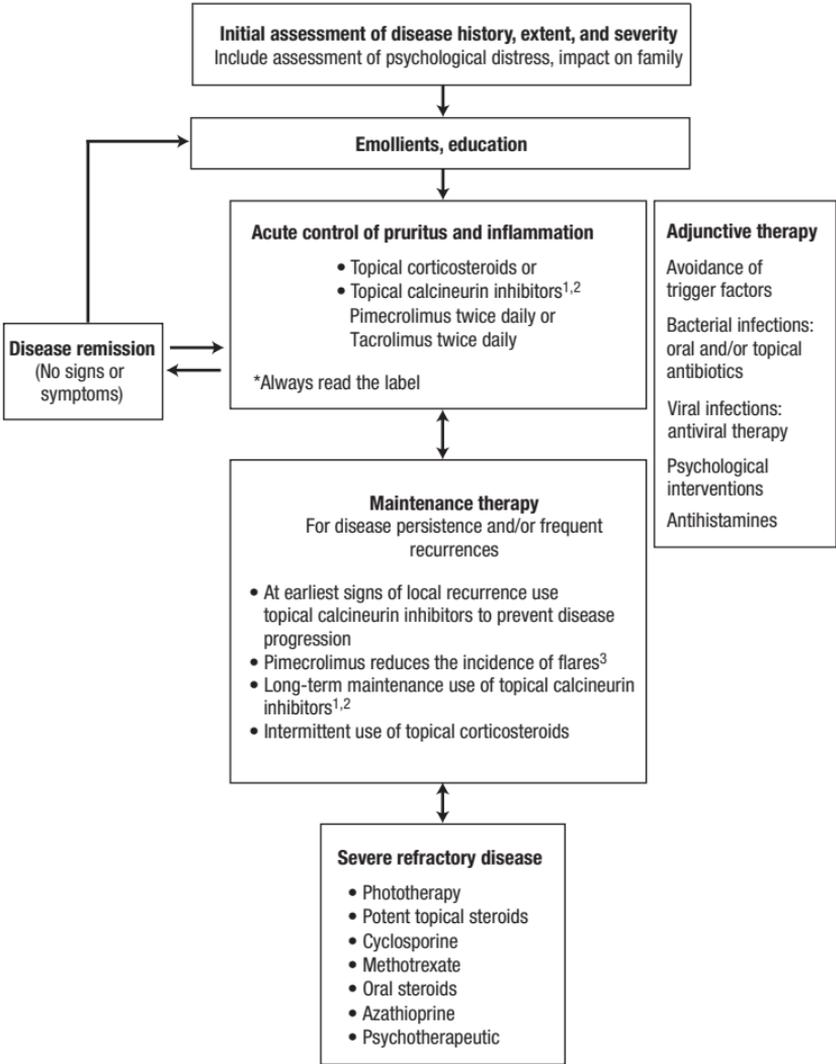
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- Effective treatment involves frequent diaper changes and keeping the area dry.
- Lukewarm water and mild soap can be used to clean the area thoroughly, which should then be allowed to dry.
- Occlusive agents (e.g., **zinc oxide**, **titanium dioxide**, **petrolatum**) should be generously applied to the area before the clean diaper is put on the child.

### ATOPIC DERMATITIS

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- An algorithm for the treatment of atopic dermatitis is provided in Fig. 17-1.
- Possible aggravating factors that may trigger a flare-up should be identified and avoided.



1. The evidence of the safety and efficacy of pimecrolimus was derived from studies primarily in patients with mild-to-moderate atopic dermatitis; tacrolimus data was derived from moderate-to-severe patients.
2. Pimecrolimus has been studied in clinical trials in infants as young as 3 months, as compared with tacrolimus from 2 years.
3. Clinical trial data have proven that pimecrolimus reduces incidence of flares, these trials have not been performed for tacrolimus.

**FIGURE 17-1.** Treatment of atopic dermatitis.

- Moisturizers, including emollients, occlusives, and humectants should be recommended based on the needs of individual patients.
- Topical corticosteroids may be used for short-term treatment of acute flare-ups (see Table 16-1 in Chap. 16 on *Psoriasis*). Most corticosteroids are applied once or twice daily. High-potency agents are used for less than 3 weeks for flare-ups or for lichenified (thickened) lesions. Moderate-potency steroids may be used for more chronic conditions, and low-

potency steroids are usually used in children. When used in combination with other topical agents such as moisturizers, the corticosteroid should be applied first, rubbed in well, and followed by the other product.

- **Antihistamines** are frequently used, but few clinical studies support their efficacy. A sedating antihistamine (e.g., **hydroxyzine**, **diphenhydramine**) can offer an advantage by facilitating sleep because pruritus is often worse at night.
- **Doxepin** is a tricyclic antidepressant that inhibits histamine receptors. It may be helpful in atopic patients who have a component of depression. Doses of 10 to 75 mg at night and up to 75 mg twice daily in adults have been used.
- The topical immunomodulators **tacrolimus** (Protopic) and **pimecrolimus** (Elidel) inhibit calcineurin, which normally initiates T-cell activation. These agents can be used on all parts of the body for prolonged periods without producing corticosteroid-induced adverse effects. Tacrolimus ointment 0.03% and 0.1% is applied twice daily; the lower strength is preferred in children with moderate to severe atopic dermatitis. The most common adverse effect is transient itching and burning at the site of application. Pimecrolimus cream 1% is applied twice daily for mild to moderate atopic dermatitis in adults and children older than age 2.
- Coal tar preparations reduce itching and skin inflammation and are available as **crude coal tar** (1% to 3%) or **liquor carbonis detergens** (5% to 20%). They have been used in combination with **topical corticosteroids**, as adjuncts to permit effective use of lower corticosteroid strengths, and in conjunction with **ultraviolet light** therapies. Patients can apply the product at bedtime and wash it off in the morning. Factors limiting coal tar use include its strong odor and staining of clothing. Coal tar preparations should not be used on acute oozing lesions, which would result in stinging and irritation.

## CUTANEOUS DRUG REACTIONS

- Most maculopapular reactions disappear within a few days after discontinuing the agent, so symptomatic control of the affected area is the primary intervention. **Topical corticosteroids** and **oral antihistamines** can relieve pruritus. In severe cases, a short course of **systemic corticosteroids** may be warranted.
- Treatment of fixed drug reactions involves removal of the offending agent. Other therapeutic measures include **corticosteroids**, **antihistamines** to relieve itching, and perhaps cool water compresses on the affected area.
- Photosensitivity reactions typically resolve with drug discontinuation. Some patients benefit from **topical corticosteroids** and **oral antihistamines**, but these are relatively ineffective. **Systemic corticosteroids** (e.g., **oral prednisone** 1 mg/kg/day tapered over 3 weeks) is more effective for these patients.

## EVALUATION OF THERAPEUTIC OUTCOMES

- Information regarding causative factors, avoidance of substances that trigger skin reactions, and the potential benefits and limitations of non-drug and drug therapy should be conveyed to patients.

## SECTION 3 | Dermatologic Disorders

- Patients with chronic skin conditions should be evaluated periodically to assess disease control, the efficacy of current therapy, and the presence of possible adverse effects.

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*See Chap. 99, Dermatologic Drug Reactions and Self-Treatable Skin Disorders, and Chap. 102, Atopic Dermatitis, both authored by Nina H. Cheigh, for a more detailed discussion of this topic.*

## DEFINITIONS

- Hyperfunction of the adrenal glands occurs in Cushing's syndrome, a disorder caused by excessive secretion of cortisol by the adrenal gland (hypercortisolism). Other causes of adrenal gland hyperfunction include primary and secondary aldosteronism (not discussed in this chapter; refer to textbook Chap. 79 for more information on these disorders).
- Adrenal gland hypofunction is associated with primary (Addison's disease) or secondary adrenal insufficiency. Adrenal insufficiency occurs when the adrenal glands do not produce enough cortisol and, in some cases, aldosterone.

## CUSHING'S SYNDROME

### PATHOPHYSIOLOGY

- Cushing's syndrome results from the effects of supraphysiologic levels of glucocorticoids originating from either exogenous administration or from endogenous overproduction by the adrenal gland (adrenocorticotrophic hormone [ACTH]-dependent) or by abnormal adrenocortical tissues (ACTH-independent).
- ACTH-dependent Cushing's syndrome is usually caused by overproduction of ACTH by the pituitary gland, causing adrenal hyperplasia (Cushing's disease). Pituitary adenomas account for about 80% of these cases. Ectopic ACTH-secreting tumors and nonneoplastic corticotropin hypersecretion are responsible for the remaining 20% of cases.
- Ectopic ACTH syndrome refers to excessive ACTH production resulting from an endocrine or nonendocrine tumor, usually of the pancreas, thyroid, or lung (e.g., small-cell lung cancer).
- ACTH-independent Cushing's syndrome is usually caused by adrenal adenomas and carcinomas.

### CLINICAL PRESENTATION

- The most common findings in Cushing's syndrome are central obesity and facial rounding (90% of patients). Peripheral obesity and fat accumulation occur in 50% of patients. Fat accumulation in the dorsocervical area (buffalo hump) is a nonspecific finding, but increased supraclavicular fat pads are more specific for Cushing's syndrome. Patients are often described as having moon facies and a buffalo hump.
- Many patients complain of myopathies (65%) or muscular weakness (85%).

- Striae are usually present along the lower abdomen and take on a red to purple color.
- Hypertension is seen in 75% to 85% of patients with diastolic blood pressures >119 mm Hg noted in over 20% of patients.
- Glucose intolerance is seen in 60% of patients.
- Psychiatric changes can occur in up to 55% of patients.
- Approximately 50% to 60% of patients develop Cushing-induced osteoporosis; about 40% present with back pain and 20% will progress to compression fractures of the spine.
- Gonadal dysfunction is common with amenorrhea seen in up to 75% of women.
- Excess androgen secretion is responsible for 80% of women presenting with hirsutism.

## DIAGNOSIS

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- The presence of hypercortisolism can be established with a midnight plasma cortisol, late-night (11 PM) salivary cortisol, 24-hour urine free cortisol, and/or low-dose dexamethasone suppression test.
- Other tests that can help determine the etiology include the high-dose dexamethasone suppression test, plasma ACTH test, metyrapone stimulation test, corticotropin-releasing hormone stimulation test or inferior petrosal sinus sampling.
- Abnormal adrenal anatomy is effectively identified using high-resolution computed tomography scanning and perhaps magnetic resonance imaging.

## DESIRED OUTCOME

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- The goals of treatment for Cushing's syndrome are to limit morbidity and mortality and return the patient to a normal functional state by removing the source of hypercortisolism without causing any pituitary or adrenal deficiencies.

## TREATMENT

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- Treatment plans in Cushing's syndrome based on etiology are included in Table 18-1.

### Nonpharmacologic Therapy

- The treatment of choice for both ACTH-dependent and ACTH-independent Cushing's syndrome is surgical resection of any offending tumors.
- Pituitary irradiation provides clinical improvement in about 50% of patients, but improvement may not be seen for 6 to 12 months and pituitary-dependent hormone deficiencies can occur.

### Pharmacotherapy

#### *Steroidogenic Inhibitors*

- These agents are used primarily in preparation for surgery, as adjunctive treatment after unsuccessful surgery or radiotherapy, or for refractory patients who are not surgical candidates. They should not be used after successful surgery.

**TABLE 18-1** Possible Treatment Plans in Cushing's Syndrome Based on Etiology

Etiology	Nondrug	Generic (Brand) Drug Name	Treatment		
			Initial	Usual	Max
Ectopic ACTH syndrome	Surgery, chemotherapy, irradiation	Metyrapone (Metopirone) 250-mg capsules	0.5–1 g/day, divided every 4–6 hours	1–2 g/day, divided every 4–6 hours	6 g/day
		Aminoglutethimide (Cytadren) 250-mg tabs	0.5–1 g/day, divided two to four times a day for 2 weeks	1 g/day, divided every 6 hours	2 g/day
Pituitary-dependent	Surgery, irradiation	Cyproheptadine (Periactin) 2 mg/5 mL syrup or 4-mg tabs	4 mg twice a day	24–32 mg/day, divided four times a day	32 mg/day
		Mitotane (Lysodren) 500-mg tabs	0.5–1 g/day, increased by 0.5–1 g/day every 1–4 weeks	1–4 g daily, with food to decrease GI effects	12 g/day
Adrenal adenoma	Surgery, postoperative replacement	Metyrapone	See above	See above	See above
Adrenal carcinoma	Surgery	Ketoconazole (Nizoral) 200-mg tabs	200 mg once or twice a day	200–1,200 mg/day, divided twice a day	1,600 mg/day divided four times a day
		Mitotane	See above	See above	See above

ACTH, adrenocorticotrop hormone.

- **Metyrapone** inhibits 11-hydroxylase activity, resulting in inhibition of cortisol synthesis. Initially, patients can demonstrate an increase in plasma ACTH concentrations because of a sudden drop in cortisol. This can cause an increase in androgenic and mineralocorticoid hormones resulting in hypertension, acne, and hirsutism. Nausea, vomiting, vertigo, headache, dizziness, abdominal discomfort, and allergic rash have been reported after oral administration.
- **Aminoglutethimide** inhibits cortisol synthesis by blocking the conversion of cholesterol to pregnenolone early in the cortisol pathway. Side effects include severe sedation, nausea, ataxia, and skin rashes. Most of these effects are dose dependent and limit aminoglutethimide use in many patients. When used alone, aminoglutethimide is indicated for short-term use in inoperable Cushing's disease with ectopic ACTH syndrome as the suspected underlying etiology. Aminoglutethimide has limited efficacy as a single agent, with relapse occurring after discontinuation of therapy.
- **Combination therapy with metyrapone and aminoglutethimide** appears more effective than either agent alone for various etiologies of Cushing's disease with fewer side effects and is useful for inoperable patients.
- **Ketoconazole** inhibits a variety of cytochrome P450 enzymes, including 11-hydroxylase and 17-hydroxylase. It is highly effective in lowering cortisol in Cushing's disease, and patients can be maintained successfully on therapy for months to years. The most common adverse effects are reversible elevation of hepatic transaminases and GI upset. It can cause gynecomastia and lower plasma testosterone values.
- **Etomidate** is an imidazole derivative similar to ketoconazole that inhibits 11-hydroxylase. Because it is only available in a parenteral formulation, its use is limited to patients with acute hypercortisolemia awaiting surgery.

### *Adrenolytic Agents*

- **Mitotane** inhibits the 11-hydroxylation of 11-desoxycortisol and 11-desoxycorticosterone in the adrenal cortex. The net result is reduced synthesis of cortisol and corticosterone. It decreases the cortisol secretion rate, plasma cortisol concentrations, urinary free cortisol, and plasma concentrations of the 17-substituted steroids. Degeneration of cells within the zona fasciculata and reticularis occurs with resultant atrophy of the adrenal cortex. The zona glomerulosa is minimally affected during acute therapy but can become damaged after long-term treatment. Because mitotane can severely reduce cortisol production, patients should be hospitalized before initiating therapy. The drug should be continued as long as clinical benefits occur. Nausea and diarrhea are common at doses  $>2$  g/day and can be avoided by gradually increasing the dose and/or administering it with food. Lethargy, somnolence, and other CNS effects are also common. Reversible hypercholesterolemia can occur.

### *Neuromodulators of ACTH Release*

- None of the neuromodulatory agents has demonstrated consistent clinical efficacy for treating Cushing's syndrome. Combination therapy with these agents may prove more efficacious than any single agent.
- **Cyproheptadine** can decrease ACTH secretion; monitoring should include morning plasma cortisol and 24-hour urinary free cortisol concen-

trations. Side effects include sedation and hyperphagia. Cyproheptadine should be reserved for nonsurgical candidates who fail more conventional therapy. Because the response rate is no more than 30%, patients should be followed closely for relapses.

- **Tretinoin** can reduce ACTH secretion through inhibition of transcriptional activities. Its use has been limited to animal models, and efficacy in humans is undetermined.
- Other neuromodulatory agents include bromocriptine, cabergoline, valproic acid, octreotide, and rosiglitazone.

### *Glucocorticoid-Receptor Blocking Agents*

- **Mifepristone** (RU-486) is a progesterone-, androgen-, and glucocorticoid-receptor antagonist that inhibits dexamethasone suppression and increases endogenous cortisol and ACTH values in normal subjects. Limited experience in Cushing's syndrome suggests that mifepristone is highly effective in reversing the manifestations of hypercortisolism.

## EVALUATION OF THERAPEUTIC OUTCOMES

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- Close monitoring of 24-hour urinary free cortisol levels and serum cortisol levels are essential to identify adrenal insufficiency in patients with Cushing's syndrome. Steroid secretion should be monitored with all drug therapy and corticosteroid replacement given if needed.

## ADRENAL INSUFFICIENCY

### PATHOPHYSIOLOGY

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- Primary adrenal insufficiency (Addison's disease) most often involves the destruction of all regions of the adrenal cortex. There are deficiencies of cortisol, aldosterone, and the various androgens. Medications that inhibit cortisol synthesis (e.g., ketoconazole) or accelerate cortisol metabolism (e.g., phenytoin, rifampin, phenobarbital) can also cause primary adrenal insufficiency.
- Secondary adrenal insufficiency most commonly results from exogenous corticosteroid use, leading to suppression of the hypothalamic-pituitary-adrenal axis and decreased release of ACTH, resulting in impaired androgen and cortisol production. Mirtazapine and progestins (e.g., medroxyprogesterone acetate, megestrol acetate) have also been reported to induce secondary adrenal insufficiency. Secondary disease typically presents with normal mineralocorticoid concentrations.

### CLINICAL PRESENTATION

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- Weight loss, dehydration, hyponatremia, hyperkalemia, and elevated blood urea nitrogen are common in Addison's disease.
- Hyperpigmentation is common in Addison's disease and may involve exposed and nonexposed parts of the body. Hyperpigmentation is usually not seen in secondary adrenal insufficiency because of low amounts of melanocyte-stimulating hormone.

## DIAGNOSIS

- The short cosyntropin-stimulation test can be used to assess patients with suspected hypocortisolism. An increase to a cortisol level  $\geq 18$  mcg/dL (500 mmol/L) rules out adrenal insufficiency.
- Patients with Addison's disease have an abnormal response to the short cosyntropin-stimulation test. Plasma ACTH levels are usually 400 to 2,000 pg/mL in primary insufficiency versus normal to low (0 to 50 pg/mL) in secondary insufficiency. A normal cosyntropin-stimulation test does not rule out secondary adrenal insufficiency.
- Other tests include the insulin hypoglycemia test, the metyrapone test, and the corticotrophin-releasing hormone stimulation test.

## DESIRED OUTCOME

- The goals of treatment for adrenal insufficiency are to limit morbidity and mortality, return the patient to a normal functional state, and prevent episodes of acute adrenal insufficiency.

## TREATMENT

### Nonpharmacologic Therapy

- Patients must be informed of treatment complications, expected outcome, proper medication administration and adherence, and possible side effects.

### Pharmacotherapy of Adrenal Insufficiency

#### Corticosteroids

- **Hydrocortisone**, **cortisone**, and **prednisone** are the glucocorticoids of choice, administered twice daily at the lowest effective dose while mimicking the normal diurnal rhythm of cortisol production.
- Recommended starting total daily doses are hydrocortisone 15 mg, cortisone acetate 20 mg, or prednisone 2.5 mg (Table 18-2). Two-thirds of the dose is given in the morning, and one-third is given in the evening.
- The patient's symptoms can be monitored every 6 to 8 weeks to assess proper glucocorticoid replacement.
- **Fludrocortisone acetate** 0.05 to 0.2 mg orally once daily can be used to replace mineralocorticoid loss. If parenteral therapy is needed, 2 to 5 mg of

**TABLE 18-2** Relative Potencies of Glucocorticoids

Glucocorticoid	Anti-inflammatory <i>Potency</i>	Equivalent Potency <i>(mg)</i>	Approximate Half-Life <i>(minutes)</i>	Sodium- Retaining <i>Potency</i>
Cortisone	0.8	25	30	2
Hydrocortisone	1	20	90	2
Prednisone	3.5	5	60	1
Prednisolone	4	5	200	1
Triamcinolone	5	4	300	0
Methylprednisolone	5	4	180	0
Betamethasone	25	0.6	100–300	0
Dexamethasone	30	0.75	100–300	0

deoxycorticosterone trimethylacetate in oil can be administered intramuscularly every 3 to 4 weeks. The major reason for adding the mineralocorticoid is to minimize development of hyperkalemia.

- Because most adrenal crises occur because of glucocorticoid dose reductions or lack of stress-related dose adjustments, patients receiving corticosteroid-replacement therapy should add 5 to 10 mg hydrocortisone (or equivalent) to their normal daily regimen shortly before strenuous activities such as exercise. During times of severe physical stress (e.g., febrile illnesses, after accidents), patients should be instructed to double their daily dose until recovery.
- Treatment of secondary adrenal insufficiency is identical to primary disease treatment with the exception that mineralocorticoid replacement is usually not necessary.

### Pharmacotherapy of Acute Adrenal Insufficiency

- Acute adrenal insufficiency (also known as adrenal crisis or Addisonian crisis) represents a true endocrine emergency.
- Stressful situations, surgery, infection, and trauma are potential events that increase adrenal requirements, especially in patients with some underlying adrenal or pituitary insufficiency.
- The most common cause of adrenal crisis is abrupt withdrawal of exogenous glucocorticoids in patients receiving chronic treatment that resulted in hypothalamic-pituitary-adrenal-axis suppression.
- **Hydrocortisone** given parenterally is the corticosteroid of choice because of its combined glucocorticoid and mineralocorticoid activity. The starting dose is 100 mg IV by rapid infusion, followed by a continuous infusion or intermittent bolus of 100 to 200 mg every 24 hours. IV administration is continued for 24 to 48 hours. If the patient is stable at that time, oral hydrocortisone can be started at a dose of 50 mg every 8 hours for another 48 hours. A hydrocortisone taper is then initiated until the dosage is 30 to 50 mg/day in divided doses.
- **Fluid replacement** often is required and can be accomplished with IV dextrose 5% in normal saline solution at a rate to support blood pressure.
- If hyperkalemia is present after the hydrocortisone maintenance phase, additional mineralocorticoid usually is required. **Fludrocortisone acetate** 0.1 mg orally once daily is the agent of choice.
- Patients with adrenal insufficiency should carry a card or wear a bracelet or necklace that contains information about their condition. They should also have easy access to injectable hydrocortisone or glucocorticoid suppositories in case of an emergency or during times of physical stress, such as febrile illness or injury.

### EVALUATION OF THERAPEUTIC OUTCOMES

- The end point of therapy for adrenal insufficiency is difficult to assess in most patients, but a reduction in excess pigmentation is a good clinical marker. Development of features of Cushing's syndrome indicates excessive replacement.

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*See Chap. 79, Adrenal Gland Disorders, authored by John G. Gums and Shawn Anderson, for a more detailed discussion of this topic.*

## DEFINITION

- Diabetes mellitus (DM) is a group of metabolic disorders characterized by hyperglycemia and abnormalities in carbohydrate, fat, and protein metabolism. It results from defects in insulin secretion, insulin sensitivity, or both. Chronic microvascular, macrovascular, and neuropathic complications may ensue.

## PATHOPHYSIOLOGY

- Type 1 DM accounts for 5% to 10% of all diabetes cases. It generally develops in childhood or early adulthood and results from immune-mediated destruction of pancreatic  $\beta$ -cells, resulting in an absolute deficiency of insulin. There is a long preclinical period (up to 9 to 13 years) marked by the presence of immune markers when  $\beta$ -cell destruction is thought to occur. Hyperglycemia occurs when 80% to 90% of  $\beta$ -cells are destroyed. There is a transient remission (“honeymoon” phase) followed by established disease with associated risks for complications and death. The factors that initiate the autoimmune process are unknown, but the process is mediated by macrophages and T lymphocytes with circulating autoantibodies to various  $\beta$ -cell antigens (e.g., islet cell antibody, insulin antibodies).
- Type 2 DM accounts for as many as 90% of DM cases and is usually characterized by the presence of both insulin resistance and relative insulin deficiency. Insulin resistance is manifested by increased lipolysis and free fatty acid production, increased hepatic glucose production, and decreased skeletal muscle uptake of glucose.  $\beta$ -Cell dysfunction is progressive and contributes to worsening blood glucose control over time. Type 2 DM occurs when a diabetogenic lifestyle (excessive calories, inadequate exercise, and obesity) is superimposed upon a susceptible genotype.
- Uncommon causes of diabetes (1% to 2% of cases) include endocrine disorders (e.g., acromegaly, Cushing’s syndrome), gestational diabetes mellitus (GDM), diseases of the exocrine pancreas (e.g., pancreatitis), and medications (e.g., glucocorticoids, pentamidine, niacin, and  $\alpha$ -interferon).
- *Impaired fasting glucose* and *impaired glucose tolerance* are terms used to describe patients whose plasma glucose levels are higher than normal but not diagnostic of DM (see Diagnosis). These disorders are risk factors for developing DM and cardiovascular disease and are associated with the insulin-resistance syndrome.
- Microvascular complications include retinopathy, neuropathy, and nephropathy. Macrovascular complications include coronary heart disease, stroke, and peripheral vascular disease.

## CLINICAL PRESENTATION

### TYPE 1 DIABETES MELLITUS

- Individuals with type 1 DM are often thin and are prone to develop diabetic ketoacidosis if insulin is withheld or under conditions of severe stress with an excess of insulin counterregulatory hormones.
- Between 20% and 40% of patients present with diabetic ketoacidosis after several days of polyuria, polydipsia, polyphagia, and weight loss.

### TYPE 2 DIABETES MELLITUS

- Patients with type 2 DM are often asymptomatic and may be diagnosed secondary to unrelated blood testing. However, the presence of complications may indicate that they have had DM for several years.
- Lethargy, polyuria, nocturia, and polydipsia can be present on diagnosis; significant weight loss is less common.

## DIAGNOSIS

- Screening for type 2 DM should be performed every 3 years in all adults beginning at the age of 45. Testing should be considered at an earlier age and more frequently in individuals with risk factors (e.g., family history of DM, obesity, signs of insulin resistance).
- The recommended screening test is a fasting plasma glucose (FPG). Normal FPG is less than 100 mg/dL (5.6 mmol/L).
- Impaired fasting glucose is defined as FPG of 100 to 125 mg/dL (5.6 to 6.9 mmol/L).
- Impaired glucose tolerance is diagnosed when the 2-hour postload sample of the oral glucose tolerance test is between 140 and 199 mg per dL (7.8 to 11.0 mmol/L).
- The diagnostic criteria for DM are contained in Table 19-1.
- Pregnant women should undergo risk assessment for GDM at their first prenatal visit and proceed with glucose testing if at high risk (e.g., positive family history, personal history of GDM, marked obesity, or member of a high-risk ethnic group).

**TABLE 19-1** Criteria for the Diagnosis of Diabetes Mellitus<sup>a</sup>

Symptoms of diabetes plus casual<sup>b</sup> plasma glucose concentration  $\geq 200$  mg/dL (11.1 mmol/L)

or

Fasting<sup>c</sup> plasma glucose  $\geq 126$  mg/dL (7.0 mmol/L)

or

2-Hour postload glucose  $\geq 200$  mg/dL (11.1 mmol/L) during an OGTT<sup>d</sup>

<sup>a</sup>In the absence of unequivocal hyperglycemia, these criteria should be confirmed by repeat testing on a different day. The third measure (oral glucose tolerance test; OGTT) is not recommended for routine clinical use.

<sup>b</sup>Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.

<sup>c</sup>Fasting is defined as no caloric intake for at least 8 hours.

<sup>d</sup>The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

**TABLE 19-2** Glycemic Goals of Therapy

Biochemical Index	ADA	ACE and AACE
Hemoglobin A1C	<7% <sup>a</sup>	≤6.5%
Preprandial plasma glucose	90–130 mg/dL (5.0–7.2 mmol/L)	<110 mg/dL (6.1 mmol/L)
Postprandial plasma glucose	<180 mg/dL <sup>b</sup> (<10 mmol/L)	<140 mg/dL (<7.8 mmol/L)

AACE, American Association of Clinical Endocrinologists; ACE, American College of Endocrinology; ADA, American Diabetes Association; DCCT, Diabetes Control and Complications Trial.

<sup>a</sup>Referenced to a nondiabetic range of 4–6% using a DCCT-based assay. More stringent glycemic goals (i.e., a normal A1C, <6%) may further reduce complications at the cost of increased risk of hypoglycemia (particularly in those with type 1 diabetes).

<sup>b</sup>Postprandial glucose measurements should be made 1–2 hours after the beginning of the meal, generally the time of peak levels in patients with diabetes.

## DESIRED OUTCOME

- The goals of therapy in DM are to ameliorate symptoms of hyperglycemia, reduce the onset and progression of microvascular and macrovascular complications, reduce mortality, and improve quality of life. Desirable plasma glucose and glycosylated hemoglobin (A1C) levels are listed in Table 19-2.

## TREATMENT

### GENERAL APPROACH

- Near-normal glycemia reduces the risk of microvascular disease complications, but aggressive management of traditional cardiovascular risk factors (i.e., smoking cessation, treatment of dyslipidemia, intensive blood pressure control, antiplatelet therapy) is needed to reduce macrovascular disease risk.
- Appropriate care requires goal setting for glycemia, blood pressure, and lipid levels; regular monitoring for complications; dietary and exercise modifications; appropriate self-monitoring of blood glucose (SMBG); and appropriate assessment of laboratory parameters.

### NONPHARMACOLOGIC THERAPY

- Medical nutrition therapy is recommended for all patients. For individuals with type 1 DM, the focus is on regulating insulin administration with a balanced diet to achieve and maintain a healthy body weight. A meal plan that is moderate in carbohydrates and low in saturated fat, with a focus on balanced meals is recommended. In addition, patients with type 2 DM often require caloric restriction to promote weight loss. Bedtime and between-meal snacks are not usually needed if pharmacologic management is appropriate.
- Aerobic exercise can improve insulin resistance and glycemic control in most patients and may reduce cardiovascular risk factors, contribute to weight loss or maintenance, and improve well-being. Exercise should be started slowly in previously sedentary patients. Older patients and those with atherosclerotic disease should have a cardiovascular evaluation prior to beginning a substantial exercise program.

## PHARMACOLOGIC THERAPY

## Insulin and Other Injectable Preparations

(Tables 19-3 and 19-4)

- **Regular insulin** has a relatively slow onset of action when given subcutaneously, requiring injection 30 minutes prior to meals to achieve optimal postprandial glucose control and to prevent delayed postmeal hypoglycemia.
- **Lispro, aspart, and glulisine insulins** are analogs that are more rapidly absorbed, peak faster, and have shorter durations of action than regular insulin. This permits more convenient dosing within 10 minutes of meals (rather than 30 minutes prior), produces better efficacy in lowering postprandial blood glucose than regular insulin in type 1 DM, and minimizes delayed postmeal hypoglycemia.

**TABLE 19-3** Available Insulins and Other Injectable Preparations

Generic Name	Analog <sup>a</sup>	Administration Options
<b>Rapid-acting insulins</b>		
Humalog (insulin lispro)	Yes	Insulin pen 3-mL, vial, and 3-mL pen cartridge
NovoLog (insulin aspart)	Yes	Insulin pen 3-mL, vial, or 3-mL pen cartridge
Apidra (insulin glulisine)	Yes	3-mL pen cartridge or OptiClik pen system
<b>Short-acting insulins</b>		
Humulin R (regular)	No	100 units, 10-mL vial; 500 units, 20-mL vial
Novolin R (regular)	No	Insulin pen, vial, or 3-mL pen cartridge, and InnoLet
<b>Intermediate-acting insulins (NPH)</b>		
Humulin N	No	Vial, prefilled pen
Novolin N	No	Vial, prefilled pen, and InnoLet
<b>Long-acting insulins</b>		
Lantus (insulin glargine)	Yes	Vial, 3-mL OptiClik pen system
Levemir (insulin detemir)	Yes	Vial, 3-mL pen cartridge and InnoLet
<b>Premixed insulins</b>		
<i>Premixed insulin analogs</i>		
Humalog Mix 75/25 (75% neutral protamine lispro, 25% lispro)	Yes	Vial, prefilled pen
Novolog Mix 70/30 (70% aspart protamine suspension, 30% aspart)	Yes	Vial, prefilled pen, 3-mL pen cartridge
Humalog Mix 50/50 (50% neutral protamine lispro, 50% lispro)	Yes	3-mL pen
<i>NPH-regular combinations</i>		
Humulin 70/30	No	Vial, prefilled pen
Novolin 70/30	No	Vial, pen cartridge, InnoLet
Humulin 50/50	No	Vial
<b>Other injectable preparations</b>		
Exenatide (Byetta)	No	5-mcg/dose and 10-mcg/dose, 60 doses prefilled pen
Pramlintide (Symlin)	Yes	5-mL vial, 1.5-mL and 2.7-mL SymlinPen

NPH, neutral protamine Hagedorn.

<sup>a</sup>All insulins available in the United States are made by human recombinant DNA technology. An insulin analog is a modified human insulin molecule that imparts particular pharmacokinetic advantages.

**TABLE 19-4** Pharmacokinetics of Various Insulins Administered Subcutaneously

Type of Insulin	Onset	Peak (hours)	Duration (hours)	Maximum Duration (hours)	Appearance
<b>Rapid-acting</b>					
Aspart	15–30 minutes	1–2	3–5	5–6	Clear
Lispro	15–30 minutes	1–2	3–4	4–6	Clear
Glulisine	15–30 minutes	1–2	3–4	5–6	Clear
<b>Short-acting</b>					
Regular	30–60 minutes	2–3	3–6	6–8	Clear
<b>Intermediate-acting</b>					
NPH	2–4 hours	4–6	8–12	14–18	Cloudy
<b>Long-acting</b>					
Glargine	4–5 hours	–	22–24	24	Clear
Detemir	2 hours	6–9	14–24	24	Clear

NPH, neutral protamine Hagedorn.

- **Neutral protamine hagedorn (NPH)** is intermediate-acting. Variability in absorption, inconsistent preparation by the patient, and inherent pharmacokinetic differences may contribute to a labile glucose response, nocturnal hypoglycemia, and fasting hyperglycemia.
- **Glargine** and **detemir** are long-acting “peakless” human insulin analogs that result in less nocturnal hypoglycemia than NPH insulin when given at bedtime.
- In type 1 DM, the average daily insulin requirement is 0.5 to 0.6 units/kg. Requirements may fall to 0.1 to 0.4 units/kg in the honeymoon phase. Higher doses (0.5 to 1 unit/kg) are warranted during acute illness or ketosis. In type 2 DM, a dosage range of 0.7 to 2.5 units/kg is often required for patients with significant insulin resistance.
- Hypoglycemia and weight gain are the most common adverse effects of insulin. Treatment of hypoglycemia is as follows:
  - ✓ **Glucose** (10 to 15 g) given orally is the recommended treatment in conscious patients.
  - ✓ **Dextrose IV** may be required in individuals who have lost consciousness.
  - ✓ **Glucagon**, 1 g intramuscular, is the treatment of choice in unconscious patients when IV access cannot be established.
- **Exenatide** is a synthetic analog of exendin-4, a 39-amino acid peptide isolated from the saliva of the Gila monster that enhances glucose-dependent insulin secretion and reduces hepatic glucose production. It also decreases appetite and slows gastric emptying, which may reduce caloric intake and cause weight loss. It significantly decreases postprandial glucose excursions but has only a modest effect on FPG values. The average A1C reduction is approximately 0.9%. The most common adverse effects are nausea, vomiting, and diarrhea. The initial dose is 5 mcg subcutaneously twice daily, titrated to 10 mcg twice daily in 1 month if needed and as tolerated. It should be injected 0 to 60 minutes before the morning and evening meals. Exenatide should be used as adjunctive therapy in patients who have not achieved adequate glycemic control despite treatment with metformin, a sulfonyleurea, and/or a thiazolidinedione.

- **Pramlintide** is a synthetic analog of amylin, a neurohormone cosecreted from  $\beta$ -cells with insulin. Pramlintide suppresses inappropriately high postprandial glucagon secretion, reduces food intake (which can cause weight loss), and slows gastric emptying. The average A1C reduction is approximately 0.6%, but optimization of concurrent insulin therapy may result in further A1C decreases. Pramlintide decreases prandial glucose excursions but has little effect on FPG concentrations. Its main advantage is in type 1 DM, where it helps stabilize wide, postprandial glycemic swings. The most common adverse effects are nausea, vomiting, and anorexia. It does not cause hypoglycemia when used alone, but it is indicated only in patients receiving insulin, so hypoglycemia can occur. If a prandial insulin dose is used, it should be reduced by 30% to 50% when pramlintide is started to minimize severe hypoglycemic reactions. In type 2 DM, the starting dose is 60 mcg subcutaneously prior to major meals; the dose is titrated up to 120 mcg per dose as tolerated and as warranted based on postprandial plasma glucose levels. In type 1 DM, dosing starts at 15 mcg prior to each meal, titrated up to a maximum of 60 mcg prior to each meal if tolerated and warranted.

### Sulfonylureas

(Table 19-5)

- Sulfonylureas exert a hypoglycemic action by stimulating pancreatic secretion of insulin. All sulfonylureas are equally effective in lowering blood glucose when administered in equipotent doses. On average, the A1C will fall by 1.5% to 2% with FPG reductions of 60 to 70 mg/dL (3.3 to 3.9 mmol/L).
- The most common side effect is hypoglycemia, which is more problematic with long half-life drugs. Individuals at high risk include the elderly, those with renal insufficiency or advanced liver disease, and those who skip meals, exercise vigorously, or lose a substantial amount of weight. Weight gain is common; less common adverse effects include skin rash, hemolytic anemia, GI upset, and cholestasis. Hyponatremia is most common with chlorpropamide but has also been reported with tolbutamide.
- The recommended starting doses (see Table 19-5) should be reduced in elderly patients who may have compromised renal or hepatic function. Dosage can be titrated every 1 to 2 weeks (longer interval with chlorpropamide) to achieve glycemic goals.

### Short-Acting Insulin Secretagogues (Meglitinides)

- Similar to sulfonylureas, meglitinides lower glucose by stimulating pancreatic insulin secretion, but insulin release is glucose dependent and diminishes at low blood glucose concentrations. Hypoglycemic risk appears to be less with meglitinides than with sulfonylureas. The average reduction in A1C is about 0.8% to 1%. These agents can be used to provide increased insulin secretion during meals (when it is needed) in patients who are close to glycemic goals. They should be administered before each meal (up to 30 minutes prior). If a meal is skipped, the medication should also be skipped.
- **Repaglinide** (Prandin) is initiated at 0.5 to 2 mg with a maximum dose of 4 mg per meal (up to four meals per day or 16 mg/day).

**TABLE 19-5** Oral Agents for the Treatment of Type 2 Diabetes Mellitus

Generic Name (generic version available?) Y = yes, N = no	Brand	Dosage Strengths (mg)	Recommended Starting Dosage (mg/day)				Duration of Action	Metabolism or Therapeutic Notes
			Nonelderly	Elderly	Equivalent Therapeutic Dose (mg)	Maximum Dose (mg/day)		
<b>Sulfonylureas</b>								
Acetohexamide (Y)	Dymelor	250, 500	250	125–250	500	1,500	Up to 16 hours	Metabolized in liver; metabolite potency equal to parent compound; renally eliminated
Chlorpropamide (Y)	Diabinese	100, 250	250	100	250	500	Up to 72 hours	Metabolized in liver; also excreted unchanged renally
Tolazamide (Y)	Tolinase	100, 250, 500	100–250	100	250	1,000	Up to 24 hours	Metabolized in liver; metabolite less active than parent compound; renally eliminated
Tolbutamide (Y)	Orinase	250, 500	1,000–2,000	500–1,000	1,000	3,000	Up to 12 hours	Metabolized in liver to inactive metabolites that are renally excreted
Glipizide (Y)	Glucotrol	5, 10	5	2.5–5	5	40	Up to 20 hours	Metabolized in liver to inactive metabolites
Glipizide (Y)	Glucotrol XL	2.5, 5, 10, 20	5	2.5–5	5	20	24 hours	Slow-release form; do not cut tablet
Glyburide (Y)	DiaBeta, Micronase	1.25, 2.5, 5	5	1.25–2.5	5	20	Up to 24 hours	Metabolized in liver; elimination $\frac{1}{2}$ renal, $\frac{1}{2}$ feces
Glyburide, micronized (Y)	Glynase	1.5, 3, 6	3	1.5–3	3	12	Up to 24 hours	Equal control, but better absorption from micronized preparation
Glimepiride (Y)	Amaryl	1, 2, 4	1–2	0.5–1	2	8	24 hours	Metabolized in liver to inactive metabolites
<b>Short-acting insulin secretagogues</b>								
Nateglinide (N)	Starlix	60, 120	120 with meals	120 with meals	NA	120 mg three times a day	Up to 4 hours	Metabolized by cytochrome P450 (CYP450) 2C9 and 3A4 to weakly active metabolites; renally eliminated
Repaglinide (N)	Prandin	0.5, 1, 2	0.5–1 with meals	0.5–1 with meals	NA	16	Up to 4 hours	Metabolized by CYP 3A4 to inactive metabolites; excreted in bile

<b>Biguanides</b>									
Metformin (Y)	Glucophage	500, 850, 1,000	500 mg twice a day	Assess renal function	NA	2,550	Up to 24 hours	No metabolism; renally secreted and excreted	
Metformin extended-release (Y)	Glucophage XR	500, 750, 1,000	500–1,000 mg with evening meal	Assess renal function	NA	2,550	Up to 24 hours	Take with evening meal or may split dose; may consider trial if intolerant to immediate-release	
<b>Thiazolidinediones</b>									
Pioglitazone (N)	Actos	15, 30, 45	15	15	NA	45	24 hours	Metabolized by CYP 2C8 and 3A4; two metabolites have longer half-lives than parent compound	
Rosiglitazone (N)	Avandia	2, 4, 8	2–4	2	NA	8 mg/day or 4 mg twice a day	24 hours	Metabolized by CYP 2C8 and 2C9 to inactive metabolites that are renally excreted	
<b>α-Glucosidase inhibitors</b>									
Acarbose (N)	Precose	25, 50, 100	25 mg 1–3 times a day	25 mg 1–3 times a day	NA	25–100 mg three times a day	1–3 hours	Eliminated in bile	
Miglitol (N)	Glyset	25, 50, 100	25 mg 1–3 times a day	25 mg 1–3 times a day	NA	25–100 mg 3 times a day	1–3 hours	Eliminated renally	
<b>Dipeptidyl peptidase-IV (DPP-IV) inhibitors</b>									
Sitagliptin (N)	Januvia	25, 50, 100	100 mg daily	25–100 mg daily based on renal function	NA	100 mg daily	24 hours	50 mg daily if creatinine clearance >30 to <50 mL/min; 25 mg daily if creatinine clearance <30 mL/min	
<b>Example combination products</b>									
Glyburide/metformin (Y)	Glucovance	1.25/250, 2.5/500, 5/500	2.5–5/500 mg twice a day	1.25/250 mg twice a day; assess renal function	NA	20 mg of glyburide, 2,000 mg of metformin	Combination medication	Used as initial therapy: 1.25/250 mg twice a day	
Glipizide/metformin (N)	Metaglip	2.5/250, 2.5/500, 5/500	2.5–5/500 mg twice a day	2.5/250 mg; assess renal function	NA	20 mg of glipizide, 2,000 mg of metformin	Combination medication	Used as initial therapy: 2.5/250 mg twice a day	
Rosiglitazone/metformin (N)	Avandamet	1/500, 2/500, 4/500, 2/1,000, 4/1,000	1–2/500 mg twice a day	1/500 mg twice a day; assess renal function	NA	8 mg of rosiglitazone; 2,000 mg of metformin	Combination medication	Can use as initial therapy	

NA, not available.

- **Nateglinide** (Starlix) dosing is 120 mg three times daily before each meal. The dose may be lowered to 60 mg per meal in patients who are near goal A1C when therapy is initiated.

### Biguanides

- **Metformin** is the only biguanide available in the United States. It enhances insulin sensitivity of both hepatic and peripheral (muscle) tissues. This allows for increased uptake of glucose into these insulin-sensitive tissues. Metformin consistently reduces A1C levels by 1.5% to 2%, FPG levels by 60 to 80 mg/dL, and retains the ability to reduce FPG levels when they are very high (>300 mg/dL). It reduces plasma triglycerides and low-density lipoprotein (LDL) cholesterol by 8% to 15% and modestly increases high-density lipoprotein (HDL) cholesterol (2%). It does not induce hypoglycemia when used alone.
- Metformin should be included in the therapy for all type 2 DM patients (if tolerated and not contraindicated) because it is the only oral antihyperglycemic medication proven to reduce the risk of total mortality and cardiovascular death.
- The most common adverse effects are abdominal discomfort, stomach upset, diarrhea, anorexia, and a metallic taste. These effects can be minimized by titrating the dose slowly and taking it with food. Extended-release metformin (Glucophage XR) may reduce some of the GI side effects. Lactic acidosis occurs rarely and can be minimized by avoiding its use in patients with renal insufficiency (serum creatinine 1.4 mg/dL or greater in women and 1.5 mg/dL or greater in men), congestive heart failure, or conditions predisposing to hypoxemia or inherent lactic acidosis. Metformin should be discontinued 2 to 3 days prior to IV radiographic dye studies and withheld until normal renal function has been documented poststudy.
- **Metformin immediate-release** is usually initiated at 500 mg twice daily with the largest meals and increased by 500 mg weekly until glycemic goals or 2,000 mg/day is achieved. Metformin 850 mg can be dosed once daily and then increased every 1 to 2 weeks to a maximum of 850 mg three times daily (2,550 mg/day).
- **Metformin extended-release** (Glucophage XR) can be initiated with 500 mg with the evening meal and increased by 500 mg weekly to a maximum dose of 2,000 mg/day. Administration two to three times a day may help minimize GI side effects and improve glycemic control. The 750-mg tablets can be titrated weekly to the maximum dose of 2,250 mg/day.

### Thiazolidinediones (Glitazones)

- These agents activate PPAR- $\gamma$ , a nuclear transcription factor important in fat cell differentiation and fatty acid metabolism. PPAR- $\gamma$  agonists enhance insulin sensitivity in muscle, liver, and fat tissues indirectly. Insulin must be present in significant quantities for these actions to occur.
- When given for about 6 months, pioglitazone and rosiglitazone reduce A1C values by about 1.5% and FPG levels by about 60 to 70 mg/dL at maximal doses. Maximal glycemic-lowering effects may not be seen until 3 to 4 months of therapy. Monotherapy is often ineffective unless the drugs

are given early in the disease course when sufficient  $\beta$ -cell function and hyperinsulinemia are present.

- Pioglitazone decreases plasma triglycerides by 10% to 20%, whereas rosiglitazone tends to have no effect. Pioglitazone does not cause significant increases in LDL cholesterol, whereas LDL cholesterol may increase by 5% to 15% with rosiglitazone.
- Fluid retention may occur, perhaps as a result of peripheral vasodilation and/or improved insulin sensitization with a resultant increase in renal sodium and water retention. A dilutional anemia may result, which does not require treatment. Edema is reported in 4% to 5% of patients when glitazones are used alone or with other oral agents. When used in combination with insulin, the incidence of edema is about 15%. Glitazones are contraindicated in patients with New York Heart Association Class III and IV heart failure and should be used with great caution in patients with Class I or II heart failure or other underlying cardiac disease.
- Weight gain is dose related, and an increase of 1.5 to 4 kg is not uncommon. Rarely, rapid gain of a large amount of weight may necessitate discontinuation of therapy. Weight gain positively predicts a larger A1C reduction but must be balanced with the potential adverse effects of long-term weight gain.
- Several case reports of hepatotoxicity with pioglitazone or rosiglitazone have been reported, but improvement in alanine aminotransferase (ALT) was consistently observed upon drug discontinuation. Baseline ALT should be obtained prior to therapy and then periodically thereafter at the practitioner's discretion. Neither drug should be started if the baseline ALT exceeds 2.5 times the upper limit of normal. The drugs should be discontinued if the ALT is more than 3 times the upper limit of normal.
- Rosiglitazone has been associated with an increased risk of myocardial ischemic events such as angina or myocardial infarction in several studies. Although causality has not been conclusively established, the FDA has required that a "black box" warning be added to the labeling. A new long-term study to evaluate potential cardiovascular risks is planned.
- **Pioglitazone** (Actos) is started at 15 mg once daily. The maximum dose is 45 mg/day.
- **Rosiglitazone** (Avandia) is initiated with 2 to 4 mg once daily. The maximum dose is 8 mg/day. A dose of 4 mg twice daily can reduce A1C by 0.2% to 0.3% more than a dose of 8 mg taken once daily.

### **$\alpha$ -Glucosidase Inhibitors**

- These agents prevent the breakdown of sucrose and complex carbohydrates in the small intestine, thereby prolonging the absorption of carbohydrates. The net effect is a reduction in the postprandial glucose concentrations (40 to 50 mg/dL) while fasting glucose levels are relatively unchanged (about 10% reduction). Efficacy on glycemic control is modest, with average reductions in A1C of 0.3% to 1%. Good candidates for these drugs are patients who are near target A1C levels with near-normal FPG levels but high postprandial levels.
- The most common side effects are flatulence, bloating, abdominal discomfort, and diarrhea, which can be minimized by slow dosage titration. If

hypoglycemia occurs when used in combination with a hypoglycemic agent (sulfonylurea or insulin), oral or parenteral glucose (dextrose) products or glucagon must be given because the drug will inhibit the breakdown and absorption of more complex sugar molecules (e.g., sucrose).

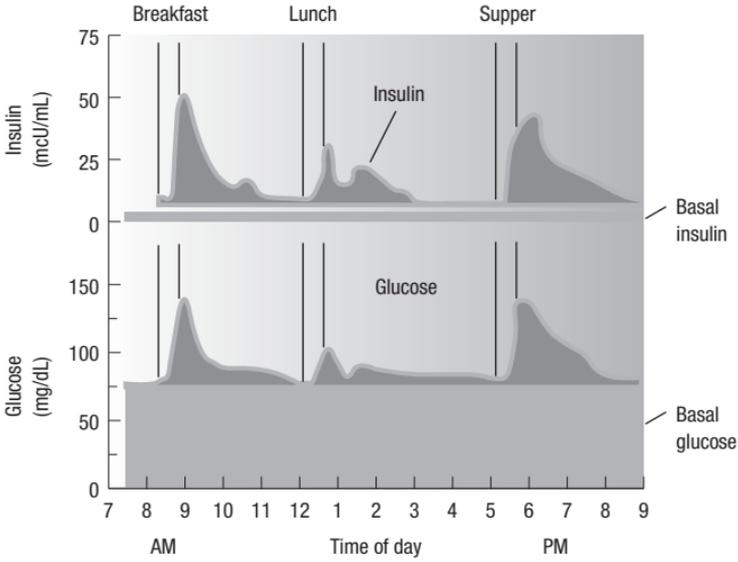
- **Acarbose** (Precose) and **miglitol** (Glyset) are dosed similarly. Therapy is initiated with a very low dose (25 mg with one meal a day) and increased very gradually (over several months) to a maximum of 50 mg three times daily for patients weighing 60 kg or more, or 100 mg three times daily for patients above 60 kg. The drugs should be taken with the first bite of the meal so that the drug is present to inhibit enzyme activity.

### Dipeptidyl Peptidase-IV Inhibitors

- Dipeptidyl peptidase-IV inhibitors prolong the half-life of an endogenously produced glucagon-like peptide-1. These agents partially reduce the inappropriately elevated glucagon postprandially and stimulate glucose-dependent insulin secretion. The average reduction in A1C is approximately 0.7% to 1% at a dose of 100 mg/day.
- The drugs are well tolerated, weight neutral, and do not cause GI side effects. Mild hypoglycemia appears to be the only significant adverse effect, but long-term safety data are limited.
- **Sitagliptin** (Januvia) is usually dosed at 100 mg orally once daily. In patients with renal impairment, the daily dose should be reduced to 50 mg (creatinine clearance 30–50 mL/min) or 25 mg (creatinine clearance <30 mL/min).
- **Vildagliptin** was not approved in the United States at the time of this writing (June 2008). The usual dose is expected to be similar to Sitagliptin.

## PHARMACOTHERAPY OF TYPE 1 DIABETES MELLITUS

- All patients with type I DM require insulin, but the type and manner of delivery differ considerably among individual patients and clinicians.
- Therapeutic strategies should attempt to match carbohydrate intake with glucose-lowering processes (usually insulin) and exercise. Dietary intervention should allow the patient to live as normal a life as possible.
- Fig. 19-1 depicts the relationship between glucose concentrations and insulin secretion over the course of a day and how various insulin regimens may be given.
- The timing of insulin onset, peak, and duration of effect must match meal patterns and exercise schedules to achieve near-normal blood glucose values throughout the day.
- A regimen of two daily injections that may roughly approximate physiologic insulin secretion is split-mixed injections of a morning dose of NPH insulin and regular insulin before breakfast and again before the evening meal (see Fig. 19-1, no. 1). This assumes that the morning NPH insulin provides basal insulin for the day and covers the midday meal, the morning regular insulin covers breakfast, the evening NPH insulin gives basal insulin for the rest of the day, and the evening regular insulin covers the evening meal. Patients may be started on 0.6 units/kg/day, with two-thirds given in the morning and one-third in the evening. Intermediate-acting insulin (e.g., NPH) should comprise two-thirds of the morning dose and one-half of the evening dose.



**Intensive insulin therapy regimens**

	7 AM	11 AM	5 PM	Bedtime
1. 2 doses, <sup>a</sup> R or rapid acting + N	R, L, A, GLU + N		R, L, A, GLU + N	
2. 3 doses, R or rapid acting + N	R, L, A, GLU + N	R, L, A, GLU	R, L, A, GLU + N	
3. 4 doses, R or rapid acting + N	R, L, A, GLU	R, L, A, GLU	R, L, A, GLU	N
4. 4 doses R or rapid acting + N	R, L, A, GLU + N	R, L, A, GLU	R, L, A, GLU	N
5. 4 doses, <sup>b</sup> R or rapid acting + long acting	R, L, A, GLU	R, L, A, GLU	R, L, A, GLU	G or D <sup>b</sup> (G may be given anytime every 24 hours)
6. CS-II pump	← Adjusted Basal →			
	Bolus	Bolus	Bolus	

<sup>a</sup>Many clinicians may not consider this intensive insulin therapy

<sup>b</sup>May be given twice daily in type 1 DM = 5 doses

**FIGURE 19-1.** Relationship between insulin and glucose over the course of a day and how various insulin regimens could be given. (A, aspart; CS-II, continuous subcutaneous insulin infusion; D, detemir; G, glargine; GLU, glulisine; L, lispro; N, neutral protamine Hagedorn; R, regular.)

However, most patients are not sufficiently predictable in their schedule and food intake to allow tight glucose control with this approach. If the fasting glucose in the morning is too high, the evening NPH dose may be moved to bedtime (now three total injections per day). This may provide sufficient intensification of therapy for some patients.

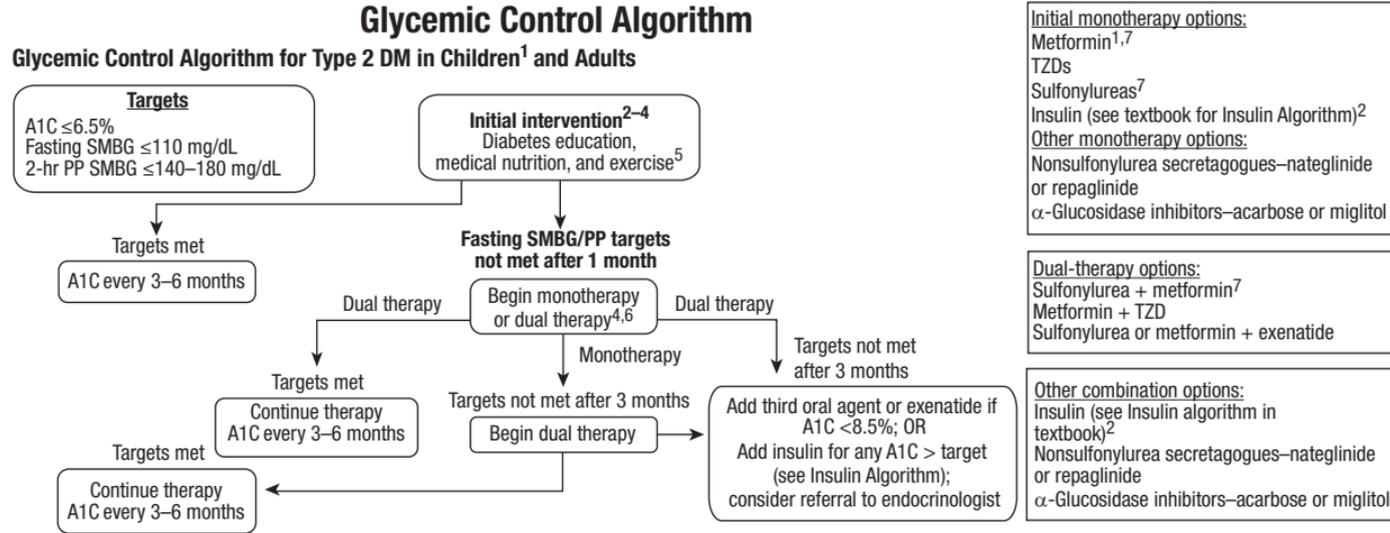
- The basal-bolus injection concept attempts to replicate normal insulin physiology by giving intermediate- or long-acting insulin as the basal component and short-acting insulin as the bolus portion (see Fig. 19-1, nos. 2, 3, 4, and 5). Intensive therapy using this approach is recommended for all adult patients at the time of diagnosis to reinforce the importance of glycemic control from the outset of treatment. Because children and prepubescent adolescents are relatively protected from microvascular complications and must be managed with a regimen that is practical for them, less intensive therapy (two injections per day of premixed insulins) is reasonable until they are postpubertal.
- The basal insulin component may be provided by once- or twice-daily **NPH** or **detemir**, or once-daily **insulin glargine**. Most type 1 DM patients require two injections of all insulins except insulin glargine. All of the insulins (with the exception of insulin glargine) have some degree of peak effect that must be considered in planning meals and activity. Insulin glargine or insulin detemir is a feasible basal insulin supplement for most patients.
- The bolus insulin component is given before meals with **regular insulin**, **insulin lispro**, **insulin aspart**, or **insulin glulisine**. The rapid onset and short duration of rapid-acting insulin analogs more closely replicate normal physiology than regular insulin, allowing the patient to vary the amount of insulin injected based on the preprandial SMBG level, upcoming activity level, and anticipated carbohydrate intake. Most patients have a prescribed dose of insulin preprandially that they vary based on an insulin algorithm. Carbohydrate counting is an effective tool for determining the amount of insulin to be injected preprandially.
- As an example, patients may begin on about 0.6 units/kg/day of insulin, with basal insulin 50% of the total dose and prandial insulin 20% of the total dose before breakfast, 15% before lunch, and 15% before dinner. Most patients require total daily doses between 0.5 and 1 unit/kg/day.
- Continuous subcutaneous insulin infusion pump therapy (generally using **insulin lispro** or **aspart** to diminish aggregation) is the most sophisticated form of basal-bolus insulin delivery (see Fig. 19-1, no. 6). The basal insulin dose may be varied, consistent with changes in insulin requirements throughout the day. In selected patients, this feature of continuous subcutaneous insulin infusion allows greater glycemic control. However, it requires greater attention to detail and frequency of SMBG more than four injections daily.
- All patients receiving insulin should have extensive education in the recognition and treatment of hypoglycemia.

## PHARMACOTHERAPY OF TYPE 2 DIABETES MELLITUS

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(Fig. 19-2)

- Symptomatic patients may initially require insulin or combination oral therapy to reduce glucose toxicity (which may reduce  $\beta$ -cell insulin secretion and worsen insulin resistance).



<sup>1</sup>Metformin is the only FDA-approved oral diabetic agent for children ( $\geq$ age 10); other agents may be used at the discretion of the clinician. <sup>2</sup>See textbook for Insulin Algorithm for Type 2 Diabetes Mellitus in Children and Adults. <sup>3</sup>If initial presentation with glucose  $\geq$ 260 mg/dL in symptomatic patient, consider insulin or insulin analog as initial intervention, probably with dual therapy. <sup>4</sup>Monotherapy with sulfonylurea or metformin does not sustain A1C reductions (UKPDS study); dual therapy certainly indicated if initial glucose  $\geq$ 210 mg/dL or A1C  $\geq$ 9.0%. <sup>5</sup>These interventions should be maintained lifelong; see Medical Nutrition, Weight Loss, and Exercise Algorithms in textbook. <sup>6</sup>If initial dual therapy is initiated, decide on add-on therapy options within 3 months if glycemic targets are not met. <sup>7</sup>Sulfonylureas and metformin are the most studied and least expensive oral diabetes agents; glipizide ER and glimepiride have a lower incidence of hypoglycemia than glyburide. **Publication #45-11265.**

**FIGURE 19-2.** Glycemic control algorithm for type 2 diabetes mellitus (DM) in children and adults. (A1C, glycosylated hemoglobin; ER, extended release; PP, postprandial; SMBG, self-monitoring of blood glucose; TZD, thiazolidinedione; UKPDS, United Kingdom Prospective Diabetes Study.) (Reprinted with permission from the Texas Diabetes Council.)

- Patients with A1C of about 7% or less are usually treated with therapeutic lifestyle measures with or without an insulin sensitizer. Those with A1C >7% but <8% are initially treated with a single oral agent. Patients with higher initial A1C values may benefit from initial therapy with two oral agents or insulin. Most patients with A1C values >9% to 10% require two or more agents to reach glycemic goals.
- Obese patients (>120% ideal body weight) without contraindications should be started on **metformin** initially, titrated to about 2,000 mg/day. A thiazolidinedione (**rosiglitazone, pioglitazone**) may be used in patients intolerant of or having a contraindication to metformin.
- Near-normal-weight patients may be treated with **insulin secretagogues**.
- Failure of initial therapy should result in addition of another class of drug. Substitution of a drug from another class should be reserved for drug intolerance. Metformin and an insulin secretagogue are often first- and second-line therapy.
- Initial combination therapy should be considered for patients with A1C >9% to 10%, and several oral combination products are available.
- If a patient has inadequate control on two drugs, adding a third class can be considered (e.g., a glitazone, exenatide, a dipeptidyl peptidase-IV inhibitor, or basal insulin). Therapy should be guided by the A1C, FPG, cost, additional benefits (e.g., weight loss), and avoidance of side effects).
- Virtually all patients ultimately become insulinopenic and require insulin therapy. Patients are often transitioned to insulin by using a bedtime injection of an intermediate- or long-acting insulin with oral agents used primarily for glycemic control during the day. This results in less hyperinsulinemia during the day and less weight gain than more traditional insulin strategies. Insulin sensitizers are commonly used with insulin because most patients are insulin resistant.
- When the combination of bedtime insulin plus daytime oral medications fails, a conventional multiple daily dose insulin regimen with an insulin sensitizer can be tried.
- Because of the variability of insulin resistance, insulin doses may range from 0.7 to 2.5 units/kg/day or more.

## TREATMENT OF COMPLICATIONS

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### Retinopathy

- Patients with established retinopathy should be examined by an ophthalmologist at least every 6 to 12 months.
- Early background retinopathy may reverse with improved glycemic control. More advanced disease will not regress with improved control and may actually worsen with short-term improvements in glycemia.
- Laser photocoagulation has markedly improved sight preservation in diabetic patients.

### Neuropathy

- Peripheral neuropathy is the most common complication in type 2 DM outpatients. Paresthesias, numbness, or pain may be predominant symptoms. The feet are involved far more often than the hands. Improved

glycemic control may alleviate some of the symptoms. Pharmacologic therapy is symptomatic and empiric, including low-dose **tricyclic antidepressants**, anticonvulsants (e.g., **gabapentin**, **pregabalin**, **carbamazepine**), **duloxetine**, **venlafaxine**, **topical capsaicin**, and various analgesics, including **tramadol** and **nonsteroidal antiinflammatory drugs**.

- Gastroparesis can be severe and debilitating. Improved glycemic control, discontinuation of medications that slow gastric motility, and use of **metoclopramide** (preferably for only a few days at a time) or **erythromycin** may be helpful.
- Patients with orthostatic hypotension may require mineralocorticoids or adrenergic agonists.
- Diabetic diarrhea is commonly nocturnal and frequently responds to a 10- to 14-day course of an antibiotic such as **doxycycline** or **metronidazole**. **Octreotide** may be useful in unresponsive cases.
- Erectile dysfunction is common, and initial treatment should include one of the oral medications currently available (e.g., **sildenafil**, **vardenafil**, **tadalafil**).

### Nephropathy

- Glucose and blood pressure control are most important for prevention of nephropathy, and blood pressure control is most important for retarding the progression of established nephropathy.
- Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers have shown efficacy in preventing the clinical progression of renal disease in patients with type 2 DM. Diuretics are frequently necessary due to volume-expanded states and are recommended second-line therapy.

### Peripheral Vascular Disease and Foot Ulcers

- Claudication and nonhealing foot ulcers are common in type 2 DM. Smoking cessation, correction of dyslipidemia, and antiplatelet therapy are important treatment strategies.
- **Pentoxifylline** (Trental) or **cilostazol** (Pletal) may be useful in selected patients. Revascularization is successful in selected patients.
- Local debridement and appropriate footwear and foot care are important in the early treatment of foot lesions. Topical treatments may be beneficial in more advanced lesions.

### Coronary Heart Disease

- Multiple-risk-factor intervention (treatment of dyslipidemia and hypertension, smoking cessation, antiplatelet therapy) reduces macrovascular events.
- The National Cholesterol Education Program Adult Treatment Panel III guidelines (see Chap. 9) classify the presence of DM as a coronary heart disease risk equivalent, and the goal LDL cholesterol is <100 mg/dL. An optional LDL goal in high-risk DM patients is <70 mg/dL. After the LDL goal is reached (usually with a **statin**), treatment of high triglycerides ( $\geq 200$  mg/dL) is considered. The non-HDL goal for patients with DM is <130 mg/dL. **Niacin** or a **fibrate** can be added to reach that goal if triglycerides are 201 to 499 mg/dL or if the patient has low HDL cholesterol (<40 mg/dL).
- The American Diabetes Association and the National Kidney Foundation recommend a goal blood pressure of <130/80 mm Hg in patients with DM.

**Angiotensin-converting enzyme inhibitors** and **angiotensin receptor blockers** are generally recommended for initial therapy. Many patients require multiple agents, so diuretics, calcium channel blockers, and  $\beta$ -**blockers** are useful as second and third agents.

## EVALUATION OF THERAPEUTIC OUTCOMES

- The A1C is the current standard for following long-term glycemic control for the previous 3 months. It should be measured at least twice a year in patients meeting treatment goals on a stable therapeutic regimen.
- Regardless of the insulin regimen chosen, gross adjustments in the total daily insulin dose can be made based on A1C measurements and symptoms such as polyuria, polydipsia, and weight gain or loss. Finer insulin adjustments can be determined on the basis of the results of frequent SMBG.
- Patients receiving insulin should be questioned about the recognition of hypoglycemia at least annually. Documentation of frequency of hypoglycemia and the treatment required should be recorded.
- Patients receiving bedtime insulin should be monitored for hypoglycemia by asking about nocturnal sweating, palpitations, and nightmares, as well as the results of SMBG.
- Patients with type 2 DM should have a routine urinalysis at diagnosis as the initial screening test for albuminuria. If positive, a 24-hour urine for quantitative assessment will assist in developing a treatment plan. If the urinalysis is negative for protein, a test to evaluate the presence of microalbuminuria is recommended.
- Fasting lipid profiles should be obtained at each follow-up visit if not at goal, annually if stable and at goal, or every 2 years if the profile suggests low risk.
- Regular frequency of foot exams (each visit), urine albumin assessment (annually), and dilated ophthalmologic exams (yearly or more frequently with abnormalities) should also be documented.
- Assessment for influenza and pneumococcal vaccine administration and assessment and management of other cardiovascular risk factors (e.g., smoking and antiplatelet therapy) are components of sound preventive medicine strategies.

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See Chap. 77, *Diabetes Mellitus*, authored by Curtis L. Triplitt, Charles A. Reasner, and William L. Isley, for a more detailed discussion of this topic.

## DEFINITION

- Thyroid disorders encompass a variety of disease states affecting thyroid hormone production or secretion that result in alterations in metabolic stability. Hyperthyroidism and hypothyroidism are the clinical and biochemical syndromes resulting from increased and decreased thyroid hormone production, respectively.

## THYROID HORMONE PHYSIOLOGY

- The thyroid hormones thyroxine ( $T_4$ ) and triiodothyronine ( $T_3$ ) are formed on thyroglobulin, a large glycoprotein synthesized within the thyroid cell. Inorganic iodide enters the thyroid follicular cell and is oxidized by thyroid peroxidase and covalently bound (organified) to tyrosine residues of thyroglobulin.
- The iodinated tyrosine residues monoiodotyrosine (MIT) and diiodotyrosine (DIT) combine (couple) to form iodothyronines in reactions catalyzed by thyroid peroxidase. Thus, two molecules of DIT combine to form  $T_4$ , and MIT and DIT join to form  $T_3$ .
- Thyroid hormone is liberated into the bloodstream by the process of proteolysis within thyroid cells.  $T_4$  and  $T_3$  are transported in the bloodstream by three proteins: thyroid-binding globulin, thyroid-binding prealbumin, and albumin. Only the unbound (free) thyroid hormone is able to diffuse into the cell, elicit a biologic effect, and regulate thyroid-stimulating hormone (TSH) secretion from the pituitary.
- $T_4$  is secreted solely from the thyroid gland, but less than 20% of  $T_3$  is produced there; the majority of  $T_3$  is formed from the breakdown of  $T_4$  catalyzed by the enzyme 5'-monodeiodinase found in peripheral tissues.  $T_3$  is about five times more active than  $T_4$ .
- $T_4$  may also be acted on by the enzyme 5'-monodeiodinase to form reverse  $T_3$ , which has no significant biologic activity.
- Thyroid hormone production is regulated by TSH secreted by the anterior pituitary, which in turn is under negative feedback control by the circulating level of free thyroid hormone and the positive influence of hypothalamic thyrotropin-releasing hormone. Thyroid hormone production is also regulated by extrathyroidal deiodination of  $T_4$  to  $T_3$ , which can be affected by nutrition, nonthyroidal hormones, drugs, and illness.

## THYROTOXICOSIS (HYPERTHYROIDISM)

## PATHOPHYSIOLOGY

- Thyrotoxicosis results when tissues are exposed to excessive levels of  $T_4$ ,  $T_3$ , or both.
- TSH-secreting pituitary tumors release biologically active hormone that is unresponsive to normal feedback control. The tumors may cosecrete

prolactin or growth hormone; therefore, patients may present with amenorrhea, galactorrhea, or signs of acromegaly.

- In Graves' disease, hyperthyroidism results from the action of thyroid-stimulating antibodies (TSAb) directed against the thyrotropin receptor on the surface of the thyroid cell. These immunoglobulin G antibodies bind to the receptor and activate the enzyme adenylate cyclase in the same manner as TSH.
- An autonomous thyroid nodule (toxic adenoma) is a discrete thyroid mass whose function is independent of pituitary control. Hyperthyroidism usually occurs with larger nodules (i.e., those greater than 3 cm in diameter).
- In multinodular goiters (Plummer's disease), follicles with a high degree of autonomous function coexist with normal or even nonfunctioning follicles. Thyrotoxicosis occurs when the autonomous follicles generate more thyroid hormone than is required.
- Painful subacute (granulomatous or de Quervain's) thyroiditis is believed to be caused by viral invasion of thyroid parenchyma.
- Painless (silent, lymphocytic, postpartum) thyroiditis is a common cause of thyrotoxicosis; its etiology is not fully understood and may be heterogeneous; autoimmunity may underlie most cases.
- Thyrotoxicosis factitia is hyperthyroidism produced by the ingestion of exogenous thyroid hormone. This may occur when thyroid hormone is used for inappropriate indications, when excessive doses are used for accepted medical indications, or when it is used surreptitiously by patients.
- Amiodarone may induce thyrotoxicosis (2% to 3% of patients) or hypothyroidism. It interferes with type I 5'-deiodinase, leading to reduced conversion of  $T_4$  to  $T_3$ , and iodide release from the drug may contribute to iodine excess. Amiodarone also causes a destructive thyroiditis with loss of thyroglobulin and thyroid hormones.

## CLINICAL PRESENTATION

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- Symptoms of thyrotoxicosis include nervousness, anxiety, palpitations, emotional lability, easy fatigability, heat intolerance, loss of weight concurrent with an increased appetite, increased frequency of bowel movements, proximal muscle weakness (noted on climbing stairs or arising from a sitting position), and scanty or irregular menses in women.
- Physical signs of thyrotoxicosis may include warm, smooth, moist skin and unusually fine hair; separation of the ends of the fingernails from the nail beds (onycholysis); retraction of the eyelids and lagging of the upper lid behind the globe upon downward gaze (lid lag); tachycardia at rest, a widened pulse pressure, and a systolic ejection murmur; occasional gynecomastia in men; a fine tremor of the protruded tongue and outstretched hands; and hyperactive deep tendon reflexes.
- Graves' disease is manifested by hyperthyroidism, diffuse thyroid enlargement, and the extrathyroidal findings of exophthalmos, pretibial myxedema, and thyroid acropachy. The thyroid gland is usually diffusely enlarged, with a smooth surface and consistency varying from soft to firm. In severe disease, a thrill may be felt and a systolic bruit may be heard over the gland.
- In subacute thyroiditis, patients complain of severe pain in the thyroid region, which often extends to the ear on the affected side. Low-grade fever

is common, and systemic signs and symptoms of thyrotoxicosis are present. The thyroid gland is firm and exquisitely tender on physical examination.

- Painless thyroiditis has a triphasic course that mimics that of painful subacute thyroiditis. Most patients present with mild thyrotoxic symptoms; lid retraction and lid lag are present but exophthalmos is absent. The thyroid gland may be diffusely enlarged, but thyroid tenderness is absent.
- Thyroid storm is a life-threatening medical emergency characterized by severe thyrotoxicosis, high fever (often greater than 39.4°C [103°F]), tachycardia, tachypnea, dehydration, delirium, coma, nausea, vomiting, and diarrhea. Precipitating factors include infection, trauma, surgery, radioactive iodine (RAI) treatment, and withdrawal from antithyroid drugs.

## DIAGNOSIS

- An elevated 24-hour radioactive iodine uptake (RAIU) indicates true hyperthyroidism: the patient's thyroid gland is overproducing  $T_4$ ,  $T_3$ , or both (normal RAIU 10% to 30%). Conversely, a low RAIU indicates that the excess thyroid hormone is not a consequence of thyroid gland hyperfunction but is likely caused by thyroiditis or hormone ingestion.
- TSH-induced hyperthyroidism is diagnosed by evidence of peripheral hypermetabolism, diffuse thyroid gland enlargement, elevated free thyroid hormone levels, and elevated serum immunoreactive TSH concentrations. Because the pituitary gland is extremely sensitive to even minimal elevations of free  $T_4$ , a "normal" or elevated TSH level in any thyrotoxic patient indicates inappropriate production of TSH.
- TSH-secreting pituitary adenomas are diagnosed by demonstrating lack of TSH response to thyrotropin-releasing hormone stimulation, inappropriate TSH levels, elevated TSH  $\alpha$ -subunit levels, and radiologic imaging.
- In thyrotoxic Graves' disease, there is an increase in the overall hormone production rate with a disproportionate increase in  $T_3$  relative to  $T_4$  (Table 20-1). Saturation of thyroid-binding globulin is increased due to the elevated levels of serum  $T_4$  and  $T_3$ , which is reflected in an elevated  $T_3$  resin uptake. As a result, the concentrations of free  $T_4$ , free  $T_3$ , and the free  $T_4$  and  $T_3$  indices are increased to an even greater extent than are the measured serum total  $T_4$  and  $T_3$  concentrations. The TSH level is undetectable due to negative feedback by elevated levels of thyroid hormone at the pituitary. In

**TABLE 20-1** Thyroid Function Test Results in Different Thyroid Conditions

	Total $T_4$	Free $T_4$	Total $T_3$	$T_3$ Resin Uptake	Free Thyroxine Index	TSH
Normal	4.5–10.9 mcg/dL	0.8–2.7 ng/dL	60–181 ng/dL	22–34%	1.0–4.3 units	0.5–4.7 milli- international units per liter
Hyperthyroid	↑↑	↑↑	↑↑↑	↑	↑↑↑	↓↓
Hypothyroid	↓↓	↓↓	↓	↓↓	↓↓↓	↑↑
Increased TBG	↑	Normal	↑	↓	Normal	Normal

TBG, thyroid-binding globulin; TSH, thyroid-stimulating hormone;  $T_3$ , triiodothyronine;  $T_4$ , thyroxine.

patients with manifest disease, measurement of the serum free  $T_4$  concentration (or total  $T_4$  and  $T_3$  resin uptake), total  $T_3$ , and TSH will confirm the diagnosis of thyrotoxicosis. If the patient is not pregnant, an increased 24-hour RAIU documents that the thyroid gland is inappropriately using the iodine to produce more thyroid hormone when the patient is thyrotoxic.

- Toxic adenomas may result in hyperthyroidism with larger nodules. Because there may be isolated elevation of serum  $T_3$  with autonomously functioning nodules, a  $T_3$  level must be measured to rule out  $T_3$  toxicosis if the  $T_4$  level is normal. After a radioiodine scan demonstrates that the toxic thyroid adenoma collects more radioiodine than the surrounding tissue, independent function is documented by failure of the autonomous nodule to decrease its iodine uptake during exogenous  $T_3$  administration.
- In multinodular goiters, a thyroid scan shows patchy areas of autonomously functioning thyroid tissue.
- A low RAIU indicates the excess thyroid hormone is not a consequence of thyroid gland hyperfunction. This may be seen in painful subacute thyroiditis, painless thyroiditis, struma ovarii, follicular cancer, and factitious ingestion of exogenous thyroid hormone.
- In subacute thyroiditis, thyroid function tests typically run a triphasic course in this self-limited disease. Initially, serum  $T_4$  levels are elevated due to release of preformed thyroid hormone from disrupted follicles. The 24-hour RAIU during this time is less than 2% because of thyroid inflammation and TSH suppression by the elevated  $T_4$  level. As the disease progresses, intrathyroidal hormone stores are depleted, and the patient may become mildly hypothyroid with an appropriately elevated TSH level. During the recovery phase, thyroid hormone stores are replenished and serum TSH elevation gradually returns to normal.
- During the thyrotoxic phase of painless thyroiditis, the 24-hour RAIU is suppressed to less than 2%. Antithyroglobulin and antimicrosomal antibody levels are elevated in more than 50% of patients.
- Thyrotoxicosis factitia should be suspected in a thyrotoxic patient without evidence of increased hormone production, thyroidal inflammation, or ectopic thyroid tissue. The RAIU is low because thyroid gland function is suppressed by the exogenous thyroid hormone. Measurement of plasma thyroglobulin reveals the presence of very low levels.

## DESIRED OUTCOME

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- The therapeutic objectives for hyperthyroidism are to normalize the production of thyroid hormone; minimize symptoms and long-term consequences; and provide individualized therapy based on the type and severity of disease, patient age and gender, existence of nonthyroidal conditions, and response to previous therapy.

## TREATMENT

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### Nonpharmacologic Therapy

- Surgical removal of the thyroid gland should be considered in patients with a large gland (>80 g), severe ophthalmopathy, or a lack of remission on antithyroid drug treatment.

- If thyroidectomy is planned, **propylthiouracil** (PTU) or **methimazole** (MMI) is usually given until the patient is biochemically euthyroid (usually 6 to 8 weeks), followed by the addition of **iodides** (500 mg/day) for 10 to 14 days before surgery to decrease the vascularity of the gland. **Levothyroxine** may be added to maintain the euthyroid state while the thionamides are continued.
- **Propranolol** has been used for several weeks preoperatively and 7 to 10 days after surgery to maintain a pulse rate less than 90 beats/min. Combined pretreatment with propranolol and 10 to 14 days of **potassium iodide** also has been advocated.
- Complications of surgery include persistent or recurrent hyperthyroidism (0.6% to 18%), hypothyroidism (up to about 49%), hypoparathyroidism (up to 4%), and vocal cord abnormalities (up to 5%). The frequent occurrence of hypothyroidism requires periodic follow-up for identification and treatment.

## Antithyroid Pharmacotherapy

### *Thioureas (Thionamides)*

- **PTU** and **MMI** block thyroid hormone synthesis by inhibiting the peroxidase enzyme system of the thyroid gland, thus preventing oxidation of trapped iodide and subsequent incorporation into iodotyrosines and ultimately iodothyronine (“organification”); and by inhibiting coupling of MIT and DIT to form  $T_4$  and  $T_3$ . PTU (but not MMI) also inhibits the peripheral conversion of  $T_4$  to  $T_3$ .
- Usual initial doses include PTU 300 to 600 mg daily (usually in three or four divided doses) or MMI 30 to 60 mg daily given in three divided doses. Evidence exists that both drugs can be given as a single daily dose.
- Improvement in symptoms and laboratory abnormalities should occur within 4 to 8 weeks, at which time a tapering regimen to maintenance doses can be started. Dosage changes should be made on a monthly basis because the endogenously produced  $T_4$  will reach a new steady-state concentration in this interval. Typical daily maintenance doses are PTU 50 to 300 mg and MMI 5 to 30 mg.
- Antithyroid drug therapy should continue for 12 to 24 months to induce a long-term remission.
- Patients should be monitored every 6 to 12 months after remission. If a relapse occurs, alternate therapy with RAI is preferred to a second course of antithyroid drugs, as subsequent courses of therapy are less likely to induce remission.
- Minor adverse reactions include pruritic maculopapular rashes, arthralgias, fever, and a benign transient leukopenia (white blood cell count less than  $4,000/\text{mm}^3$ ). The alternate thiourea may be tried in these situations, but cross-sensitivity occurs in about 50% of patients.
- Major adverse effects include agranulocytosis (with fever, malaise, gingivitis, oropharyngeal infection, and a granulocyte count less than  $250/\text{mm}^3$ ), aplastic anemia, a lupus-like syndrome, polymyositis, GI intolerance, hepatotoxicity, and hypoprotrombinemia. If it occurs, agranulocytosis almost always develops in the first 3 months of therapy; routine monitor-

ing is not recommended because of its sudden onset. Patients who have experienced a major adverse reaction to one thiourea should not be converted to the alternate drug because of cross-sensitivity.

### *Iodides*

- **Iodide** acutely blocks thyroid hormone release, inhibits thyroid hormone biosynthesis by interfering with intrathyroidal iodide use, and decreases the size and vascularity of the gland.
- Symptom improvement occurs within 2 to 7 days of initiating therapy, and serum  $T_4$  and  $T_3$  concentrations may be reduced for a few weeks.
- Iodides are often used as adjunctive therapy to prepare a patient with Graves' disease for surgery, to acutely inhibit thyroid hormone release and quickly attain the euthyroid state in severely thyrotoxic patients with cardiac decompensation, or to inhibit thyroid hormone release after RAI therapy.
- **Potassium iodide** is available as a saturated solution (**SSKI**, 38 mg iodide per drop) or as **Lugol's solution**, containing 6.3 mg of iodide per drop.
- The typical starting dose of SSKI is 3 to 10 drops daily (120 to 400 mg) in water or juice. When used to prepare a patient for surgery, it should be administered 7 to 14 days preoperatively.
- As an adjunct to RAI, SSKI should not be used before but rather 3 to 7 days after RAI treatment so that the RAI can concentrate in the thyroid.
- Adverse effects include hypersensitivity reactions (skin rashes, drug fever, rhinitis, conjunctivitis); salivary gland swelling; "iodism" (metallic taste, burning mouth and throat, sore teeth and gums, symptoms of a head cold, and sometimes stomach upset and diarrhea); and gynecomastia.

### *Adrenergic Blockers*

- $\beta$ -Blockers have been used widely to ameliorate thyrotoxic symptoms such as palpitations, anxiety, tremor, and heat intolerance. They have no effect on peripheral thyrotoxicosis and protein metabolism and do not reduce TSAbs or prevent thyroid storm. **Propranolol** and **nadolol** partially block the conversion of  $T_4$  to  $T_3$ , but this contribution to the overall therapeutic effect is small.
- $\beta$ -Blockers are usually used as adjunctive therapy with antithyroid drugs, RAI, or iodides when treating Graves' disease or toxic nodules; in preparation for surgery; or in thyroid storm.  $\beta$ -Blockers are primary therapy only for thyroiditis and iodine-induced hyperthyroidism.
- **Propranolol** doses required to relieve adrenergic symptoms vary, but an initial dose of 20 to 40 mg four times daily is effective for most patients (heart rate less than 90 beats/min). Younger or more severely toxic patients may require as much as 240 to 480 mg/day.
- $\beta$ -Blockers are contraindicated in patients with decompensated heart failure unless it is caused solely by tachycardia (high output). Other contraindications include sinus bradycardia, concomitant therapy with monoamine oxidase inhibitors or tricyclic antidepressants, and patients with spontaneous hypoglycemia. Side effects include nausea, vomiting, anxiety, insomnia, lightheadedness, bradycardia, and hematologic disturbances.
- Centrally acting sympatholytics (e.g., **clonidine**) and calcium channel antagonists (e.g., **diltiazem**) may be useful for symptom control when contraindications to  $\beta$ -blockade exist.

### Radioactive Iodine

- **Sodium iodide 131** is an oral liquid that concentrates in the thyroid and initially disrupts hormone synthesis by incorporating into thyroid hormones and thyroglobulin. Over a period of weeks, follicles that have taken up RAI and surrounding follicles develop evidence of cellular necrosis and fibrosis of the interstitial tissue.
- RAI is the agent of choice for Graves' disease, toxic autonomous nodules, and toxic multinodular goiters. Pregnancy is an absolute contraindication to the use of RAI.
- $\beta$ -Blockers are the primary adjunctive therapy to RAI, since they may be given anytime without compromising RAI therapy.
- Patients with cardiac disease and elderly patients are often treated with thionamides prior to RAI ablation because thyroid hormone levels will transiently increase after RAI treatment due to release of preformed thyroid hormone.
- Antithyroid drugs are not routinely used after RAI because their use is associated with a higher incidence of posttreatment recurrence or persistent hyperthyroidism.
- If iodides are administered, they should be given 3 to 7 days after RAI to prevent interference with the uptake of RAI in the thyroid gland.
- The goal of therapy is to destroy overactive thyroid cells, and a single dose of 4,000 to 8,000 rad results in a euthyroid state in 60% of patients at 6 months or less. A second dose of RAI should be given 6 months after the first RAI treatment if the patient remains hyperthyroid.
- Hypothyroidism commonly occurs months to years after RAI. The acute, short-term side effects include mild thyroidal tenderness and dysphagia. Long-term follow-up has not revealed an increased risk for development of thyroid carcinoma, leukemia, or congenital defects.

### Treatment of Thyroid Storm

- The following therapeutic measures should be instituted promptly: (1) suppression of thyroid hormone formation and secretion; (2) antiadrenergic therapy; (3) administration of corticosteroids; and (4) treatment of associated complications or coexisting factors that may have precipitated the storm (Table 20-2).

**TABLE 20-2** Drug Dosages Used in the Management of Thyroid Storm

Drug	Regimen
Propylthiouracil	900–1,200 mg/day orally in four or six divided doses
Methimazole	90–120 mg/day orally in four or six divided doses
Sodium iodide	Up to 2 g/day IV in single or divided doses
Lugol's solution	5–10 drops three times a day in water or juice
Saturated solution of potassium iodide	1–2 drops three times a day in water or juice
Propranolol	40–80 mg every 6 hours
Dexamethasone	5–20 mg/day orally or IV in divided doses
Prednisone	25–100 mg/day orally in divided doses
Methylprednisolone	20–80 mg/day IV in divided doses
Hydrocortisone	100–400 mg/day IV in divided doses

- **PTU** in large doses is the preferred thionamide because it interferes with the production of thyroid hormones and blocks the peripheral conversion of  $T_4$  to  $T_3$ .
- **Iodides**, which rapidly block the release of preformed thyroid hormone, should be administered after PTU is initiated to inhibit iodide use by the overactive gland.
- Antiadrenergic therapy with the short-acting agent **esmolol** is preferred because it can be used in patients with pulmonary disease or at risk for cardiac failure and because its effects can be rapidly reversed.
- **Corticosteroids** are generally recommended, but there is no convincing evidence of adrenocortical insufficiency in thyroid storm; their benefits may be attributed to their antipyretic action and stabilization of blood pressure.
- General supportive measures, including **acetaminophen** as an antipyretic (aspirin or other nonsteroidal antiinflammatory drugs may displace bound thyroid hormone), **fluid and electrolyte replacement**, **sedatives**, **digoxin**, **antiarrhythmics**, **insulin**, and **antibiotics** should be given as indicated. Plasmapheresis and peritoneal dialysis have been used to remove excess hormone in patients not responding to more conservative measures.

## EVALUATION OF THERAPEUTIC OUTCOMES

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- After therapy (thionamides, RAI, or surgery) for hyperthyroidism has been initiated, patients should be evaluated on a monthly basis until they reach a euthyroid condition.
- Clinical signs of continuing thyrotoxicosis or the development of hypothyroidism should be noted.
- After  $T_4$  replacement is initiated, the goal is to maintain both the free  $T_4$  level and the TSH concentration in the normal range. Once a stable dose of  $T_4$  is identified, the patient may be followed every 6 to 12 months.

## HYPOTHYROIDISM

### PATHOPHYSIOLOGY

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- The vast majority of hypothyroid patients have thyroid gland failure (primary hypothyroidism). The causes include chronic autoimmune thyroiditis (Hashimoto's disease), iatrogenic hypothyroidism, iodine deficiency, enzyme defects, thyroid hypoplasia, and goitrogens.
- Pituitary failure (secondary hypothyroidism) is an uncommon cause resulting from pituitary tumors, surgical therapy, external pituitary radiation, postpartum pituitary necrosis, metastatic tumors, tuberculosis, histiocytosis, and autoimmune mechanisms.

### CLINICAL PRESENTATION

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- Adult manifestations of hypothyroidism include dry skin, cold intolerance, weight gain, constipation, weakness, lethargy, fatigue, muscle cramps, myalgia, stiffness, and loss of ambition or energy. In children, thyroid hormone deficiency may manifest as growth retardation.

- Physical signs include coarse skin and hair, cold or dry skin, periorbital puffiness, bradycardia, and slowed or hoarse speech. Objective weakness (with proximal muscles being affected more than distal muscles) and slow relaxation of deep tendon reflexes are common. Reversible neurologic syndromes such as carpal tunnel syndrome, polyneuropathy, and cerebellar dysfunction may also occur.
- Most patients with pituitary failure (secondary hypothyroidism) have clinical signs of generalized pituitary insufficiency such as abnormal menses and decreased libido, or evidence of a pituitary adenoma such as visual field defects, galactorrhea, or acromegaloid features.
- Myxedema coma is a rare consequence of decompensated hypothyroidism manifested by hypothermia, advanced stages of hypothyroid symptoms, and altered sensorium ranging from delirium to coma. Untreated disease is associated with a high mortality rate.

## DIAGNOSIS

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- A rise in the TSH level is the first evidence of primary hypothyroidism. Many patients have a free  $T_4$  level within the normal range (compensated hypothyroidism) and few, if any, symptoms of hypothyroidism. As the disease progresses, the free  $T_4$  concentration drops below the normal level. The  $T_3$  concentration is often maintained in the normal range despite a low  $T_4$ . Antithyroid peroxidase antibodies and antithyroglobulin antibodies are likely to be elevated. The RAIU is not a useful test in the evaluation of hypothyroidism because it can be low, normal, or even elevated.
- Pituitary failure (secondary hypothyroidism) should be suspected in a patient with decreased levels of  $T_4$  and inappropriately normal or low TSH levels.

## DESIRED OUTCOME

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- The treatment goals for hypothyroidism are to normalize thyroid hormone concentrations in tissue, provide symptomatic relief, prevent neurologic deficits in newborns and children, and reverse the biochemical abnormalities of hypothyroidism.

## TREATMENT OF HYPOTHYROIDISM

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(See Table 20-3)

- Levothyroxine (L-thyroxine,  $T_4$ ) is the drug of choice for thyroid hormone replacement and suppressive therapy because it is chemically stable, relatively inexpensive, free of antigenicity, and has uniform potency; however, any of the commercially available thyroid preparations can be used. Once a particular product is selected, therapeutic interchange is discouraged.
- Because  $T_3$  (and not  $T_4$ ) is the biologically active form, levothyroxine administration results in a pool of thyroid hormone that is readily and consistently converted to  $T_3$ .
- Young patients with long-standing disease and patients older than 45 years without known cardiac disease should be started on 50 mcg daily of levothyroxine and increased to 100 mcg daily after 1 month.

**TABLE 20-3** Thyroid Preparations Used in the Treatment of Hypothyroidism

Drug/Dosage Form	Content	Relative Dose
<b>Thyroid USP</b>		
Armour Thyroid (T <sub>4</sub> :T <sub>3</sub> ratio) 9.5 mcg:2.25 mcg, 19 mcg:4.5 mcg, 38 mcg:9 mcg, 57 mcg:13.5 mcg, 76 mcg:18 mcg, 114 mcg:27 mcg, 152 mcg:36 mcg, 190 mcg:45 mcg tablets	Desiccated beef or pork thyroid gland	1 grain (equivalent to 60 mcg of T <sub>4</sub> )
<b>Thyroglobulin</b>		
Proloid 32-, 65-, 100-, 130-, 200-mg tablets	Partially purified pork thyroglobulin	1 grain
<b>Levothyroxine</b>		
Synthroid, Levothroid, Levoxyl, Unithroid, and other generics 25-, 50-, 75-, 88-, 100-, 112-, 125-, 137-, 150-, 175-, 200-, 300-mcg tablets; 200- and 500-mcg/vial injection	Synthetic T <sub>4</sub>	50–60 mcg
<b>Liothyronine</b>		
Cytomel 5-, 25-, and 50-mcg tablets	Synthetic T <sub>3</sub>	15–37.5 mcg
<b>Liotrix</b>		
Thyrolar 1/4-, 1/2-, 1-, 2-, and 3-strength tablets	Synthetic T <sub>4</sub> :T <sub>3</sub> in 4:1 ratio	50–60 mcg T <sub>4</sub> and 12.5–15 mcg T <sub>3</sub>

T<sub>3</sub>, triiodothyronine; T<sub>4</sub>, thyroxine.

- The recommended initial daily dose for older patients or those with known cardiac disease is 25 mcg/day titrated upward in increments of 25 mcg at monthly intervals to prevent stress on the cardiovascular system.
- The average maintenance dose for most adults is about 125 mcg/day, but there is a wide range of replacement doses, necessitating individualized therapy and appropriate monitoring to determine an appropriate dose.
- Patients with subclinical hypothyroidism and marked elevations in TSH (greater than 10 milli-international units per liter [mIU/L]) and high titers of TSAb or prior treatment with sodium iodide 131 may benefit from treatment with levothyroxine.
- Levothyroxine is the drug of choice for pregnant women, and the objective of the treatment is to decrease TSH to 1 mIU/L and to maintain free T<sub>4</sub> concentrations in the normal range.
- Cholestyramine, calcium carbonate, sucralfate, aluminum hydroxide, ferrous sulfate, soybean formula, and dietary fiber supplements may impair the absorption of levothyroxine from the GI tract. Drugs that increase nondeiodinative T<sub>4</sub> clearance include rifampin, carbamazepine, and possibly phenytoin. Amiodarone may block the conversion of T<sub>4</sub> to T<sub>3</sub>.
- **Thyroid, USP** (or desiccated thyroid) is derived from hog, beef, or sheep thyroid gland. It may be antigenic in allergic or sensitive patients. Inexpensive generic brands may not be bioequivalent.
- **Thyroglobulin** is a purified hog-gland extract that is standardized biologically to give a T<sub>4</sub>:T<sub>3</sub> ratio of 2.5:1. It has no clinical advantages and is not widely used.

- **Liothyronine** (synthetic  $T_3$ ) has uniform potency but has a higher incidence of cardiac adverse effects, higher cost, and difficulty in monitoring with conventional laboratory tests.
- **Liotrix** (synthetic  $T_4:T_3$  in a 4:1 ratio) is chemically stable, pure, and has a predictable potency but is expensive. It lacks therapeutic rationale because about 35% of  $T_4$  is converted to  $T_3$  peripherally.
- Excessive doses of thyroid hormone may lead to heart failure, angina pectoris, and myocardial infarction. Allergic or idiosyncratic reactions can occur with the natural animal-derived products such as desiccated thyroid and thyroglobulin, but they are extremely rare with the synthetic products used today. Excess exogenous thyroid hormone may reduce bone density and increase the risk of fracture.

### TREATMENT OF MYXEDEMA COMA

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- Immediate and aggressive therapy with IV bolus **levothyroxine**, 300 to 500 mcg, has traditionally been used. Initial treatment with IV **liothyronine** or a combination of both hormones has also been advocated because of impaired conversion of  $T_4$  to  $T_3$ .
- Glucocorticoid therapy with IV **hydrocortisone** 100 mg every 8 hours should be given until coexisting adrenal suppression is ruled out.
- Consciousness, lowered TSH concentrations, and normal vital signs are expected within 24 hours.
- Maintenance levothyroxine doses are typically 75 to 100 mcg IV until the patient stabilizes and oral therapy is begun.
- Supportive therapy must be instituted to maintain adequate ventilation, euglycemia, blood pressure, and body temperature. Underlying disorders such as sepsis and myocardial infarction must be diagnosed and treated.

### EVALUATION OF THERAPEUTIC OUTCOMES

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- Serum TSH concentration is the most sensitive and specific monitoring parameter for adjustment of levothyroxine dose. Concentrations begin to fall within hours and are usually normalized within 2 to 6 weeks.
- TSH and  $T_4$  concentrations should both be checked every 6 weeks until a euthyroid state is achieved. An elevated TSH level indicates insufficient replacement. Serum  $T_4$  concentrations can be useful in detecting noncompliance, malabsorption, or changes in levothyroxine product bioequivalence. TSH may also be used to help identify noncompliance.
- In patients with hypothyroidism caused by hypothalamic or pituitary failure, alleviation of the clinical syndrome and restoration of serum  $T_4$  to the normal range are the only criteria available for estimating the appropriate replacement dose of levothyroxine.

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See Chap. 78, *Thyroid Disorders*, authored by Steven I. Sherman and Robert L. Talbert, for a more detailed discussion of this topic.

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SECTION 5  
GASTROINTESTINAL DISORDERS

*Edited by Joseph T. DiPiro and Terry L. Schwinghammer*

CHAPTER

21

## Cirrhosis and Portal Hypertension

### DEFINITIONS

- Cirrhosis is defined as a diffuse process characterized by fibrosis and a conversion of the normal hepatic architecture into structurally abnormal nodules. The end result is destruction of hepatocytes and their replacement by fibrous tissue.
- The resulting resistance to blood flow results in portal hypertension and the development of varices and ascites. Hepatocyte loss and intrahepatic shunting of blood results in diminished metabolic and synthetic function, which leads to hepatic encephalopathy (HE) and coagulopathy.
- Cirrhosis has many causes (Table 21-1). In the United States, excessive alcohol intake and chronic viral hepatitis (types B and C) are the most common causes.

### PATHOPHYSIOLOGY

- Cirrhosis results in elevation of portal blood pressure because of fibrotic changes within the hepatic sinusoids, changes in the levels of vasodilatory and vasoconstrictor mediators, and an increase in blood flow to the splanchnic vasculature. The pathophysiologic abnormalities that cause it result in the commonly encountered problems of ascites, portal hypertension and esophageal varices, HE, and coagulation disorders.

### ASCITES

- Ascites is the pathologic accumulation of lymph fluid within the peritoneal cavity. It is one of the earliest and most common presentations of cirrhosis.
- The development of ascites is related to systemic arterial vasodilation that leads to the activation of the baroreceptors in the kidney and an activation of the renin-angiotensin system, with sodium and water retention and vasoconstrictor production.

### PORTAL HYPERTENSION AND VARICES

- The most important sequelae of portal hypertension are the development of varices and alternative routes of blood flow. Patients with cirrhosis are at risk for varices when portal pressures exceed the vena cava pressure by greater than or equal to 12 mm Hg.
- Hemorrhage from varices occurs in 25% to 40% of patients with cirrhosis, and each episode of bleeding carries a 25% to 30% risk of death.

**TABLE 21-1** Etiology of Cirrhosis

Chronic alcohol consumption
Chronic viral hepatitis (types B, C, and D)
Metabolic liver disease
Hemochromatosis
Wilson's disease
$\alpha_1$ -Antitrypsin deficiency
Nonalcoholic steatohepatitis ("fatty liver")
Cholestatic liver diseases
Primary biliary cirrhosis
Secondary biliary cirrhosis (possible causes: gallstones, strictures, parasitic infection)
Primary sclerosing cholangitis (associated with ulcerative colitis and cholangiocarcinoma)
Budd-Chiari's syndrome
Severe congestive heart failure and constrictive pericarditis
Drugs and herbals
Isoniazid, methyl dopa, amiodarone, methotrexate, phenothiazine, estrogen, anabolic steroids, black cohosh, Jamaican bush tea

## HEPATIC ENCEPHALOPATHY

- HE is a central nervous system disturbance with a wide range of neuropsychiatric symptoms associated with hepatic insufficiency and liver failure.
- The symptoms of HE are thought to result from an accumulation of gut-derived nitrogenous substances in the systemic circulation as a consequence of shunting through portosystemic collaterals bypassing the liver. These substances then enter the CNS and result in alterations of neurotransmitters that affect consciousness and behavior.
- Altered ammonia, glutamate, benzodiazepine receptor agonists, and manganese are associated with HE. However, serum ammonia levels are poorly correlated with mental status in HE.
- Type A HE is induced by acute liver failure, Type B results from portal-systemic bypass without intrinsic liver disease, and Type C occurs with cirrhosis. HE may be classified as episodic, persistent, or minimal.

## COAGULATION DEFECTS

- Complex coagulation derangements can occur in cirrhosis. These derangements include the reduction in the synthesis of coagulation factors, excessive fibrinolysis, disseminated intravascular coagulation, thrombocytopenia, and platelet dysfunction.
- Vitamin K–dependent clotting factor, including factor VII, is affected early.
- The net effect of these events is the development of bleeding diathesis.

## CLINICAL PRESENTATION

- The range of presentation of patients with cirrhosis may be from asymptomatic with abnormal laboratory tests to acute life-threatening hemorrhage.
- Table 21-2 describes the presenting signs and symptoms of cirrhosis.
- Jaundice is often a late manifestation of cirrhosis, and its absence does not exclude the diagnosis. The classic signs of cirrhosis, such as palmar

**TABLE 21-2** Clinical Presentation of Cirrhosis**Signs and symptoms**

Asymptomatic  
 Hepatomegaly, splenomegaly  
 Pruritus, jaundice, palmar erythema, spider angiomata, hyperpigmentation  
 Gynecomastia, reduced libido  
 Ascites, edema, pleural effusion, and respiratory difficulties  
 Malaise, anorexia, and weight loss  
 Encephalopathy

**Laboratory tests**

Hypoalbuminemia  
 Elevated prothrombin time  
 Thrombocytopenia  
 Elevated alkaline phosphatase  
 Elevated aspartate transaminase (AST), alanine transaminase (ALT), and  $\gamma$ -glutamyl transpeptidase (GGT)

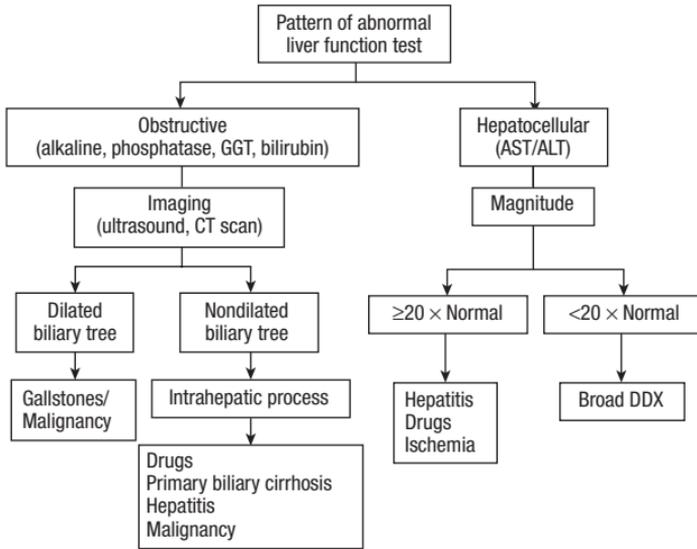
erythema, spider angiomata, and gynecomastia, are neither sensitive nor specific for the disease.

- On questioning, a patient who abuses alcohol will often underestimate the amount of alcohol consumed.
- An elevation of prothrombin time was the single most reliable manifestation of cirrhosis. The combination of thrombocytopenia, encephalopathy, and ascites had the highest predictive value.

## LABORATORY ABNORMALITIES

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- Routine liver assessment tests include alkaline phosphatase, bilirubin, aspartate transaminase, alanine transaminase, and  $\gamma$ -glutamyl transpeptidase (GGT). Additional markers of hepatic synthetic activity include albumin and prothrombin time. The substances are typically elevated in chronic inflammatory liver diseases such as hepatitis C, but may be normal in others with resolved infectious processes.
- The aminotransferases, aspartate transaminase and alanine transaminase, are enzymes that have increased concentrations in plasma following hepatocellular injury. The highest concentrations are seen in acute viral infections, or ischemic or toxic liver injury.
- Alkaline phosphatase levels and GGT are elevated in plasma with obstructive disorders that disrupt the flow of bile from hepatocytes to the bile ducts or from the biliary tree to the intestines in condition such as primary biliary cirrhosis, sclerosing cholangitis, drug-induced cholestasis, gallstone disease, and autoimmune cholestatic liver disease.
- The levels of GGT in plasma correlate well with elevations of alkaline phosphatase and are a sensitive marker for cholestatic liver disease.
- Elevations of serum bilirubin are common in end-stage liver disease and obstruction of the common bile duct, but other causes of hyperbilirubinemia are numerous.
- Fig. 21-1 describes a general algorithm for the interpretation of liver function tests.
- Albumin and coagulation factors are markers of hepatic synthetic activity and are used to estimate hepatocyte functioning in cirrhosis.



**FIGURE 21-1.** Interpretation of liver function tests. (ALT, alanine transaminase; AST, aspartate transaminase; CT, computed tomography; DDX, differential diagnosis; GGT,  $\gamma$ -glutamyl transpeptidase.)

- Thrombocytopenia is a relatively common feature in chronic liver disease found in 30% to 64% of cirrhotic patients.
- Liver biopsy plays a central role in the diagnosis and staging of liver disease.
- The Child-Pugh classification system uses a combination of physical and laboratory findings to assess and define the severity of cirrhosis and is a predictor of patient survival, surgical outcome, and risk of variceal bleeding (Table 21-3).

## TREATMENT

### DESIRED OUTCOME

- Clinical improvement or resolution of acute complications, such as variceal bleeding, and resolution of hemodynamic instability for an episode of acute variceal hemorrhage.
- Prevention of complications, achieving adequate lowering of portal pressure with medical therapy using  $\beta$ -adrenergic blocker therapy, or supporting abstinence from alcohol.

### GENERAL APPROACHES

- Identify and eliminate the causes of cirrhosis (e.g., alcohol abuse).
- Assess the risk for variceal bleeding and begin pharmacologic prophylaxis where indicated, reserving endoscopic therapy for high-risk patients or acute bleeding episodes.
- The patient should be evaluated for clinical signs of ascites and managed with pharmacologic treatment (e.g., diuretics) and paracentesis. Careful

**TABLE 21-3** Criteria and Scoring for the Child-Pugh Grading of Chronic Liver Disease

Score	1	2	3
Bilirubin (mg/dL)	1–2	2–3	>3
Albumin (mg/dL)	>3.5	2.8–3.5	<2.8
Ascites	None	Mild	Moderate
Encephalopathy (grade)	None	1 and 2	3 and 4
Prothrombin time (sec prolonged)	1–4	4–6	>6

Grade A, 1–6 points; grade B, 7–9 points; grade C, 10–15 points.

monitoring for spontaneous bacterial peritonitis (SBP) should be employed in patients with ascites who undergo acute deterioration.

- HE is a common complication of cirrhosis and requires clinical vigilance and treatment with dietary restriction, elimination of CNS depressants, and therapy to lower ammonia levels.
- Frequent monitoring for signs of hepatorenal syndrome, pulmonary insufficiency, and endocrine dysfunction is necessary.

## MANAGEMENT OF PORTAL HYPERTENSION AND VARICEAL BLEEDING

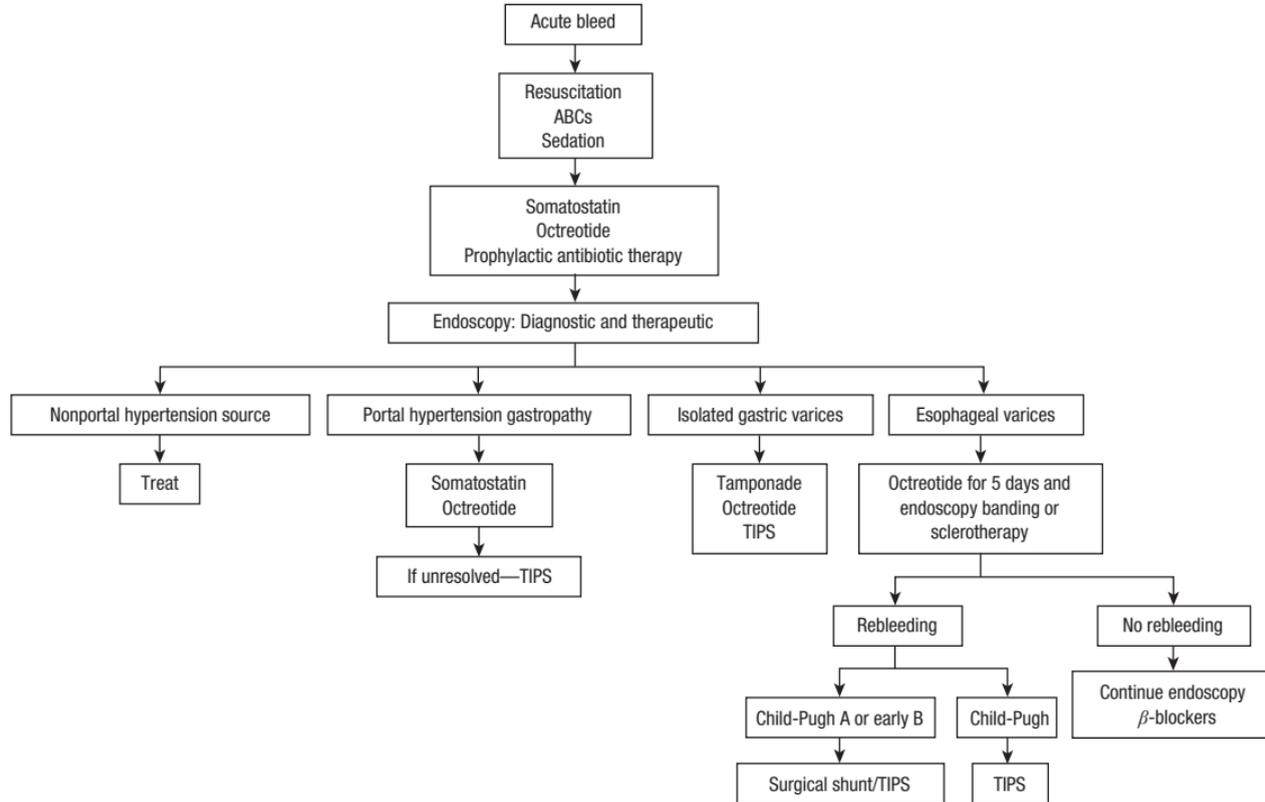
- The management of varices involves three strategies: (1) primary prophylaxis to prevent rebleeding, (2) treatment of variceal hemorrhage, and (3) secondary prophylaxis to prevent rebleeding in patients who have already bled.

### Primary Prophylaxis

- The mainstay of primary prophylaxis is the use of nonselective  $\beta$ -adrenergic blocking agents such as **propranolol** or **nadolol**. These agents reduce portal pressure by reducing portal venous inflow via two mechanisms: decrease in cardiac output, and decrease in splanchnic blood flow. They prevent bleeding, and there is a trend toward reduced mortality.
- $\beta$ -Adrenergic blocker therapy should be continued for life, unless it is not tolerated, because bleeding can occur when therapy is abruptly discontinued.
- All patients with cirrhosis and portal hypertension should be considered for endoscopic screening, and patients with large varices should receive primary prophylaxis with  $\beta$ -adrenergic blockers.
- Therapy should be initiated with **propranolol**, 10 mg three times daily, or **nadolol**, 20 mg once daily, and titrated to a reduction in resting heart rate of 20% to 25%, an absolute heart rate of 55 to 60 beats/min, or the development of adverse effects.
- Endoscopic band ligation (EBL) should be considered in patients with contraindications or intolerance to  $\beta$ -adrenergic blockers.
- There is insufficient evidence to recommend nitrates in addition to  $\beta$ -adrenergic blockers to further lower portal pressure.

### Acute Variceal Hemorrhage

- Fig. 21-2 presents an algorithm for the management of variceal hemorrhage. Evidence-based recommendations for selected treatments are presented in Table 21-4.



**FIGURE 21-2.** Management of acute variceal hemorrhage. (ABCs, airway, breathing, and circulation; TIPS, transjugular intrahepatic portosystemic shunt.)

**TABLE 21-4** Evidence-Based Table of Selected Treatment Recommendations: Variceal Bleeding in Portal Hypertension

Recommendation	Grade
Prevention of variceal bleeding	
Nonselective $\beta$ -blockers should be initiated in patients with medium or large esophageal varices	1A
EBL should be offered to patients who have contraindications or intolerance to nonselective $\beta$ -blockers	5D
Treatment of variceal bleeding	
Antibiotic prophylaxis should be instituted on admission	1A
Vasoactive drugs should be started as soon as possible, prior to endoscopy, and maintained for 2–5 days	1A
EBL is the recommended form of endoscopic therapy for acute esophageal variceal bleeding and should be used in conjunction with vasoactive drug therapy	1A
Secondary prophylaxis of variceal bleeding	
Nonselective $\beta$ -blockers, EBL, or both should be used for prevention of recurrent variceal bleeding	1A

EBL, endoscopic band ligation.

Recommendation Grading: Level of Evidence 1 = highest; 5 = lowest; Grade of Recommendation: A = strongest; D = weakest. Data from DeFranchis R. Updating consensus in portal hypertension. Report of the Baveno III consensus workshop on definitions, methodology and therapeutic strategies in portal hypertension. *J Hepatol* 2000;33:846–852.

- Initial treatment goals include: (1) adequate fluid resuscitation, (2) correction of coagulopathy and thrombocytopenia, (3) control of bleeding, (4) prevention of rebleeding, and (5) preservation of liver function.
- Prompt stabilization and aggressive fluid resuscitation of patients with active bleeding are followed by endoscopic examination. Airway management is critical.
- The American College of Gastroenterology recommends esophagogastroduodenoscopy employing endoscopic injection sclerotherapy or EBL of varices as the primary diagnostic and treatment strategy for upper GI tract hemorrhage secondary to portal hypertension and varices.
- Fluid resuscitation involves colloids initially and subsequent blood products.
- Vasoactive drug therapy (somatostatin, octreotide, or terlipressin) to stop or slow bleeding is routinely employed early in patient management to allow stabilization of the patient and to permit endoscopy to proceed under more favorable conditions. These agents decrease splanchnic blood flow and reduce portal and variceal pressures, without significant adverse effects.
- Treatment with octreotide or somatostatin should be initiated early to control bleeding and facilitate endoscopy. Octreotide is preferred and is administered as an IV bolus of 50 to 100 mcg and is followed by a continuous infusion of 25 mcg/hour, up to a maximum rate of 50 mcg/hour. Patients should be monitored for hypo- or hyperglycemia.
- **Vasopressin**, alone or in combination with nitroglycerin, can no longer be recommended as first-line therapy for the management of variceal hemorrhage. Vasopressin causes nonselective vasoconstriction and can result in hypertension, severe headaches, coronary ischemia, myocardial infarction, and arrhythmias.

- Antibiotic therapy should be used early to prevent sepsis in patients with signs of infection or ascites.
- EBL is the recommended form of endoscopic therapy for acute variceal bleeding, although endoscopic injection sclerotherapy (injection of 1 to 4 mL of a sclerosing agent into the lumen of the varices) may be used if the ligation is technically difficult. EBL is often used for upper GI tract hemorrhage secondary to portal hypertension and varices.
- If standard therapy fails to control bleeding, a salvage procedure such as balloon tamponade (with a Sengstaken-Blakemore tube), transjugular intrahepatic portosystemic shunt, or surgical shunting is necessary.

### Prevention of Rebleeding

- $\beta$ -Adrenergic blockers along with EBL is the best treatment option for prevention of rebleeding.
- In patients without contraindications,  $\beta$ -adrenergic blocking agents should be the initial step in prevention of rebleeding, along with EBL. Use of a long-acting  $\beta$ -adrenergic blocker (such as nadolol) is usually recommended to improve compliance, and gradual, individualized dose escalation may help to minimize side effects. A decrease in hepatic venous pressure gradient to <12 mm Hg or a reduction of more than 20% from baseline are considered therapeutic targets.
- **Propranolol** may be given at 20 mg three times daily (or **nadolol**, 20 to 40 mg once daily) and titrated weekly to achieve a goal of heart rate 55 to 60 beats/min or a heart rate that is 25% lower than the baseline heart rate. Patients should be monitored for evidence of heart failure, bronchospasm, or glucose intolerance.
- For patients who fail to achieve sufficient reductions in portal pressure with  $\beta$ -blocker therapy alone, combination therapy with **isosorbide mononitrate** may more effectively lower portal pressures.

### ASCITES

- For patients with ascites, a serum-ascites albumin gradient should be determined. If the serum-ascites albumin gradient is greater than 1.1, portal hypertension is present with 97% accuracy.
- The treatment of ascites secondary to portal hypertension includes abstinence from alcohol, sodium restriction, and diuretics. Sodium chloride should be restricted to 2 g/day.
- Diuretic therapy should be initiated with single morning doses of **spironolactone**, 100 mg, and **furosemide**, 40 mg, with a goal of 0.5-kg maximum daily weight loss. The dose of each can be increased together, maintaining the 100:40 mg ratio, to a maximum daily dose of 400 mg spironolactone and 160 mg furosemide.
- If tense ascites is present, a 4- to 6-L paracentesis should be performed prior to institution of diuretic therapy and salt restriction.
- Patients who experience encephalopathy, severe hyponatremia despite fluid restriction, or renal insufficiency should have diuretic therapy discontinued.
- Liver transplantation should be considered in patients with refractory ascites.

**TABLE 21-5** Treatment Goals: Acute and Chronic Hepatic Encephalopathy

Acute Hepatic Encephalopathy	Chronic Hepatic Encephalopathy
Control precipitating factor	Reverse encephalopathy
Reverse encephalopathy	Avoid recurrence
Hospital/inpatient therapy	Home/outpatient therapy
Maintain fluid and hemodynamic support	Manage persistent neuropsychiatric abnormalities
Expect normal mentation after recovery	Manage chronic liver disease
	High prevalence of abnormal mentation after recovery

## SPONTANEOUS BACTERIAL PERITONITIS

- Antibiotic therapy for prevention of SBP should be considered in all patients who are at high risk for this complication (those who experience a prior episode of SBP or variceal hemorrhage, and those with low-protein ascites).
- Patients with documented or suspected SBP should receive broad-spectrum antibiotic therapy to cover *Escherichia coli*, *Klebsiella pneumoniae*, and *Streptococcus pneumoniae*.
- **Cefotaxime**, 2 g every 8 hours, or a similar third-generation cephalosporin is considered the drug of choice. **Oral ofloxacin**, 400 mg every 12 hours, is equivalent to IV cefotaxime.

## Hepatic Encephalopathy

- Table 21-5 describes the treatment goals for HE.
- The first approach to treatment of HE is to identify any precipitating causes. Precipitating factors and therapy alternatives are presented in Table 21-6.

**TABLE 21-6** Portosystemic Encephalopathy: Precipitating Factors and Therapy

Factor	Therapy Alternatives
GI bleeding	Band ligation/sclerotherapy
Variceal	Octreotide
Nonvariceal	Endoscopic therapy
	Proton pump inhibitors
Infection/sepsis	Antibiotics
	Paracentesis
Electrolyte abnormalities	Discontinue diuretics
	Fluid and electrolyte replacement
Sedative ingestion	Discontinue sedatives/tranquilizers
	Consider reversal (flumazenil/naloxone)
Dietary excesses	Limit daily protein
	Lactulose
Constipation	Cathartics
	Bowel cleansing/enema
Renal insufficiency	Discontinue diuretics
	Discontinue nonsteroidal antiinflammatory drugs, nephrotoxic antibiotics
	Fluid resuscitation

**TABLE 21-7** Management Approach and Outcome Assessments

Complication	Treatment Approach	Monitoring Parameter	Outcome Assessment
Ascites	Diet, diuretics, paracentesis, TIPS	Daily assessment of weight	Prevent or eliminate ascites and its secondary complications
Spontaneous bacterial peritonitis	Antibiotic therapy, prophylaxis if undergoing paracentesis	Evidence of clinical deterioration (e.g., abdominal pain, fever, anorexia, malaise, fatigue)	Prevent/treat infection to decrease mortality
Variceal bleeding	Pharmacologic prophylaxis	Child-Pugh score, endoscopy, CBC	Appropriate reduction in heart rate and portal pressure
	Endoscopy, vasoactive drug therapy (octreotide), sclerotherapy, volume resuscitation, pharmacologic prophylaxis	CBC, evidence of overt bleeding	Acute: control acute bleed. Chronic: variceal obliteration, reduce portal pressures
Coagulation disorders	Blood products (PPF, platelets), vitamin K	CBC, prothrombin time, platelet count	Normalize PT, maintain/improve hemostasis
Hepatic encephalopathy	Ammonia reduction (lactulose, cathartics), elimination of drugs causing CNS depression, limit excess protein in diet	Grade of encephalopathy, EEG, psychological testing, mental status changes, concurrent drug therapy	Maintain functional capacity, prevent hospitalization for encephalopathy, decrease ammonia levels, provide adequate nutrition
Hepatorenal syndrome	Eliminate concurrent nephrotoxins (NSAIDs), decrease or discontinue diuretics, volume resuscitation, liver transplantation	Serum and urine electrolytes, concurrent drug therapy	Prevent progressive renal injury by preventing dehydration and avoiding other nephrotoxins Liver transplantation for refractory hepatorenal syndrome
Hepatopulmonary syndrome	Paracentesis, O <sub>2</sub> therapy	Dyspnea, presence of ascites	Acute: relief of dyspnea and hypoxia. Chronic: manage ascites as above

CBC, complete blood cell count; EEG, electroencephalogram; NSAIDs, nonsteroidal antiinflammatory drugs; O<sub>2</sub>, oxygen; PPF, plasma protein fraction; PT, prothrombin time; TIPS, transjugular intrahepatic portosystemic shunt.

- Treatment approaches include: (1) reduction of blood ammonia concentrations by dietary restrictions, and drug therapy aimed at inhibiting ammonia production or enhancing its removal (lactulose and antibiotics) and (2) inhibition of  $\gamma$ -aminobutyric acid–benzodiazepine receptors by flumazenil.
- Approaches to reducing blood ammonia concentrations include: In patients with acute HE, limit protein intake to 10 to 20 g/day while maintaining the total caloric intake. Protein intake can be titrated by increasing 10 to 20 g/day every 3 to 5 days to a total of 0.8 to 1 g/kg/day. With chronic HE, restrict protein intake to 40 g/day.
- In episodic HE, lactulose is initiated at 45 mL every hour (or 300 mL lactulose syrup with 700 mL water given as a retention enema) until catharsis begins. The dose is then decreased to 15 to 30 mL orally every 8 to 12 hours and titrated to produce two to three soft, acidic stools per day.

- Antibiotic therapy with **metronidazole** or **neomycin** is reserved for patients who have not responded to diet and lactulose.
- Zinc acetate supplementation (220 mg twice daily) is recommended for long-term management in patients with cirrhosis who are zinc deficient.
- Other adjunctive therapies that may be considered for patient's refractory to standard therapy include L-ornithine L-aspartate or flumazenil 0.2 mg up to 15 mg IV.

## EVALUATION OF THERAPEUTIC OUTCOMES

- Table 21-7 summarizes the management approach for patients with cirrhosis, including monitoring parameters and therapeutic outcomes.

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*See Chap. 39, Portal Hypertension and Cirrhosis, authored by Julie M. Sease, Edward G. Timm, and James J. Stragand, for a more detailed discussion of this topic.*

## DEFINITION

- Constipation does not have a single, generally agreed upon definition. Normal people pass at least three stools per week. Some of the definitions of constipation include: fewer than three stools per week for women and five for men despite a high-residue diet or a period of greater than 3 days without a bowel movement; straining at stool greater than 25% of the time and/or two or fewer stools per week; or straining at defecation and less than one stool daily with minimal effort.

## PATHOPHYSIOLOGY

- Constipation is not a disease but a symptom of an underlying disease or problem.
- Disorders of the GI tract (e.g., irritable bowel syndrome or diverticulitis), metabolic disorders (e.g., diabetes), or endocrine disorders (e.g., hypothyroidism) may cause constipation.
- Constipation commonly results from a diet low in fiber or from use of constipating drugs such as opiates. Constipation may sometimes be psychogenic in origin.
- Diseases or conditions that may cause constipation are:
  - ✓ GI disorders.
    - Irritable bowel syndrome, diverticulitis, upper and lower GI tract diseases, hemorrhoids, anal fissures, ulcerative proctitis, tumors, hernia, volvulus of the bowel, syphilis, tuberculosis, lymphogranuloma venereum, Hirschsprung's disease.
  - ✓ Metabolic and endocrine disorders.
    - Diabetes mellitus with neuropathy, hypothyroidism, panhypopituitarism, pheochromocytoma, hypercalcemia, enteric glucagons excess.
  - ✓ Pregnancy.
  - ✓ Neurogenic constipation.
    - Head trauma, CNS tumors, spinal cord injury, cerebrospinal accidents, Parkinson's disease.
  - ✓ Psychiatric disorders.
  - ✓ Inappropriate bowel habits.
  - ✓ Causes of drug-induced constipation are listed in Table 22-1.
  - ✓ All opiate derivatives are associated with constipation, but the degree of intestinal inhibitory effects seems to differ between agents. Orally administered opiates appear to have greater inhibitory effect than parenterally administered agents; oral codeine is well known as a potent antimotility agent.

## CLINICAL PRESENTATION

- The laxative abuser may present with contradictory findings, sometimes diarrhea or weight loss. Laxative abusers may also have vomiting, abdom-

**TABLE 22-1** Drugs Causing Constipation

Analgesics
Inhibitors of prostaglandin synthesis
Opiates
Anticholinergics
Antihistamines
Antiparkinsonian agents (e.g., benztropine or trihexyphenidyl)
Phenothiazines
Tricyclic antidepressants
Antacids containing calcium carbonate or aluminum hydroxide
Barium sulfate
Calcium channel blockers
Clonidine
Diuretics (nonpotassium-sparing)
Ganglionic blockers
Iron preparations
Muscle blockers (D-tubocurarine, succinylcholine)
Nonsteroidal antiinflammatory agents
Polystyrene sodium sulfonate

inal pain, lassitude, thirst, edema, and bone pain (due to osteomalacia). With prolonged abuse, patients may have fluid and electrolyte imbalances (most commonly hypokalemia), protein-losing gastroenteropathy with hypoalbuminemia, and syndromes resembling colitis. Laxative abusers frequently deny laxative use (Table 22-2).

## DESIRED OUTCOME

- A major goal for treatment of constipation is prevention of constipation by alteration of lifestyle (particularly diet) to prevent further episodes of constipation. For acute constipation, the goal is to relieve symptoms and restore normal bowel function.

## TREATMENT

### GENERAL APPROACH TO TREATMENT

- The patient should be asked about the frequency of bowel movements and the chronicity of constipation. The patient should also be carefully ques-

**TABLE 22-2** Clinical Presentation of Constipation

#### Signs and symptoms

It is important to ascertain whether the patient perceives the problem as infrequent bowel movements, stools of insufficient size, a feeling of fullness, or difficulty and pain on passing stool.

Signs and symptoms include hard, small or dry stools, bloated stomach, cramping abdominal pain and discomfort, straining or grunting, sensation of blockage, fatigue, headache, and nausea and vomiting.

#### Laboratory tests

A series of examinations, including proctoscopy, sigmoidoscopy, colonoscopy, or barium enema, may be necessary to determine the presence of colorectal pathology.

Thyroid function studies may be performed to determine the presence of metabolic or endocrine disorders.

tioned about usual diet and laxative regimens. Does the patient have a diet consistently deficient in high-fiber items and containing mainly highly refined foods? What laxatives or cathartics has the patient used to attempt relief of constipation? The patient should be questioned about other concurrent medications, with interest toward agents that might cause constipation.

- General measures believed to be beneficial in managing constipation include dietary modification to increase the amount of fiber consumed daily, exercise, adjustment of bowel habits so that a regular and adequate time is made to respond to the urge to defecate, and increasing fluid intake.
- If an underlying disease is recognized as the cause of constipation, attempts should be made to correct it. GI malignancies may be removed through a surgical resection. Endocrine and metabolic derangements are corrected by the appropriate methods.
- Potential drug causes of constipation should be identified. For some medications (e.g., antacids), nonconstipating alternatives exist. If no reasonable alternatives exist to the medication thought to be responsible for constipation, consideration should be given to lowering the dose. If a patient must remain on constipating medications, then more attention must be paid to general measures for prevention of constipation, as discussed in Dietary Modification and Bulk-Forming Agents below.
- In a small percentage of patients presenting with complaints of constipation, surgical procedures (such as intestinal resection) are necessary. Surgery is usually necessary with most colonic malignancies and with GI obstruction from a number of causes.

## DIETARY MODIFICATION AND BULK-FORMING AGENTS

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- The most important aspect of the therapy for constipation for the majority of patients is dietary modification to increase the amount of fiber consumed. Patients should be advised to include at least 10 g of crude fiber in their daily diets. Fruits, vegetables, and cereals have the highest fiber content.
- A trial of dietary modification with high-fiber content should be continued for at least 1 month before effects on bowel function are determined.
- The patient should be cautioned that abdominal distention and flatus may be particularly troublesome in the first few weeks, particularly with high bran consumption.

## PHARMACOLOGIC THERAPY

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- The various types of laxatives are discussed in this section. The agents are divided into three general classifications: (1) those causing softening of feces in 1 to 3 days (bulk-forming laxatives, **docusates**, and **lactulose**); (2) those that result in soft or semifluid stool in 6 to 12 hours (bisacodyl and senna); and (3) those causing water evacuation in 1 to 6 hours (**saline cathartics**, **castor oil**, and **polyethylene glycol-electrolyte lavage solution**).
- Dosage recommendations for laxatives and cathartics are provided in Table 22-3.

**TABLE 22-3** Dosage Recommendations for Laxatives and Cathartics

Agent	Recommended Dose
<b>Agents that cause softening of feces in 1–3 days</b>	
Bulk-forming agents/osmotic laxatives	
Methylcellulose	4–6 g/day
Polycarbophil	4–6 g/day
Psyllium	Varies with product
Emollients	
Docusate sodium	50–360 mg/day
Docusate calcium	50–360 mg/day
Docusate potassium	100–300 mg/day
Lactulose	15–30 mL orally
Sorbitol	30–50 g/day orally
Mineral oil	15–30 mL orally
<b>Agents that result in soft or semifluid stool in 6–12 hours</b>	
Bisacodyl (oral)	5–15 mg orally
Senna	Dose varies with formulation
Magnesium sulfate (low dose)	<10 g orally
<b>Agents that cause watery evacuation in 1–6 hours</b>	
Magnesium citrate	18 g 300 mL water
Magnesium hydroxide	2.4–4.8 g orally
Magnesium sulfate (high dose)	10–30 g orally
Sodium phosphates	Varies with salt used
Bisacodyl	10 mg rectally
Polyethylene glycol-electrolyte preparations	4 L

## Recommendations

- The basis for treatment and prevention of constipation should consist of bulk-forming agents in addition to dietary modifications that increase dietary fiber.
- For most nonhospitalized persons with acute constipation, the infrequent use (less than every few weeks) of most laxative products is acceptable; however, before more potent laxative or cathartics are used, relatively simple measures may be tried. For example, acute constipation may be relieved by the use of a **tap-water enema** or a **glycerin** suppository; if neither is effective, the use of oral sorbitol, low doses of bisacodyl or senna, or saline laxatives (e.g., **milk of magnesia**) may provide relief.
- If laxative treatment is required for longer than 1 week, the person should be advised to consult a physician to determine if there is an underlying cause of constipation that requires treatment with agents other than laxatives.
- For some bedridden or geriatric patients, or others with chronic constipation, bulk-forming laxatives remain the first line of treatment, but the use of more potent laxatives may be required relatively frequently. Agents that may be used in these situations include **milk of magnesia** and **lactulose**.
- In the hospitalized patient without GI disease, constipation may be related to the use of general anesthesia and/or opiate substances. Most orally or rectally administered laxatives may be used. For prompt initiation of a bowel movement, a **tap-water enema** or **glycerin** suppository is recommended, or **milk of magnesia**.

- The approach to the treatment of constipation in infants and children should consider neurologic, metabolic, or anatomic abnormalities when constipation is a persistent problem. When not related to an underlying disease, the approach to constipation is similar to that in an adult. High-fiber diet should be emphasized.

### **Emollient Laxatives (Docusates)**

- These surfactant agents, **docusate** in its various salts, work by facilitating the mixing of aqueous and fatty materials within the intestinal tract. They may increase water and electrolyte secretion in the small and large bowel.
- These products result in a softening of stools within 1 to 3 days.
- Emollient laxatives are not effective in treating constipation but are used mainly to prevent constipation. They may be helpful in situations where straining at stool should be avoided, such as after recovery from myocardial infarction, with acute perianal disease, or after rectal surgery.
- It is unlikely that these agents are effective in preventing constipation if major causative factors (e.g., heavy opiate use, uncorrected pathology, inadequate dietary fiber) are not concurrently addressed.

### **Lubricants**

- **Mineral oil** is the only lubricant laxative in routine use and acts by coating stool and allowing easier passage. It inhibits colonic absorption of water, thereby increasing stool weight and decreasing stool transit time. Generally, the effect on bowel function is noted after 2 or 3 days of use.
- Mineral oil is helpful in situations similar to those suggested for docusates: to maintain a soft stool and avoid straining for relatively short periods of time (a few days to 2 weeks).
- Mineral oil may be absorbed systemically and cause a foreign-body reaction in lymphoid tissue. Also, in debilitated or recumbent patients, mineral oil may be aspirated, causing lipid pneumonia.

### **Lactulose and Sorbitol**

- **Lactulose** is a disaccharide that causes an osmotic effect retained in the colon. It is generally not recommended as a first-line agent for the treatment of constipation because it is costly and not necessarily more effective than agents such as milk of magnesia. It may be justified as an alternative for acute constipation and has been found to be particularly useful in elderly patients.
- Occasionally, the use of lactulose may result in flatulence, cramps, diarrhea, and electrolyte imbalances.
- **Sorbitol**, a monosaccharide, has been recommended as a primary agent in the treatment of functional constipation in cognitively intact patients. It is as effective as lactulose and much less expensive.

### **Saline Cathartics**

- Saline cathartics are composed of relatively poorly absorbed ions such as magnesium, sulfate, phosphate, and citrate, which produce their effects primarily by osmotic action to retain fluid in the GI tract. These agents may be given orally or rectally.
- A bowel movement may result within a few hours of oral doses and in 1 hour or less after rectal administration.

- These agents should be used primarily for acute evacuation of the bowel, which may be necessary before diagnostic examinations, after poisonings, and in conjunction with some anthelmintics to eliminate parasites.
- Agents such as **milk of magnesia** (an 8% suspension of magnesium hydroxide) may be used occasionally (every few weeks) to treat constipation in otherwise healthy adults.
- Saline cathartics should not be used on a routine basis to treat constipation. With fecal impactions, the enema formulations of these agents may be helpful.

### Castor Oil

- **Castor oil** is metabolized in the GI tract to an active compound, ricinoleic acid, which stimulates secretory processes, decreases glucose absorption, and promotes intestinal motility, primarily in the small intestine. Castor oil usually results in a bowel movement within 1 to 3 hours of administration. Because the agent has such a strong purgative action, it should not be used for the routine treatment of constipation.

### Glycerin

- This agent is usually administered as a 3-g suppository and exerts its effect by osmotic action in the rectum. As with most agents given as suppositories, the onset of action is usually less than 30 minutes.
- **Glycerin** is considered a safe laxative, although it may occasionally cause rectal irritation. Its use is acceptable on an intermittent basis for constipation, particularly in children.

### Polyethylene Glycol-Electrolyte Lavage Solution

- Whole-bowel irrigation with **polyethylene glycol-electrolyte lavage solution** has become popular for colon cleansing before diagnostic procedures or colorectal operations.
- Four liters of this solution is administered over 3 hours to obtain complete evacuation of the GI tract. The solution is not recommended for the routine treatment of constipation, and its use should be avoided in patients with intestinal obstruction.

### Lubiprostone

- Lubiprostone is a chloride channel activator that acts locally on the gut to accelerate genitourinary transit time and delay gastric emptying. It is approved for chronic idiopathic constipation in adults. The dose is 24 mg capsule twice daily with food. Lubiprostone may cause headache, diarrhea, and nausea.

### Other Agents

- Tap-water enemas may be used to treat simple constipation. The administration of 200 mL of water by enema to an adult often results in a bowel movement within 1.5 hours. Soapsuds are no longer recommended for use in enemas because their use may result in proctitis or colitis.

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See Chap. 38, *Diarrhea and Constipation*, authored by William J. Spruill and William E. Wade, for a more detailed discussion of this topic.

**DEFINITION**

- Diarrhea is an increased frequency and decreased consistency of fecal discharge as compared with an individual's normal bowel pattern. Frequency and consistency are variable within and between individuals. For example, some individuals defecate as many as three times a day, while others defecate only two or three times per week. Most cases of acute diarrhea are caused by infections with viruses, bacteria, or protozoa and are generally self-limited.

**PATHOPHYSIOLOGY**

- Diarrhea is an imbalance in absorption and secretion of water and electrolytes. Diarrhea may be associated with a specific disease of the GI tract or with a disease outside the GI tract.
- Four general pathophysiologic mechanisms disrupt water and electrolyte balance, leading to diarrhea. These four mechanisms are the basis of diagnosis and therapy. They are (1) a change in active ion transport by either decreased sodium absorption or increased chloride secretion; (2) a change in intestinal motility; (3) an increase in luminal osmolarity; and (4) an increase in tissue hydrostatic pressure. These mechanisms have been related to four broad clinical diarrheal groups: secretory, osmotic, exudative, and altered intestinal transit.
- Secretory diarrhea occurs when a stimulating substance (e.g., vasoactive intestinal peptide [VIP], laxatives, or bacterial toxin) increases secretion or decreases absorption of large amounts of water and electrolytes.
- Poorly absorbed substances retain intestinal fluids, resulting in osmotic diarrhea.
- Inflammatory diseases of the GI tract can cause exudative diarrhea by discharge of mucus, proteins, or blood into the gut.
- Intestinal motility can be altered by reduced contact time in the small intestine, premature emptying of the colon, and by bacterial overgrowth.

**CLINICAL PRESENTATION**

- The clinical presentation of diarrhea is shown in Table 23-1.
- Many agents, including antibiotics and other drugs, cause diarrhea (Table 23-2). Laxative abuse for weight loss may also result in diarrhea.

**DESIRED OUTCOME**

- The therapeutic goals of diarrhea treatment are to manage the diet; prevent excessive water, electrolyte, and acid–base disturbances; provide symptomatic relief; treat curable causes of diarrhea; and manage secondary

**TABLE 23-1** Clinical Presentation of Diarrhea**General**

Usually, acute diarrheal episodes subside within 72 hours of onset, whereas chronic diarrhea involves frequent attacks over extended time periods.

**Signs and symptoms**

Abrupt onset of nausea, vomiting, abdominal pain, headache, fever, chills, and malaise.

Bowel movements are frequent and never bloody, and diarrhea lasts 12–60 hours.

Intermittent periumbilical or lower right quadrant pain with cramps and audible bowel sounds is characteristic of small intestinal disease.

When pain is present in large intestinal diarrhea, it is a gripping, aching sensation with tenesmus (straining, ineffective and painful stooling). Pain localizes to the hypogastric region, right or left lower quadrant, or sacral region.

In chronic diarrhea, a history of previous bouts, weight loss, anorexia, and chronic weakness are important findings.

**Physical examination**

Typically demonstrates hyperperistalsis with borborygmi and generalized or local tenderness.

**Laboratory tests**

Stool analysis studies include examination for microorganisms, blood, mucus, fat, osmolality, pH, electrolyte and mineral concentration, and cultures.

Stool test kits are useful for detecting GI viruses, particularly rotavirus.

Antibody serologic testing shows rising titers over a 3- to 6-day period, but this test is not practical and is nonspecific.

Occasionally, total daily stool volume is also determined.

Direct endoscopic visualization and biopsy of the colon may be undertaken to assess for the presence of conditions such as colitis or cancer.

Radiographic studies are helpful in neoplastic and inflammatory conditions.

**TABLE 23-2** Drugs Causing Diarrhea

## Laxatives

Antacids containing magnesium

Antineoplastics

Auranofin (gold salt)

## Antibiotics

Clindamycin

Tetracyclines

Sulfonamides

Any broad-spectrum antibiotic

## Antihypertensives

Reserpine

Guanethidine

Methyldopa

Guanabenz

Guanadrel

Angiotensin-converting enzyme inhibitors

## Cholinergics

Bethanechol

Neostigmine

## Cardiac agents

Quinidine

Digitalis

Digoxin

## Nonsteroidal antiinflammatory drugs

Misoprostol

Colchicine

Proton pump inhibitors

H<sub>2</sub>-receptor blockers

disorders causing diarrhea. Clinicians must clearly understand that diarrhea, like a cough, may be a body defense mechanism for ridding itself of harmful substances or pathogens. The correct therapeutic response is not necessarily to stop diarrhea at all costs!

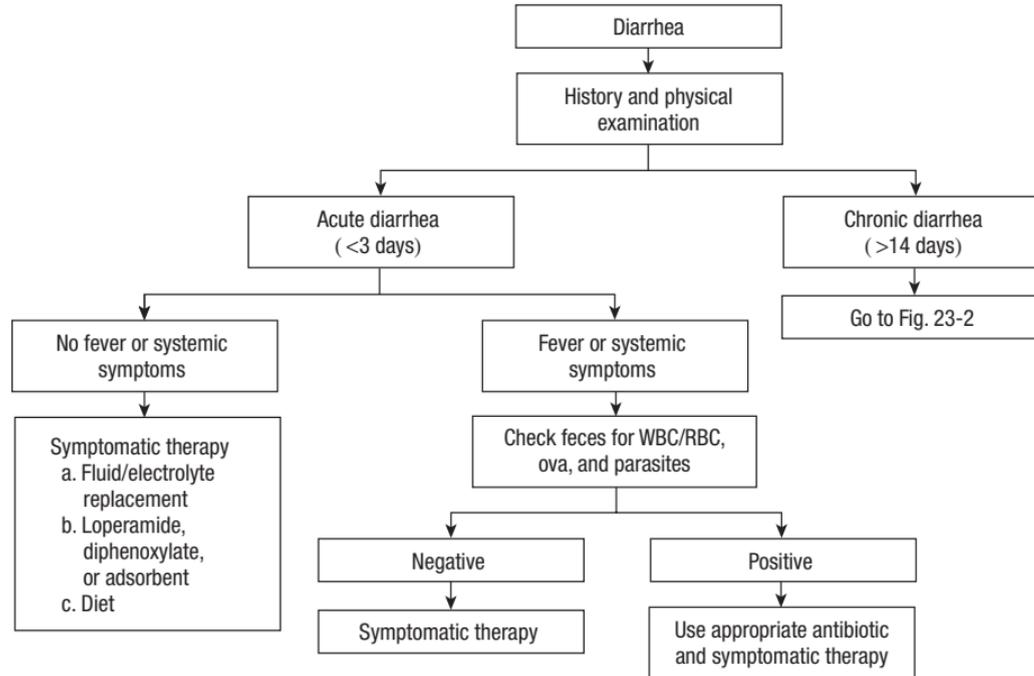
## TREATMENT

### GENERAL PRINCIPLES

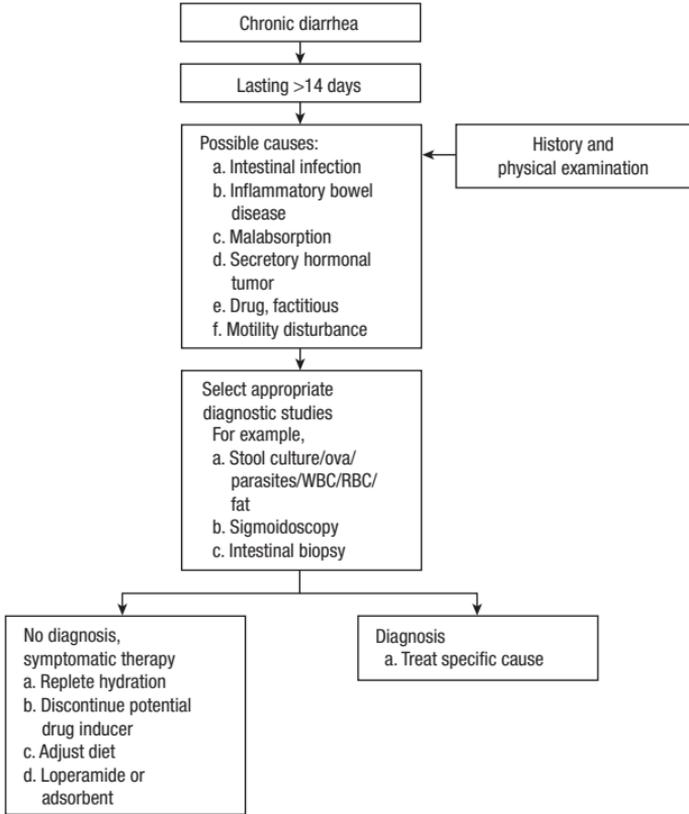
- Management of the diet is a first priority for treatment of diarrhea (Figs. 23-1 and 23-2). Most clinicians recommend stopping solid foods for 24 hours and avoiding dairy products.
- When nausea or vomiting is mild, a digestible low-residue diet is administered for 24 hours.
- If vomiting is present and is uncontrollable with antiemetics, nothing is taken by mouth. As bowel movements decrease, a bland diet is begun. Feeding should continue in children with acute bacterial diarrhea.
- Rehydration and maintenance of water and electrolytes are the primary treatment measures until the diarrheal episode ends. If vomiting and dehydration are not severe, enteral feeding is the less costly and preferred method. In the United States, many commercial oral rehydration preparations are available (Table 23-3).

### PHARMACOLOGIC THERAPY

- Various drugs have been used to treat diarrhea (Table 23-4). These drugs are grouped into several categories: antimotility, adsorbents, antisecretory compounds, antibiotics, enzymes, and intestinal microflora. Usually, these drugs are not curative but palliative.
- Opiates and opioid derivatives delay the transit of intraluminal content or increase gut capacity, prolonging contact and absorption. The limitations of the opiates are addiction potential (a real concern with long-term use) and worsening of diarrhea in selected infectious diarrheas.
- **Loperamide** is often recommended for managing acute and chronic diarrhea. Diarrhea lasting 48 hours beyond initiating loperamide warrants medical attention.
- Adsorbents (such as **kaolin-pectin**) are used for symptomatic relief (see Table 23-4). Adsorbents are nonspecific in their action; they adsorb nutrients, toxins, drugs, and digestive juices. Coadministration with other drugs reduces their bioavailability.
- **Bismuth subsalicylate** is often used for treatment or prevention of diarrhea (traveler's diarrhea) and has antisecretory, antiinflammatory, and antibacterial effects. Bismuth subsalicylate contains multiple components that might be toxic if given in excess to prevent or treat diarrhea.
- **Lactobacillus** preparation is intended to replace colonic microflora. This supposedly restores intestinal functions and suppresses the growth of pathogenic microorganisms. However, a dairy product diet containing 200 to 400 g of lactose or dextrin is equally effective in recolonization of normal flora.



**FIGURE 23-1.** Recommendations for treating acute diarrhea. Follow these steps: (1) Perform a complete history and physical examination. (2) Is the diarrhea acute or chronic? If chronic diarrhea, go to Fig. 23-2. (3) If acute diarrhea, check for fever and/or systemic signs and symptoms (i.e., toxic patient). If systemic illness (fever, anorexia, or volume depletion), check for an infectious source. If positive for infectious diarrhea, use appropriate antibiotic/anthelmintic drug and symptomatic therapy. If negative for infectious cause, use only symptomatic treatment. (4) If no systemic findings, then use symptomatic therapy based on severity of volume depletion, oral or parenteral fluid/electrolytes, antidiarrheal agents (see Table 23-4), and diet. (RBC, red blood cells; WBC, white blood cells.)



**FIGURE 23-2.** Recommendations for treating chronic diarrhea. Follow these steps: (1) Perform a careful history and physical examination. (2) The possible causes of chronic diarrhea are many. These can be classified into intestinal infections (bacterial or protozoal), inflammatory disease (Crohn’s disease or ulcerative colitis), malabsorption (lactose intolerance), secretory hormonal tumor (intestinal carcinoid tumor or vasoactive intestinal peptide-secreting tumors), drug (antacid), factitious (laxative abuse), or motility disturbance (diabetes mellitus, irritable bowel syndrome, or hyperthyroidism). (3) If the diagnosis is uncertain, selected appropriate diagnostic studies should be ordered. (4) Once diagnosed, treatment is planned for the underlying cause with symptomatic antidiarrheal therapy. (5) If no specific cause can be identified, symptomatic therapy is prescribed. (RBC, red blood cells; WBC, white blood cells.)

**TABLE 23-3** Oral Rehydration Solutions

	WHO-ORS	Pedialyte <sup>a</sup> (Abbott)	Rehydralyte <sup>a</sup> (Abbott)	Infalyte (Mead Johnson)	Resol <sup>a</sup> (Wyeth)
Osmolality (mOsm/L)	311	249	304	200	269
Carbohydrates <sup>a</sup> (g/L)	13.5	25	25	30 <sup>b</sup>	20
Calories (cal/L)	65	100	100	126	80
Electrolytes (mEq/L)					
Sodium	75	45	75	50	50
Potassium	20	20	20	25	20
Chloride	65	35	65	45	50
Citrate	—	30	30	34	34
Bicarbonate	30	—	—	—	—
Calcium	—	—	—	—	4
Magnesium	—	—	—	—	4
Sulfate	—	—	—	—	—
Phosphate	—	—	—	—	5

WHO-ORS, World Health Organization Oral Rehydration Solution.

<sup>a</sup>Carbohydrate is glucose.

<sup>b</sup>Rice syrup solids are carbohydrate source.

- Anticholinergic drugs, such as **atropine**, block vagal tone and prolong gut transit time. Their value in controlling diarrhea is questionable and limited by side effects.
- **Octreotide**, a synthetic octapeptide analog of endogenous somatostatin, is prescribed for the symptomatic treatment of carcinoid tumors and VIP-secreting tumors. Octreotide is used in selected patients with carcinoid syndrome. Octreotide blocks the release of serotonin and other active peptides and is effective in controlling diarrhea and flushing. Dosage range for managing diarrhea associated with carcinoid tumors is 100 to 600 mcg/day in two to four divided doses, subcutaneously for 2 weeks. Octreotide is associated with adverse effects such as cholelithiasis, nausea, diarrhea, and abdominal pain.

## EVALUATION OF THERAPEUTIC OUTCOMES

- Therapeutic outcomes are directed to key symptoms, signs, and laboratory studies. The constitutional symptoms usually improve within 24 to 72 hours.
- One should check the frequency and character of bowel movements each day along with the vital signs and improving appetite.
- The clinician also needs to monitor body weight, serum osmolality, serum electrolytes, complete blood cell count, urinalysis, and cultures (if appropriate). With an urgent or emergency situation, evaluation of the volume status of the patient is the most important outcome.
- Toxic patients (those with fever, dehydration, and hematochezia and those who are hypotensive) require hospitalization; they need IV electrolyte solutions and empiric antibiotics while awaiting cultures. With quick management, they usually recover within a few days.

**TABLE 23-4** Selected Antidiarrheal Preparations

	<b>Dose Form</b>	<b>Adult Dose</b>
<b>Antimotility</b>		
Diphenoxylate	2.5 mg/tablet 2.5 mg/5 mL	5 mg four times daily; do not exceed 20 mg/day
Loperamide	2 mg/capsule 1 mg/5 mL	Initially 4 mg, then 2 mg after each loose stool; do not exceed 16 mg/day
Paregoric	2 mg/5 mL (morphine)	5–10 mL 1–4 times daily
Opium tincture	5 mg/mL (morphine)	0.6 mL four times daily
Difenoxin	1 mg/tablet	Two tablets, then one tablet after each loose stool; up to 8 tablets/day
<b>Adsorbents</b>		
Kaolin-pectin mixture	5.7 g kaolin + 130.2 mg pectin/30 mL	30–120 mL after each loose stool
Polycarbophil	500 mg/tablet	Chew 2 tablets four times daily or after each loose stool; do not exceed 12 tablets/day
Attapulgit	750 mg/15 mL 300 mg/7.5 mL 750 mg/tablet 600 mg/tablet 300 mg/tablet	1,200–1,500 mg after each loose bowel movement or every 2 hours; up to 9,000 mg/day
<b>Antisecretory</b>		
Bismuth subsalicylate	1,050 mg/30 mL 262 mg/15 mL 524 mg/15 mL 262 mg/tablet	Two tablets or 30 mL every 30 minutes to 1 hour as needed up to 8 doses/day
Enzymes (lactase)	1,250 neutral lactase units/4 drops 3,300 FCC lactase units per tablet	3–4 drops taken with milk or dairy product One or two tablets as above
Bacterial replacement ( <i>Lactobacillus acidophilus</i> , <i>L. bulgaricus</i> )		Two tablets or 1 granule packet 3–4 times daily; give with milk, juice, or water
<b>Octreotide</b>	0.05 mg/mL 0.1 mg/mL 0.5 mg/mL	Initial: 50 mcg subcutaneously 1–2 times per day and titrate dose based on indication up to 600 mcg/day in 2–4 divided doses

FCC, Food Chemical Codex.

See Chap. 38, *Diarrhea and Constipation*, authored by William J. Spruill and William E. Wade, for a more detailed discussion of this topic.

## DEFINITION

- *Gastroesophageal reflux disease (GERD)* refers to symptoms or mucosal damage resulting from the abnormal retrograde movement of gastric contents from the stomach into the esophagus. When the esophagus is repeatedly exposed to refluxed material for prolonged periods, inflammation of the esophagus (reflux esophagitis) can occur and in some cases it progresses to erosion of the squamous epithelium (erosive esophagitis). Severe reflux symptoms associated with normal endoscopic findings are referred to as “symptomatic GERD,” nonerosive reflux disease, or endoscopy-negative reflux disease.

## PATHOPHYSIOLOGY

- The key factor in the development of GERD is the abnormal reflux of gastric contents from the stomach into the esophagus.
- In some cases, gastroesophageal reflux is associated with defective lower esophageal sphincter (LES) pressure or function. Patients may have decreased LES pressures related to spontaneous transient LES relaxations, transient increases in intraabdominal pressure, or an atonic LES. A variety of foods and medications may decrease LES pressure (Table 24-1).
- Problems with other normal mucosal defense mechanisms may also contribute to the development of GERD, including prolonged acid clearance time from the esophagus, delayed gastric emptying, and reduced mucosal resistance.
- Aggressive factors that may promote esophageal damage upon reflux into the esophagus include gastric acid, pepsin, bile acids, and pancreatic enzymes. The composition and volume of the refluxate and the duration of exposure are the most important aggressive factors in determining the consequences of gastroesophageal reflux.

## CLINICAL PRESENTATION

- The hallmark symptom of gastroesophageal reflux and esophagitis is heartburn, or pyrosis. It is classically described as a substernal sensation of warmth or burning that may radiate to the neck. It is waxing and waning in character and is often aggravated by activities that worsen gastroesophageal reflux (e.g., recumbent position, bending over, eating a high-fat meal). Other symptoms include water brash (hypersalivation), belching, and regurgitation.
- Atypical symptoms include nonallergic asthma, chronic cough, hoarseness, pharyngitis, dental erosions, and chest pain that mimics angina.
- Inadequately treated GERD may lead to complications from long-term acid exposure such as continual pain, dysphagia, and odynophagia. Other severe complications include esophageal strictures, hemorrhage, Barrett’s esophagus, and esophageal adenocarcinoma.

**TABLE 24-1** Foods and Medications That May Worsen Gastroesophageal Reflux Disease Symptoms**Decreased lower esophageal sphincter pressure**

## Foods

Fatty meal	Garlic
Carminatives (peppermint, spearmint)	Onions
Chocolate	Chili peppers
Coffee, cola, tea	

## Medications

Anticholinergics	Ethanol
Barbiturates	Nicotine (smoking)
Caffeine	Nitrates
Dihydropyridine calcium channel blockers	Progesterone
Dopamine	Tetracycline
Estrogen	Theophylline

**Direct irritants to the esophageal mucosa**

## Foods

Spicy foods	Tomato juice
Orange juice	Coffee

## Medications

Aspirin	Iron
Bisphosphonates (e.g., alendronate)	Quinidine
Nonsteroidal antiinflammatory drugs	Potassium chloride

**DIAGNOSIS**

- The most useful tool in the diagnosis of gastroesophageal reflux is the clinical history, including both presenting symptoms and associated risk factors. Patients with mild, typical reflux symptoms do not usually require invasive evaluation; a clinical diagnosis of GERD can be assumed in patients who respond to appropriate therapy.
- Further diagnostic evaluation should be performed in those who do not respond to therapy, who present with alarm symptoms (e.g., dysphagia, weight loss), or who have long-standing GERD symptoms.
- Endoscopy is the preferred technique for assessing the mucosa for esophagitis and complications such as Barrett's esophagus. It enables visualization and biopsy of the esophageal mucosa, but the mucosa may appear relatively normal in mild cases of GERD.
- A camera-containing capsule swallowed by the patient is a new technology for visualizing the esophageal mucosa (PillCam ESO). The procedure is less invasive than endoscopy and takes about 20 minutes to perform in the clinician's office. Images of the esophagus are downloaded through sensors placed on the patient's chest that are connected to a data collector. The camera-containing capsule is passed in the stool.
- Barium radiography is less expensive than endoscopy but lacks the sensitivity and specificity needed to accurately determine the presence of mucosal injury or to distinguish Barrett's esophagus from esophagitis.
- Twenty-four-hour ambulatory pH monitoring is useful in patients who continue to have symptoms without evidence of esophageal damage, patients who are refractory to standard treatment, and patients who

present with atypical symptoms (e.g., chest pain or pulmonary symptoms). The test helps to correlate symptoms with abnormal esophageal acid exposure, documents the percentage of time the intraesophageal pH is low, and determines the frequency and severity of reflux.

- **Omeprazole** given empirically in standard or double doses as a “therapeutic trial” for diagnosing GERD may be as beneficial as ambulatory pH monitoring while also being less expensive, more convenient, and more readily available. However, there is no standard dosing regimen; standard-dose or double-dose omeprazole has been used.
- Esophageal manometry to evaluate motility should be performed in any patient who is a candidate for antireflux surgery. It is useful in determining which surgical procedure is best for the patient.

## DESIRED OUTCOME

- The goals of treatment are to reduce or eliminate symptoms, decrease the frequency and duration of gastroesophageal reflux, promote healing of the injured mucosa, and prevent the development of complications.

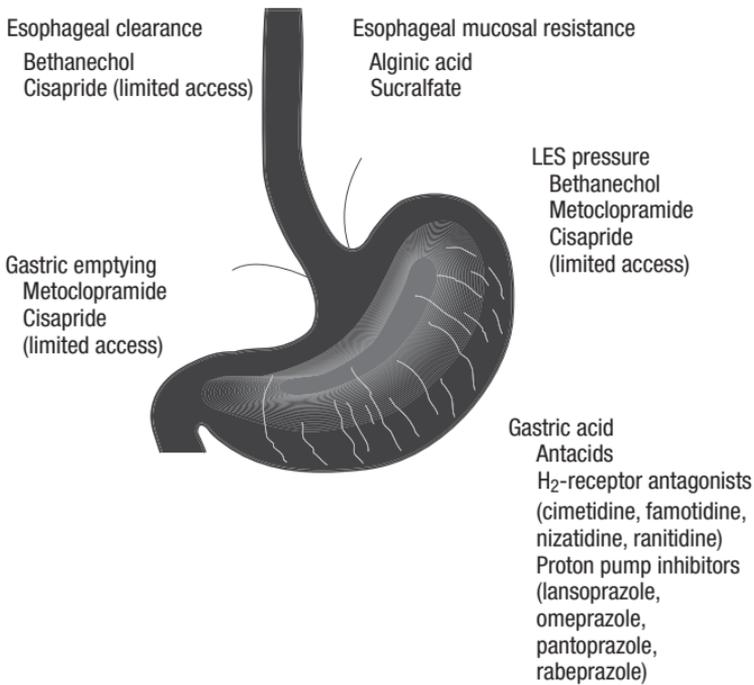
## TREATMENT

### GENERAL APPROACH

- Therapeutic modalities are targeted at reversing the pathophysiologic abnormalities. These include decreasing the acidity of the refluxate, decreasing the gastric volume available to be refluxed, improving gastric emptying, increasing LES pressure, enhancing esophageal acid clearance, and protecting the esophageal mucosa (Fig. 24-1).
- Treatment is categorized into the following modalities:
  - ✓ Phase I: Lifestyle changes and patient-directed therapy with **antacids** and/or nonprescription **histamine<sub>2</sub>-receptor antagonists (H<sub>2</sub>RA)** or **proton pump inhibitors (PPIs)**.
  - ✓ Phase II: Pharmacologic interventions with standard or high-dose acid-suppressing agents.
  - ✓ Phase III: Interventional therapies (antireflux surgery or endoluminal therapies).
- The initial therapeutic modality depends in part on the patient’s condition (symptom frequency, degree of esophagitis, presence of complications). Historically, a step-up approach has been used, starting with phase I and then progressing through phases II and III if necessary (Table 24-2). A step-down approach is also effective, starting with a PPI once or twice daily instead of an H<sub>2</sub>RA and then stepping down to the lowest acid suppression needed to control symptoms.
- Lifestyle modifications should be started initially and continued throughout the treatment course (Table 24-3).

### ANTACIDS AND ANTACID-ALGINIC ACID PRODUCTS

- **Antacids** provide immediate, symptomatic relief for mild GERD and are often used concurrently with other acid-suppressing therapies. Patients



**FIGURE 24-1.** Therapeutic interventions in the management of gastroesophageal reflux disease. Pharmacologic interventions are targeted at improving defense mechanisms or decreasing aggressive factors. (LES, lower esophageal sphincter.)

who require frequent use for chronic symptoms should receive prescription-strength, acid-suppressing therapy instead.

- An **antacid with alginate acid** (Gaviscon) is not a potent acid-neutralizing agent, but it does form a viscous solution that floats on the surface of the gastric contents. This serves as a protective barrier for the esophagus against reflux of gastric contents and reduces the frequency of reflux episodes. The combination product may be superior to antacids alone in relieving symptoms, but efficacy data indicating endoscopic healing are lacking.
- Antacids have a short duration, which necessitates frequent administration throughout the day to provide continuous acid neutralization. Typical doses are two tablets or 1 tablespoonful four times daily (after meals and at bedtime). Nighttime acid suppression cannot be maintained with bedtime doses of antacids.

### H<sub>2</sub>-RECEPTOR ANTAGONISTS: CIMETIDINE, RANITIDINE, FAMOTIDINE, AND NIZATIDINE

- The H<sub>2</sub>RAs in divided doses are effective for treating mild to moderate GERD. Low-dose nonprescription products may be beneficial for symptomatic relief of intermittent heartburn and for preventing meal-provoked

**TABLE 24-2** Therapeutic Approach to Gastroesophageal Reflux Disease (GERD)

<b>Patient Presentation</b>	<b>Recommended Treatment Regimen</b>	<b>Comments</b>
<b>Intermittent, mild heartburn</b>	<p><b>Lifestyle modifications</b> <b>plus</b> <b>patient-directed therapy</b></p> <p>Antacids</p> <ul style="list-style-type: none"><li>• Maalox or Mylanta 30 mL as needed or after meals and at bedtime</li><li>• Gaviscon 2 tabs after meals and at bedtime</li><li>• Calcium carbonate 500 mg, 2–4 tablets as needed</li></ul> <p><b>and/or</b></p> <p>Nonprescription H<sub>2</sub>-receptor antagonists (taken up to twice daily)</p> <ul style="list-style-type: none"><li>• Cimetidine 200 mg</li><li>• Famotidine 10 mg</li><li>• Nizatidine 75 mg</li><li>• Ranitidine 75 mg</li></ul> <p><b>or</b></p> <p>Nonprescription proton pump inhibitor (taken once daily)</p> <ul style="list-style-type: none"><li>• Omeprazole 20 mg</li></ul>	<p>Lifestyle modifications should be started initially and continued throughout the course of treatment. If symptoms are unrelieved with lifestyle modifications and nonprescription medications after 2 weeks, patient should seek medical attention.</p>
<b>Symptomatic relief of GERD</b>	<p><b>Lifestyle modifications</b> <b>plus</b> <b>prescription-strength acid suppression therapy</b></p> <p>H<sub>2</sub>-receptor antagonists (for 6–12 weeks)</p> <ul style="list-style-type: none"><li>• Cimetidine 400 mg twice daily</li><li>• Famotidine 20 mg twice daily</li><li>• Nizatidine 150 mg twice daily</li><li>• Ranitidine 150 mg twice daily</li></ul>	<p>For typical symptoms, treat empirically with prescription-strength acid-suppression therapy. If symptoms recur, consider maintenance therapy (MT). <i>Note:</i> Most patients will require standard doses for MT.</p> <p>Mild GERD can usually be treated effectively with H<sub>2</sub>-receptor antagonists.</p>

(continued)

**TABLE 24-2** Therapeutic Approach to Gastroesophageal Reflux Disease (GERD) (Continued)

Patient Presentation	Recommended Treatment Regimen	Comments
	<p><b>or</b></p> <p>Proton pump inhibitors (for 4–8 weeks); all are given once daily</p> <ul style="list-style-type: none"><li>• Esomeprazole 20 mg</li><li>• Lansoprazole 15 mg</li><li>• Omeprazole 20 mg</li><li>• Pantoprazole 40 mg</li><li>• Rabeprazole 20 mg</li></ul>	<p>Patients with moderate to severe symptoms should receive a proton pump inhibitor as initial therapy.</p>
<b>Healing of erosive esophagitis or treatment of patients presenting with moderate to severe symptoms or complications</b>	<p><b>Lifestyle modifications plus</b></p> <p>Proton pump inhibitors for 4–16 weeks (up to twice daily)</p> <ul style="list-style-type: none"><li>• Esomeprazole 20–40 mg daily</li><li>• Lansoprazole 30 mg daily</li><li>• Omeprazole 20 mg daily</li><li>• Rabeprazole 20 mg daily</li><li>• Pantoprazole 40 mg daily</li></ul> <p><b>or</b></p> <p>High-dose H<sub>2</sub>-receptor antagonist (for 8–12 weeks)</p> <ul style="list-style-type: none"><li>• Cimetidine 400 mg four times daily or 800 mg twice daily</li><li>• Famotidine 40 mg twice daily</li><li>• Nizatidine 150 mg four times daily</li><li>• Ranitidine 150 mg four times daily</li></ul>	<p>For atypical or alarm symptoms, obtain endoscopy (if possible) to evaluate mucosa. Give a trial of a proton pump inhibitor. If symptoms are relieved, consider MT. Proton pump inhibitors are the most effective maintenance therapy in patients with atypical symptoms, complications, and erosive disease.</p> <p>Patients not responding to pharmacologic therapy, including those with persistent atypical symptoms, should be evaluated via ambulatory reflux monitoring to confirm the diagnosis of GERD (if possible).</p>
<b>Interventional therapies</b>	Antireflux surgery or endoscopic therapies	

**TABLE 24-3** Nonpharmacologic Treatment of Gastroesophageal Reflux Disease with Lifestyle Modifications

- Elevate the head of the bed (increases esophageal clearance). Use 6- to 8-inch blocks under the head of the bed. Sleep on a foam wedge.
- Dietary changes:
  - Avoid foods that may decrease lower esophageal sphincter pressure (fats, chocolate, alcohol, peppermint, and spearmint).
  - Avoid foods that have a direct irritant effect on the esophageal mucosa (spicy foods, orange juice, tomato juice, and coffee).
  - Include protein-rich meals in diet (augments lower esophageal sphincter pressure).
  - Eat small meals and avoid eating immediately prior to sleeping (within 3 hours if possible) (decreases gastric volume).
  - Weight reduction (reduces symptoms).
- Stop smoking (decreases spontaneous esophageal sphincter relaxation).
- Avoid alcohol (increases amplitude of the lower esophageal sphincter, peristaltic waves, and frequency of contraction).
- Avoid tight-fitting clothes.
- Discontinue, if possible, drugs that may promote reflux (calcium channel blockers,  $\beta$ -blockers, nitrates, theophylline).
- Take drugs that have a direct irritant effect on the esophageal mucosa with plenty of liquid if they cannot be avoided (bisphosphonates, tetracyclines, quinidine, potassium chloride, iron salts, aspirin, nonsteroidal antiinflammatory drugs).

heartburn in patients with mild disease. For nonerosive disease, H<sub>2</sub>RAs are given in standard doses twice daily. For nonresponding patients and those with erosive disease, higher doses and/or four times daily dosing provide better acid control (see Table 23-2).

- The efficacy of H<sub>2</sub>RAs in GERD is highly variable; although standard doses produce symptomatic improvement in about 60% of patients, endoscopic healing rates average only about 50%. The more severe the esophageal damage, the poorer the response. Higher doses and prolonged courses (8 weeks or more) are frequently required.
- The H<sub>2</sub>RAs are generally well tolerated. The most common adverse effects are headache, somnolence, fatigue, dizziness, and either constipation or diarrhea. Cimetidine may inhibit the metabolism of theophylline, warfarin, phenytoin, nifedipine, and propranolol, among other drugs.
- Because all of the H<sub>2</sub>RAs are equally efficacious, selection of the specific agent should be based on differences in pharmacokinetics, safety profile, and cost.

### PROTON PUMP INHIBITORS: ESOMEPRAZOLE, LANSOPRAZOLE, OMEPRAZOLE, PANTOPRAZOLE, AND RABEPRAZOLE

- PPIs block gastric acid secretion by inhibiting hydrogen potassium adenosine triphosphatase in gastric parietal cells, which results in profound and long-lasting antisecretory effects.
- PPIs are superior to H<sub>2</sub>RAs in patients with moderate to severe GERD, including those with erosive esophagitis, complicated symptoms (Barrett's esophagus, strictures), and nonerosive GERD with moderate to severe symptoms. Relapse is common in these patients, and long-term mainte-

nance therapy is generally indicated. Symptomatic relief is achieved in approximately 83% of patients, and endoscopic healing rates are about 78% at 8 weeks.

- PPIs are also efficacious in patients refractory to H<sub>2</sub>RAs and are more cost effective than H<sub>2</sub>RAs in patients with severe disease.
- PPIs are usually well tolerated. Potential adverse effects include headache, dizziness, somnolence, diarrhea, constipation, nausea, and vitamin B<sub>12</sub> deficiency. All PPIs can decrease the absorption of drugs such as **ketconazole** or **itraconazole** that require an acidic environment for absorption. Other drug interactions vary with each agent.
- The PPIs degrade in acidic environments and are therefore formulated in delayed-release capsules or tablets. **Lansoprazole**, **esomeprazole**, and **omeprazole** contain enteric-coated (pH-sensitive) granules in a capsule form. In patients unable to swallow the capsules, the contents can be mixed in applesauce or placed in orange juice. In patients with nasogastric tubes, the contents should be mixed in 8.4% sodium bicarbonate solution. **Esomeprazole** granules can be dispersed in water. Lansoprazole is also available in packets for oral suspension and delayed-release orally disintegrating tablets; the packet for oral suspension should not be placed through nasogastric tubes. Patients taking **pantoprazole** or **rabeprazole** should be instructed not to crush, chew, or split the delayed-release tablets.
- **Zegerid** is a combination product containing omeprazole 20 or 40 mg with sodium bicarbonate in immediate-release oral capsules and powder for oral suspension. It should be taken on an empty stomach at least 1 hour before a meal. Zegerid offers an alternative to the delayed-release capsules or the IV formulation in adult patients with nasogastric tubes.
- **Lansoprazole**, **esomeprazole**, and **pantoprazole** are available in IV formulations for patients who cannot take oral medications, but they are not more efficacious than oral preparations and are significantly more expensive.
- Patients should be instructed to take oral PPIs in the morning 15 to 30 minutes before breakfast to maximize efficacy, because these agents inhibit only actively secreting proton pumps. If dosed twice daily, the second dose should be taken approximately 10 to 12 hours after the morning dose and prior to a meal or snack.
- All of the PPIs are safe and effective, and the choice of a particular agent is likely to be based on cost.

## PROMOTILITY AGENTS

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- Promotility agents may be useful as adjuncts to acid suppression therapy in patients with a known motility defect (e.g., LES incompetence, decreased esophageal clearance, delayed gastric emptying). However, these agents are generally not as effective as acid suppression therapy and have undesirable side effects.
- **Cisapride** has comparable efficacy to H<sub>2</sub>RAs in patients with mild esophagitis. It is no longer available for routine use because of life-threatening arrhythmias when combined with certain medications and other disease states. It is currently available only through a limited access program from the manufacturer.

- **Metoclopramide**, a dopamine antagonist, increases LES pressure in a dose-related manner and accelerates gastric emptying. Unlike cisapride, it does not improve esophageal clearance. Metoclopramide provides symptomatic improvement for some patients with GERD, but substantial evidence of endoscopic healing is lacking. Tachyphylaxis and side effects limit its usefulness. Commonly reported adverse reactions include somnolence, nervousness, fatigue, dizziness, weakness, depression, diarrhea, and rash.
- **Bethanechol** has very limited value and is not routinely recommended for the treatment of GERD because of unwanted side effects.

## MUCOSAL PROTECTANTS

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- **Sucralfate** is a nonabsorbable aluminum salt of sucrose octasulfate that has limited value and is not routinely recommended for treatment of GERD.

## COMBINATION THERAPY

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- Combination therapy with an acid-suppressing agent and a prokinetic agent or mucosal protectant seems logical, but data supporting such therapy are limited. This approach should be reserved for patients who have esophagitis plus concurrent motor dysfunction or for those who have failed high-dose PPI therapy.

## MAINTENANCE THERAPY

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- Although healing and/or symptomatic improvement may be achieved via many different therapeutic modalities, 70% to 90% of patients relapse within 1 year of discontinuation of therapy.
- Long-term maintenance therapy should be considered to prevent complications and worsening of esophageal function in patients who have symptomatic relapse after discontinuation of therapy or dosage reduction, including patients with complications such as Barrett's esophagus, strictures, or hemorrhage.
- Most patients require standard doses to prevent relapses. **H<sub>2</sub>RAs** may be an effective maintenance therapy in patients with mild disease. The **PPIs** are the drugs of choice for maintenance treatment of moderate to severe esophagitis. Usual once-daily doses are **omeprazole** 20 mg, **lansoprazole** 30 mg, **rabeprazole** 20 mg, or **esomeprazole** 20 mg. Lower doses of a PPI or alternate-day regimens may be effective in some patients with less severe disease.
- "On-demand" maintenance therapy, by which patients take their PPI only when they have symptoms, may be effective for patients with endoscopy-negative GERD.

## EVALUATION OF THERAPEUTIC OUTCOMES

- The short-term goals are to relieve symptoms such as heartburn and regurgitation so that they do not impair the patient's quality of life.
- The frequency and severity of symptoms should be monitored, and patients should be counseled on symptoms that suggest the presence of

complications requiring immediate medical attention, such as dysphagia or odynophagia. Patients with persistent symptoms should be evaluated for the presence of strictures or other complications.

- Patients should also be monitored for the presence of atypical symptoms such as cough, nonallergic asthma, or chest pain. These symptoms require further diagnostic evaluation.

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*See Chap. 34, Gastroesophageal Reflux Disease, authored by Dianne B. Williams and Robert R. Schade, for a more detailed discussion of this topic.*

## DEFINITION

- *Viral hepatitis* refers to the clinically important hepatotropic viruses responsible for hepatitis A (HAV), hepatitis B (HBV), delta hepatitis, hepatitis C (HCV), and hepatitis E.

## HEPATITIS A

- HAV infection primarily occurs through transmission by the fecal–oral route, person-to-person, or by ingestion of contaminated food or water. The incidence of HAV correlates directly with low socioeconomic status, poor sanitary conditions, and overcrowding. Rates of HAV infection have increased among international travelers, injection drug users, and men who have sex with men.
- HAV infection usually produces a self-limited disease and acute viral infection with a low case-fatality rate, and confers lifelong immunity.
- The disease exhibits three phases: incubation (averaging 28 days, with a range of 15 to 50 days), acute hepatitis (generally lasting 2 months), and convalescence. Most patients have full clinical and biochemical recovery within 12 weeks. Nearly all individuals will have clinical resolution within 6 months of the infection. HAV does not lead to chronic infections.
- The clinical presentation of HAV infection is given in Table 25-1.
- The diagnosis of acute HAV infection is based on clinical criteria of acute onset of fatigue, abdominal pain, loss of appetite, intermittent nausea and vomiting, jaundice or elevated serum aminotransferase levels, and serologic testing for immunoglobulin (Ig) G anti-HAV.

## TREATMENT

- No specific treatment options exist for HAV. Management of HAV infection is primarily supportive. Steroid use is not recommended.

## PREVENTION

- The spread of HAV can be best controlled by avoiding exposure. The most important measures to avoid exposure include good hand-washing techniques and good personal hygiene practices.
- The current vaccination strategy in the United States includes vaccinating all children at 1 year of age. Groups who should receive HAV vaccine are shown in Table 25-2.
- Two inactivated virus vaccines are currently licensed in the United States, Havrix and Vaqta. Approved dosing recommendations are shown in Table 25-3. Seroconversion rates >94% are achieved with the first dose.
- IG is used when pre- or postexposure prophylaxis against HAV infection is needed. It is most effective if given during the incubation phase of infection. A single dose of IG of 0.02 mL/kg intramuscularly is recom-

**TABLE 25-1** Clinical Presentation of Acute Hepatitis A**Signs and symptoms**

- The preicteric phase brings nonspecific influenza-like symptoms consisting of anorexia, nausea, fatigue, and malaise.
- Abrupt onset of anorexia, nausea, vomiting, malaise, fever, headache, and right upper quadrant abdominal pain with acute illness.
- Icteric hepatitis is generally accompanied by dark urine, acholic (light-colored) stools, and worsening of systemic symptoms.
- Pruritus is often a major complaint of icteric patients.

**Physical examination**

- Icteric sclera, skin, and secretions
- Mild weight loss of 2–5 kg
- Hepatomegaly

**Laboratory tests**

- Positive serum immunoglobulin M anti-hepatitis A virus.
- Mild elevations of serum bilirubin,  $\gamma$ -globulin, and hepatic transaminase (alanine transaminase and aspartate transaminase) values to about twice normal in acute anicteric disease.
- Elevations of alkaline phosphatase,  $\gamma$ -glutamyl transferase, and total bilirubin in patients with cholestatic illness.

**TABLE 25-2** Recommendations for Hepatitis A Vaccination

All children at 1 year of age

In areas without existing hepatitis A vaccination programs, catch-up vaccination of children ages 2–18 years can be considered.

Persons traveling to or working in countries that have high or intermediate endemicity of infection.<sup>a</sup>

Men who have sex with men.

Illegal-drug users.

Persons who have occupational risk for infection (e.g., persons who work with HAV-infected primates or HAV in a research laboratory setting).

Persons who have clotting-factor disorders.

Persons who have chronic liver disease (e.g., persons with chronic liver disease caused by hepatitis B or C and persons awaiting liver transplants).

HAV, hepatitis A virus.

<sup>a</sup>Travelers to Canada, Western Europe, Japan, Australia, or New Zealand are at no greater risk for HAV infection than they are while in the United States. All other travelers should be assessed for hepatitis A risk.

From Centers for Disease Control and Prevention. This is found at [www.cdc.gov](http://www.cdc.gov).

**TABLE 25-3** Recommended Dosing of Havrix and Vaqta

Vaccine	Vaccinee's Age (years)	Dose	Volume (mL)	Number Doses	Schedule (months)
Havrix	2–18	720 ELISA units	0.5	2	0, 6–12
	≥19	1,440 ELISA units	1	2	0, 6–12
Vaqta	1–18	25 units	0.5	2	0, 6–18
	≥19	50 units	1	2	0, 6–18

ELISA, enzyme-linked immunosorbent assay.

From Centers for Disease Control and Prevention. Prevention of hepatitis A through active or passive immunizations: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 2006;55(RR-7):1–23.

mended for travelers to high-risk areas if travel is for less than 3 months. For lengthy stays, a single dose of 0.06 mL/kg is used.

- For people recently exposed to HAV and not previously vaccinated, IG is indicated for:
  - ✓ Those in close contact with an HAV-infected person, all staff and attendees of daycare centers when HAV is documented, if involved in a common source exposure (such as a food-borne outbreak), classroom contacts of an index case patient, and schools, hospitals, and work settings where close personal contact occurred with the case patient.
- Common vaccine side effects include soreness and warmth at the injection site, headache, malaise, and pain.

## HEPATITIS B

- HBV is a leading cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma.
- Transmission of HBV occurs sexually, parenterally, and perinatally. In the United States, transmission occurs predominantly through sexual contact or injection-drug use. International travel is also an important risk factor.
- Approximately 20% of patients with chronic HBV infection develop complications of decompensated cirrhosis, including hepatic insufficiency and portal hypertension. HBV is a risk factor for development of hepatocellular carcinoma.
- There are three phases of HBV infection. The incubation period for HBV is 4 to 10 weeks during which patients are highly infective. This is followed by a symptomatic phase with intermittent flares of hepatitis and marked increases in aminotransferase serum levels. The final phase is seroconversion to anti-hepatitis B core antigen (anti-Hb<sub>c</sub>Ag). Patients who continue to have detectable hepatitis B surface antigen (Hb<sub>s</sub>Ag) and HB<sub>c</sub>Ag and a high serum titer of HBV DNA for more than 6 months have chronic HBV.
- The interpretation of serologic markers for HBV is given in Table 25-4.
- Clinical manifestations of acute HBV infection are age dependent. Infants infected with HBV are generally asymptomatic, while about 85% to 95% of children aged 1 to 5 years are asymptomatic.
- The clinical presentation of chronic HBV is given in Table 25-5.

## PREVENTION

- Prophylaxis of HBV can be achieved by vaccination or by passive immunity in postexposure cases with hepatitis B immunoglobulin.
- Two products are available for prevention of hepatitis B infection: **hepatitis B vaccine**, which provides active immunity, and **hepatitis B immune-globulin (HBIG)**, which provides temporary passive immunity.
- The goals of immunization against viral hepatitis include prevention of the short-term viremia that can lead to transmission of infection, clinical disease, and chronic HBV infection.
- Persons who should receive HBV vaccine are listed in Table 25-6.
- Side effects of the vaccines are soreness at the injection site, headache, fatigue, irritability, and fever.

**TABLE 25-4** Interpretation of Serologic Tests in Hepatitis B Virus

Tests	Result	Interpretation
HB <sub>s</sub> Ag	(-)	Susceptible
Anti-HB <sub>c</sub>	(-)	
Anti-HB <sub>s</sub>	(-)	
HB <sub>s</sub> Ag	(-)	Immune because of natural infection
Anti-HB <sub>c</sub>	(+)	
Anti-HB <sub>s</sub>	(+)	
HB <sub>s</sub> Ag	(-)	Immune because of vaccination (valid only if test performed 1–2 months after third vaccine dose)
Anti-HB <sub>c</sub>	(-)	
Anti-HB <sub>s</sub>	(+)	
HB <sub>s</sub> Ag	(+)	Acute infection
Anti-HB <sub>c</sub>	(+)	
IgM anti-HB <sub>c</sub>	(+)	
HB <sub>s</sub> Ag	(+)	Chronic infection
Anti-HB <sub>c</sub>	(+)	
IgM anti-HB <sub>c</sub>	(-)	
Anti-HB <sub>s</sub>	(-)	Four interpretations possible:
HB <sub>s</sub> A	(-)	
Anti-HB <sub>c</sub>	(+)	
Anti-HB <sub>s</sub>	(-)	
		1. Recovery from acute infection
		2. Distant immunity and test not sensitive enough to detect low level of HB <sub>s</sub> Ag in serum
		3. Susceptible with false-positive anti-HB <sub>c</sub>
		4. May have undetectable level of HB <sub>s</sub> Ag in serum and be chronically infected

HB<sub>c</sub>, hepatitis B core; HB<sub>s</sub>, hepatitis B surface; HB<sub>s</sub>A, hepatitis B surface associated; HB<sub>s</sub>Ag, hepatitis B surface antigen; IgM, immunoglobulin M.

From Centers for Disease Control and Prevention: *Hepatitis B Serology*, <http://www.cdc.gov/ncidod/diseases/hepatitis/b/BSerology.htm>.

## Hepatitis B Immune Globulin

- HBIg is used only for postexposure prophylaxis for HBV for perinatal exposure of infants of HBV-carrier mothers, sexual exposure to HB<sub>s</sub>Ag-

**TABLE 25-5** Clinical Presentation of Chronic Hepatitis B<sup>a</sup>

### Signs and symptoms

- Easy fatigability, anxiety, anorexia, and malaise.
- Ascites, jaundice, variceal bleeding, and hepatic encephalopathy can manifest with liver decompensation.
- Hepatic encephalopathy is associated with hyperexcitability, impaired mentation, confusion, obtundation, and eventually coma.
- Vomiting and seizures.

### Physical examination

- Icteric sclera, skin, and secretions.
- Decreased bowel sounds, increased abdominal girth, and detectable fluid wave.
- Asterixis.
- Spider angiomas.

### Laboratory tests

- Presence of hepatitis B surface antigen for at least 6 months.
- Intermittent elevations of hepatic transaminase (alanine transaminase and aspartate transaminase) and hepatitis B virus DNA greater than 10<sup>5</sup> copies/mL.
- Liver biopsies for pathologic classification as chronic persistent hepatitis, chronic active hepatitis, or cirrhosis.

<sup>a</sup>Chronic hepatitis B can be present even without all the signs, symptoms, and physical examination findings listed being apparent.

**TABLE 25-6** Recommendations for Hepatitis B Virus (HBV) Vaccination

Infants
Adolescents, including all previously unvaccinated children <19 years old
All unvaccinated adults at risk for infection
All unvaccinated adults seeking vaccination (specific risk factor not required)
Men and women with a history of other sexually transmitted diseases and persons with a history of multiple sex partners (>1 partner/6 months)
Men who have sex with men
Injection-drug users
Household contacts and sex partners of persons with chronic hepatitis B infection and health care and public safety workers with exposure to blood in the workplace
Clients and staff of institutions for the developmentally disabled
International travelers who plan to spend >6 months in countries with high rates of HBV infection and who will have close contact with the local population
Recipients of clotting-factor concentrates
Sexually transmitted disease clinic patients
HIV patient/HIV-testing patients
Drug-abuse treatment and prevention clinic patients
Correctional facilities inmates
Chronic dialysis/ESRD patients

ESRD, end-stage renal disease; HIV, human immunodeficiency virus.

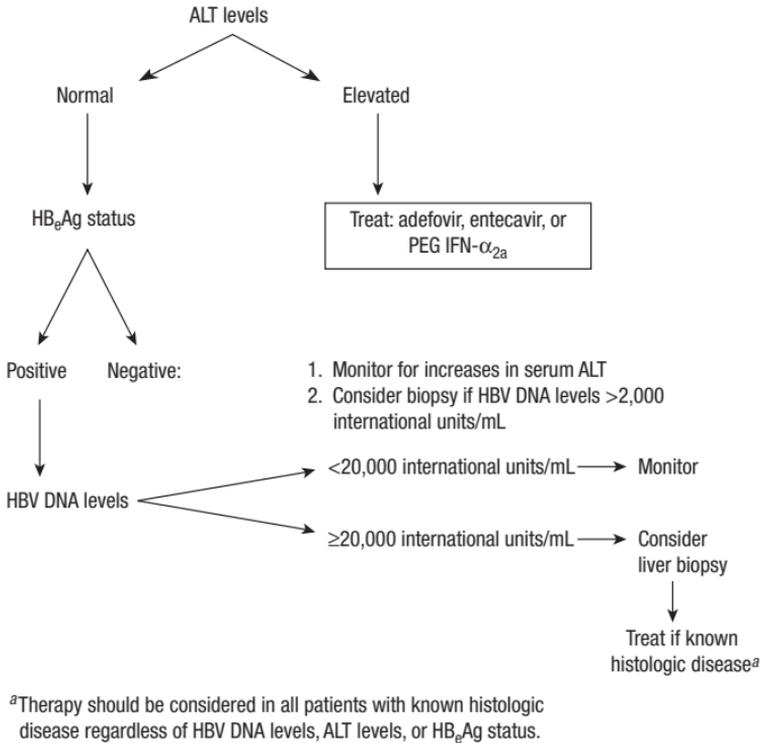
From Centers for Disease Control and Prevention. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: Recommendations of the Advisory Committee on Immunization Practices (ACIP) Part 1: Immunization of infants, children, and adolescents. *MMWR Morb Mortal Wkly Rep* 2005;54(RR-16):1-31.

positive persons, percutaneous or permucosal exposure to HB<sub>s</sub>Ag-positive blood, and exposure of an infant to a caregiver who has acute hepatitis B.

- The recommended dose is 0.06 mL/kg administered intramuscularly.

## TREATMENT

- The key goals of therapy are to increase the likelihood of immunoclearance of the virus, prevent disease progression to cirrhosis or hepatocellular carcinoma, and to minimize further liver injury. Successful therapy is associated with loss of HB<sub>c</sub>Ag status and seroconversion to anti-HB<sub>c</sub>Ag.
- No specific therapy is available for the management of acute HBV infection. Some patients with chronic HBV infection should be treated. A suggested treatment algorithm for chronic HBV is as shown for patients without (Fig. 25-1) and with cirrhosis (Fig. 25-2).
- All chronic HBV infection patients should avoid alcohol and be immunized against HAV.
- Drug therapy is used to suppress viral replication by immune mediating or antiviral effects. **Interferon  $\alpha_{2b}$**  (IFN- $\alpha_{2b}$ ), **lamivudine**, **telbivudine**, **adefovir entecavir**, and **pegylated IFN- $\alpha_{2a}$**  (PEG-IFN) are approved in the United States for first-line treatment of chronic HBV.
- Several factors correlate with improved response to IFN therapy, including increased alanine transaminases and HBV DNA levels, high histologic activity score at biopsy, and being non-Asian. Treatment for a minimum of 12 months is associated with greater sustained virologic response rates than treatment for 4 to 6 months. Conventional IFN therapy has been



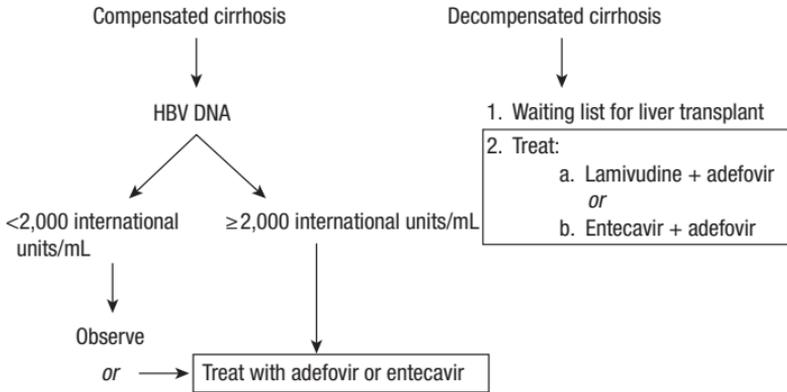
**FIGURE 25-1.** Suggested treatment algorithm for patients with chronic hepatitis B virus (HBV) infection. (ALT, alanine transaminase; Hb<sub>s</sub>Ag; hepatitis B e antigen; PEG IFN, pegylated interferon.) (Data from Keeffe EB, Dieterich DT, Han SB, et al. A treatment algorithm for the management of chronic hepatitis B virus infection in the United States: An update. *Clin Gastroenterol Hepatol* 2006;4:936–962.)

virtually replaced with pegylated IFN, because of the ease of administration (once-weekly injections), fewer side effects, and improved efficacy.

- Lamivudine (100 mg daily given orally) may be used alone or in combination with PEG-IFN for chronic HBV.

## HEPATITIS C

- HCV is the most common blood-borne pathogen. Screening for HCV infection is recommended in selected groups who are at high risk for infection (Table 25-7).
- HCV is most often acquired through IV drug use; sexual contact; hemodialysis; or household, occupational, or perinatal exposure.
- In the vast majority of patients (up to 85%) acute HCV infection leads to chronic infection defined by persistently detectable HCV RNA for 6 months or more.
- Patients with acute HCV are often asymptomatic and undiagnosed. One-third of adults will experience some mild and nonspecific symptoms, including fatigue, anorexia, weakness, jaundice, abdominal pain, or dark urine.



**FIGURE 25-2.** Suggested treatment algorithm for patients with chronic hepatitis B virus (HBV) infection. (Data from Keeffe EB, Dieterich DT, Han SB, et al. A treatment algorithm for the management of chronic hepatitis B virus infection in the United States: An update. *Clin Gastroenterol Hepatol* 2006;4:936–962.)

- The most common symptom of chronic HCV infection is persistent fatigue. An estimated 20% of patients with chronic HCV infection will develop cirrhosis and half of those patients will progress to decompensated cirrhosis or hepatocellular carcinoma.
- The diagnosis of HCV infection is confirmed with a reactive enzyme immunoassay for anti-HCV. Serum transaminase values are elevated within 4 to 12 weeks after exposure.

## TREATMENT

- The goal of treating HCV is to eradicate HCV infection, which prevents the development of chronic HCV infection and sequelae.
- Treatment for HCV infection is necessary because a high percentage of acutely infected patients develop chronic infections. Treatment is indicated in patients previously untreated who have chronic HCV, circulating HCV RNA, increased alanine transaminases levels, evidence on biopsy of moderate to severe hepatic grade and stage, and compensated liver disease.

**TABLE 25-7** Recommendations for Hepatitis C Virus (HCV) Screening

Current or past injection drug use
Coinfection with HIV
Received blood transfusions or organ transplantations before 1992
Received clotting factors before 1987
Ever on chronic hemodialysis
Patients with unexplained elevated ALT levels or evidence of liver disease
Health care and public safety workers after an occupational exposure
Children born to HCV-positive mothers
Immigrants from countries with a high prevalence of HCV infection

ALT, alanine transaminase; HIV, human immunodeficiency virus.

Data from Hoofnagle JH. Course and outcome of hepatitis C. *Hepatology* 2002;36(5 Suppl 1):S21–S29.

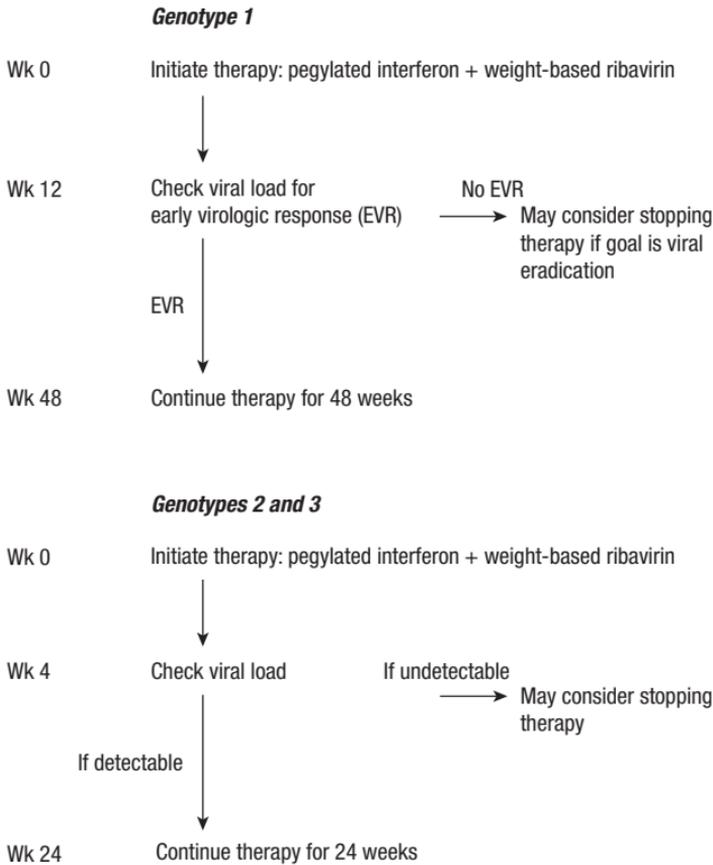
**TABLE 25-8** Recommended Hepatitis C Virus Treatment Dosing

Genotype	Pegylated-IFN Dose	Ribavirin Dose	Duration <sup>a</sup>	
1	Peginterferon $\alpha_{2a}$ 180 mcg/wk	<75 kg <sup>b</sup>	1,000 mg	48 weeks
	or Peginterferon $\alpha_{2b}$ 1.5 mcg/wk	$\geq$ 75 kg	1,200 mg	
2, 3	Peginterferon $\alpha_{2a}$ 180 mcg/wk		800 mg	24 weeks
	or Peginterferon $\alpha_{2b}$ 1.5 mcg/wk			

<sup>a</sup>Actual treatment duration may be reduced depending on early virologic response.

<sup>b</sup>Patient weight.

- Contraindications to treatment include: autoimmune hepatitis, decompensated liver disease, women who are pregnant or patients whose female partners are pregnant, hemoglobinopathies, creatinine clearance <50 mL/min, hemodialysis, or ischemic cardiovascular or cerebrovascular disease.



**FIGURE 25-3.** Suggested response-optimized chronic hepatitis C virus infection treatment regimens. (Data from Dienstag JL, McHutchinson JG. *American Gastroenterological Association technical review of the management of hepatitis C. Gastroenterology* 2006;130:231–264.)

**TABLE 25-9** Pegylated Interferon Comparison

	<b>Pegasys</b>	<b>PEG-Intron</b>
Interferon	Alpha-2a	Alpha-2b
Indications	HBV, HCV	HCV
PEG moiety (weight)	Branched (40 kDa)	Linear (12 kDa)
Distribution	8–12 L; highest concentration in liver, spleen, kidneys	Body-weight dependent: 1 L/kg; distributes throughout body
Metabolism	Liver	Liver
Excretion	Renal	Renal
Dosing	Fixed: 180 mcg/wk subcutaneously	Weight dependent: 1.5 mcg/kg/wk subcutaneously

HBV, hepatitis B virus; HCV, hepatitis C virus.

**TABLE 25-10** Common Side Effects Associated with Peginterferon Therapy (Experienced by >20% of Patients)

Fatigue	Arthralgia
Fever	Musculoskeletal pain
Headache	Insomnia
Nausea	Depression
Anorexia	Anxiety/emotional lability
Rigors	Alopecia
Myalgia	Injection site reactions

- Treatment response is best in patients with HCV genotype 1 and those who take at least 80% of their medications for at least 80% of the treatment time.
- All patients with chronic HCV infection should be vaccinated for hepatitis A and B. Patients should be advised to maintain good overall health, stop smoking, and avoid alcohol and illicit drugs.
- The current standard of treatment for chronic HCV infection is a combination of once-weekly **PEG-IFN** and a daily oral dose of **ribavirin**. Sustained virologic response rates are 54% to 56%. Therapy is optimized based on genotype, patient weight, and response to therapy. Recommended treatment regimens for HCV infection are given in Table 25-8 and Fig. 25-3.
- Two PEG-IFNs are available, Pegasys and PEG-Intron (Table 25-9). It is unclear which is superior.
- Common side effects of peginterferon are given in Table 25-10. Common side effects of ribavirin are fatigue, flu-like symptoms, neutropenia, thrombocytopenia, and anemia.

## PREVENTION

- No HCV vaccine is currently available.

*See Chap. 42, Viral Hepatitis, authored by Paulina Deming, Renee-Claude Mercier and Manjunath P. Pai, for a more detailed discussion of this topic.*

## DEFINITION

- There are two forms of idiopathic inflammatory bowel disease (IBD): ulcerative colitis, a mucosal inflammatory condition confined to the rectum and colon, and Crohn's disease, a transmural inflammation of GI mucosa that may occur in any part of the GI tract. The etiologies of both conditions are unknown, but they may have a common pathogenetic mechanism.

## PATHOPHYSIOLOGY

- The major theories of the cause of IBD involve a combination of infectious, genetic, and immunologic causes. The inflammatory response with IBD may indicate abnormal regulation of the normal immune response or an autoimmune reaction to self-antigens. Microflora of the GI tract may provide a trigger to activate inflammation. Crohn's disease may involve a T lymphocyte disorder that arises in genetically susceptible individuals as a result of a breakdown in the regulatory constraints on mucosal immune responses to enteric bacteria. Proposed etiologies for IBD are found in Table 26-1.
- Smoking appears to be protective for ulcerative colitis but associated with increased frequency of Crohn's disease.
- Ulcerative colitis and Crohn's disease differ in two general respects: anatomic sites and depth of involvement within the bowel wall. There is, however, overlap between the two conditions, with a small fraction of patients showing features of both diseases (Table 26-2).

## ULCERATIVE COLITIS

- Ulcerative colitis is confined to the colon and rectum and affects primarily the mucosa and the submucosa. The primary lesion occurs in the crypts of the mucosa (crypts of Lieberkühn) in the form of a crypt abscess.
- Local complications (involving the colon) occur in the majority of ulcerative colitis patients. Relatively minor complications include hemorrhoids, anal fissures, or perirectal abscesses.
- A major complication is toxic megacolon, a severe condition that occurs in up to 7.9% of ulcerative colitis patients admitted to hospitals. The patient with toxic megacolon usually has a high fever, tachycardia, distended abdomen, elevated white blood cell count, and a dilated colon.
- The risk of colonic carcinoma is much greater in patients with ulcerative colitis as compared with the general population.
- Approximately 11% of patients with ulcerative colitis have hepatobiliary complications including fatty liver, pericholangitis, chronic active hepatitis, cirrhosis, sclerosing cholangitis, cholangiocarcinoma, and gallstones.
- Arthritis commonly occurs in IBD patients and is typically asymptomatic and migratory. Arthritis typically involves one or a few large joints such as the knees, hips, ankles, wrists, and elbows.

**TABLE 26-1** Proposed Etiologies for Inflammatory Bowel Disease

Infectious agents
Viruses (e.g., measles)
L-Forms of bacteria
Mycobacteria
Chlamydia
Genetics
Metabolic defects
Connective tissue disorders
Environmental factors
Diet
Smoking (Crohn's disease)
Immune defects
Altered host susceptibility
Immune-mediated mucosal damage
Psychologic factors
Stress
Emotional or physical trauma
Occupation

- Ocular complications (iritis, episcleritis, and conjunctivitis) occur in up to 10% of patients. Five percent to 10% of patients experience dermatologic or mucosal complications (erythema nodosum, pyoderma gangrenosum, aphthous stomatitis).

**TABLE 26-2** Comparison of the Clinical and Pathologic Features of Crohn's Disease and Ulcerative Colitis

Feature	Crohn's Disease	Ulcerative Colitis
<b>Clinical</b>		
Malaise, fever	Common	Uncommon
Rectal bleeding	Common	Common
Abdominal tenderness	Common	May be present
Abdominal mass	Common	Absent
Abdominal pain	Common	Unusual
Abdominal wall and internal fistulas	Common	Absent
Distribution	Discontinuous	Continuous
Aphthous or linear ulcers	Common	Rare
<b>Pathologic</b>		
Rectal involvement	Rare	Common
Ileal involvement	Very common	Rare
Strictures	Common	Rare
Fistulas	Common	Rare
Transmural involvement	Common	Rare
Crypt abscesses	Rare	Very common
Granulomas	Common	Rare
Linear clefts	Common	Rare
Cobblestone appearance	Common	Absent

## CROHN'S DISEASE

- Crohn's disease is a transmural inflammatory process. The terminal ileum is the most common site of the disorder but it may occur in any part of the GI tract.
- About two-thirds of patients have some colonic involvement, and 15% to 25% of patients have only colonic disease.
- Patients often have normal bowel separating segments of diseased bowel; that is, the disease is often discontinuous.
- Complications of Crohn's disease may involve the intestinal tract or organs unrelated to it. Small-bowel stricture and subsequent obstruction is a complication that may require surgery. Fistula formation is common and occurs much more frequently than with ulcerative colitis.
- Systemic complications of Crohn's disease are common and similar to those found with ulcerative colitis. Arthritis, iritis, skin lesions, and liver disease often accompany Crohn's disease.
- Nutritional deficiencies are common with Crohn's disease.

## CLINICAL PRESENTATION

### ULCERATIVE COLITIS

- There are a wide range of ulcerative colitis presentations. Symptoms may range from mild abdominal cramping with frequent small-volume bowel movements to profuse diarrhea (Table 26-3). Many patients have disease confined to the rectum (proctitis).
- Most patients with ulcerative colitis experience intermittent bouts of illness after varying intervals of no symptoms.
- Mild disease, which afflicts two-thirds of patients, has been defined as fewer than four stools daily, with or without blood, with no systemic disturbance and a normal erythrocyte sedimentation rate.

**TABLE 26-3** Clinical Presentation of Ulcerative Colitis

#### Signs and symptoms

- Abdominal cramping
- Frequent bowel movements, often with blood in the stool
- Weight loss
- Fever and tachycardia in severe disease
- Blurred vision, eye pain, and photophobia with ocular involvement
- Arthritis
- Raised, red, tender nodules that vary in size from 1 cm to several centimeters

#### Physical examination

- Hemorrhoids, fissures, or perirectal abscesses may be present
- Iritis, uveitis, episcleritis, and conjunctivitis with ocular involvement
- Dermatologic findings with erythema nodosum, pyoderma gangrenosum, or aphthous ulceration

#### Laboratory tests

- Decreased hematocrit/hemoglobin
- Increased erythrocyte sedimentation rate
- Leukocytosis and hypoalbuminemia with severe disease

**TABLE 26-4** Clinical Presentation of Crohn's Disease**Signs and symptoms**

- Malaise and fever
- Abdominal pain
- Frequent bowel movements
- Hematochezia
- Fistula
- Weight loss
- Arthritis

**Physical examination**

- Abdominal mass and tenderness
- Perianal fissure or fistula

**Laboratory tests**

- Increased white blood cell count and erythrocyte sedimentation rate

- Patients with moderate disease have more than four stools per day but with minimal systemic disturbance.
- With severe disease, the patient has more than six stools per day with blood, with evidence of systemic disturbance as shown by fever, tachycardia, anemia, or erythrocyte sedimentation rate greater than 30.

**CROHN'S DISEASE**

- As with ulcerative colitis, the presentation of Crohn's disease is highly variable (Table 26-4). A single episode may not be followed by further episodes, or the patient may experience continuous, unremitting disease. A patient may present with diarrhea and abdominal pain or a perirectal or perianal lesion.
- The course of Crohn's disease is characterized by periods of remission and exacerbation. Some patients may be free of symptoms for years, while others experience chronic problems in spite of medical therapy.

**DESIRED OUTCOME**

- Goals of treatment include resolution of acute inflammatory processes, resolution of attendant complications (e.g., fistulas, abscesses), alleviation of systemic manifestations (e.g., arthritis), maintenance of remission from acute inflammation, or surgical palliation or cure.

**TREATMENT****GENERAL APPROACH**

- Treatment of IBD centers on agents used to relieve the inflammatory process. Salicylates, glucocorticoids, antimicrobials, and immunosuppressive agents are commonly used to treat active disease and, for some agents, to lengthen the time of disease remission.
- In addition to the use of drugs, surgical procedures are sometimes performed when active disease is not adequately controlled or when the required drug dosages pose an unacceptable risk of adverse effects.

## NONPHARMACOLOGIC TREATMENT

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### Nutritional Support

- Patients with moderate to severe IBD are often malnourished.
- The nutritional needs of the majority of patients can be adequately addressed with enteral supplementation. Patients who have severe disease may require a course of parenteral nutrition.
- Probiotic formulas have been effective in maintaining remission in ulcerative colitis.

### Surgery

- For ulcerative colitis, colectomy may be performed when the patient has disease uncontrolled by maximum medical therapy or when there are complications of the disease such as colonic perforation, toxic dilatation (megacolon), uncontrolled colonic hemorrhage, or colonic strictures.
- The indications for surgery with Crohn's disease are not as well established as they are for ulcerative colitis, and surgery is usually reserved for the complications of the disease. There is a high recurrence rate of Crohn's disease after surgery.

## PHARMACOLOGIC THERAPY

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- The major types of drug therapy used in IBD include **aminosalicylates**, **glucocorticoids**, immunosuppressive agents (**azathioprine**, **mercaptopurine**, **cyclosporine**, and **methotrexate**), antimicrobials (**metronidazole** and **ciprofloxacin**), and agents to inhibit tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) (anti-TNF- $\alpha$  antibodies).
- **Sulfasalazine**, an agent that combines a sulfonamide (sulfapyridine) antibiotic and mesalamine (5-aminosalicylic acid) in the same molecule, has been used for many years to treat IBD. Mesalamine-based products are listed in Table 26-5.
- Corticosteroids and adrenocorticotropic hormone have been widely used for the treatment of ulcerative colitis and Crohn's disease and are used in moderate to severe disease. Prednisone is most commonly used. Budesonide is an oral controlled-release formulation that minimizes systemic effects.
- Immunosuppressive agents such as **azathioprine** and **mercaptopurine** (a metabolite of azathioprine) are sometimes used for the treatment of IBD. These agents are generally reserved for cases that are refractory to steroids and may be associated with serious adverse effects such as lymphomas, pancreatitis, or nephrotoxicity. Cyclosporine has been of short-term benefit in acute, severe ulcerative colitis when used in a continuous infusion.
- Methotrexate given 15 to 25 mg intramuscularly once weekly is useful for treatment and maintenance of Crohn's disease.
- Antimicrobial agents, particularly **metronidazole**, are frequently used in attempts to control Crohn's disease, particularly when it involves the perineal area or fistulas.
- Infliximab is an anti-TNF antibody that is useful in moderate to severe active disease and steroid-dependent or fistulizing disease but the cost far exceeds that of other regimens. Adalimumab is another anti-TNF antibody

**TABLE 26-5** Mesalamine Derivatives for Treatment of Inflammatory Bowel Disease

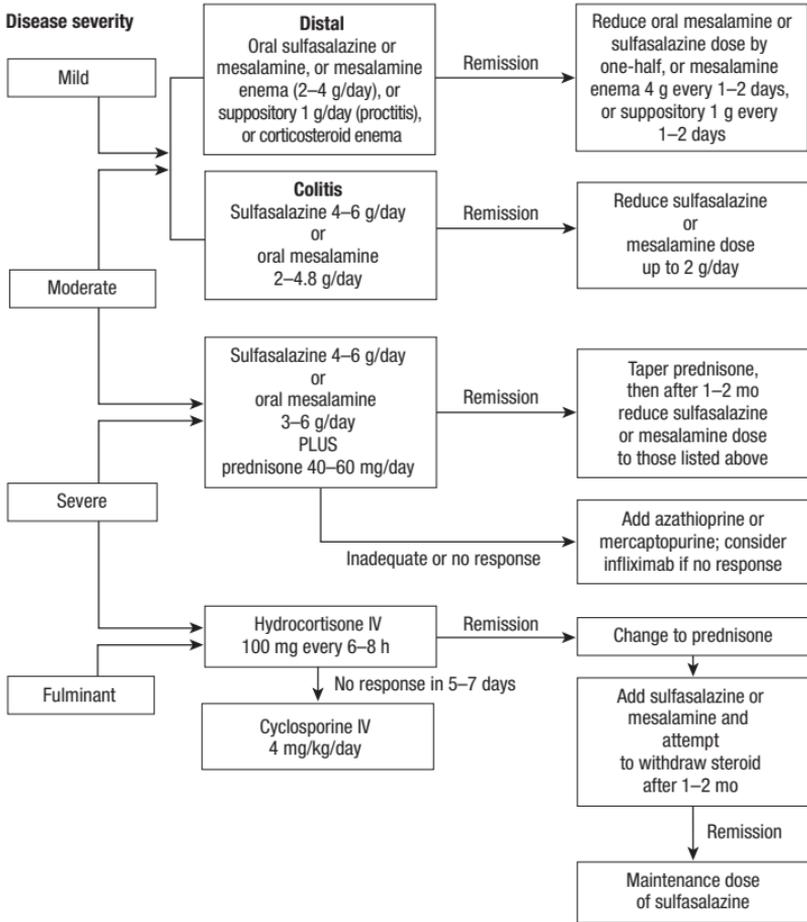
Product	Trade Name(s)	Formulation	Dose/Day	Site of Action
Sulfasalazine	Azulfidine	Tablet	4–6 g	Colon
Mesalamine	Azulfidine EN-tabs			
	Rowasa, Salofalk, Claversal, Pentasa	Enema	1–4 g	Rectum, terminal colon
	Asacol	Mesalamine tablet coated with Eudragit-S (delayed-release acrylic resin)	2.4–4.8 g	Distal ileum and colon
	Pentasa	Mesalamine capsules encapsulated in ethylcellulose microgranules	2–4 g	Small bowel and colon
	Lialda	Mesalamine tablet formulated with Multi Matrix System™ delayed-release technology, allows for once-daily dosing	2.4–4.8 g	Colon
Olsalazine	Canasa	Mesalamine suppository	500–1,000 mg	Rectum
	Dipentum	Dimer of 5-aminosalicylic acid oral capsule	1.5–3 g	Colon
Balsalazide	Colazal	Capsule	6.75 g	Colon

that is an option for patients with moderate to severe active Crohn's disease previously treated with infliximab who have lost response.

## Ulcerative Colitis

### Mild to Moderate Disease

- The first line of drug therapy for the patient with mild to moderate colitis is oral **sulfasalazine** or an oral **mesalamine** derivative, or topical mesalamine or steroids for distal disease (Fig. 26-1).
- When given orally, usually 4 g/day, up to 8 g/day of sulfasalazine is required to attain control of active inflammation. **Sulfasalazine** therapy should be instituted at 500 mg/day and increased every few days up to 4 g/day or the maximum tolerated.
- Oral **mesalamine** derivatives (such as those listed in Table 26-5) are reasonable alternatives to sulfasalazine for treatment of ulcerative colitis but they are not more effective than sulfasalazine.
- Steroids have a place in the treatment of moderate to severe ulcerative colitis that is unresponsive to maximal doses of oral and topical mesalamine. **Prednisone** up to 1 mg/kg/day or 40 to 60 mg daily may be used for patients who do not have an adequate response to sulfasalazine or mesalamine.
- Steroids and sulfasalazine appear to be equally efficacious; however, the response to steroids may be evident sooner.
- Rectally administered steroids or mesalamine can be used as initial therapy for patients with ulcerative proctitis or distal colitis.
- Transdermal **nicotine** improved symptoms of patients with mild to moderate active ulcerative colitis in daily doses of 15 to 25 mg.



**FIGURE 26-1.** Treatment approaches for ulcerative colitis.

### Severe or Intractable Disease

- Patients with uncontrolled severe colitis or incapacitating symptoms require hospitalization for effective management. Most medication is given by the parenteral route.
- With severe colitis, there is a much greater reliance on parenteral steroids and surgical procedures. Sulfasalazine or mesalamine derivatives have not been proven beneficial for treatment of severe colitis.
- Steroids have been valuable in the treatment of severe disease because the use of these agents may allow some patients to avoid colectomy. A trial of steroids is warranted in most patients before proceeding to colectomy, unless the condition is grave or rapidly deteriorating.
- Continuous IV infusion of **cyclosporine** (4 mg/kg/day) is recommended for patients with acute severe ulcerative colitis refractory to steroids.

### Maintenance of Remission

- Once remission from active disease has been achieved, the goal of therapy is to maintain the remission.

- The major agents used for maintenance of remission are **sulfasalazine** (2 g/day) and the **mesalamine** derivatives, although mesalamine is not as effective as sulfasalazine.
- Steroids do not have a role in the maintenance of remission with ulcerative colitis because they are ineffective. Steroids should be gradually withdrawn after remission is induced (over 3 to 4 weeks). If they are continued, the patient will be exposed to steroid side effects without likelihood of benefits.
- **Azathioprine** is effective in preventing relapse of ulcerative colitis for periods exceeding 4 years. However, 3 to 6 months may be required for beneficial effect. For patients who initially respond to infliximab, continued administration of 5 mg/kg every 8 weeks as maintenance therapy is an alternative for steroid dependent patients.

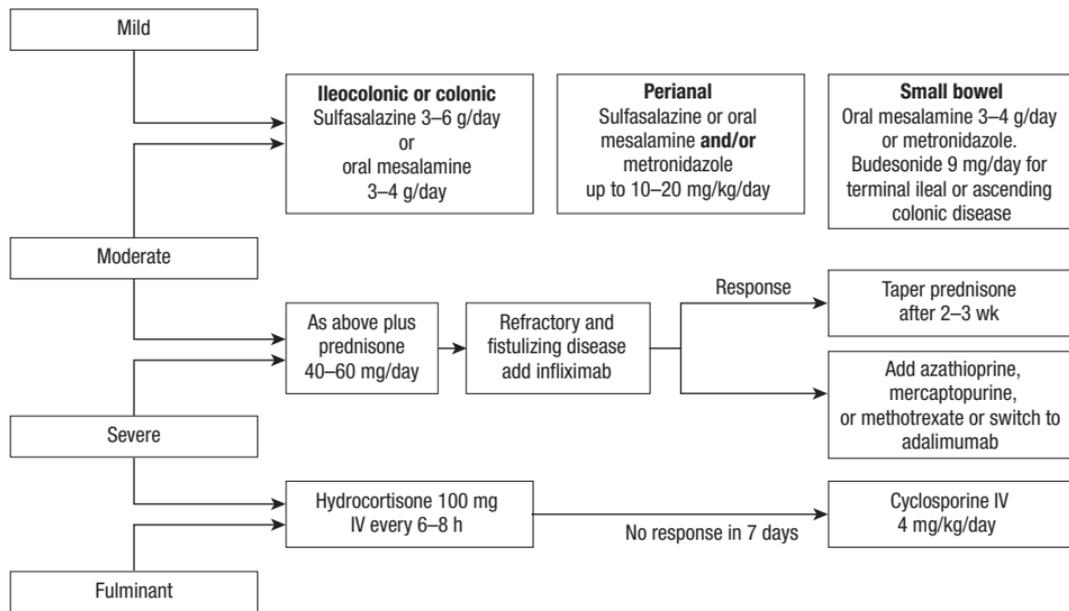
## Crohn's Disease

### (Fig. 26-2)

#### *Active Crohn's Disease*

- The goal of treatment for active Crohn's disease is to achieve remission; however, in many patients, reduction of symptoms so that the patient may carry out normal activities or reduction of the steroid dose required for control is a significant accomplishment.
- In the majority of patients, active Crohn's disease is treated with **sulfasalazine**, **mesalamine** derivatives, or **steroids**, although **azathioprine**, **mercaptopurine**, **methotrexate**, **infliximab**, and **metronidazole** are frequently used.
- **Sulfasalazine** is more effective when Crohn's disease involves the colon.
- Mesalamine derivatives (such as **Pentasa** or **Asacol**) that release mesalamine in the small bowel may be more effective than sulfasalazine for ileal involvement.
- **Steroids** are frequently used for the treatment of active Crohn's disease, particularly with more severe presentations, or in those patients unresponsive to aminosalicylates. Budesonide is a viable first-line option for patients with mild to moderate ileal or right-sided disease. Systemic steroids induce remission in up to 70% of patients and should be reserved for patients with moderate to severe disease who have failed aminosalicylates or budesonide.
- **Metronidazole** (given orally up to 20 mg/kg/day) may be useful in some patients with Crohn's disease, particularly in patients with colonic or ileocolonic involvement or those with perineal disease. The combination of metronidazole with ciprofloxacin is efficacious in some patients.
- The immunosuppressive agents (**azathioprine** and **mercaptopurine**) are generally limited to use in patients not achieving adequate response to standard medical therapy, or to reduce steroid doses when toxic doses are required. The usual dose of azathioprine is 2 to 3 mg/kg/day and 1 to 1.5 mg/kg/day for mercaptopurine. Up to 3 to 4 months may be required to observe a response. Starting doses are typically 50 mg/day and increased at 2-week intervals while monitoring complete blood count with differential.
- Patients deficient in thiopurine S-methyltransferase (TPMT) are at greater risk of bone marrow suppression from azathioprine and mercaptopurine. Determination of TPMT or TPMT genotype is recommended to guide dosage.

**Disease severity**



**FIGURE 26-2.** Treatment approaches for Crohn's disease.

- **Cyclosporine** is not recommended for Crohn's disease except for patients with symptomatic and severe perianal or cutaneous fistulas. The dose of cyclosporine is important in determining efficacy. An oral dose of 5 mg/kg/day was not effective, whereas 7.9 mg/kg/day was effective. However, toxic effects limit application of the higher dosage. Dosage should be guided by cyclosporine whole-blood concentrations.
- **Methotrexate**, given as a weekly injection of 5 to 25 mg, has demonstrated efficacy for induction of remission in Crohn's disease as well as for maintenance therapy. The risks are bone marrow suppression, hepatotoxicity, and pulmonary toxicity.
- **Infliximab** is used for moderate to severe active Crohn's disease in patients failing immunosuppressive therapy, in those who are corticosteroid dependent, and for treatment of fistulizing disease. A single, 5 mg/kg infusion is effective when given every day for 8 weeks. Additional doses at 2 and 6 weeks following the initial dose results in higher response rates.
- **Adalimumab** is effective in 54% of patients with moderate to severe Crohn's disease who have lost response to infliximab. The typical dosage is 160 mg subcutaneously initially, followed by 80 mg subcutaneously at week 2, with subsequent doses of 40 mg subcutaneously every other week thereafter.

### *Maintenance of Remission*

- Prevention of recurrence of disease is clearly more difficult with Crohn's disease than with ulcerative colitis. **Sulfasalazine** and oral **mesalamine** derivatives are effective in preventing acute recurrences in quiescent Crohn's disease.
- **Steroids** also have no place in the prevention of recurrence of Crohn's disease; these agents do not appear to alter the long-term course of the disease.
- Although the published data are not consistent, there is evidence to suggest that **azathioprine**, **mercaptopurine**, **methotrexate**, **infliximab**, and **adalimumab** are effective in maintaining remission in Crohn's disease.

## SELECTED COMPLICATIONS

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### **Toxic Megacolon**

- The treatment required for toxic megacolon includes general supportive measures to maintain vital functions, consideration for early surgical intervention, and antimicrobials.
- Aggressive fluid and electrolyte management are required for dehydration.
- When the patient has lost significant amounts of blood (through the rectum), blood replacement is also necessary.
- Steroids in high dosages (hydrocortisone 100 mg every 8 hours) should be administered intravenously to reduce acute inflammation.
- Antimicrobial regimens that are effective against enteric aerobes and anaerobes should be administered as preemptive therapy in the event that perforation occurs.

### **Systemic Manifestations**

- The common systemic manifestations of IBD include arthritis, anemia, skin manifestations such as erythema nodosum and pyoderma gangrenosum, uveitis, and liver disease.

- Anemia may be a common problem where there is significant blood loss from the GI tract. When the patient can consume oral medication, **ferrous sulfate** should be administered. Vitamin B<sub>12</sub> or folic acid may also be required.

## SPECIAL CONSIDERATIONS

### PREGNANCY

- Drug therapy for IBD is not a contraindication for pregnancy, and most pregnancies are well managed in patients with these diseases. The indications for medical and surgical treatment are similar to those in the nonpregnant patient. If a patient has an initial bout of IBD during pregnancy, a standard approach to treatment with sulfasalazine or steroids should be initiated.
- Folic acid supplementation, 1 mg twice daily, should be given.
- **Metronidazole** or **methotrexate** should not be used during pregnancy. Azathioprine and mercaptopurine may be associated with fetal deformities.

### ADVERSE DRUG REACTIONS TO AGENTS USED FOR TREATMENT OF INFLAMMATORY BOWEL DISEASE

- Sulfasalazine is often associated with either dose-related or idiosyncratic adverse drug effects. Dose-related side effects usually include GI disturbances such as nausea, vomiting, diarrhea, or anorexia, but may also include headache and arthralgia.
- Patients receiving sulfasalazine should receive oral **folic acid** supplementation since sulfasalazine inhibits folic acid absorption.
- Non-dose-related adverse effects of sulfasalazine include rash, fever, or hepatotoxicity most commonly, as well as relatively uncommon but serious reactions such as bone marrow suppression, thrombocytopenia, pancreatitis, pneumonitis, interstitial nephritis, and hepatitis.
- Oral mesalamine derivatives may impose a lower frequency of adverse effects compared with sulfasalazine. Up to 90% of patients who are intolerant to sulfasalazine will tolerate oral mesalamine derivatives. Olsalazine may cause watery diarrhea in up to 25% of patients.
- The well-appreciated adverse effects of glucocorticoids include hyperglycemia, hypertension, osteoporosis, fluid retention and electrolyte disturbances, myopathies, psychosis, and reduced resistance to infection. In addition, glucocorticoid use may cause adrenocortical suppression. Specific regimens for withdrawal of glucocorticoid therapy have been suggested.
- Immunosuppressants such as azathioprine and mercaptopurine have a significant potential for adverse reactions, including bone marrow suppression, and have been associated with lymphomas (in renal transplant patients) and pancreatitis. Myelosuppression resulting in leukopenia is related to a deficiency in TPMT in some patients.
- Infliximab has been associated with infusion reactions, serum sickness, sepsis, and reactivation of latent tuberculosis. Adalimumab carries risks similar to infliximab.

## EVALUATION OF THERAPEUTIC OUTCOMES

- The success of therapeutic regimens to treat IBDs can be measured by patient-reported complaints, signs and symptoms, direct physician examination (including endoscopy), history and physical examination, selected laboratory tests, and quality of life measures.
- To create more objective measures, disease-rating scales or indices have been created. The Crohn's Disease Activity Index is a commonly used scale, particularly for evaluation of patients during clinical trials. The scale incorporates eight elements: (1) number of stools in the past 7 days; (2) sum of abdominal pain ratings from the past 7 days; (3) rating of general well-being in the past 7 days; (4) use of antidiarrheals; (5) body weight; (6) hematocrit; (7) finding of abdominal mass; and (8) a sum of symptoms present in the past week. Elements of this index provide a guide for those measures that may be useful in assessing the effectiveness of treatment regimens.
- Standardized assessment tools have also been constructed for ulcerative colitis. Elements in these scales include (1) stool frequency; (2) presence of blood in the stool; (3) mucosal appearance (from endoscopy); and (4) physician's global assessment based on physical examination, endoscopy, and laboratory data.

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*See Chap. 36, Inflammatory Bowel Disease, authored by Brian A. Hemstreet and Joseph T. DiPiro, for a more detailed discussion of this topic.*

## DEFINITION

- Nausea is usually defined as the inclination to vomit or as a feeling in the throat or epigastric region alerting an individual that vomiting is imminent. Vomiting is defined as the ejection or expulsion of gastric contents through the mouth, often requiring a forceful event.

## PATHOPHYSIOLOGY

- Specific etiologies associated with nausea and vomiting are presented in Table 27-1.
- Table 27-2 presents specific cytotoxic agents categorized by their emetogenic potential. Although some agents may have greater emetogenic potential than others, combinations of agents, high doses, clinical settings, psychological conditions, prior treatment experiences, and unusual stimuli to sight, smell, or taste may alter a patient's response to a drug treatment.
- A variety of other common etiologies have been proposed for the development of nausea and vomiting in cancer patients. These are presented in Table 27-3.
- The three consecutive phases of emesis include nausea, retching, and vomiting. Nausea, the imminent need to vomit, is associated with gastric stasis. Retching is the labored movement of abdominal and thoracic muscles before vomiting. The final phase of emesis is vomiting, the forceful expulsion of gastric contents due to GI retroperistalsis.
- Vomiting is triggered by afferent impulses to the vomiting center, a nucleus of cells in the medulla. Impulses are received from sensory centers, such as the chemoreceptor trigger zone (CTZ), cerebral cortex, and visceral afferents from the pharynx and GI tract. When excited, afferent impulses are integrated by the vomiting center, resulting in efferent impulses to the salivation center, respiratory center, and the pharyngeal, GI, and abdominal muscles, leading to vomiting.
- The CTZ, located in the area postrema of the fourth ventricle of the brain, is a major chemosensory organ for emesis and is usually associated with chemically induced vomiting.
- Numerous neurotransmitter receptors are located in the vomiting center, CTZ, and GI tract. Examples of such receptors include cholinergic and histaminic, dopaminergic, opiate, serotonin, neurokinin (NK), and benzodiazepine receptors. Theoretically, chemotherapeutic agents, their metabolites, or other emetic compounds trigger the process of emesis through stimulation of one or more of these receptors.

## CLINICAL PRESENTATION

- The clinical presentation of nausea and vomiting is given in Table 27-4. Nausea and vomiting may be classified as either simple or complex.

**TABLE 27-1** Specific Etiologies of Nausea and Vomiting**Gastrointestinal mechanisms**

- Mechanical obstruction
  - Gastric outlet obstruction
  - Small bowel obstruction
- Functional gastrointestinal disorders
- Gastroparesis
  - Nonulcer dyspepsia
  - Chronic intestinal pseudoobstruction
  - Irritable bowel syndrome
- Organic gastrointestinal disorders
  - Peptic ulcer disease
  - Pancreatitis
  - Pyelonephritis
  - Cholecystitis
  - Cholangitis
  - Hepatitis
- Acute gastroenteritis
  - Viral
  - Bacterial

**Cardiovascular diseases**

- Acute myocardial infarction
- Congestive heart failure
- Radiofrequency ablation

**Neurologic processes**

- Increased intracranial pressure
- Migraine headache
- Vestibular disorders

**Metabolic disorders**

- Diabetes mellitus (diabetic ketoacidosis)
- Addison's disease
- Renal disease (uremia)

**Psychiatric causes**

- Psychogenic vomiting
- Anxiety disorders
- Anorexia nervosa

**Therapy-induced causes**

- Cytotoxic chemotherapy
- Radiation therapy
- Theophylline preparations
- Anticonvulsant preparations
- Digitalis preparations
- Opiates
- Antibiotics

**Drug withdrawal**

- Opiates
- Benzodiazepines

**Miscellaneous causes**

- Pregnancy
- Noxious odors
- Operative procedures

Reprinted and adapted from Hasler WL, Chey WD. *Gastroenterology*, 2003, Vol. 25, 1860–1867.

**DESIRED OUTCOME**

- The overall goal of antiemetic therapy is to prevent or eliminate nausea and vomiting; this should be accomplished without adverse effects or with clinically acceptable adverse effects.

**TREATMENT****GENERAL APPROACH TO TREATMENT**

- Treatment options for nausea and vomiting include drug and nondrug modalities. The treatment depends on associated medical conditions.
- For patients with simple complaints, perhaps related to food or beverage consumption, avoidance or moderation of dietary intake may be preferable.
- Nonpharmacologic interventions are classified as behavioral interventions and include relaxation, biofeedback, self-hypnosis, cognitive distraction, guided imagery, and systematic desensitization.
- Psychogenic vomiting may benefit from psychological interventions.

**TABLE 27-2** Emetogenicity of Chemotherapeutic Agents

<b>Emetic Risk (if no prophylactic medication is administered)</b>	<b>Cytotoxic Agent (in alphabetical order)</b>	
High (>90%)	Carmustine	
	Cisplatin	
	Cyclophosphamide $\geq 1,500$ mg/m <sup>2</sup>	
	Dacarbazine	
	Dactinomycin	
	Mechlorethamine	
	Streptozotocin	
	Moderate (30–90%)	Carboplatin
		Cytarabine $>1$ g/m <sup>2</sup>
		Cyclophosphamide $<1,500$ mg/m <sup>2</sup>
Daunorubicin		
Doxorubicin		
Epirubicin		
Idarubicin		
Ifosfamide		
Irinotecan		
Oxaliplatin		
Low (10–30%)	Bortezomib	
	Cetuximab	
	Cytarabine $\leq 1$ g/m <sup>2</sup>	
	Docetaxel	
	Etoposide	
	Fluorouracil	
	Gemcitabine	
	Methotrexate	
	Mitomycin	
	Mitoxantrone	
Minimal (<10%)	Paclitaxel	
	Pemetrexed	
	Topotecan	
	Trastuzumab	
	Bevacizumab	
	Bleomycin	
	Busulfan	
	2-Chlorodeoxyadenosine	
	Fludarabine	
	Rituximab	
Vinblastine		
Vincristine		
Vinorelbine		

*Adapted from Results of the 2004 Perugia International Antiemetic Consensus Conference.*

## PHARMACOLOGIC MANAGEMENT

- Information concerning commonly available antiemetic preparations is compiled in Table 27-5.
- For most conditions, a single-agent antiemetic is preferred; however, for those patients not responding to such therapy and those receiving highly emetogenic chemotherapy, multiple-agent regimens are usually required.

**TABLE 27-3** Nonchemotherapy Etiologies of Nausea and Vomiting in Cancer Patients

Fluid and electrolyte abnormalities
Hypercalcemia
Volume depletion
Water intoxication
Adrenocortical insufficiency
Drug-induced
Opiates
Antibiotics
Antifungals
GI obstruction
Increased intracranial pressure
Peritonitis
Metastases
Brain
Meninges
Hepatic
Uremia
Infections (septicemia, local)
Radiation therapy

- The treatment of simple nausea and vomiting usually requires minimal therapy. Both nonprescription and prescription drugs useful in the treatment of simple nausea and vomiting are usually effective in small, infrequently administered doses.
- The management of complex nausea and vomiting, for example, in patients who are receiving cytotoxic chemotherapy, may require combination therapy.

**TABLE 27-4** Presentation of Nausea and Vomiting**General**

Depending on severity of symptoms, patients may present in mild to severe distress

**Symptoms**

Simple: Self-limiting, resolves spontaneously and requires only symptomatic therapy

Complex: Not relieved after administration of antiemetics; progressive deterioration of patient secondary to fluid-electrolyte imbalances; usually associated with noxious agents or psychogenic events

**Signs**

Simple: Patient complaint of queasiness or discomfort

Complex: Weight loss; fever; abdominal pain

**Laboratory tests**

Simple: None

Complex: Serum electrolyte concentrations; upper/lower GI evaluation

**Other information**

Fluid input and output

Medication history

Recent history of behavioral or visual changes, headache, pain, or stress

Family history positive for psychogenic vomiting

**TABLE 27-5** Common Antiemetic Preparations and Adult Dosage Regimens

Drug	Adult Dosage Regimen	Dosage Form/Route	Availability
<b>Antacids</b>			
Antacids (various)	15–30 mL every 2–4 h prn	Liquid	OTC
<b>Histamine (H<sub>2</sub>) antagonists</b>			
Cimetidine (Tagamet HB)	200 mg twice daily prn	Tab	OTC
Famotidine (Pepcid AC)	10 mg twice daily prn	Tab	OTC
Nizatidine (Axid AR)	75 mg twice daily prn	Tab	OTC
Ranitidine (Zantac 75)	75 mg twice daily prn	Tab	OTC
<b>Antihistaminic-anticholinergic agents</b>			
Cyclizine (Marezine)	50 mg before departure; may repeat in 4–6 hour prn	Tab	OTC
Dimenhydrinate (Dramamine)	50–100 mg q 4–6 h prn	Tab, chew tab, cap	OTC
Diphenhydramine (Benadryl)	25–50 mg q 4–6 h prn	Tab, cap, liquid	Rx/OTC
	10–50 mg q 2–4 h prn	IM, IV	
Hydroxyzine (Vistaril, Atarax)	25–100 mg q 4–6 h prn	IM (unlabeled use)	Rx
Meclizine (Bonine, Antivert)	12.5–25 mg 1 h before travel; repeat q 12–24 h prn	Tab, chew tab	Rx/OTC
Scopolamine (Transderm Scop)	1.5 mg q 72 hour	Transdermal patch	Rx
Trimethobenzamide (Tigan)	300 mg three to four times daily	Cap	Rx
	200 mg three to four times daily	IM, supp	
<b>Phenothiazines</b>			
Chlorpromazine (Thorazine)	10–25 mg q 4–6 h prn	Tab, liquid	Rx
	25–50 mg q 4–6 h prn	IM, IV	

Prochlorperazine (Compazine)	5–10 mg three to four times daily prn 5–10 mg q 3 to 4 h prn 2.5–10 mg q 3 to 4 h prn 25 mg twice daily prn	Tab, liquid IM IV Supp	Rx Rx Rx
Promethazine (Phenergan)	12.5–25 mg q 4–6 h prn	Tab, liquid, IM, IV, supp	Rx
Thiethylperazine (Torecan)	10 mg one to six times daily prn	Tab, IM, IV	Rx
<b>Cannabinoids</b>			
Dronabinol (Marinol)	5–15 mg/m <sup>2</sup> q 2–4 h prn	Cap	Rx (C-III)
Nabilone (Cesamet)	1–2 mg twice daily	Cap	Rx (C-II)
<b>Butyrophenones</b>			
Haloperidol (Haldol)	1–5 mg q 12 h prn	Tab, liquid, IM, IV	Rx
Droperidol (Inapsine) <sup>d</sup>	2.5 mg; additional 1.25 mg may be given	IM, IV	Rx
<b>Benzodiazepines</b>			
Alprazolam (Xanax)	0.5–2 mg three times per day prior to chemotherapy	Tab	Rx (C-IV)
Lorazepam (Ativan)	0.5–2 mg on night before and morning of chemotherapy	Tab	Rx (C-IV)
<b>Miscellaneous agents</b>			
Metoclopramide (Reglan), for delayed CINV	20–40 mg three to four times daily	Tab	Rx

C-II, C-III, C-IV, controlled substance schedule 2, 3, and 4, respectively; cap, capsule; chew tab, chewable tablet; CINV, chemotherapy-induced nausea and vomiting; liquid, oral syrup, concentrate, or suspension; OTC, nonprescription; Rx, prescription; supp, rectal suppository; tab, tablet.

<sup>d</sup>See text for current warnings.

## Drug Class Information

### *Antacids*

- Single or combination nonprescription antacid products, especially those containing magnesium hydroxide, aluminum hydroxide, and/or calcium carbonate, may provide sufficient relief from simple nausea or vomiting, primarily through gastric acid neutralization.
- Common antacid dosage regimens for the relief of nausea and vomiting include one or more small doses of single- or multiple-agent products.

### *Histamine-2 Receptor Antagonists*

- Histamine-2 antagonists (cimetidine, famotidine, nizatidine, ranitidine) may be used in low doses to manage simple nausea and vomiting associated with heartburn or gastroesophageal reflux.

### *Antihistamine–Anticholinergic Drugs*

- Antiemetic drugs from the antihistaminic–anticholinergic category may be appropriate in the treatment of simple symptomatology.
- Adverse reactions that may be apparent with the use of the antihistaminic–anticholinergic agents primarily include drowsiness or confusion, blurred vision, dry mouth, urinary retention, and possibly tachycardia, particularly in elderly patients.

### *Phenothiazines*

- **Phenothiazines** are most useful in patients with simple nausea and vomiting.
- Rectal administration is a reasonable alternative in patients in whom oral or parenteral administration is not feasible.
- Problems associated with these drugs include troublesome and potentially dangerous side effects, including extrapyramidal reactions, hypersensitivity reactions with possible liver dysfunction, marrow aplasia, and excessive sedation.

### *Corticosteroids*

- **Dexamethasone** has been used successfully in the management of chemotherapy-induced nausea and vomiting (CINV) and postoperative nausea and vomiting (PONV), either as a single agent or in combination with selective serotonin reuptake inhibitors (SSRIs). For CINV, dexamethasone is effective in the prevention of both cisplatin-induced acute emesis and when used alone or in combination for the prevention of delayed nausea and vomiting associated with CINV.

### *Metoclopramide*

- **Metoclopramide** increases lower esophageal sphincter tone, aids gastric emptying, and accelerates transit through the small bowel, possibly through the release of acetylcholine.
- Metoclopramide is used for its antiemetic properties in patients with diabetic gastroparesis and with dexamethasone for prophylaxis of delayed nausea and vomiting associated with chemotherapy administration.

### *Cannabinoids*

- When compared with conventional antiemetics, oral **nabilone** and oral **dronabinol** were slightly more effective than active comparators in patients receiving moderately emetogenic chemotherapy regimens.
- The efficacy of cannabinoids as compared to SSRIs for CINV has not been studied. They should be considered for the treatment of refractory nausea and vomiting in patients receiving chemotherapy.

### *Substance P/Neurokinin 1 Receptor Antagonists*

- Substance P is a peptide neurotransmitter in the NK family whose preferred receptor is the NK<sub>1</sub> receptor. Substance P is believed to be the primary mediator of the delayed phase of CINV and one of two mediators of the acute phase of CINV.
- **Aprepitant** is the first approved member of this class of drugs and is indicated as part of a multiple drug regimen for prophylaxis of nausea and vomiting associated with high-dose cisplatin-based chemotherapy.
- Numerous potential drug interactions are possible; clinically significant drug interactions with oral contraceptives, warfarin, and oral dexamethasone have been described.

### *Selective Serotonin Receptor Inhibitors (Ondansetron, Granisetron, Dolasetron, and Palonosetron)*

- SSRIs (**dolasetron**, **granisetron**, **ondansetron**, and **palonosetron**) act by blocking presynaptic serotonin receptors on sensory vagal fibers in the gut wall.
- The most common side effects associated with these agents are constipation, headache, and asthenia.

## CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

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- Nausea and vomiting that occur within 24 hours of chemotherapy administration is defined as acute, whereas when it starts more than 24 hours after chemotherapy administration, it is defined as delayed. The emetogenic potential of the chemotherapeutic agent or regimen (see Table 27-2) is the primary factor to consider when selecting an antiemetic for **prophylaxis** of CINV.
- Recommendations for antiemetics in patients receiving chemotherapy are presented in Table 27-6, and doses are shown in Table 27-7.

### **Prophylaxis of Chemotherapy-Induced Nausea and Vomiting**

- Patients receiving chemotherapy that is classified as being of high emetic risk should receive a combination antiemetic regimen containing three drugs on the day of chemotherapy administration (day 1)—an SSRI plus dexamethasone plus aprepitant.
- Patients receiving regimens that are classified as being of moderate emetic risk should receive a combination antiemetic regimen containing an SSRI plus dexamethasone on day 1.
- Dexamethasone alone is recommended for prophylaxis prior to regimens of low emetic risk.

**TABLE 27-6** Recommendations for the Use of Antiemetics in Patients Receiving Chemotherapy

Emetic Risk	Prophylaxis of Acute Phase of CINV on Day of Chemotherapy Administration (Day 1)	Prophylaxis of Delayed Phase of CINV
<b>High</b>	SSRI + dexamethasone + aprepitant	Days 2 and 3 after chemotherapy: dexamethasone + aprepitant
<b>Moderate</b>	<b>Anthracycline + cyclophosphamide:</b> SSRI + dexamethasone + aprepitant <b>All other regimens of moderate emetic risk:</b> SSRI + dexamethasone	Days 2 and 3 after chemotherapy: aprepitant Days 2–4 after chemotherapy: dexamethasone or SSRI
<b>Low</b>	Dexamethasone	None
<b>Minimal</b>	None	None

CINV, chemotherapy-induced nausea and vomiting; SSRI, selective serotonin reuptake inhibitor.

**TABLE 27-7** Dosage Recommendations for CINV

Emetic Risk	Prophylaxis of Acute Phase of CINV (one dose administered prior to chemotherapy)	Prophylaxis of Delayed Phase of CINV
<b>High</b>	SSRI: Dolasetron 100 mg po or 100 mg IV or 1.8 mg/kg IV Granisetron 2 mg po or 1 mg IV or 0.01 mg/kg IV Ondansetron 24 mg po or 8 mg IV or 0.15 mg/kg IV Palonosetron 0.25 mg IV <b>and</b> Dexamethasone 12 mg po (with aprepitant) or 20 mg PO <b>and</b> Aprepitant 125 mg po	Dexamethasone 8 mg po days 2 and 3 after chemotherapy Aprepitant 80 mg po days 2 and 3 after chemotherapy
<b>Moderate</b>	Anthracycline + cyclophosphamide: SSRI: (as above) <b>and</b> Dexamethasone 12 mg po (with aprepitant) <b>and</b> Aprepitant 125 mg po  <b>All other regimens of moderate emetic risk:</b> SSRI: Dolasetron 100 mg po or 100 mg IV or 1.8 mg/kg IV Granisetron 2 mg po or 1 mg IV or 0.01 mg/kg IV Ondansetron 16 mg po or 8 mg IV or 0.15 mg/kg IV  Palonosetron 0.25 mg IV <b>and</b> Dexamethasone 8 mg IV	Aprepitant 80 mg po days 2 and 3 after chemotherapy  SSRI: Dolasetron 100 mg po daily <sup>a</sup> Granisetron 1 mg po daily <sup>a</sup> Ondansetron 8 mg po daily or twice daily <sup>a</sup>  or Dexamethasone 8 mg po daily <sup>a</sup>
<b>Low</b>	Dexamethasone 8 mg po	None
<b>Minimal</b>	None	None

CINV, chemotherapy-induced nausea and vomiting; SSRI, selective serotonin reuptake inhibitor.

<sup>a</sup>For 2–4 days following chemotherapy.

Doses included in the above table reflect the recommendations from published guidelines. These doses may differ from manufacturer labeling; they reflect the consensus of the guideline participants.

Adapted from Stephenson J, Davies A. An assessment of etiology-based guidelines for the management of nausea and vomiting in patients with advanced cancer. *Support Care Cancer* 2006;14:348–353; Kovac AL. Prevention and treatment of postoperative nausea and vomiting. *Drugs* 2000;59:213–243; and Gan TJ, Meyer T, Apfel CC, et al. Consensus guidelines for managing postoperative nausea and vomiting. *Anesth Analg* 2003;97:62–71.

## Treatment of Chemotherapy-Induced Nausea and Vomiting

- Chlorpromazine, prochlorperazine, promethazine, methylprednisolone, lorazepam, metoclopramide, dexamethasone, or dronabinol may be used for adult patients. Around the clock dosing should be considered. The choice of specific agent should be based on patient specific factors, including potential for adverse drug reactions, and cost. SSRIs are effective for breakthrough nausea and vomiting but they are not superior to the less expensive antiemetics above.
- Aprepitant, dexamethasone, or metoclopramide have demonstrated efficacy in preventing CINV, whereas the results with SSRIs are inconsistent.
- Aprepitant and dexamethasone can be used on the 2 days following administration of high emetic risk chemotherapy.

## POSTOPERATIVE NAUSEA AND VOMITING

- A variety of pharmacologic approaches are available and may be prescribed as single or combination therapy for prophylaxis of PONV. See Table 27-8 for doses of specific agents.
- Most patients undergoing an operative procedure do not require preoperative prophylactic antiemetic therapy and universal PONV prophylaxis is not cost effective.
- SSRIs in doses of dolasetron 12.5 mg, granisetron 0.1 mg, ondansetron 1 mg, or tropisetron 0.5 mg are recommended in patients who experience PONV despite prophylactic dexamethasone or when no prophylactic agent was used.

## RADIATION-INDUCED NAUSEA AND VOMITING

- Patients receiving single-exposure, high-dose radiation therapy to the upper abdomen, or total- or hemibody irradiation, should receive prophylactic antiemetics. Preventive therapy with an SSRI and dexamethasone is recommended in patients receiving total-body irradiation.

## DISORDERS OF BALANCE

- Beneficial therapy for patients with nausea and vomiting associated with disorders of balance can reliably be found among the antihistaminic–

**TABLE 27-8** Recommended Prophylactic Doses of Antiemetics for PONV

Drug	Adult Dose (IV)	Pediatric Dose (IV)	Timing of Dose <sup>a</sup>
Dolasetron	12.5 mg	350 mcg/kg up to 12.5 mg	At end of surgery
Granisetron	0.35–1 mg		At end of surgery
Ondansetron	4–8 mg	50–100 mcg/kg up to 4 mg	At end of surgery
Tropisetron	5 mg	–	At end of surgery
Dexamethasone	5–10 mg	150 mcg/kg up to 8 mg	At induction
Droperidol	0.625–1.25 mg	50–70 mcg/kg up to 1.25 mg	At end of surgery

PONV, postoperative nausea and vomiting.

<sup>a</sup>Based on recommendations from consensus guidelines; may differ from manufacturer's recommendations.

anticholinergic agents. Neither the antihistaminic nor the anticholinergic potency appears to correlate well with the ability of these agents to prevent or treat the nausea and vomiting associated with motion sickness.

- Scopolamine is commonly used to prevent nausea or vomiting caused by motion.

### ANTIEMETIC USE DURING PREGNANCY

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- Initial management of nausea and vomiting of pregnancy often involves dietary changes and/or lifestyle modifications.
- Pyridoxine (10 to 25 mg one to four times daily) is recommended as first-line therapy. If symptoms persist, addition of a histamine-1 receptor antagonist, such as dimenhydrinate, diphenhydramine, or meclizine, is recommended.

### ANTIEMETIC USE IN CHILDREN

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- For children receiving chemotherapy of high or moderate risk, a corticosteroid plus SSRI should be administered. The best doses or dosing strategy has not been determined.
- For nausea and vomiting associated with pediatric gastroenteritis, there is greater emphasis on rehydration measures than on pharmacologic intervention.

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*See Chap. 37, Nausea and Vomiting, authored by Cecily V. DiPiro, for a more detailed discussion of this topic.*

**DEFINITION**

- Acute pancreatitis (AP) is an inflammatory disorder of the pancreas characterized by severe pain in the upper abdomen and increased serum concentrations of pancreatic lipase and amylase.
- Chronic pancreatitis (CP) is a syndrome of destructive and inflammatory conditions resulting from long-standing pancreatic injury. It is characterized by irreversible fibrosis and destruction of exocrine and endocrine tissue but is not invariably progressive.

**ACUTE PANCREATITIS****PATHOPHYSIOLOGY**

- Gallstones and alcohol abuse account for most cases in the United States. A cause cannot be identified in some patients (idiopathic pancreatitis).
- Many medications have been implicated (Table 28-1), but a causal association is difficult to confirm because ethical and practical considerations prevent rechallenge.
- AP is initiated by premature activation of pancreatic zymogens (inactive enzymes) within the acinar cells, pancreatic ischemia, or pancreatic duct obstruction.
- Release of active pancreatic enzymes directly causes local or distant tissue damage. Trypsin digests cell membranes and leads to the activation of other pancreatic enzymes. Lipase damages fat cells, producing noxious substances that cause further pancreatic and peripancreatic injury.
- Release of cytokines injures acinar cells and enhances the inflammatory response. Injured acinar cells liberate chemoattractants that attract neutrophils, macrophages, and other cells to the area of inflammation, and increased vascular permeability promotes tissue edema.
- Pancreatic infection may result from increased intestinal permeability and translocation of colonic bacteria.
- Local complications in severe AP may include acute fluid collection, pancreatic necrosis, abscess, pseudocyst formation, and pancreatic ascites.
- Systemic complications may include cardiovascular, renal, pulmonary, metabolic, hemorrhagic, and CNS abnormalities.

**CLINICAL PRESENTATION**

- The clinical presentation depends on the severity of the inflammatory process and whether damage is confined to the pancreas or involves contiguous organs.
- The initial presentation ranges from moderate abdominal discomfort to excruciating pain, shock, and respiratory distress. Abdominal pain occurs in 95% of patients and is usually epigastric, often radiating to the upper

**TABLE 28-1** Medications Associated with Acute Pancreatitis

<b>Class I: Definite Association</b>	<b>Class II: Probable Association</b>	<b>Class III: Possible Association</b>	
5-Aminosalicylic acid	Acetaminophen	Amiodarone	Indomethacin
Asparaginase	Carbamazepine	Calcium	Indinavir
Azathioprine	Cisplatin	Celecoxib	Aldesleukin
Corticosteroids	Enalapril	Clozapine	Infliximab
Cytarabine	Erythromycin	Cholestyramine	Ketoprofen
Didanosine	Hydrochlorothiazide	Cimetidine	Ketorolac
Estrogens	Interferon $\alpha_2b$	Ciprofloxacin	Lipid emulsion
Furosemide	Lamivudine	Clarithromycin	Lisinopril
Mercaptopurine	Octreotide	Clonidine	Mefenamic acid
Opiates		Cyclosporine	Metolazone
Pentamidine		Danazol	Nitrofurantoin
Pentavalent antimonials		Diazoxide	Ondansetron
Sulfasalazine		Etanercept	Omeprazole
Sulfamethoxazole and trimethoprim		Ethacrynic acid	Oxyphenbutazone
Sulindac		Famciclovir	Pravastatin
Tetracycline		Glyburide	Paclitaxel
Valproic acid/salts		Gold therapy	Propofol
		Granisetron	Propoxyphene
		Metformin	Rifampin
		Methyldopa	Sertraline
		Metronidazole	Zalcitabine
		Ibuprofen	

quadrants or back. The onset is usually sudden and the intensity is often described as “knife-like” or “boring.” The pain usually reaches its maximum intensity within 30 minutes and may persist for hours or days. Nausea and vomiting occur in 85% of patients and usually follow the onset of pain.

- Clinical signs associated with widespread pancreatic inflammation and necrosis include marked epigastric tenderness, abdominal distention, hypotension, and low-grade fever. In severe disease, bowel sounds are diminished or absent. Dyspnea and tachypnea are signs of acute respiratory complications.

## DIAGNOSIS

- A definitive diagnosis of AP is made by surgical examination of the pancreas or pancreatic histology. In the absence of these procedures, the diagnosis depends on recognition of an etiologic factor, clinical signs and symptoms, abnormal laboratory tests, and imaging techniques that predict disease severity.
- The serum amylase concentration usually rises 4 to 8 hours after symptom onset, peaks at 24 hours, and returns to normal over the next 8 to 14 days. Serum amylase concentrations greater than three times the upper limit of normal are highly suggestive of AP.
- Serum lipase is specific to the pancreas, and concentrations are usually elevated. The increases persist longer than serum amylase elevations and can be detected after the amylase has returned to normal.

- AP may be associated with leukocytosis, hyperglycemia, hypoalbuminemia, mild hyperbilirubinemia, and elevations in serum alkaline phosphatase and hepatic transaminases.
- Marked hypocalcemia indicates severe necrosis and is a poor prognostic sign.
- Dehydration may lead to hemoconcentration with elevated hemoglobin, hematocrit, blood urea nitrogen, and serum creatinine.
- C-reactive protein increases by 48 hours after the onset of symptoms and may be useful in distinguishing mild from severe pancreatitis.
- Some patients with severe pancreatitis develop thrombocytopenia and a prolonged prothrombin time.
- Contrast-enhanced computed tomography (CT) is used to identify the cause of pancreatitis and confirm the diagnosis. Magnetic resonance imaging is used to grade the severity of AP and identify bile duct abnormalities not seen on CT. Ultrasonography is useful to determine pancreatic enlargement and peripancreatic fluid collections.

## DESIRED OUTCOME

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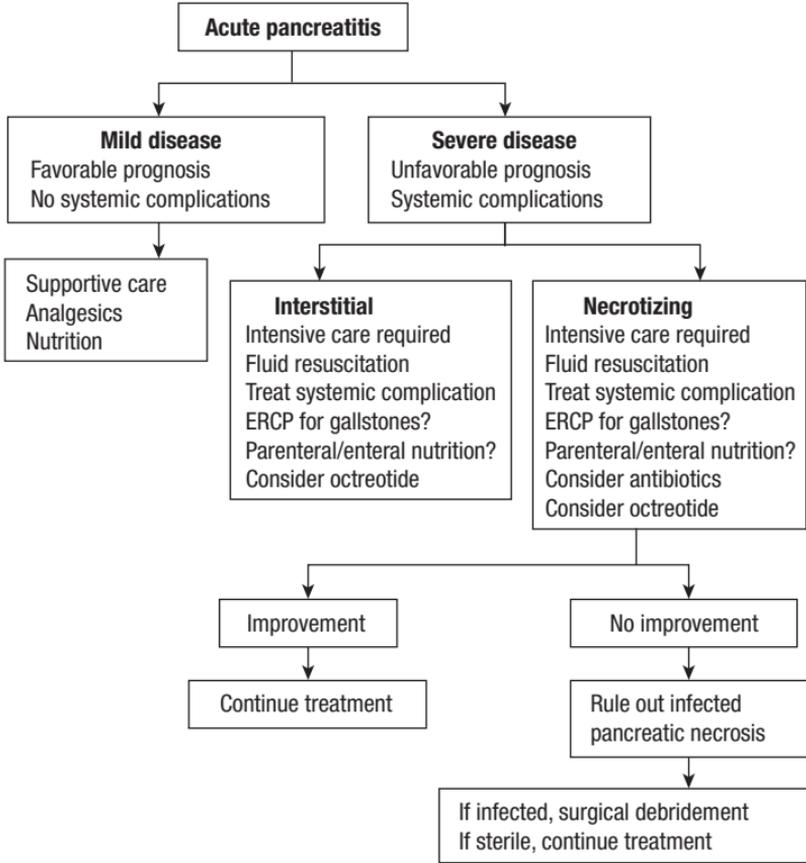
- Treatment of AP is aimed at relieving abdominal pain and nausea, replacing fluids, minimizing systemic complications, and preventing pancreatic necrosis and infection.

## PHARMACOLOGIC TREATMENT

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(Fig. 28-1)

- Medications listed in Table 28-1 should be discontinued, if possible.
- Initial treatment usually involves withholding food or liquids to minimize exocrine stimulation of the pancreas.
- Nasogastric aspiration is beneficial in patients with profound pain, severe disease, paralytic ileus, and intractable vomiting.
- Patients predicted to follow a severe course require treatment of any cardiovascular, respiratory, renal, and metabolic complications. Aggressive fluid resuscitation is essential to correct intravascular volume depletion and maintain blood pressure. **IV colloids** may be required because fluid losses are rich in protein. **Drotrecogin alfa** may benefit patients with pancreatitis and systemic inflammatory response syndrome. **IV potassium, calcium, and magnesium** are used to correct deficiency states. **Insulin** is used to treat hyperglycemia. Patients with necrotizing pancreatitis may require antibiotics and surgical intervention.
- Nutritional support with enteral or parenteral nutrition should be initiated if it is anticipated that oral nutrition will be withheld for more than 1 week.
- Analgesics are given to reduce abdominal pain. In the past, parenteral **meperidine** (50 to 100 mg) every 3 to 4 hours was usually used because it causes less spasm of the sphincter of Oddi than other opioids. Meperidine is used less frequently today because it is not as effective as other opioids and is contraindicated in renal failure. Parenteral **morphine** is sometimes used, but it is thought to cause spasm of the sphincter of Oddi, increases in serum amylase and, rarely, pancreatitis. **Hydromorphone** may also be



**FIGURE 28-1.** Algorithm of guidelines for evaluation and treatment of acute pancreatitis. (ERCP, endoscopic retrograde cholangiopancreatography.)

used because it has a longer half-life than meperidine. Patient-controlled analgesia should be considered in patients who require frequent opioid dosing (e.g., every 2 to 3 hours).

- There is no evidence that inhibiting gastric acid secretion by antisecretory drugs prevents exacerbations of abdominal pain, but they may be used to prevent stress-related mucosal bleeding.
- **Octreotide**, 0.1 mg subcutaneously every 8 hours, may decrease sepsis, length of hospital stay, and perhaps mortality in patients with severe AP, but there are insufficient data to support its routine use in treating AP.
- Only patients with severe AP complicated by necrosis should receive infection prophylaxis with broad-spectrum antibiotics. Agents that cover the range of enteric aerobic gram-negative bacilli and anaerobic organisms should be started within the first 48 hours and continued for 2 to 3 weeks. **Imipenem–cilastatin** (500 mg every 8 hours) may be most effective; a fluoroquinolone (e.g., **ciprofloxacin**, **levofloxacin**) with **metronidazole** should be considered for penicillin-allergic patients.

## SURGERY

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- Removal of biliary tract gallstones with endoscopic retrograde cholangiopancreatography or surgery usually resolves AP and reduces the risk of recurrence. Surgery may be indicated in AP to treat pseudocyst, pancreatic abscess, and to drain the pancreatic bed if hemorrhagic or necrotic material is present.

## EVALUATION OF THERAPEUTIC OUTCOMES

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- In patients with mild AP, pain control, fluid and electrolyte status, and nutrition should be assessed periodically depending on the degree of abdominal pain and fluid loss.
- Patients with severe AP should be transferred to an intensive care unit for close monitoring of vital signs, fluid and electrolyte status, white blood cell count, blood glucose, lactate dehydrogenase, aspartate aminotransferase, serum albumin, hematocrit, blood urea nitrogen, serum creatinine, and international normalized ratio. Continuous hemodynamic and arterial blood gas monitoring is essential. Serum lipase, amylase, and bilirubin require less frequent monitoring. The patient should be monitored for signs of infection, relief of abdominal pain, and adequate nutritional status.

## CHRONIC PANCREATITIS

### PATHOPHYSIOLOGY

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- In most individuals, CP is progressive and loss of pancreatic function is irreversible. Permanent destruction of pancreatic tissue usually leads to exocrine and endocrine insufficiency.
- Prolonged ethanol consumption accounts for 70% of all cases in the United States; 10% result from other causes, and 20% are idiopathic.
- Ethanol-induced pancreatitis appears to progress from inflammation to cellular necrosis, and fibrosis occurs over time. Chronic alcohol ingestion causes changes in pancreatic fluid that create intraductal protein plugs that block small ductules. This results in progressive structural damage in the ducts and acinar tissue. Calcium complexes with the protein plugs, eventually resulting in destruction of pancreatic tissue.
- Abdominal pain may be related in part to increased intraductal pressure secondary to continued pancreatic secretion, pancreatic inflammation, and abnormalities of pancreatic nerves.
- Malabsorption of protein and fat occurs when the capacity for enzyme secretion is reduced by 90%. A minority of patients develop complications including pancreatic pseudocyst, abscess, and ascites or common bile duct obstruction leading to cholangitis or secondary biliary cirrhosis.

### CLINICAL PRESENTATION

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- The main features are abdominal pain, malabsorption, weight loss, and diabetes. Jaundice occurs in about 10% of patients.
- Patients typically report dull epigastric or abdominal pain that radiates to the back. It may be either consistent or episodic. The pain is deep-seated,

positional, frequently nocturnal, and unresponsive to medication. Nausea and vomiting often accompany the pain. Severe attacks last from several days to weeks and may be aggravated by eating and relieved by abstinence from alcohol.

- Steatorrhea (excessive loss of fat in the feces) and azotorrhea (excessive loss of protein in the feces) are seen in most patients. Steatorrhea is often associated with diarrhea and bloating. Weight loss may occur.
- Pancreatic diabetes is usually a late manifestation that is commonly associated with pancreatic calcification. Neuropathy is sometimes seen.

## DIAGNOSIS

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- Most patients have a history of heavy ethanol use and attacks of recurrent upper abdominal pain. The classic triad of pancreatic calcification, steatorrhea, and diabetes usually confirms the diagnosis.
- Serum amylase and lipase concentrations usually remain normal unless the pancreatic duct is blocked or a pseudocyst is present.
- The white blood cell count, fluid balance, and electrolyte concentrations usually remain normal unless fluids and electrolytes are lost due to vomiting and diarrhea.
- Malabsorption of fat can be detected by Sudan staining of the feces or a 72-hour quantitative measurement of fecal fat.
- Surgical biopsy of pancreatic tissue through laparoscopy or laparotomy is the gold standard for confirming the diagnosis of CP.
- In the absence of histologic samples, imaging techniques are helpful in detecting calcification of the pancreas and other causes of pain (ductal obstruction secondary to stones, strictures, or pseudocysts) and in differentiating CP from pancreatic cancer. Ultrasonography is the simplest and least expensive imaging technique, and abdominal CT is often used if the ultrasound examination is negative or unsatisfactory.
- Endoscopic retrograde cholangiopancreatography is the most sensitive and specific diagnostic test, but it is reserved for patients in whom the diagnosis cannot be established by imaging techniques because of the potential for complications.

## DESIRED OUTCOME

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- The goals of treating uncomplicated CP are control of chronic abdominal pain and correction of malabsorption and glucose intolerance.

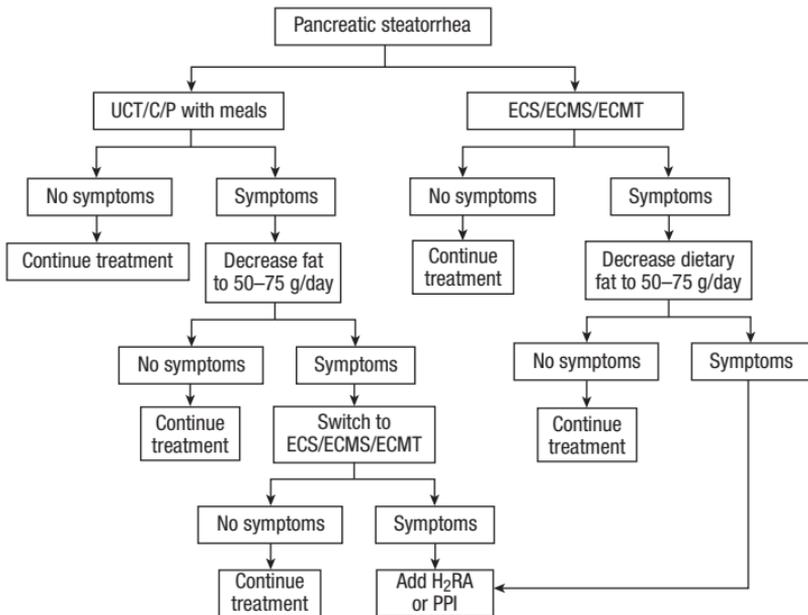
## PHARMACOLOGIC TREATMENT

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- In patients with ethanol-induced CP, abstinence is the most important factor in preventing abdominal pain in the early stages of the disease.
- Small and frequent meals (six meals/day) and a diet restricted in fat (50 to 75 g/day) are recommended to minimize postprandial pancreatic secretion and pain.
- Pain management should begin with nonnarcotic analgesics such as **acetaminophen** or a **nonsteroidal antiinflammatory drug** administered on a scheduled basis before meals to prevent postprandial exacerbation of

pain. If pain persists, the response to exogenous non-enteric-coated pancreatic enzymes should be evaluated in patients with mild to moderate CP. If these measures fail, consideration may be given to use of **tramadol** or addition of a low-dose opioid to the regimen (e.g., **acetaminophen plus codeine**). Parenteral opioids are reserved for patients with severe pain unresponsive to oral analgesics. In patients with pain that is difficult to manage, nonnarcotic modulators of chronic pain (e.g., selective serotonin reuptake inhibitors, tricyclic antidepressants) may be considered.

- Most patients with malabsorption require pancreatic enzyme supplementation (Fig. 28-2). The combination of pancreatic enzymes (lipase, amylase, and protease) and a reduction in dietary fat (to less than 25 g/meal) enhances nutritional status and reduces steatorrhea. An initial dose containing about 30,000 international units of lipase and 10,000 international units of trypsin should be given with each meal.
- Oral pancreatic enzyme supplements are available as powders, uncoated or coated tablets, capsules, enteric-coated spheres and microspheres, or enteric-coated microtablets encased in a cellulose or gelatin capsule (Table 28-2). Microencapsulated enteric-coated products are not superior to recommended doses of conventional non-enteric-coated enzyme preparations. The quantity of active lipase delivered to the duodenum appears to be a more important determinant in pancreatic enzyme replacement therapy than the dosage form. GI side effects appear to be dose related but occur less frequently with enteric-coated products.



**FIGURE 28-2.** Algorithm of guidelines for the treatment of pancreatic steatorrhea in chronic pancreatitis. (C, capsule; ECMS, enteric-coated microsphere; ECMT, enteric-coated microtablet; ECS, enteric-coated sphere; H<sub>2</sub>RA, histamine-2 receptor antagonist; P, powder; PPI, proton pump inhibitor; UCT, uncoated tablet.)

**TABLE 28-2** Enzyme Content of Selected Pancreatic Enzyme Preparations

Product	Dosage Form	Enzyme Contents (units) <sup>a</sup>		
		Lipase	Amylase	Protease
Creon-10	ECMS	10,000	33,200	37,500
Creon-20	ECMS	20,000	66,400	75,000
Ku-Zyme HP	C	8,000	30,000	30,000
Lipram-CR10	ECMS	10,000	33,200	37,500
Lipram-PN16	ECMS	16,000	48,000	48,000
Lipram-CR20	ECMS	20,000	66,400	75,000
Lipram-PN20	ECMS	20,000	56,000	44,000
Lipram-UL12	ECMS	12,000	39,000	39,000
Lipram-PN10	ECMS	10,000	30,000	30,000
Lipram-UL18	ECMS	18,000	58,500	58,500
Lipram-UL20	ECMS	20,000	65,000	65,000
Pancrease	ECMS	4,500	20,000	25,000
Pancrease MT-4	ECMT	4,000	12,000	12,000
Pancrease MT-10	ECMT	10,000	30,000	30,000
Pancrease MT-16	ECMT	16,000	48,000	48,000
Pancrease MT-20	ECMT	20,000	56,000	44,000
Ultrase MT 12	ECMT	12,000	39,000	39,000
Ultrase MT 18	ECMT	18,000	58,500	58,500
Ultrase MT 20	ECMT	20,000	65,000	65,000
Viokase <sup>b</sup>	P	16,800	70,000	70,000
Viokase 8	UCT	8,000	30,000	30,000
Viokase 16	UCT	16,000	60,000	60,000

C, powder encased in a cellulose capsule; ECMS, enteric-coated microspheres encased in a cellulose or gelatin capsule; ECMT, enteric-coated microtablets encased in a cellulose capsule; UCT, uncoated tablet; P, powder.

<sup>a</sup>All listed products contain pancrelipase. Pancrelipase contains not less than 24 USP units of lipase activity, not less than 100 USP units of amylase activity, and not less than 100 USP units of protease activity per mg.

<sup>b</sup>Units of 0.7 g of powder.

- Concurrent use of an H<sub>2</sub> receptor antagonist or proton pump inhibitor may improve the efficacy of pancreatic enzyme supplementation by both increasing pH and decreasing intragastric volume. Antacids have little or no added effect in reducing steatorrhea. Addition of an H<sub>2</sub> receptor antagonist may be beneficial for symptomatic patients whose steatorrhea is not corrected by enzyme replacement therapy and reducing dietary fat. A proton pump inhibitor should be considered in patients who fail to benefit from an H<sub>2</sub> receptor antagonist.

## SURGERY

- The most common indication for surgery in CP is abdominal pain refractory to medical therapy. Surgical procedures that alleviate pain include a subtotal pancreatectomy, decompression of the main pancreatic duct, or interruption of the splanchnic nerves.

## EVALUATION OF THERAPEUTIC OUTCOMES

- The severity and frequency of abdominal pain should be assessed periodically to determine the efficacy of the analgesic regimen.

- The effectiveness of pancreatic enzyme supplementation is measured by improvement in body weight and stool consistency or frequency. The 72-hour stool test for fecal fat may be used when the adequacy of treatment is in question.
- Serum uric acid and folic acid concentrations should be monitored yearly in patients prone to hyperuricemia or folic acid deficiency. Blood glucose must be monitored carefully in diabetic patients.

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*See Chap. 41, Pancreatitis, authored by Rosemary R. Berardi and Patricia A. Montgomery, for a more detailed discussion of this topic.*

## DEFINITION

- *Peptic ulcer disease* (PUD) refers to a group of ulcerative disorders of the upper GI tract that require acid and pepsin for their formation. Ulcers differ from gastritis and erosions in that they extend deeper into the muscularis mucosa. The three common forms of peptic ulcers include *Helicobacter pylori* (HP)–associated ulcers, nonsteroidal antiinflammatory drug (NSAID)–induced ulcers, and stress-related mucosal damage (also called stress ulcers).

## PATHOPHYSIOLOGY

- The pathogenesis of duodenal ulcers (DU) and gastric ulcers (GU) is multifactorial and most likely reflects a combination of pathophysiologic abnormalities and environmental and genetic factors.
- Most peptic ulcers occur in the presence of acid and pepsin when HP, NSAIDs, or other factors disrupt normal mucosal defense and healing mechanisms. Acid is an independent factor that contributes to disruption of mucosal integrity. Increased acid secretion has been observed in patients with DU and may result from HP infection. Patients with GU usually have normal or reduced rates of acid secretion.
- Alterations in mucosal defense induced by HP or NSAIDs are the most important cofactors in peptic ulcer formation. Mucosal defense and repair mechanisms include mucus and bicarbonate secretion, intrinsic epithelial cell defense, and mucosal blood flow. Maintenance of mucosal integrity and repair is mediated by endogenous prostaglandin production.
- HP infection causes gastritis in all infected individuals and is causally linked to PUD. However, only about 20% of infected persons develop symptomatic PUD. Most non-NSAID ulcers are infected with HP, and HP eradication markedly decreases ulcer recurrence. HP may cause ulcers by direct mucosal damage, altering the immune/inflammatory response, and by hypergastrinemia leading to increased acid secretion.
- Nonselective NSAIDs (including aspirin) cause gastric mucosal damage by two mechanisms: (1) a direct or topical irritation of the gastric epithelium, and (2) systemic inhibition of the cyclooxygenase-1 (COX-1) enzyme, which results in decreased synthesis of protective prostaglandins.
- Use of corticosteroids alone does not increase the risk of ulcer or complications, but ulcer risk is doubled in corticosteroid users taking NSAIDs concurrently.
- Epidemiologic evidence links cigarette smoking to PUD, impaired ulcer healing, and ulcer-related GI complications. The risk is proportional to the amount smoked per day.
- Although clinical observation suggests that ulcer patients are adversely affected by stressful life events, controlled studies have failed to document a cause-and-effect relationship.

- Coffee, tea, cola beverages, beer, milk, and spices may cause dyspepsia but do not increase PUD risk. Ethanol ingestion in high concentrations is associated with acute gastric mucosal damage and upper GI bleeding but is not clearly the cause of ulcers.

## CLINICAL PRESENTATION

- Abdominal pain is the most frequent symptom of PUD. The pain is often epigastric and described as burning but can present as vague discomfort, abdominal fullness, or cramping. A typical nocturnal pain may awaken patients from sleep, especially between 12 AM and 3 AM.
- Pain from DU often occurs 1 to 3 hours after meals and is usually relieved by food, whereas food may precipitate or accentuate ulcer pain in GU. Antacids provide rapid pain relief in most ulcer patients.
- Heartburn, belching, and bloating often accompany the pain. Nausea, vomiting, and anorexia are more common in GU than DU.
- The severity of symptoms varies from patient to patient and may be seasonal, occurring more frequently in the spring or fall.
- Pain does not always correlate with the presence of an ulcer. Asymptomatic patients may have an ulcer at endoscopy, and patients may have persistent symptoms even with endoscopically proven healed ulcers. Many patients (especially older adults) with NSAID-induced, ulcer-related complications have no prior abdominal symptoms.
- Complications of ulcers caused by HP and NSAIDs include upper GI bleeding, perforation into the peritoneal cavity, penetration into an adjacent structure (e.g., pancreas, biliary tract, or liver), and gastric outlet obstruction. Bleeding may be occult or present as melena or hematemesis. Perforation is associated with sudden, sharp, severe pain, beginning first in the epigastrium but quickly spreading over the entire abdomen. Symptoms of gastric outlet obstruction typically occur over several months and include early satiety, bloating, anorexia, nausea, vomiting, and weight loss.

## DIAGNOSIS

- The physical examination may reveal epigastric tenderness between the umbilicus and the xiphoid process that less commonly radiates to the back.
- Routine laboratory tests are not helpful in establishing a diagnosis of uncomplicated PUD. The hematocrit, hemoglobin, and stool hemoccult tests are used to detect bleeding.
- The diagnosis of HP infection can be made using endoscopic or nonendoscopic tests. The tests that require upper endoscopy are invasive, more expensive, uncomfortable, and usually require a mucosal biopsy for histology, culture, or detection of urease activity. The nonendoscopic tests include serologic antibody detection tests, the urea breath test (UBT), and the stool antigen test. Serologic tests detect circulating immunoglobulin G directed against HP but are of limited value in evaluating posttreatment eradication. The UBT is based on urease production by HP.

- Testing for HP is only recommended if eradication therapy is considered. If endoscopy is not planned, serologic antibody testing is reasonable to determine HP status. The UBT is the preferred nonendoscopic method to verify HP eradication after treatment.
- The diagnosis of PUD depends on visualizing the ulcer crater either by upper GI radiography or endoscopy. Radiography may be the preferred initial diagnostic procedure in patients with suspected uncomplicated PUD. Upper endoscopy should be performed if complications are thought to exist or if an accurate diagnosis is warranted. If a GU is found on radiography, malignancy should be excluded by direct endoscopic visualization and histology.

## DESIRED OUTCOME

- The goals of treatment are relieving ulcer pain, healing the ulcer, preventing ulcer recurrence, and reducing ulcer-related complications. In HP-positive patients with an active ulcer, a previously documented ulcer, or a history of an ulcer-related complication, the goals are to eradicate the organism, heal the ulcer, and cure the disease with a cost-effective drug regimen.

## TREATMENT

### NONPHARMACOLOGIC TREATMENT

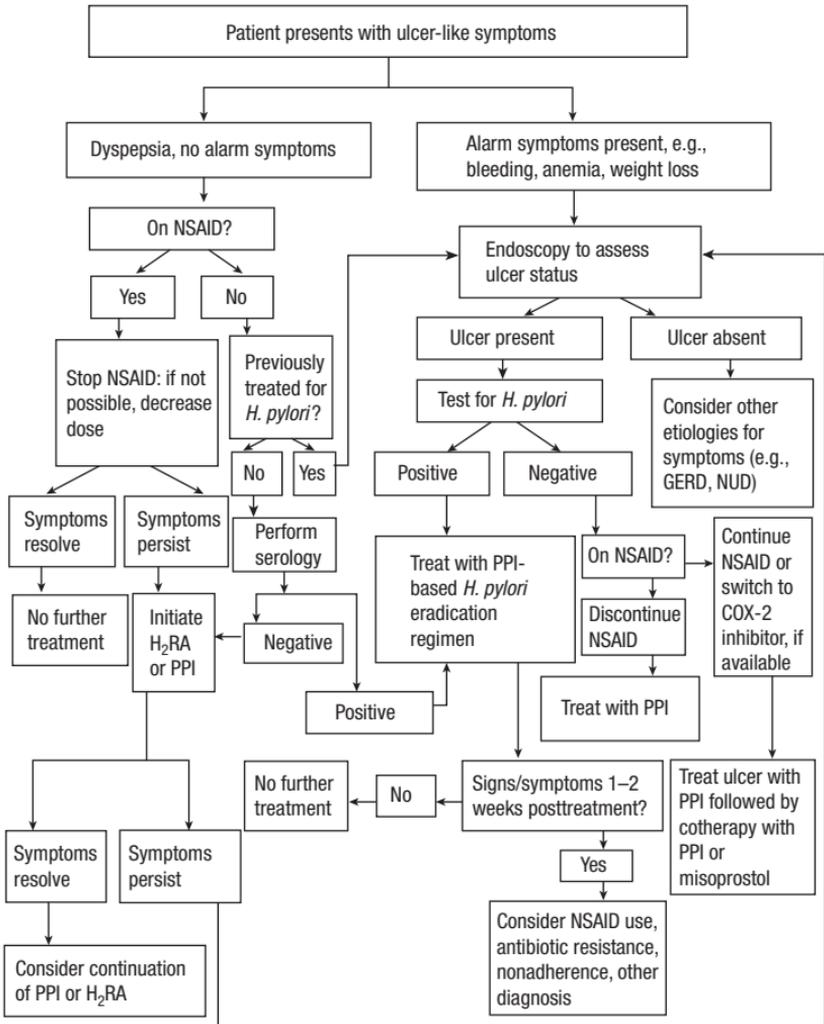
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- Patients with PUD should eliminate or reduce psychological stress, cigarette smoking, and the use of nonselective NSAIDs (including aspirin). If possible, alternative agents such as **acetaminophen**, a nonacetylated salicylate (e.g., **salsalate**), or a COX-2 selective inhibitor should be used for pain relief.
- Although there is no need for a special diet, patients should avoid foods and beverages that cause dyspepsia or exacerbate ulcer symptoms (e.g., spicy foods, caffeine, alcohol).

### PHARMACOLOGIC TREATMENT

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- An algorithm for the evaluation and management of a patient with dyspeptic or ulcer-like symptoms is presented in Fig. 29-1.
- Eradication of HP is recommended for HP-infected patients with GU, DU, ulcer-related complications, and in some other situations. Treatment should be effective, well tolerated, easy to comply with, and cost-effective (Table 29-1).
- First-line eradication therapy is a proton pump inhibitor (PPI)-based, three-drug regimen containing two antibiotics, usually **clarithromycin** and **amoxicillin**, reserving **metronidazole** for back-up therapy (e.g., clarithromycin–metronidazole in penicillin-allergic patients). The PPI should be taken 30 to 60 minutes before a meal along with the two antibiotics. Although an initial 7-day course provides minimally acceptable eradication rates, longer treatment periods (10 to 14 days) are associated with higher eradication rates and less antimicrobial resistance.



**FIGURE 29-1.** Algorithm for the evaluation and management of a patient who presents with dyspeptic or ulcer-like symptoms. (COX-2, cyclooxygenase-2; GERD, gastroesophageal reflux disease; *H. pylori*, *Helicobacter pylori*; H<sub>2</sub>RA, histamine-2 receptor antagonist; NSAID, nonsteroidal antiinflammatory drug; NUD, nonulcer dyspepsia; PPI, proton pump inhibitor.)

- First-line treatment with quadruple therapy using a PPI (with **bismuth**, **metronidazole**, and **tetracycline**) achieves similar eradication rates as PPI-based triple therapy and permits a shorter treatment duration (7 days). However, this regimen is often recommended as second-line treatment when a clarithromycin–amoxicillin regimen is used initially. All medications except the PPI should be taken with meals and at bedtime.
- If the initial treatment fails to eradicate HP, second-line empiric treatment should: (1) use antibiotics that were not included in the initial regimen;

**TABLE 29-1** Drug Regimens to Eradicate *Helicobacter pylori*<sup>a</sup>

Drug 1	Drug 2	Drug 3	Drug 4
<b>Proton pump inhibitor–based three-drug regimens</b>			
Omeprazole 20 mg twice daily <b>or</b> lansoprazole 30 mg twice daily <b>or</b> pantoprazole 40 mg twice daily <b>or</b> esomeprazole 40 mg daily <b>or</b> rabeprazole 20 mg daily	Clarithromycin 500 mg twice daily	Amoxicillin 1 g twice daily <b>or</b> metronidazole 500 mg twice daily	
<b>Bismuth-based four-drug regimens<sup>b</sup></b>			
Omeprazole 40 mg twice daily <b>or</b> lansoprazole 30 mg twice daily <b>or</b> pantoprazole 40 mg twice daily <b>or</b> esomeprazole 40 mg daily <b>or</b> rabeprazole 20 mg daily <b>or</b> standard ulcer-healing dosages of an histamine-2 receptor antagonist taken for 4–6 weeks (see Table 29-2)	Bismuth subsalicylate 525 mg four times daily	Metronidazole 250–500 mg four times daily	Tetracycline 500 mg four times daily <b>or</b> amoxicillin 500 mg four times daily, <b>or</b> clarithromycin 250–500 mg four times daily

<sup>a</sup>Although treatment is minimally effective if used for 7 days, 10–14 days of treatment is recommended. The antisecretory drug may be continued beyond antimicrobial treatment in patients with a history of complicated ulcer (e.g., bleeding or in heavy smokers).

<sup>b</sup>In the setting of an active ulcer, acid suppression is added to hasten pain relief.

(2) include antibiotics that do not have resistance problems; (3) use a drug that has a topical effect (e.g., bismuth); and (4) be extended to 14 days. Thus, if a PPI–amoxicillin–clarithromycin regimen fails, therapy should be instituted with a PPI, bismuth subsalicylate, metronidazole, and tetracycline for 14 days.

- Treatment with a conventional antiulcer drug (e.g., PPI, histamine-2 receptor antagonist [H<sub>2</sub>RA], or sucralfate alone) is an alternative to HP eradication but is discouraged because of the high rate of ulcer recurrence and ulcer-related complications. Dual therapy (e.g., H<sub>2</sub>RA plus sucralfate, H<sub>2</sub>RA plus PPI) is not recommended because it increases cost without enhancing efficacy.
- Maintenance therapy with a PPI or H<sub>2</sub>RA (Table 29-2) is recommended for high-risk patients with ulcer complications, patients who fail HP eradication, and those with HP-negative ulcers.
- For treatment of NSAID-induced ulcers, nonselective NSAIDs should be discontinued (when possible) if an active ulcer is confirmed. Most uncomplicated NSAID-induced ulcers heal with standard regimens of an H<sub>2</sub>RA, PPI, or sucralfate (see Table 29-2) if the NSAID is discontinued. If the NSAID must be continued, consideration should be given to reducing the

**TABLE 29-2** Oral Drug Regimens Used to Heal Peptic Ulcers or Maintain Ulcer Healing

Drug	Duodenal or Gastric Ulcer Healing (mg/dose)	Maintenance of Duodenal or Gastric Ulcer Healing (mg/dose)
<b>Proton pump inhibitors</b>		
Omeprazole	20–40 daily	20–40 daily
Lansoprazole	15–30 daily	15–30 daily
Rabeprazole	20 daily	20 daily
Pantoprazole	40 daily	40 daily
Esomeprazole	20–40 daily	20–40 daily
<b>Histamine-2 receptor antagonists</b>		
Cimetidine	300 four times daily	400–800 at bedtime
	400 twice daily	
	800 at bedtime	
Famotidine	20 twice daily	20–40 at bedtime
	40 at bedtime	
Nizatidine	150 twice daily	150–300 at bedtime
	300 at bedtime	
Ranitidine	150 twice daily	150–300 at bedtime
	300 at bedtime	
<b>Promote mucosal defense</b>		
Sucralfate (g/dose)	1 g four times daily	1–2 g twice daily
	2 g twice daily	1 g four times daily

NSAID dose or switching to acetaminophen, a nonacetylated salicylate, a partially selective COX-2 inhibitor, or a selective COX-2 inhibitor. PPIs are the drugs of choice when NSAIDs must be continued because potent acid suppression is required to accelerate ulcer healing. If HP is present, treatment should be initiated with an eradication regimen that contains a PPI. Patients at risk of developing serious ulcer-related complications while on NSAIDs should receive prophylactic cotherapy with misoprostol or a PPI.

- Patients with ulcers refractory to treatment should undergo upper endoscopy to confirm a nonhealing ulcer, exclude malignancy, and assess HP status. HP-positive patients should receive eradication therapy. In HP-negative patients, higher PPI doses (e.g., omeprazole 40 mg/day) heal the majority of ulcers. Continuous PPI treatment is often necessary to maintain healing.

## EVALUATION OF THERAPEUTIC OUTCOMES

- Patients should be monitored for symptomatic relief of ulcer pain as well as potential adverse effects and drug interactions related to drug therapy.
- Ulcer pain typically resolves in a few days when NSAIDs are discontinued and within 7 days upon initiation of antiulcer therapy. Most patients with uncomplicated PUD will be symptom-free after treatment with any one of the recommended antiulcer regimens.
- The persistence or recurrence of symptoms within 14 days after the end of treatment suggests failure of ulcer healing or HP eradication, or an alternative diagnosis such as gastroesophageal reflux disease.

- Most patients with uncomplicated HP-positive ulcers do not require confirmation of ulcer healing or HP eradication.
- High-risk patients on NSAIDs should be closely monitored for signs and symptoms of bleeding, obstruction, penetration, and perforation.
- Follow-up endoscopy is justified in patients with frequent symptomatic recurrence, refractory disease, complications, or suspected hypersecretory states.

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*See Chap. 35, Peptic Ulcer Disease, authored by Rosemary R. Berardi and Lynda S. Welage, for a more detailed discussion of this topic.*

SECTION 6  
GYNECOLOGIC AND OBSTETRIC DISORDERS

*Edited by Barbara G. Wells*

CHAPTER

30

## Contraception

### DEFINITION

- Contraception is the prevention of pregnancy following sexual intercourse by inhibiting sperm from reaching a mature ovum (i.e., methods that act as barriers or prevent ovulation) or by preventing a fertilized ovum from implanting in the endometrium (i.e., mechanisms that create an unfavorable uterine environment).
- Method failure (perfect-use failure) is a failure inherent to the proper use of the contraceptive alone.
- User failure (typical use failure) takes into account the user's ability to follow directions correctly and consistently.

### THE MENSTRUAL CYCLE

- The median length of the menstrual cycle is 28 days (range 21 to 40). The first day of menses is day 1 of the follicular phase. Ovulation usually occurs on day 14 of the menstrual cycle. After ovulation, the luteal phase lasts until the beginning of the next cycle.
- Epinephrine and norepinephrine stimulate the hypothalamus to secrete gonadotropin-releasing hormone, which stimulates the anterior pituitary to secrete bursts of gonadotropins, follicle-stimulating hormone (FSH), and luteinizing hormone (LH).
- In the follicular phase, FSH causes recruitment of a small group of follicles for continued growth. Between 5 and 7 days, one of these becomes the dominant follicle, which later ruptures to release the oocyte. The dominant follicle develops increasing amounts of estradiol and inhibin, which cause a negative feedback on the secretion of gonadotropin-releasing hormone and FSH, causing atresia of the remaining follicles recruited earlier.
- The dominant follicle continues to grow and synthesizes estradiol, progesterone, and androgen. Estradiol stops the menstrual flow from the previous cycle, thickens the endometrial lining, and produces thin, watery cervical mucus. FSH regulates aromatase enzymes that induce conversion of androgens to estrogens in the follicle.
- The pituitary releases a mid-cycle LH surge that stimulates the final stages of follicular maturation and ovulation. Ovulation occurs 24 to 36 hours after the estradiol peak and 10 to 16 hours after the LH peak.
- The LH surge, occurring 28 to 32 hours before a follicle ruptures, is the most clinically useful predictor of approaching ovulation. Conception is

most successful when intercourse takes place from 2 days before ovulation to the day of ovulation.

- After ovulation, the remaining luteinized follicles become the corpus luteum, which synthesizes androgen, estrogen, and progesterone (Fig. 30-1).
- If pregnancy occurs, human chorionic gonadotropin prevents regression of the corpus luteum and stimulates continued production of estrogen and progesterone. If pregnancy does not occur, the corpus luteum degenerates, and progesterone declines. As progesterone levels decline, menstruation occurs.

## TREATMENT

### NONPHARMACOLOGIC THERAPY

- A comparison of methods of nonhormonal contraception is shown in Table 30-1.

#### Periodic Abstinence

- The abstinence (rhythm) method is not well accepted, as it is associated with relatively high pregnancy rates and necessitates avoidance of intercourse for several days in each cycle.

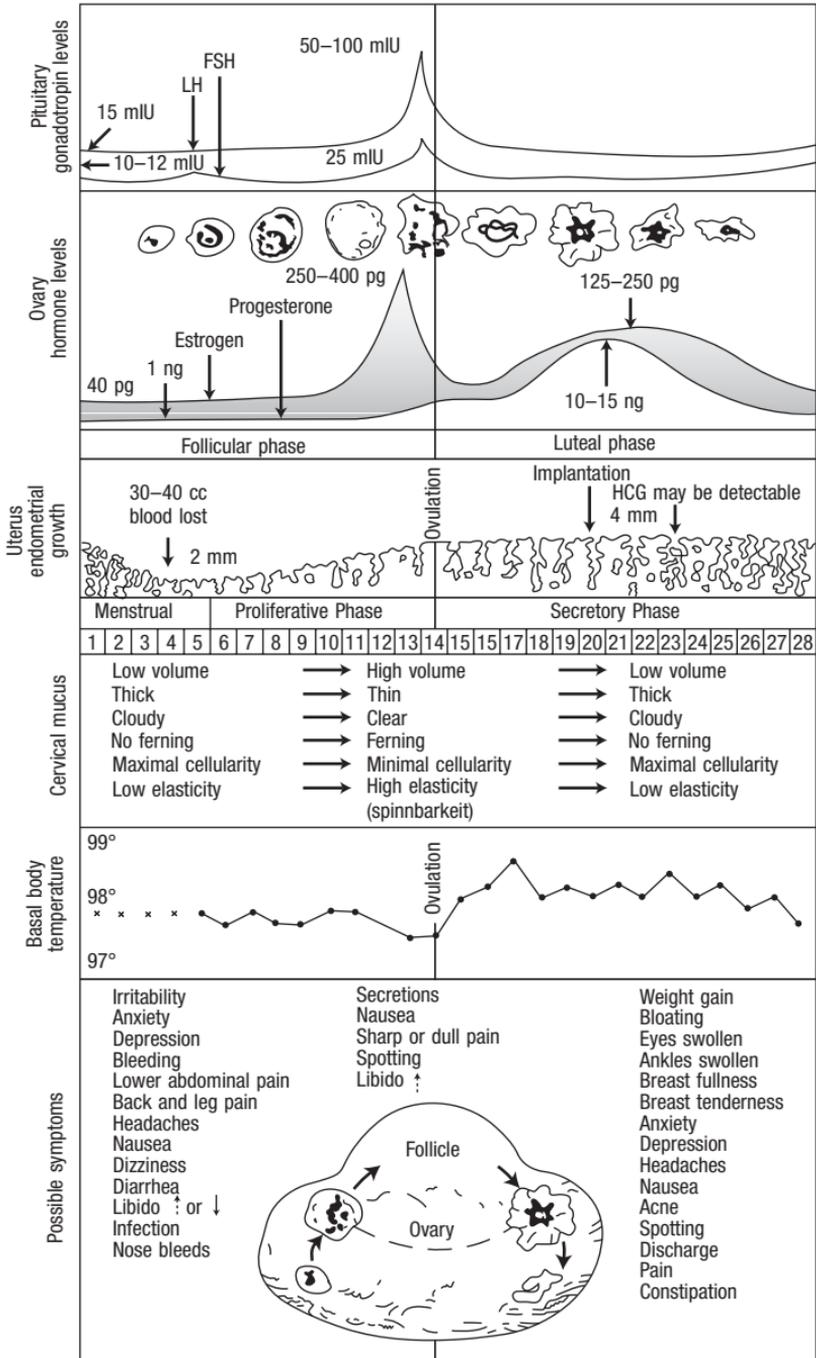
#### Barrier Techniques

- The effectiveness of the diaphragm depends on its function as a barrier and on the spermicidal cream or jelly placed in the diaphragm before insertion.
- The cervical cap, smaller and less messy than the diaphragm, fits over the cervix like a thimble. Caps can be inserted 6 hours prior to intercourse, and women should not wear the cap for longer than 48 hours to reduce the risk of toxic shock syndrome.
- Most condoms made in the United States are latex rubber, which is impermeable to viruses, but about 5% are made from lamb intestine, which is not impermeable to viruses. Mineral oil-based vaginal drug formulations (e.g., Cleocin vaginal cream, Premarin vaginal cream, Vagistat 1, Femstat, and Monistat Vaginal suppositories) can decrease barrier strength of latex by 90% in 60 seconds. Condoms with spermicides are no longer recommended, as they provide no additional protection against pregnancy or sexually transmitted diseases (STDs) and may increase vulnerability to human immunodeficiency virus (HIV).
- The female condom (Reality) covers the labia as well as the cervix, thus it may be more effective than the male condom in preventing transmission of STDs. However, the pregnancy rate is reported to be 21% in the first year of use.

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#### Spermicides

- Spermicides, most of which contain nonoxynol-9, are surfactants that destroy sperm cell walls. They offer no protection against STDs, and when



**FIGURE 30-1.** Menstrual cycle events, idealized 28-day cycle. (FSH, follicle-stimulating hormone; HCG, human chorionic gonadotropin; LH, luteinizing hormone.) (From Hatcher RA, Ziemann M, Cwiak, C et al. *A Pocket Guide to Managing Contraception*. Tiger, GA: Bridging the Gap Foundation, 2005. This figure may be reproduced at no cost to the reader.)

**TABLE 30-1** Comparison of Methods of Nonhormonal Contraception

<b>Method</b>	<b>Absolute Contraindications</b>	<b>Advantages</b>	<b>Disadvantages</b>	<b>Percent of Women with Pregnancy<sup>a</sup></b>	
				<b>Perfect Use</b>	<b>Typical Use</b>
Condoms, male	Allergy to latex or rubber	Inexpensive STD protection, including HIV (latex only)	High user failure rate Poor acceptance Possibility of breakage Efficacy decreased by oil-based lubricants Possible allergic reactions to latex in either partner	2	15
Condoms, female (Reality)	Allergy to polyurethane History of TSS	Can be inserted just before intercourse or ahead of time STD protection, including HIV Low cost	High user failure rate Dislike ring hanging outside vagina Cumbersome	5	21
Diaphragm with spermicide	Allergy to latex, rubber, or spermicide Recurrent UTIs History of TSS Abnormal gynecologic anatomy	Decreased incidence of cervical neoplasia Some protection against STDs	High user failure rate Decreased efficacy with increased frequency of intercourse Increased incidence of vaginal yeast UTIs, TSS Efficacy affected by oil-based lubricants Cervical irritation	6	16

Cervical cap (FemCap, Leah's Shield)	Allergy to spermicide History of TSS Abnormal gynecologic anatomy Abnormal Papanicolaou smear	Low cost Latex-free Some protection against STDs FemCap reusable for up to 2 years	High user failure rate Decreased efficacy with parity Cannot be used during menses	9	16 <sup>b</sup>
Spermicides alone	Allergy to spermicide	Inexpensive	High user failure rate Must be reapplied before each act of intercourse May enhance HIV transmission No protection against STDs	18	29
Sponge (Today)	Allergy to spermicide Recurrent UTIs History of TSS Abnormal gynecologic anatomy	Inexpensive	High user failure rate Decreased efficacy with parity Cannot be used during menses No protection against STDs	9	16

HIV, human immunodeficiency virus; STD, sexually transmitted disease; TSS, toxic shock syndrome; UTI, urinary tract infection.

<sup>a</sup>Failure rates in the United States during first year of use.

<sup>b</sup>Failure rate with FemCap reported to be 29% per package insert.

Data from Hatcher RA, Ziemann M, Gwiak C et al. *A Pocket Guide to Managing Contraception*. Tiger, GA: Bridging the Gap Foundation, 2005; Hatcher RA, Trussell J, Stewart F, et al. *Contraceptive Technology*, 18th ed. New York: Ardent Media, 2004; Dickey RP. *Managing Contraceptive Pill Patients*, 12th ed. Dallas, TX: Essential Medical Information Systems, 2004.

used more than two times daily, they may increase the transmission of HIV. Women at high risk for HIV should not use spermicides.

### **Spermicide-Implanted Barrier Techniques**

- The vaginal contraceptive sponge (Today) contains 1 g of nonoxynol-9 and provides protection for 24 hours. After intercourse, the sponge must be left in place for at least 6 hours before removal. It is available without a prescription.

### **Hormonal Contraception**

#### *Composition and Formulations*

- Hormonal contraceptives contain either a combination of synthetic estrogen and synthetic progestin or a progestin alone.
- Progestins thicken cervical mucus, delay sperm transport, and induce endometrial atrophy. They also block the LH surge and thus inhibit ovulation. Estrogens suppress FSH release, which may contribute to blocking the LH surge, and also stabilizes the endometrial lining and provides cycle control.

#### *Components*

- Two synthetic estrogens are used in hormonal contraceptives in the United States, ethinyl estradiol (EE) and mestranol. Mestranol must be converted to EE in the liver to be active. It is approximately 50% less potent than EE. Most combined oral contraceptives (OCs) contain estrogen at doses of 20 to 50 mcg of EE daily. The contraceptive ring produces one-half the serum concentration of EE derived from a 30-mcg OC.
- Progestins vary in their progestational activity and differ with respect to inherent estrogenic, antiestrogenic, and androgenic effects. Their estrogenic and antiestrogenic properties occur because progestins are metabolized to estrogenic substances. Androgenic properties occur because of the structural similarity of the progestin to testosterone.
- Progestins include desogestrel, drospirenone, ethynodiol diacetate, norgestimate, norethindrone, norethindrone acetate, norethynodrel, norgestrel, and levonorgestrel, the active isomer of norgestrel. The patch contains norelgestromin, the active metabolite of norgestimate. The vaginal ring contains etonogestrel, the metabolite of desogestrel.
- Table 30-2 lists available OCs by brand name and hormonal composition.

#### *Considerations with Oral Contraceptive Use*

- The recommendation of the American College of Obstetricians and Gynecologists is to allow provision of hormonal contraception after a simple medical history and blood pressure measurement.
- Noncontraceptive benefits of OCs include decreased menstrual cramps and ovulatory pain; decreased menstrual blood loss; improved menstrual regularity; increased hemoglobin concentration; improvement in acne; reduced risk of ovarian and endometrial cancer; and reduced risk of ovarian cysts, ectopic pregnancy, pelvic inflammatory disease, and benign breast disease.
- The transdermal patch may cause less breast discomfort and dysmenorrhea than OCs.

**TABLE 30-2** Composition of Commonly Prescribed Oral Contraceptives<sup>a</sup>

Product	Estrogen	Micrograms <sup>b</sup>	Progestin	Milligrams <sup>b</sup>	Spotting and Breakthrough Bleeding (%)
<b>50 mcg estrogen</b>					
Necon, Nelova, Norethin, Norinyl, Ortho-Novum 1/50	Mestranol	50	Norethindrone	1	10.6
Norlestrin 1/50	Ethinyl estradiol	50	Norethindrone acetate	1	13.6
Ovcon 50	Ethinyl estradiol	50	Norethindrone	1	11.9
Ovral, Ogestrel	Ethinyl estradiol	50	Norgestrel	0.5	4.5
Demulen 50, Zovia 1/50	Ethinyl estradiol	50	Ethinodiol diacetate	1	13.9
<b>Sub-50 mcg estrogen monophasic</b>					
Alesse, Aviana, Lessina, Levlite	Ethinyl estradiol	20	Levonorgestrel	0.1	26.5
Brevicon, Modicon, Necon, Nortrel 0.5/30	Ethinyl estradiol	35	Norethindrone	0.5	24.6
Demulen, Zovia 1/35	Ethinyl estradiol	37.4	Ethinodiol diacetate	1	37.4
Apri, Desogen, Ortho-Cept	Ethinyl estradiol	30	Desogestrel	0.15	13.1
Levlen, Levora, Nordette, Portia	Ethinyl estradiol	30	Levonorgestrel	0.15	14
Loestrin 1/20 (check)	Ethinyl estradiol	20	Norethindrone acetate	1	29.7
Microgestin 1/20 (check)	Ethinyl estradiol	20	Norethindrone acetate	1	29.7
Loestrin, Microgestin 1.5/30	Ethinyl estradiol	30	Norethindrone acetate	1.5	25.2
Cryselle, Lo-Ovral, Low-Ogestrel	Ethinyl estradiol	30	Norgestrel	0.3	9.6
Necon, Nelova, Norinyl, Norethin, Nortrel, Ortho-Novum 1/35	Ethinyl estradiol	35	Norethindrone	1	14.7
Ortho-Cyclen, Sprintec	Ethinyl estradiol	35	Norgestimate	0.25	14.3
Ovcon-35	Ethinyl estradiol	35	Norethindrone	0.4	11
Yasmin	Ethinyl estradiol	30	Drospirenone	3	14.5

*(continued)*

**TABLE 30-2** Composition of Commonly Prescribed Oral Contraceptives<sup>a</sup> (Continued)

Product	Estrogen	Micrograms <sup>b</sup>	Progestin	Milligrams <sup>b</sup>	Spotting and Breakthrough Bleeding (%)	
<b>Sub-50 mcg estrogen monophasic extended cycle</b>						
Loestrin-24 FE <sup>c</sup>	Ethinyl estradiol	20	Norethindrone	1		
Lybrel	Ethinyl estradiol	20	Levonorgestrel	0.09	52 <sup>e</sup>	
Seasonale <sup>d</sup>	Ethinyl estradiol	30	Levonorgestrel	0.15	58.5 <sup>e</sup>	
Yaz <sup>c</sup>	Ethinyl estradiol	20	Drospirenone	3		
<b>Sub-50 mcg estrogen multiphasic</b>						
Cyclessa	Ethinyl estradiol	25 (7)	Desogestrel	0.1 (7)	11.1	
		25 (7)		0.125 (7)		
		25 (7)		0.15 (7)		
Estrostep	Ethinyl estradiol	20 (5)	Norethindrone acetate	1 (5)	21.7	
		30 (7)		1 (7)		
		35 (9)		1 (9)		
Kariva, Mircette	Ethinyl estradiol	20 (21)	Desogestrel	0.15 (21)	19.7	
		10 (5)		Desogestrel		
Necon, Nelova, Ortho-Novum 10/11	Ethinyl estradiol	35 (10)	Norethindrone	0.5 (10)	17.6	
		35 (11)		Norethindrone		1 (11)
Nortrel, Ortho-Novum 7/7/7	Ethinyl estradiol	35 (7)	Norethindrone	0.5 (7)	14.5	
		35 (7)		Norethindrone		0.75 (7)
		35 (7)		Norethindrone		1 (7)
Ortho Tri-Cyclen	Ethinyl estradiol	35 (7)	Norgestimate	0.18 (7)	17.7	
		35 (7)		Norgestimate		0.215 (7)
		35 (7)		Norgestimate		0.25 (7)
		35 (7)		Norgestimate		

Ortho Tri-Cyclen LO	Ethinyl estradiol	25 (7)	Norgestimate	0.18 (7)	11.5
	Ethinyl estradiol	25 (7)	Norgestimate	0.215 (7)	
	Ethinyl estradiol	25 (7)	Norgestimate	0.25 (7)	
Tri-Norinyl	Ethinyl estradiol	35 (7)	Norethindrone	0.5 (7)	25.5
	Ethinyl estradiol	35 (9)	Norethindrone	1 (9)	
	Ethinyl estradiol	35 (5)	Norethindrone	0.5 (5)	
<b>Sub-50 mcg estrogen multiphasic extended cycle</b>					
Seasonique	Ethinyl estradiol	30 (84)	Levonorgestrel	0.15 (84)	42.5 <sup>e</sup>
	Ethinyl estradiol	10 (7)	Levonorgestrel	0.15 (7)	
<b>Progestin only</b>					
Camila, Errin, Micronor, Nor-QD	Ethinyl estradiol	—	Norethindrone	0.35	42.3
Ovrette	Ethinyl estradiol	—	Norgestrel	0.075	34.9

<sup>a</sup>28-day regimens (21-day active pills, then 7-day pill-free interval) unless otherwise noted.

<sup>b</sup>Number in parentheses refers to the number of days the dose is received in multiphasic oral contraceptives.

<sup>c</sup>28-day regimen (24-day active pills, then 4-day pill-free interval).

<sup>d</sup>91-day regimen (84-day active pills, then 7-day pill-free interval).

<sup>e</sup>Percent reporting after 6–12 months of use.

Data from Hatcher RA, Ziemann M, Cwiak C et al. *A Pocket Guide to Managing Contraception*. Tiger, GA: Bridging the Gap Foundation, 2005; Hatcher RA, Trussell J, Stewart F, et al. *Contraceptive Technology*, 18th ed. New York: Ardent Media, 2004; Dickey RP. *Managing Contraceptive Pill Patients*, 12th ed. Dallas, TX: Essential Medical Information Systems, 2004; Anonymous. *Choice of contraceptives*. *Treat Guidel Med Lett* 2004;2:55–62.

**TABLE 30-3** Adverse Effects of Combined Hormonal Contraception (CHC) and Management<sup>a</sup>

Adverse Effects	Management
<b>Estrogen excess</b>	
Nausea, breast tenderness, headaches, cyclic weight gain due to fluid retention	Decrease estrogen content in CHC Consider progestin-only methods or IUD
Dysmenorrhea, menorrhagia, uterine fibroid growth	Decrease estrogen content in CHC Consider extended-cycle or continuous regimen OC Consider progestin-only methods or IUD NSAIDs for dysmenorrhea
<b>Estrogen deficiency</b>	
Vasomotor symptoms, nervousness, decreased libido	Increase estrogen content in CHC
Early-cycle (days 1–9) breakthrough bleeding and spotting	Increase estrogen content in CHC
Absence of withdrawal bleeding (amenorrhea)	Exclude pregnancy Increase estrogen content in CHC if menses is desired Continue current CHC if amenorrhea acceptable
<b>Progestin excess</b>	
Increased appetite, weight gain, bloating, constipation	Decrease progestin content in CHC
Acne, oily skin, hirsutism	Decrease progestin content in CHC Choose less androgenic progestin in CHC
Depression, fatigue, irritability	Decrease progestin content in CHC
<b>Progestin deficiency</b>	
Dysmenorrhea, menorrhagia	Increase progestin content in CHC Consider extended-cycle or continuous regimen OC Consider progestin-only methods or IUD NSAIDs for dysmenorrhea
Late-cycle (days 10–21) breakthrough bleeding and spotting	Increase progestin content in CHC

IUD, intrauterine device; NSAID, nonsteroidal antiinflammatory drug; OC, oral contraceptive.

<sup>a</sup>CHC regimens should be continued for at least 3 months before adjustments are made based on adverse effects.

Data from Hatcher RA, Ziemann M, Cwiak C et al. *A Pocket Guide to Managing Contraception*. Tiger, GA: Bridging the Gap Foundation, 2005; Hatcher RA, Trussel J, Stewart F, et al. *Contraceptive Technology*, 18th ed. New York: Ardent Media, 2004; Dickey RP. *Managing Contraceptive Pill Patients*, 12th ed. Dallas, TX: Essential Medical Information Systems, 2004.

- Adverse effects associated with combined hormonal contraceptives (CHCs) and their management are shown in Table 30-3.
- The main safety concern about CHCs is their lack of protection against STDs.
- The World Health Organization (WHO) developed a graded list of precautions for clinicians to consider when initiating CHCs (Table 30-4).

### Women over 35 Years of Age

- CHCs containing less than 50 mcg EE are an acceptable form of contraception for nonsmoking women up to the time of menopause.
- Studies have not demonstrated an increased risk of myocardial infarction (MI) or stroke in healthy, nonsmoking women older than 35 years of age using low-dose OCs.

### Smoking Women

- Women over 35 years who smoke and take OCs have an increased risk of MI; therefore, clinicians should prescribe CHCs with caution, if at all, in women

**TABLE 30-4** World Health Organization Precautions in the Provision of Combined Hormonal Contraceptives (CHCs)

**Category 4: Refrain from providing CHCs for women with the following diagnoses**

- Thrombophlebitis or thromboembolic disorder, or a history of these conditions
- Cerebrovascular disease, coronary artery disease, peripheral vascular disease
- Valvular heart disease with thrombogenic complications (e.g., pulmonary hypertension, atrial fibrillation, history of endocarditis)
- Diabetes with vascular involvement (e.g., nephropathy, retinopathy, neuropathy, other vascular disease or diabetes >20 years' duration)
- Migraine headaches with focal aura
- Migraine headaches without aura in women  $\geq 35$  years old should discontinue CHC
- Uncontrolled hypertension ( $\geq 160$  mm Hg systolic or  $\geq 90$  mm Hg diastolic)
- Major surgery with prolonged immobilization
- Thrombogenic mutations (e.g., factor V Leiden, protein C or S deficiency, antithrombin III deficiency, prothrombin deficiency)
- Breast cancer
- Acute or chronic hepatocellular disease with abnormal liver function, cirrhosis, hepatic adenomas, or hepatic carcinomas
- Age  $> 35$  years and currently smoking  $\geq 15$  cigarettes per day
- Known or suspected pregnancy
- Breast-feeding women  $< 6$  weeks postpartum

**Category 3: Conditions may be adversely impacted by CHCs, and the risks generally outweigh the benefits; providers should exercise caution if combined CHCs are used in these situations and carefully monitor for adverse effects**

- Multiple risk factors for arterial cardiovascular disease
- Known hyperlipidemia
- Migraine headache without aura in women  $\geq 35$  years old
- History of hypertension (systolic 140–159 mm Hg or diastolic 90–99 mm Hg)
- History of cancer, but no evidence of current disease for 5 years
- Cirrhosis, mild and compensated
- Symptomatic gallbladder disease
- Cholestatic jaundice with prior pill use
- Age  $> 35$  years and currently smoking  $< 15$  cigarettes per day
- Postpartum  $< 21$  days, not breast-feeding
- Breast-feeding women 6 weeks to 6 months postpartum
- Commonly used drugs that induce liver enzymes (rifampin, phenytoin, carbamazepine, barbiturates, primidone, topiramate) and reduce efficacy of CHC

*(continued)*

**TABLE 30-4** World Health Organization Precautions in the Provision of Combined Hormonal Contraceptives (CHCs) (Continued)**Category 2: Some conditions may trigger potential concerns with CHCs, but benefits usually outweigh risks**

- Family history of thromboembolism
- Superficial thrombophlebitis
- Uncomplicated valvular heart disease
- Diabetes without vascular disease
- Sickle cell disease
- Migraine headaches without aura in women <35 years old
- Nonmigrainous headaches at any age should discontinue CHC
- Hypertension during pregnancy, resolved postpartum
- Major surgery without prolonged immobilization
- Gallbladder disease (symptomatic and treated by cholecystectomy or asymptomatic)
- Cholestatic jaundice of pregnancy
- Undiagnosed breast mass
- Undiagnosed abnormal genital bleeding
- Cervical intraepithelial neoplasia or cervical cancer
- Obesity (body mass index  $\geq 30$  kg/m<sup>2</sup>)
- Age <35 years and currently smoking
- Breastfeeding women  $\geq 6$  months postpartum
- Age  $\geq 40$  years
- Drugs that may induce metabolism of CHC and reduce efficacy (griseofulvin, antiretroviral therapy)

**Category 1: Do not restrict use of combined oral contraceptives for the following conditions**

- Varicose veins
- History of gestational diabetes
- Nonmigrainous headaches
- Thyroid disease
- Thalassemia
- Iron deficiency anemia
- Depression
- Epilepsy
- Infectious diseases (HIV, schistosomiasis, tuberculosis, malaria)
- Minor surgery without immobilization
- Endometriosis
- Irregular or heavy vaginal bleeding, severe dysmenorrhea
- Sexually transmitted diseases
- Uterine fibroids
- Pelvic inflammatory disease
- Endometrial cancer
- Ovarian cancer
- History of pelvic surgery
- Trophoblast disease
- History of ectopic pregnancy
- Postabortion
- Postpartum women  $\geq 21$  weeks, not breast-feeding
- Menarche to 40 years of age
- Drug interactions with antibiotics other than rifampin and griseofulvin

HIV, human immunodeficiency virus.

Data from Hatcher RA, Ziemann M, Cwiak C et al. *A Pocket Guide to Managing Contraception*. Tiger, GA: Bridging the Gap Foundation, 2005; Hatcher RA, Trussell J, Stewart F, et al. *Contraceptive Technology*, 18th ed. New York: Ardent Media, 2004; Dickey RP. *Managing Contraceptive Pill Patients*, 12th ed. Dallas, TX: Essential Medical Information Systems, 2004; World Health Organization. *Medical Eligibility Criteria for Contraceptive Use*, 3rd ed. 2004, <http://www.who.int/reproductive-health/publications/mec/index.htm>; Roddy RE, Zekeng L, Ryan KA, et al. *A controlled trial of nonoxynol 9 film to reduce male-to-female transmission of sexually transmitted diseases*. *N Engl J Med* 1998;339:504–510; Pettiti DB. *Combination estrogen-progestin oral contraceptives*. *N Engl J Med* 2003;349:1443–1450.

older than 35 years who smoke. The WHO states that smoking 15 or more cigarettes per day by women over 35 years is a contraindication to the use of CHCs, and that the risks generally outweigh the benefits even in those who smoke fewer than 15 cigarettes per day. Progestin-only contraceptive methods should be considered for women in this group.

### *Hypertension*

- CHCs, even those with less than 35 mcg estrogen, can cause small increases in blood pressure (6 to 8 mm Hg) in both normotensive and hypertensive women. In women with hypertension, OCs have been associated with an increased risk of MI and stroke. Use of CHCs is acceptable in women younger than 35 years with well-controlled and monitored hypertension. Hypertensive women with end-organ disease or who smoke should not use CHCs. Progestin-only pills and depot medroxyprogesterone acetate (DMPA) are choices for women with hypertension.

### *Diabetes*

- The new progestins are believed to have little, if any, effect on carbohydrate metabolism. Nonsmoking women younger than 35 years with diabetes, but no vascular disease, can safely use CHCs, but diabetic women with vascular disease or diabetes of more than 20 years' duration should not use OCs.

### *Dyslipidemia*

- Generally, synthetic progestins decrease high-density lipoprotein (HDL) and increase low-density lipoprotein (LDL). Estrogens decrease LDL but increase HDL and triglycerides. Most low-dose CHCs (with the possible exception of levonorgestrel pills, which may reduce HDL levels in some patients) have no significant impact on HDL, LDL, triglycerides, or total cholesterol.
- However, the mechanism for the increased incidence of cardiovascular disease in CHC users is believed to be thromboembolic and thrombotic changes, not atherosclerosis.
- Women with controlled dyslipidemias can use low-dose CHCs, with periodic monitoring of fasting lipid profiles. Women with uncontrolled dyslipidemia (LDL greater than 160 mg/dL, HDL less than 35 mg/dL, triglycerides greater than 250 mg/dL) and additional risk factors (e.g., coronary artery disease, diabetes, hypertension, smoking, or a positive family history) should use an alternative method of contraception.

### *Thromboembolism*

- Estrogens have a dose-related effect in the development of venous thromboembolism (VTE) and pulmonary embolism. This is especially true in women with underlying hypercoagulable states or who have acquired conditions (e.g., obesity, pregnancy, immobility, trauma, surgery, and certain malignancies.)
- The risk of VTE in women using low-dose OCs (less than 50 mcg EE with norethindrone or levonorgestrel) was four times the risk in nonusers. However, this risk is less than the risk of thromboembolic events during pregnancy. OCs containing desogestrel have been associated with a 1.7 to 19 times higher risk of VTE than OCs containing levonorgestrel.

- CHCs are contraindicated in women with a history of thromboembolic events and in those at risk due to prolonged immobilization with major surgery unless they are taking anticoagulants.
- Emergency contraception (EC) has not been associated with an increased risk of thromboembolic events.

### *Migraine Headache*

- Women with migraines may experience a decreased or increased frequency of migraine headaches when using CHCs.
- CHCs may be considered for healthy, nonsmoking women with migraines if they do not have focal neurologic signs; however, women of any age who have migraine with aura should not use CHCs. Women who develop migraines (with or without aura) while receiving CHCs should immediately discontinue their use.

### *Breast Cancer*

- A U.S. study found no association between overall breast cancer and current or past OC use. Although some studies have found differences in risk of breast cancer based on the presence of BRCA1 and BRCA2 mutations, the most recent cohort study found no association with low-dose OCs and the presence of either mutation.
- The choice to use CHCs should not be affected by the presence of benign breast disease or a family history of breast cancer with either mutation. The WHO precautions state that women with recent personal history of breast cancer should not use CHCs, but that CHCs can be considered in women without evidence of disease for 5 years.

### *Systemic Lupus Erythematosus*

- OCs do not increase the risk of flare among women with stable systemic lupus erythematosus (SLE) and without antiphospholipid/anticardiolipin antibodies.
- CHCs should be avoided in women with SLE and antiphospholipid antibodies or vascular complications. Progestin-only contraceptives can be used in these women.

### ***General Considerations for Oral Contraceptives***

- With perfect use, their efficacy is greater than 99%, but with typical use, up to 8% of women may experience unintended pregnancy.
- Monophasic OCs contain the same amounts of estrogen and progestin for 21 days, followed by 7 days of placebo. Biphasic and triphasic pills contain variable amounts of estrogen and progestin for 21 days and are followed by a 7-day placebo phase.
- Extended-cycle pills and continuous combination regimens may offer some side-effect benefits. Extended-cycle OCs increase the number of hormone-containing pills from 21 to 84 days, followed by a 7-day placebo phase, resulting in four menstrual cycles per year. One product provides hormone-containing pills daily throughout the year. Continuous combination regimens provide OCs for 21 days, then very-low-dose estrogen and progestin for an additional 4 to 7 days.

- Third generation OCs contain newer progestins (e.g., desogestrel, drospirenone, gestodene, and norgestimate). These potent progestins have no estrogenic effects and are less androgenic, and thus are thought to have fewer side effects (e.g., less likelihood or severity of acne). Drospirenone may also cause less weight gain compared to levonorgestrel.
- The progestin-only “Minipills” tend to be less effective than combination OCs, and they are associated with irregular and unpredictable menstrual bleeding. They must be taken every day of the menstrual cycle at approximately the same time of day to maintain contraceptive efficacy. They are associated with more ectopic pregnancies than other hormonal contraceptives.
- In the “quick-start” method for initiating OCs, the woman takes the first pill on the day of her office visit (after a negative urine pregnancy test). In the first-day start method, women take the first pill on the first day of the next menstrual cycle. The Sunday start method was used for many years, whereby the first pill was taken on the first Sunday after starting the menstrual cycle.
- Specific instructions should be provided about what to do if a pill is missed (Table 30-5).

### Choice of an Oral Contraceptive

- In women without coexisting medical conditions, an OC containing 35 mcg or less of EE and less than 0.5 mg of norethindrone is recommended.

**TABLE 30-5** Recommendations for Missed Oral Contraceptive Doses

Number of Pills Missed	Week in Which Pills Were Missed	Recommendation	Use of 7-Day Backup Method
1	1	Take two pills as soon as possible Finish the pill pack Use emergency contraception if necessary	Yes
1	2–3	Take two pills as soon as possible Finish the pill pack	No
1	4	Skip placebo pills Finish the pill pack	No
2–4	1	Take two pills as soon as possible <sup>a</sup> Finish the pill pack Use emergency contraception if necessary	Yes
2–4	2	Take two pills as soon as possible <sup>a</sup> Finish the pill pack Use emergency contraception if necessary	Yes
2–4	3	Start a new pill pack <sup>a</sup>	No
2–4	4	Skip placebo pills Finish the pill pack	No
5	Any	Take two pills as soon as possible Start a new pill pack Use emergency contraception if necessary	Yes

<sup>a</sup>Alternative recommendation is to take one of the missed pills every 12 hours until caught up, then continue the rest of the pill pack. Data from Hatcher RA, Ziemann M, Cwiak C et al. *A Pocket Guide to Managing Contraception*. Tiger, GA: Bridging the Gap Foundation, 2005; Hatcher RA, Trussell J, Stewart F, et al. *Contraceptive Technology*, 18th ed. New York: Ardent Media, 2004; Dickey RP. *Managing Contraceptive Pill Patients*, 12th ed. Dallas, TX: Essential Medical Information Systems, 2004.

- Adolescents, underweight women (<110 lb [50 kg]), women older than 35 years, and those who are perimenopausal may have fewer side effects with OCs containing 20 to 25 mcg of EE. However, these low-estrogen OCs are associated with more breakthrough bleeding and an increased risk of contraceptive failure if doses are missed.
- Women weighing more than 160 lb (72.7 kg) may have higher contraceptive failure rates with low-dose OCs and may benefit from pills containing 35 to 50 mcg of EE.
- Women with migraine headaches, history of thromboembolic disease, heart disease, cerebrovascular disease, SLE with vascular disease, and hypertriglyceridemia are good candidates for progestin-only methods (e.g., minipills, DMPA, and the levonorgestrel intrauterine system). Women older than 35 years who are smokers or are obese, or who have hypertension or vascular disease, should use progesterone-only methods.

### Managing Side Effects

- Many symptoms occurring in the first cycle of OC use (e.g., breakthrough bleeding, nausea, bloating), improve by the second or third cycle of use.
- Table 30-6 shows symptoms of a serious or potentially serious nature associated with CHC.
- Women should be instructed to immediately discontinue CHCs if they experience warning signs often called ACHES (*abdominal pain, chest pain, headaches, eye problems, and severe leg pain*).

### Drug Interactions

- Table 30-7 shows drug–drug interaction of OCs. Women should be told to use an alternative method of contraception if there is a possibility of a drug interaction compromising OC efficacy.
- Rifampin reduces the efficacy of OCs.
- Case reports have shown a reduction in EE levels when CHCs are taken with tetracyclines and penicillin derivatives. The Council on Scientific

**TABLE 30-6** Serious Symptoms That May Be Associated with Combined Hormonal Contraception

Serious Symptoms	Possible Underlying Problem
Blurred vision, diplopia, flashing lights, blindness, papilledema	Stroke, hypertension, temporary vascular problem of many possible sites, retinal artery thrombosis
Numbness, weakness, tingling in extremities, slurred speech	Hemorrhagic or thrombotic stroke
Migraine headaches	Vascular spasm, stroke
Breast mass, pain, or swelling	Breast cancer
Chest pain (radiating to left arm or neck), shortness of breath, coughing up blood	Pulmonary embolism, myocardial infarction
Abdominal pain, hepatic mass or tenderness, jaundice, pruritus	Gallbladder disease, hepatic adenoma, pancreatitis, thrombosis of abdominal artery or vein
Excessive spotting, breakthrough bleeding	Endometrial, cervical, or vaginal cancer
Severe leg pain (calf, thigh), tenderness, swelling, warmth	Deep vein thrombosis

Data from Hatcher RA, Trussel J, Stewart F, et al. *Contraceptive Technology*, 18th ed. New York: Ardent Media, 2004; Dickey RP. *Managing Contraceptive Pill Patients*, 12th ed. Dallas, TX: Essential Medical Information Systems, 2004.

**TABLE 30-7** Interactions of Oral Contraceptives (OCs) with Other Drugs

Interacting Drugs	Outcome and Recommendation
Anticonvulsants (barbiturates, including phenobarbital and primidone; carbamazepine; felbamate; phenytoin; topiramate; vigabatrin)	Decreased contraceptive effect Use OCs containing 50 mcg ethinyl estradiol and a second method of contraception or IUD
Griseofulvin (Fulvicin, Grifulvin V, and others)	Possible decreased contraceptive effect Use second method of contraception
Nonnucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine)	Possible decreased contraceptive effect Use IUD
Protease inhibitors (amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir)	Increased or decreased contraceptive effect Use IUD
Rifampin	Decreased contraceptive effect Use second method of contraception or alternate method (IUD) if concomitant use is long term

IUD, intrauterine device.

Data from Hatcher RA, Trussell J, Stewart F, et al. *Contraceptive Technology*, 18th ed. New York: Ardent Media, 2004; World Health Organization. *Medical Eligibility Criteria for Contraceptive Use*, 3rd ed. 2004, <http://www.who.int/reproductive-health/publications/mec/index.htm>; Use of hormonal contraception in women with coexisting medical conditions. *ACOG Practice Bulletin No 73*.

American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2006;107:1453-1472; Dickinson BD, Altman RD, Neilsen NH, Sterling ML. Drug interactions between oral contraceptives and antibiotics. *Obstet Gynecol* 2001;98:853-860; Archer JS, Archer DF. Oral contraceptive efficacy and antibiotic interaction: A myth debunked. *J Am Acad Dermatol* 2002;46:917-923.

Affairs of the American Medical Association recommends that women be informed about the small risk of interactions with antibiotics, and, if desired, appropriate additional nonhormonal contraceptive agents should be considered. Women who develop breakthrough bleeding during concomitant use of antibiotics and CHCs should be told to use an alternate method of contraception during the period of concomitant use.

- Phenobarbital, carbamazepine, and phenytoin potentially reduce efficacy of OCs, and many anticonvulsants are known teratogens. The use of condoms in conjunction with high-estrogen OCs or intrauterine devices (IUDs) may be considered for women taking these drugs.

### ***Discontinuation of the Oral Contraceptive, Return of Fertility***

- Traditionally, women are advised to allow two to three normal menstrual periods after discontinuing CHCs before becoming pregnant. However, in several large cohort and case-controlled studies, infants conceived in the first month after an OC was discontinued had no greater chance of miscarriage or a birth defect than those born in the general population. The average delay in ovulation after discontinuing OCs is 1 to 2 weeks.

### ***Emergency Contraception***

- Plan B is the only product approved for EC and is the regimen of choice. Plan B contains two tablets, each containing 0.75 mg levonorgestrel. The first tablet is to be taken within 72 hours of unprotected intercourse (the sooner, the more effective); the second dose is taken 12 hours later. It is available without a prescription for women at least 18 years old and for those less than 18 years old by prescription. It is sold only in pharmacies and must be kept behind the counter.
- The FDA has also approved the following regimens for EC (first dose within 72 hours of unprotected intercourse and a followup dose 12 hours later):

- ✓ Ovral (two tablets/dose)
- ✓ Nordette, Levlen, Levora, Lo/Ovral, Triphasil, Tri-Levlen, or Trivora (four tablets/dose)
- ✓ Alesse or Levlite (five tablets/dose)
- In addition, progestin-only pills can be used as EC (Ovrette [20 tablets/dose]). Common side effects of EC are nausea, vomiting, and irregular bleeding.

### *Transdermal Contraceptives*

- A combination contraceptive is available as a transdermal patch (Ortho Evra), which may have improved adherence compared to OCs. Efficacy seems to be compromised in women over 198 lb (90 kg). The patch should be applied to the abdomen, buttocks, upper torso, or upper arm at the beginning of the menstrual cycle and replaced every week for 3 weeks.
- The package insert provides preliminary data indicating a higher incidence of thromboembolic events with the patch. The benefits of increased compliance must be weighed against the risk of increased estrogen exposure and possibly more thromboembolic events.

### *Contraceptive Rings*

- The first vaginal ring (NuvaRing) releases approximately 15 mcg/day of EE and 120 mcg/day of etonogestrel over a 3-week period. On first use, the ring should be inserted on or prior to the fifth day of the cycle, remain in place for 3 weeks, then be removed. One week should lapse before the new ring is inserted on the same day of the week as it was for the last cycle. A second form of contraception should be used for the first 7 days of ring use or if the ring has been expelled for more than 3 hours.

### *Long-Acting Injectable and Implantable Contraceptives*

- Women who particularly benefit from progestin-only methods, including minipills, are those who are breast-feeding, those who are intolerant to estrogens, and those with concomitant medical conditions in which estrogen is not recommended. Also injectable and implantable contraceptives are beneficial for women with compliance issues.
- Pregnancy failure rates with the long-acting progestin contraception are comparable to that of female sterilization.

### *Injectable Progestins*

- DMPA 150 administered by deep intramuscular injection in the gluteal or deltoid muscle within 5 days of the onset of menstrual bleeding inhibits ovulation for more than 3 months, and the dose should be repeated every 12 weeks to ensure continuous contraception. A new formulation contains 104 mg of DMPA (Depo-SubQ Provera 104), which is injected subcutaneously into the thigh or abdomen. The manufacturer recommends excluding pregnancy in women more than 1 week late for repeat injection of the intramuscular formulation or 2 weeks late for repeat injection of the subcutaneous formulation.
- DMPA can be given immediately postpartum in women who are not breast-feeding, but in women who are breast-feeding, it should not be given until 6 weeks postpartum.

- Women using DMPA have a lower incidence of *Candida* vulvovaginitis, ectopic pregnancy, pelvic inflammatory disease, and endometrial and ovarian cancer compared to women using no contraception. The median time to conception from the first omitted dose is 10 months.
- The most frequent adverse effect of DMPA is menstrual irregularities, which decrease after the first year. Breast tenderness, weight gain, and depression occur less frequently.
- DMPA has been associated with a reduction in bone mineral density (BMD), but it has not been associated with the development of osteoporosis or fractures. Recent evidence suggests that BMD loss may slow after 1 to 2 years of DMPA use.

### *Subdermal Progestin Implants*

- Implanon is a single, 4-cm implant, containing 68 mg of etonogestrel that is placed under the skin of the upper arm. It releases 60 mcg daily for the first month, decreasing gradually to 30 mcg/daily at the end of the 3 years of recommended use. With perfect use efficacy approaches 100%, but may be less in women weighing more than 130% of their ideal body weight.
- The major adverse effect is irregular menstrual bleeding. Other side effects are headache, vaginitis, weight gain, acne, and breast and abdominal pain. It does not appear to decrease BMD. It is contraindicated in women who are pregnant, have active liver disease, a history of thromboembolic events, or a history of breast cancer.
- As fertility returns soon after removal, and since Implanon does not affect bone health, it may be preferred over DMPA.

### *Intrauterine Devices*

- IUDs cause low-grade, intrauterine inflammation and increased prostaglandin formation. In addition, endometrial suppression is caused by the progestin-releasing IUD. They are spermicidal and also interfere with implantation of the fertilized ovum. Efficacy rates are greater than 99% with both perfect use and typical use.
- The risk of pelvic inflammatory disease among users ranges from 1% to 2.5%; the risk is highest during the first 20 days after the insertion procedure.
- Ideal patients for an IUD are nulligravid women who are monogamous and are not at risk for STDs or pelvic inflammatory disease.
- ParaGard (copper) can be left in place for 10 years. A disadvantage of ParaGard is increased menstrual blood flow and dysmenorrhea. The average monthly blood loss increased by 35% in clinical trials.
- Mirena releases levonorgestrel over 5 years. It causes a reduction in menstrual blood loss.

## EVALUATION OF THERAPEUTIC OUTCOMES

- All CHC users should have at least annual blood pressure monitoring.
- Glucose levels should be monitored closely when CHCs are started or stopped in patients with a history of glucose intolerance or diabetes mellitus.
- Contraceptive users should have at least annual cytologic screening (more often if they are at risk for STDs), and they should also be regularly

evaluated for problems that may relate to the CHCs (e.g., breakthrough bleeding, amenorrhea, weight gain, and acne).

- Women using DMPA should be evaluated every 3 months for weight gain, menstrual cycle disturbances, and STD risks.
- Patients on DMPA also should be weighed, have their blood pressure monitored, and have a physical exam, and Papanicolaou smear annually, as well as mammogram as indicated based on the patient's age.

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*See Chap. 82, Contraception, authored by Lori M. Dickerson, Sarah P. Shrader, and Vanessa A. Diaz, for a more detailed discussion of this topic.*

- Menopause is the permanent cessation of menses following the loss of ovarian follicular activity. Perimenopause is the period immediately prior to the menopause and the first year after menopause. Indications of postmenopausal hormone therapy include the short-term treatment of menopausal symptoms (i.e., hot flashes, night sweats, and urogenital atrophy).

## PHYSIOLOGY

- The hypothalamic–pituitary–ovarian axis controls reproductive physiology through the reproductive years. Follicle-stimulating hormone (FSH) and luteinizing hormone, produced by the pituitary in response to gonadotropin-releasing hormone from the hypothalamus, regulate ovarian function. Gonadotropins are also influenced by negative feedback from the sex steroids estradiol (produced by the dominant follicle) and progesterone (produced by the corpus luteum). Other sex steroids are androgens, primarily testosterone and androstenedione, secreted by the ovarian stroma and the adrenal gland.
- Pathophysiologic changes associated with menopause are caused by loss of ovarian follicular activity. The postmenopausal ovary is no longer the primary site of estradiol or progesterone synthesis.
- As women age, circulating FSH progressively rises and ovarian inhibin declines. When ovarian function has ceased, serum FSH concentrations are greater than 40 international units/L. Menopause is characterized by a 10- to 15-fold increase in circulating FSH concentrations compared with concentrations of FSH in the follicular phase, a four- to fivefold increase in luteinizing hormone, and a greater than 90% decrease in circulating estradiol concentrations.

## CLINICAL PRESENTATION

- Vasomotor symptoms (e.g., hot flashes and night sweats) are common short-term symptoms of estrogen withdrawal, which usually disappear within 1 to 2 years but sometimes persist for 20 years.
- Other symptoms include vaginal dryness, dyspareunia, urogenital atrophy, sleep disturbances, sexual dysfunction, and impaired concentration and memory.
- Other symptoms, including mood swings, depression, insomnia, migraine, formication, arthralgia, myalgia, and urinary frequency, are attributed to menopause, but the relationship between these symptoms and estrogen deficiency is controversial.
- Long-term morbidity associated with menopause includes accelerated bone loss and osteoporosis (see Chap. 3 “Osteoporosis”).
- Dysfunctional uterine bleeding may occur during perimenopause.

## DIAGNOSIS

- Menopause is determined retrospectively after 12 consecutive months of amenorrhea. FSH on day 2 or 3 of the menstrual cycle greater than 10 to 12 international units/L suggests presence of perimenopause.
- The diagnosis of menopause should include a comprehensive medical history and physical examination, complete blood count, and measurement of serum FSH. When ovarian function has ceased, serum FSH concentrations exceed 40 international units/L. Altered thyroid function and pregnancy must be excluded.

## TREATMENT

- Mild menopausal symptoms can often be alleviated by lifestyle modification, weight control, smoking cessation, exercise, and a healthy diet.
- Mild vaginal dryness can sometimes be relieved by nonestrogenic vaginal creams, but significant vaginal dryness often requires local or systemic estrogen therapy.
- Current data suggest that **phytoestrogens** are no more effective than placebo for hot flashes or other symptoms of menopause.
- Phytoestrogens decrease low-density lipoprotein and triglyceride concentrations, do not change high-density lipoprotein concentrations, and may improve bone density.
- The three main classes of phytoestrogens (and common food sources) are **isoflavones** (soybeans), **lignans** (cereals and oilseeds such as flaxseed), and **coumestans** (alfalfa sprouts). The biologic potency of phytoestrogens varies and is less than that of synthetic estrogen.

## HORMONAL REGIMENS

- In women with an intact uterus, hormone therapy consists of an estrogen plus a progestogen. In women who have undergone hysterectomy, estrogen therapy is given unopposed by a progestogen.
- The **continuous combined oral estrogen–progestogen** arm of the Women's Health Initiative (WHI) study was terminated prematurely after a mean of 5.2-year follow-up because of the occurrence of a prespecified level of invasive breast cancer. The study also found increased coronary disease events, stroke, and pulmonary embolism. Beneficial effects included decreases in hip fracture and colorectal cancer.
- The oral estrogen-alone arm was stopped early after a mean of 7 years of follow-up. Estrogen-only therapy had no effect on coronary heart disease risk and caused no increase in breast cancer risk.
- A subsequent large epidemiologic study found a greater risk for breast cancer with combined estrogen–progestogen use, as well as increased risk for estrogen-only therapy and tibolone, but selection bias was found in the study population.

## ESTROGENS

- Preparations suitable for replacement therapy are shown in Table 31-1. The oral and transdermal routes are used most frequently. There is no evidence that one estrogen compound is more effective than another in relieving menopausal symptoms or preventing osteoporosis.
- **Conjugated equine estrogens** are composed of **estrone sulfate** (50% to 60%) and other estrogens such as **equilin** and **17  $\alpha$ -dihydroequilin**.
- **Estradiol** is the predominant and most active form of endogenous estrogens. Given orally, it is metabolized by intestinal mucosa and liver (10% reaches the circulation as free estradiol), and resultant estrone concentrations are three to six times those of estradiol.
- **Ethinyl estradiol** is a semisynthetic estrogen that has similar activity following administration by the oral and parenteral routes.
- **Parenteral estrogens**, including transdermal, intranasal, and vaginal, avoid first-pass metabolism and result in a more physiologic estradiol-to-estrone ratio (i.e., estradiol concentrations greater than estrone concentrations). These routes also are less likely to affect sex hormone-binding globulin, circulating lipids, coagulation parameters, or C-reactive protein levels.
- Variability in absorption is common with the **percutaneous preparations** (gels, creams, and emulsions).

**TABLE 31-1** Selected Systemic Estrogen Products<sup>a,b</sup>

Estrogen	Dosage Strength	Comments
<b>Oral estrogens</b>		
Conjugated equine estrogens	0.3, 0.45, 0.625, 0.9, 1.25 mg	Orally administered estrogens stimulate synthesis of hepatic proteins and increase circulating concentrations of sex hormone-binding globulin, which, in turn, may compromise the bioavailability of androgens and estrogens
Synthetic conjugated estrogens	0.3, 0.45, 0.625, 0.9, 1.25 mg	
Esterified estrogens	0.3, 0.625, 1.25, 2.5 mg	
Estropate (piperazine estrone sulfate)	0.625, 1.25, 2.5, 5 mg	
Micronized estradiol	0.5, 1, 1.5, 2 mg	
Estradiol acetate	0.45, 0.9, 1.8 mg	
<b>Parenteral estrogens</b>		
Transdermal 17 $\beta$ -estradiol (patch)	14, 25, 37.5, 50, 60, 75, 100 mcg per 24 hours	Women with elevated triglyceride concentrations or significant liver function abnormalities may benefit from parenteral therapy
Estradiol vaginal ring	0.05, 0.1 mg per 24 hours (replaced every 3 months)	
Estradiol topical emulsion	4.35 mg of estradiol hemihydrate per foil-laminated pouch	Single approved dose is 8.7 mg of estradiol hemihydrate per day (two pouches)
Estradiol topical gel	0.25 to 1 mg of estradiol per dose	Apply to skin once daily
Estradiol topical solution	1.53 mg of estradiol per spray	Spray on inner surface of forearm once daily
Intranasal estradiol <sup>c</sup>	One spray per nostril delivers 150 mcg	—

<sup>a</sup>Systemic oral and transdermal estrogen and progestogen combination products are available in the United States.<sup>b</sup>Systemic oral estrogen and androgen combination products are available in the United States.<sup>c</sup>Not available in the United States.

- **Estradiol pellets** (implants) contain pure **crystalline 17  $\beta$ -estradiol** and are placed subcutaneously into the anterior abdominal wall or buttock. They are difficult to remove.
- **Intranasal 17  $\beta$ -estradiol** spray is given once or twice daily, and is clinically equivalent to oral or transdermal estradiol, but causes less mastalgia.
- **Vaginal creams, tablets, and rings** are used for treatment of urogenital atrophy. Systemic estrogen absorption is lower with the vaginal tablets and rings, compared to the vaginal creams.
- New evidence indicates that lower doses of estrogens are effective in controlling postmenopausal symptoms and reducing bone loss (see Table 31-2). Even ultralow doses of 17  $\beta$ -estradiol delivered by vaginal ring improved serum lipid profiles and prevented bone loss in elderly women.
- Adverse effects of **estrogen** include nausea, headache, breast tenderness, and heavy bleeding. More serious adverse effects include increased risk for coronary heart disease, stroke, venous thromboembolism, breast cancer, and gallbladder disease. Transdermal estrogen is less likely than oral estrogen to cause nausea, headache, breast tenderness, gallbladder disease, and deep vein thrombosis.

## PROGESTOGENS

- In women who have not undergone hysterectomy, a **progestogen** should be added because estrogen monotherapy is associated with endometrial hyperplasia and cancer.
- The most commonly used oral progestogens are **medroxyprogesterone acetate, micronized progesterone, and norethisterone acetate**.

**TABLE 31-2** Estrogen for Treatment of Menopausal Symptoms and Osteoporosis Prevention

Regimen	Standard Dose	Low Dose	Route	Frequency
Conjugated equine estrogens	0.625 mg	0.3 or 0.45 mg	Oral	Once daily
Synthetic conjugated estrogens	0.625 mg	0.3 mg	Oral	Once daily
Esterified estrogens	0.625 mg	0.3 mg	Oral	Once daily
Estropipate (piperazine estrone sulfate)	1.5 mg	0.625 mg	Oral	Once daily
Ethinyl estradiol	5 mcg	2.5 mcg	Oral	Once daily
Micronized 17 $\beta$ -estradiol	1–2 mg	0.25–0.5 mg	Oral	Once daily
Transdermal 17 $\beta$ -estradiol	50 mcg	25 mcg	Transdermal (patch)	Once or twice weekly
Intranasal 17 $\beta$ -estradiol <sup>a</sup>	150 mcg per nostril	–	Intranasally	Once daily
Implanted 17 $\beta$ -estradiol	50–100-mg pellets	25-mg pellets	Pellets implanted subcutaneously	Every 6 months
Percutaneous 17 $\beta$ -estradiol	0.04 mg (gel) 0.05 mg (emulsion)		Transdermal (emulsion, gel)	Once daily

<sup>a</sup>Not available in the United States.

**TABLE 31-3** Progestogen Doses for Endometrial Protection (Oral Cyclic Administration)

Progestogen	Dose
Dydrogesterone <sup>d</sup>	10–20 mg for 12–14 days per calendar month
Medroxyprogesterone acetate	5–10 mg for 12–14 days per calendar month
Micronized progesterone	200 mg for 12–14 days per calendar month
Norethisterone <sup>d</sup>	0.7–1 mg for 12–14 days per calendar month
Norethindrone acetate	5 mg for 12–14 days per calendar month
Norgestrel <sup>d</sup>	0.15 mg for 12–14 days per calendar month
Levonorgestrel <sup>d</sup>	150 mcg for 12–14 days per calendar month

<sup>d</sup>Not available in a progestogen-only oral dosage form in the United States.

- Several progestogen regimens to prevent endometrial hyperplasia are shown in Table 31-3.
- Four **combination estrogen and progestogen** regimens are currently in use (Table 31-4).
- Continuous-cyclic (sequential)—results in scheduled vaginal withdrawal bleeding in approximately 90% of women, but it may be scant or absent in older women.
- Continuous-combined—prevents monthly bleeding. It may initially cause unpredictable spotting or bleeding; thus, it is best reserved for women who are at least 2 years postmenopause.
- Continuous long-cycle (cyclic withdrawal)—reduces monthly bleeding. Estrogen is given daily, and progestogen is given six times yearly (every other month) for 12 to 14 days, resulting in six periods/year.
- Intermittent-combined (continuous-pulsed)—prevents monthly bleeding. It consists of 3 days of estrogen therapy alone, followed by 3 days of combined

**TABLE 31-4** Common Combination Postmenopausal Hormone Therapy Regimens

Regimen	Doses
<b>Oral continuous-cyclic regimens</b>	
CEE + MPA <sup>d</sup>	0.625 mg + 5 mg; 0.625 mg + 10 mg
<b>Oral continuous-combined regimens</b>	
CEE + MPA	0.625 mg + 2.5 mg; 0.625 mg + 5 mg; 0.45 mg + 2.5 mg; 0.3 mg + 1.5 mg/day
17 $\beta$ -Estradiol + NETA	1 mg + 0.1 mg; 1 mg + 0.25 mg; 1 mg + 0.5 mg/day
Ethinyl estradiol + NETA	1 mcg + 0.2 mg; 2.5 mcg + 0.5 mg; 5 mcg + 1 mg; 10 mcg + 1 mg/day
<b>Transdermal continuous-cyclic regimens</b>	
17 $\beta$ -Estradiol + NETA <sup>d</sup>	50 mcg + 0.14 mg; 50 mcg + 0.25 mg
<b>Transdermal continuous-combined regimens</b>	
17 $\beta$ -Estradiol + NETA	50 mcg + 0.14 mg; 50 mcg + 0.25 mg; 25 mcg + 0.125 mg

CEE, conjugated equine estrogens; MPA, medroxyprogesterone acetate; NETA, norethindrone acetate.

Other oral (drospirenone and norgestimate) and transdermal (levonorgestrel) progestogens also are available in combination with an estrogen.

<sup>d</sup>Estrogen alone for days 1–14, followed by estrogen–progestogen on days 15–28.

estrogen and progestogen, which is then repeated without interruption. It causes fewer side effects than regimens with higher progestogen doses.

- Adverse effects of progestogens are irritability, depression, headache, mood swings, fluid retention, and sleep disturbance.
- Low-dose hormone therapy (**conjugated equine estrogen 0.45 mg and medroxyprogesterone acetate 1.5 mg/day**) has demonstrated equivalent symptom relief and bone density preservation without an increase in endometrial hyperplasia. Whether such lower doses will be safer (cause less venous thromboembolism and breast cancer) remains to be seen.

## ANDROGENS

- The therapeutic use of **testosterone** in women, although controversial, is becoming more widespread. Data supporting an androgen deficiency syndrome are lacking, and the American Endocrine Society recommend against making a diagnosis of androgen deficiency in women at this time. Evidence of short-term efficacy of testosterone has been seen in surgically menopausal women. At present, use of testosterone is not recommended because clear indications and evidence evaluating safety are inadequate.
- Androgen regimens are shown in Table 31-5.
- Testosterone treatment should not be given to postmenopausal women who are not receiving concurrent **estrogen** until completion of studies on the use of testosterone without estrogen.
- Absolute contraindications to androgen therapy include pregnancy or lactation and known or suspected androgen-dependent neoplasia. Relative contraindications are concurrent use of conjugated equine estrogens (for parenteral testosterone therapy), low sex hormone binding globulin level, moderate to severe acne, clinical hirsutism, and androgenic alopecia.
- Adverse effects from excessive dosage include virilization, fluid retention, and potentially adverse lipoprotein lipid effects, which are more likely with oral administration.

## SELECTIVE ESTROGEN-RECEPTOR MODULATORS

- Selective estrogen-receptor modulators prevent bone loss and vertebral fractures. They bind to estrogen receptors and function as tissue-specific estrogen antagonists (in breast) or agonists (in bone).

**TABLE 31-5** Androgen Regimens Used for Women

Regimen	Dose	Frequency	Route
Methyltestosterone in combination with esterified estrogen	1.25–2.5 mg	Daily	Oral
Mixed testosterone esters	50–100 mg	Every 4–6 weeks	Intramuscular
Testosterone pellets	50 mg	Every 6 months	Subcutaneous (implanted)
Transdermal testosterone system <sup>a</sup>	150–300 mcg/day	Every 3–4 days	Transdermal patch
Nandrolone decanoate	50 mg	Every 8–12 weeks	Intramuscular

<sup>a</sup>Undergoing clinical trials in the United States.

- **Tamoxifen** is discussed in Chap. 61, “Breast Cancer”; **raloxifene** is discussed in Chap. 3, “Osteoporosis.” Raloxifene decreases bone loss in recently menopausal women without affecting the endometrium and has estrogen-like actions on lipid metabolism. It may exacerbate vasomotor symptoms, and it increases the risk of venous thromboembolism and stroke.

## TIBOLONE

- **Tibolone** has combined estrogenic, progestogenic, and androgenic activity. Its effects depend on metabolism and activation in peripheral tissues. Tibolone has beneficial effects on mood and libido and improves menopausal symptoms and vaginal atrophy. It protects against bone loss and reduces the risk of vertebral fractures. It reduces total cholesterol, triglyceride, lipoprotein (a), and, unfortunately, high-density lipoprotein concentrations. It may increase cardiovascular risk, breast cancer risk, and endometrial cancer risk.
- Major adverse effects include weight gain and bloating. It may increase the risk of stroke in elderly women.

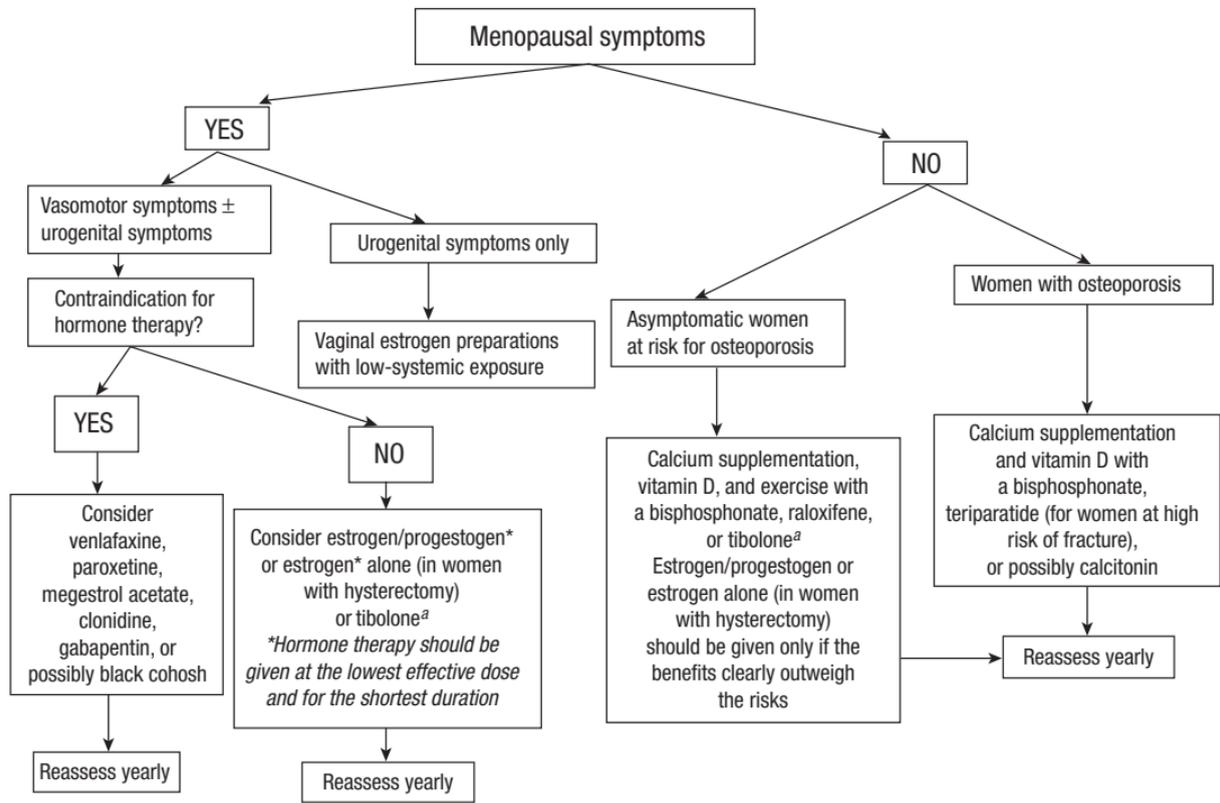
## TREATMENT CONSIDERATIONS

- An algorithm for the management of postmenopausal women is shown in Fig. 31-1. Hormone therapy is contraindicated in women with endometrial or breast cancer, undiagnosed vaginal bleeding, coronary heart disease, thromboembolism (including recent spontaneous thrombosis or presence of thrombophilia), stroke, transient ischemic attack, and active liver disease. Relative contraindications include uterine leiomyoma, migraine headaches, and seizure disorder. Oral estrogen should also be avoided in women with hypertriglyceridemia, liver disease, and gallbladder disease. For these women, transdermal administration is safer.

## BENEFITS OF HORMONE REPLACEMENT THERAPY

### RELIEF OF MENOPAUSAL SYMPTOMS

- Most women with vasomotor symptoms need hormone treatment for less than 5 years. Without treatment, hot flashes usually disappear within 1 to 2 years. Hormone therapy can usually be tapered and stopped after about 2 or 3 years.
- **Estrogen** is more effective than any other therapy in relieving vasomotor symptoms, and all types and routes of systemic administration are equally effective in a dose-dependent fashion. If treatment can be tapered and stopped within 5 years, no evidence of increased risk of breast cancer is seen.
- Alternatives to estrogen for hot flashes are shown in Table 31-6. Progesterone alone may be an option in women with a history of breast cancer or venous thrombosis, but side effects limit their use. For women with contraindications to hormone therapy, selective serotonin reuptake inhibitors and venlafaxine are considered by some to be first-line therapy, but efficacy of venlafaxine beyond 12 weeks has not been shown.



**FIGURE 31-1.** Algorithm for management of postmenopausal women. <sup>a</sup>Tibolone is currently not approved for use in the United States.

**TABLE 31-6** Alternatives to Estrogen for Treatment of Hot Flashes

Drug	Dose (Oral)	Interval	Comments
Tibolone	2.5–5 mg	Once daily	Tibolone is not recommended during the perimenopause because it may cause irregular bleeding
Venlafaxine	37.5–150 mg	Once daily	Side effects include dry mouth, decreased appetite, nausea, and constipation
Paroxetine	12.5–25 mg	Once daily	12.5 mg is an adequate, well-tolerated starting dose for most women; adverse effects include headache, nausea, and insomnia
Fluoxetine	20 mg	Once daily	Modest improvement seen in hot flashes
Megestrol acetate	20–40 mg	Once daily	Progesterone may be linked to breast cancer etiology; also, there is concern regarding the safety of progestational agents in women with preexisting breast cancer
Clonidine	0.1 mg	Once daily	Can be administered orally or transdermally; drowsiness and dry mouth can occur, especially with higher doses
Gabapentin	900 mg	Divided in three daily doses	Adverse effects include somnolence and dizziness; these symptoms often can be obviated with a gradual increase in dosing

- Significant vaginal dryness because of vaginal atrophy requires use of local or systemic estrogen therapy. It can be treated with topical estrogen cream, tablets, or vaginal ring. Topical estrogen may be better than systemic estrogen for these symptoms and avoids high levels of circulating estrogen.
- Concomitant progestogen therapy generally is unnecessary with **low-dose micronized 17  $\beta$ -estradiol**, but regular use of **conjugated equine estrogen creams** and other products that may promote endometrial proliferation in women with an intact uterus requires intermittent progestogen challenges (i.e., for 10 days every 12 weeks).
- The benefits of hormonal therapies for osteoporosis prevention are discussed in Chap. 3. Hormone therapy should be considered for osteoporosis prevention only in women at significant risk for osteoporosis who cannot take nonestrogen regimens.
- The WHI study was the first randomized, controlled trial to confirm that hormone therapy reduces colon cancer risk.

## RISKS OF HORMONE THERAPY

- The American Heart Association recommends against postmenopausal hormone therapy for reducing the risk of coronary heart disease.
- The WHI trial showed an overall increase in the risk of coronary heart disease in healthy postmenopausal women aged 50 to 79 years taking **estrogen–progestogen therapy** compared with those taking placebo. The increased risk of coronary heart disease was most apparent at 1 year. The estrogen-alone arm of the WHI showed no effect (either increase or decrease) in the risk of coronary heart disease. Recent analysis showed that women who started hormone therapy closer to the time of menopause tended to have decreased coronary heart disease risk compared to the

increased risk seen among women who started therapy more distant from menopause.

- In the estrogen plus progestogen arm, the increased risk for ischemic stroke and venous thromboembolism continued throughout the 5 years of therapy. In the estrogen-alone arm, there was a similar increase in risk for stroke.
- Raloxifene does not significantly affect the risk for coronary heart disease.
- In the WHI study, **estrogen plus progestogen therapy** had an increased risk for invasive breast cancer, which did not appear until after 3 years of study participation. The estrogen-only arm of the WHI showed no increase in risk for breast cancer during the 7-year follow-up.
- The Million Women Study reported that current use of hormone therapy increased breast cancer risk and breast cancer mortality. Increased incidence was observed for **estrogen only, estrogen plus progestogen, and for tibolone**.
- In a reanalysis of 51 studies, less than 5 years of therapy with **combined estrogen and progestogen** was associated with a 15% increase in risk for breast cancer, and the risk increased with greater duration of treatment. Five years after discontinuation of hormone replacement therapy, the risk of breast cancer was no longer increased.
- Addition of progestogen to estrogen may increase breast cancer risk beyond that observed with estrogen alone.
- **Raloxifene** treatment of osteoporosis was associated with a 76% risk reduction for estrogen-receptor positive breast cancer. An additional study showed that this reduced risk continues for up to 8 years. Among women at high risk for breast cancer, raloxifene was as effective as tamoxifen in reducing the risk of invasive breast cancer and had a lower risk of thromboembolic events.
- **Estrogen alone** given to women with an intact uterus increases uterine cancer risk, and this increased risk begins within 2 years of treatment and persists for many years after estrogen is discontinued. The sequential addition of **progestin** to estrogen for at least 10 days of the cycle or continuous combined estrogen-progestogen does not increase the risk of endometrial cancer. A 4-year trial of **raloxifene** in women with osteoporosis showed no increased risk of endometrial cancer.
- **Combined hormone therapy** may increase the risk of ovarian cancer, but more study is needed to confirm these findings.
- Women taking hormone therapy have a twofold increase in risk for thromboembolic events, with the highest risk occurring in the first year of use. The increased risk is dose dependent.
- Women taking **estrogen or estrogen-progestogen combined therapy** are at increased risk for cholecystitis, cholelithiasis, and cholecystectomy. Transdermal estrogen is an alternative to oral therapy for women at high risk for cholelithiasis.

## OTHER EFFECTS OF HORMONE THERAPY

- Women with vasomotor symptoms taking hormone therapy have better mental health and less depressive symptoms compared to those taking

placebo, but hormone therapy may worsen quality of life in women without vasomotor symptoms.

- The WHI study found that postmenopausal women 65 years or older taking **estrogen plus progestogen** therapy had twice the rate of dementia, including Alzheimer's disease. Combined therapy also did not prevent mild cognitive impairment.

## EVALUATION OF THERAPEUTIC OUTCOMES

- After initiating hormone therapy, follow-up at 6 months is advisable to assess for efficacy, side effects, and patterns of withdrawal bleeding.
- With estrogen-based therapy, there should be yearly breast exams, monthly breast self-examinations, and periodic mammograms. Women on hormonal therapy should undergo annual monitoring, including pelvic examination, blood pressure checks, and routine endometrial cancer surveillance.
- Bone mineral density should be measured in women older than 65 years and in women younger than 65 years with risk factors for osteoporosis. Repeat testing should be done as clinically indicated.

## PREMATURE OVARIAN FAILURE AND PREMENOPAUSAL HORMONE REPLACEMENT

### DEFINITION

- **Premature ovarian failure** is a condition characterized by sex-steroid deficiency, amenorrhea, and infertility in women younger than 40 years of age. It affects 1% of women. Premature ovarian failure is associated with a significantly higher risk for osteoporosis and cardiovascular disease and increased mortality.
- In cases of secondary amenorrhea, symptoms may include hot flashes, night sweats, fatigue, and mood changes. In primary amenorrhea, incomplete development of secondary sex characteristics may occur.
- It is defined by presence of at least 4 months of amenorrhea and at least 2 serum FSH concentrations greater than 40 international units/L in women younger than 40 years.
- The goal of therapy is to provide a hormone replacement regimen that maintains sex steroid status as effectively as the normal, functioning ovary.
- Young women with primary amenorrhea (i.e., absence of menses in a girl who is 16 years or older) in whom secondary sex characteristics have failed to develop should receive initially **very low doses of estrogen (e.g., 0.3 mg of conjugated equine estrogen)** (with no **progestogen**) daily for 6 months, with dose increases at 6-month intervals until the required dose is achieved. Toward the end of the second year of treatment, **cyclic progestogen therapy** can be given 12 to 14 days/month.
- Women with secondary amenorrhea (i.e., cessation of menses in a woman who was previously menstruating for 6 months or more) who have been estrogen deficient for 12 months or longer should also receive **low-dose estrogen** initially, but the dose can be increased up to maintenance levels

over a 6-month period, and progestin therapy can be instituted with the initiation of estrogen therapy.

- An **estrogen** dose equivalent to at least 1.25 mg conjugated equine estrogen (or 100 mcg transdermal estradiol) is needed to achieve adequate replacement in young women, and a **progestogen** should be given for 12 to 14 days per calendar month to prevent endometrial hyperplasia.
- Testosterone replacement in addition to estrogen may be important.
- If these patients miss an expected menses, they should be tested for pregnancy and discontinue hormone therapy. Hormone therapy must be continued at least until the average age of natural menopause, and long-term follow-up is necessary.

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*See Chap. 85, Hormone Therapy in Women, authored by Sophia N. Kalantari-dou, Susan R. Davis, and Karim Anton Calis, for a more detailed discussion of this topic.*

## DEFINITION

- Therapeutic considerations associated with pregnancy and lactation encompass many complex issues that affect both the mother and her child, from planning for pregnancy through lactation. Resources on the use of drugs in pregnancy and lactation include the FDA categorization system, the primary literature, textbooks, and computerized databases (e.g., the Canadian database, <http://www.motherisk.org>).

## PHYSIOLOGIC AND PHARMACOKINETIC FACTORS

- The duration of pregnancy is approximately 280 days; this time period extends from the first day of the last menstrual period to birth. Pregnancy is divided into three periods of three calendar months; each 3-month period is called a trimester.
- Drug absorption during pregnancy may be altered by delayed gastric emptying and vomiting. An increased gastric pH may affect absorption of weak acids and bases. Higher estrogen and progesterone levels may alter liver enzyme activity and increase elimination of some drugs, but cause accumulation of others.
- Maternal plasma volume, cardiac output, and glomerular filtration increase by 30% to 50% during pregnancy, possibly lowering the plasma concentration of renally cleared drugs. Body fat increases; thus volume of distribution of fat-soluble drugs may increase. Plasma albumin concentrations decrease; thus volume of distribution of highly protein bound drugs may increase. However, there may be little change in serum concentration, as these unbound drugs are more rapidly cleared by the liver and kidney.
- The placenta is the organ of exchange between the mother and fetus for a number of substances, including drugs. Drug molecular weights affect drug transfer across the placenta:
  - ✓ Molecular weights less than 500 daltons cross readily.
  - ✓ Molecular weights 600 to 1,000 daltons cross more slowly.
  - ✓ Molecular weights greater than 1,000 daltons (e.g., insulin and heparin) do not cross in significant amounts.
- Lipophilic drugs (e.g., opiates and antibiotics) cross more easily than do water-soluble drugs. Certain protein-bound drugs may achieve higher plasma concentrations in the fetus than in the mother.

## DRUG SELECTION DURING PREGNANCY

- The incidence of congenital malformation is approximately 3% to 5%, and it is estimated that 1% of all birth defects are caused by medication exposure.
- Adverse fetal drug effects depend on dosage, route of administration, concomitant exposure to other agents, and stage of pregnancy when the exposure occurred.

- Exposure to the fetus in the first 2 weeks after conception may have an “all or nothing” effect (i.e., could destroy the embryo or have no ill effect). Exposure during the period of organogenesis (18 to 60 days postconception) may result in structural anomalies (e.g., **methotrexate**, **cyclophosphamide**, **diethylstilbestrol**, **lithium**, **retinoids**, **thalidomide**, certain **antiepileptic drugs**, and **coumarin derivative**).
- Exposure after this point may result in growth retardation, CNS or other abnormalities, or death (e.g., **nonsteroidal antiinflammatory drugs [NSAIDs]**, **angiotensin-converting enzyme inhibitors [ACEIs]**, and **tetracycline derivatives**).
- Principles for selecting medications for use during pregnancy include:
  - ✓ Select drugs that have been used safely for long periods of time.
  - ✓ Prescribe doses at the lower end of the dosing range.
  - ✓ Eliminate nonessential medication and discourage self-medication.
  - ✓ Avoid medications known to be harmful.
  - ✓ Adjust doses to optimize health of mother while minimizing risk to fetus.

## PRECONCEPTION PLANNING

- Preconception interventions have been shown to improve pregnancy outcomes.
- Ingestion of **folic acid** by all women of childbearing potential should be encouraged, as it reduces the risk for neural tube defects in offspring. Women at low risk should take 400 mcg/day throughout the reproductive years. Women at high risk (e.g., those who take certain seizure medications or who have had a previously affected pregnancy) should take 4 mg/day.
- Assessment and reduction in the use of alcohol, tobacco, and other substances prior to pregnancy improve outcomes. For smoking cessation, behavioral interventions are preferred. Intermittent delivery formulations of **nicotine replacement therapies** are preferred over the patches. If patches are used, 16-hour patches are preferred over 24-hour patches.

## PREGNANCY-INFLUENCED ISSUES

### GASTROINTESTINAL TRACT

#### Constipation

- Constipation commonly occurs during pregnancy. Nondrug modalities such as education, physical exercise, biofeedback, and increased intake of dietary fiber and fluid should be instituted first.
- If additional therapy is warranted, the use of **supplemental fiber** with or without a stool softener is appropriate. Lactulose, sorbitol, bisacodyl, or **senna** can be used occasionally.
- **Castor oil** and **mineral oil** should be avoided.

#### Gastroesophageal Reflux Disease

- Therapy includes lifestyle and dietary modifications such as small, frequent meals; alcohol, tobacco, and caffeine avoidance; food avoidance 3 hours before bedtime; and elevation of the head of the bed.

- Drug therapy, if necessary, may be initiated with **aluminum, calcium, or magnesium antacids; sucralfate;** or **cimetidine** or **ranitidine**. **Lansoprazole, omeprazole, and metoclopramide** are also options if the patient does not respond to histamine-2 receptor blockers.
- **Sodium bicarbonate** and **magnesium trisilicate** should be avoided.

### Hemorrhoids

- Hemorrhoids during pregnancy are common.
- Therapy includes high intake of dietary fiber, adequate oral fluid intake, use of sitz baths; topical anesthetics, skin protectants and astringents may also be used. Treatment for refractory hemorrhoids includes rubber band ligation, sclerotherapy, and surgery.

### Nausea and Vomiting

- Up to 80% of all pregnant women experience some degree of nausea and vomiting. Hyperemesis gravidarum (i.e., severe nausea and vomiting requiring hospitalization for hydration and nutrition) occurs in only about 1% to 3% of pregnant women.
- Nonpharmacologic treatments include eating small, frequent meals; avoiding fatty foods; acupressure; and acustimulation. Pharmacotherapy may include the following: antihistamines (e.g., **doxylamine**), vitamins (e.g., **pyridoxine, cyanocobalamin**), anticholinergics (e.g., **dicyclomine, scopolamine**), dopamine antagonists (e.g., **metoclopramide**). **Ondansetron** can be used when other agents have failed, and **ginger** is considered safe and effective. **Dexamethasone** or **prednisolone** have been effective for hyperemesis gravidarum, but the risk of oral clefts is increased.

## GESTATIONAL DIABETES MELLITUS

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- Screening for gestational diabetes mellitus utilizes the oral glucose challenge test. Groups at high risk are African Americans, Native Americans, Asian Americans, Latino Americans, and Pacific Islanders.
- First-line therapy includes nutritional and exercise interventions for all women, and caloric restrictions for obese women. If nutritional intervention fails to achieve fasting plasma glucose levels less than or equal to 105 mg/dL, 1-hour post-prandial plasma glucose concentrations less than or equal to 155 mg/dL, or 2-hour postprandial levels less than or equal to 130 mg/dL, then therapy with **recombinant human insulin** should be instituted; **glyburide** may be considered after 11 weeks of gestation.
- Goals for self-monitored blood glucose levels while on insulin therapy are a preprandial plasma glucose level between 80 and 110 mg/dL, and a 2-hour postprandial plasma glucose level less than 155 mg/dL.

## HYPERTENSION

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- Hypertension during pregnancy includes gestational hypertension (pregnancy-induced hypertension without proteinuria), preeclampsia (hypertension with proteinuria), and chronic hypertension (diagnosed prior to pregnancy with or without overlying preeclampsia). Eclampsia, a medical emergency, is preeclampsia with seizures.

- For women at high risk for preeclampsia, low-dose **aspirin** after 12 weeks' gestation reduces the risk for preeclampsia by 19%. Aspirin may reduce the risk of preterm birth by 7% and fetal or neonatal death by 16%. **Calcium**, 1 g/day, is recommended for all pregnant women, as it may help prevent hypertension in pregnant women and reduce the risk of preeclampsia by 31% to 67%.
- Antihypertensive drug therapy for mild to moderate hypertension in pregnancy has not been shown to improve pregnancy outcomes, except in the case of hypertensive crisis. Commonly used drugs for hypertension in pregnancy include **methyldopa**, **labetalol**, and calcium channel blockers. ACEIs should probably be avoided throughout pregnancy. For very high blood pressure in pregnancy, drugs to avoid are magnesium sulfate (except for eclampsia prevention), high-dose diazoxide, nimodipine, and chlorpromazine.
- The cure for preeclampsia is delivery of the fetus if the pregnancy is at term. Drug therapy for hypertension in preeclampsia includes **methyldopa**, **labetalol**, and **calcium channel blockers**. **Magnesium sulfate** is used to prevent eclampsia and to treat eclamptic seizures.

## VENOUS THROMBOEMBOLISM

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- Risk factors for venous thromboembolism in pregnancy include increasing age, history of thromboembolism, hypercoagulable conditions, operative vaginal delivery or cesarean section, obesity, and a family history of thrombosis.
- For treatment of acute thromboembolism, adjusted-dose **low-molecular-weight heparin** or **unfractionated heparin** should be used for the duration of pregnancy and for 6 weeks after delivery. **Warfarin** should be avoided after the first 6 weeks of gestation because it may cause fetal bleeding, malformations of the nose, stippled epiphyses, or CNS anomalies.

## ACUTE CARE ISSUES IN PREGNANCY

### HEADACHE

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- For tension headaches during pregnancy, nonpharmacologic approaches are first-line therapies, including exercise, biofeedback, and massage. If drug therapy is needed, **acetaminophen** is the first choice.
- For migraine headache during pregnancy, rest, reassurance, and ice packs should be used initially. If drug therapy is needed, **acetaminophen** is first-line therapy.
- NSAIDs are contraindicated after 37 weeks' gestation. For refractory migraines, narcotics may be used. **Salicylates** and **indomethacin** should be avoided throughout pregnancy if possible. The use of **sumatriptan** is controversial. Nausea of migraines may be treated with **metoclopramide**.

### URINARY TRACT INFECTION

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- The principal infecting organism is *Escherichia coli*, but *Proteus mirabilis* and *Klebsiella pneumoniae* account for some infections. Untreated bacteriuria may result in pyelonephritis, preterm labor, preeclampsia, transient renal failure, and low birth weight.

- Group B *Streptococcus* bacteriuria should be treated to reduce the rate of preterm delivery. These women should also receive antibiotics at delivery to prevent infection in the newborn.
- Treatment of asymptomatic bacteriuria is necessary to reduce the risk of pyelonephritis and premature delivery. A course of 7 to 10 days of treatment is common. A repeat culture 10 days after completion of treatment is recommended.
- **Cephalexin** is considered safe and effective. **Nitrofurantoin** should not be used after week 37 due to concern for hemolytic anemia in the newborn. **Sulfa-containing drugs** may increase risk for kernicterus in the newborn and should be avoided during the last weeks of gestation. **Folate antagonists**, such as **trimethoprim**, are relatively contraindicated during the first trimester because of their association with cardiovascular malformations. **Fluoroquinolones** and **tetracyclines** are contraindicated.

## SEXUALLY TRANSMITTED DISEASES

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### Chlamydia

- Chlamydia infection can be transmitted at birth to the neonate and cause conjunctivitis and a subacute, afebrile pneumonia with onset at 1 to 3 months.
- The current recommendation for the treatment of *Chlamydia* cervicitis is **azithromycin**, 1 g orally as a single dose, or **amoxicillin**, 500 mg three times daily for 7 days.
- Other options include **erythromycin base** or **ethylsuccinate**.

### Syphilis

- **Penicillin** is the drug of choice, and it is effective for preventing transmission to the fetus and treating the already infected fetus. No alternatives to penicillin are available for the pregnant woman who is allergic to penicillin.

### *Neisseria gonorrhoeae*

- *Neisseria gonorrhoeae* is a risk factor for preterm delivery. Symptoms in the neonate usually start within 2 to 5 days of birth.
- The treatment of choice is **ceftriaxone**, 125 mg intramuscularly (IM) as a single dose or cefixime, 400 mg orally in a single dose. **Spectinomycin** 2 g IM as a single dose is appropriate as a second choice.

### Genital Herpes

- The overriding concern with genital herpes is transmission of the virus to the neonate during birth.
- **Acyclovir** has been used safely, and most women will receive oral acyclovir therapy for first episodes or for recurrence. IV acyclovir can be used for severe infections. For **valacyclovir** and **famciclovir**, safety data are more limited.

### Bacterial Vaginosis

- Bacterial vaginosis is a risk factor for premature rupture of membranes, preterm labor, preterm birth, spontaneous abortion, and postpartum endometritis.

- The recommended regimen for treatment is **metronidazole**, 500 mg twice daily for 7 days; metronidazole, 250 mg three times daily for 7 days; or **clindamycin**, 300 mg twice daily for 7 days.

## CHRONIC ILLNESSES IN PREGNANCY

### ALLERGIC RHINITIS, ASTHMA

- All pregnant patients with asthma should have access to a short-acting  $\beta_2$ -agonist (**albuterol** is the preferred agent).
- Low-dose **inhaled corticosteroids** are the treatment of choice for women with mild persistent asthma. **Budesonide** is preferred, but other inhaled corticosteroids that were used effectively prior to pregnancy can be continued.
- **Cromolyn**, **leukotriene receptor antagonists**, and **theophylline** are considered alternative agents, but they are not preferred.
- For moderate persistent asthma, either a combination of low-dose inhaled corticosteroids with a long-acting  $\beta_2$ -agonist or an increase in the dose of inhaled corticosteroids is recommended.
- For severe, persistent asthma, the inhaled corticosteroid dose should be increased to the high-dose range, and addition of systemic corticosteroids may be needed.
- **Intranasal corticosteroids** are the most effective treatment for allergic rhinitis during pregnancy. **Beclomethasone** and **budesonide** have been used most. **Nasal cromolyn** and first-generation antihistamines (**chlorpheniramine**, **tripelennamine**, and **hydroxyzine**) are also considered first-line therapy. **Loratadine** and **cetirizine** have not been as extensively studied.
- Short-term **topical oxymetazoline** or **inhaled corticosteroids** may be preferred over oral decongestants, especially during early pregnancy.

### DERMATOLOGIC CONDITIONS

- Topical agents with minimal pregnancy risk include **bacitracin**, **benzoyl peroxide**, **ciclopirox**, **clindamycin**, **erythromycin**, **metronidazole**, **mupirocin**, **permethrin**, and **terbinafine**.
- **Topical corticosteroids** are considered to have minimal pregnancy risk, but should be applied at the lowest possible dose for the shortest time.
- Systemic agents that are considered safe in pregnancy include **acyclovir**, **amoxicillin**, **azithromycin**, **cephalosporins**, **chlorpheniramine**, **cyproheptadine**, **dicloxacillin**, **diphenhydramine**, **erythromycin** (except estolates), **nystatin**, and **penicillin**.
- **Lidocaine** and **lidocaine with epinephrine** are also considered safe during pregnancy.
- **Acitretin**, **fluorouracil**, **isotretinoin**, **methotrexate**, and **thalidomide** should be avoided during pregnancy.

### DIABETES

- **Insulin** is the drug treatment of choice for patients with either type 1 or type 2 diabetes during pregnancy; **glyburide** can be used for type 2 diabetes after the eleventh week of gestation. **Metformin** is also an option.

- Goals for self-monitoring of blood glucose are the same as for gestational diabetes.

## EPILEPSY

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- Major malformations occur in 4% to 6% of the offspring of women taking **benzodiazepines, carbamazepine, phenobarbital, phenytoin, or valproic acid**.
- Minor malformations occur in 6% to 20% of pregnancies affected by epilepsy; this is twice the rate in the general population. The increase is considered to be a result of fetal exposure to antiepileptic drugs. Regimens consisting of combinations of antiepileptic drugs are associated with higher malformation rates.
- Drug therapy should be optimized prior to conception, and antiepileptic drug monotherapy is recommended when possible.
- If drug withdrawal is planned, it should be done at least 6 months prior to conception.
- All women with epilepsy should take a **folic acid** supplement, 0.4 to 5 mg daily.
- To correct vitamin K deficiency in newborns, women should take 10 mg oral **vitamin K<sub>1</sub>** daily during the last month of gestation.

## HUMAN IMMUNODEFICIENCY VIRUS INFECTIONS

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- If the pregnant woman has been on prior antiretroviral therapy, continuation should be considered. Without prior therapy, the regimen should be selected from those suggested for nonpregnant adults. Current **zidovudine** dosing recommendations during pregnancy are 100 mg five times daily, 200 mg three times daily, or 300 mg twice daily. It should be initiated at the beginning of the second trimester and continued throughout pregnancy. It is also recommended during labor, delivery, and the postpartum period.
- The infant should receive **zidovudine** beginning 8 to 12 hours after birth and continued for the first 6 weeks of life.

## HYPERTENSION

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- For women with 140 to 179 mm Hg systolic or 90 to 109 mm Hg diastolic, the decision to continue or stop antihypertensive therapy during pregnancy is controversial. Antihypertensive drugs may be continued during pregnancy except for **ACEIs** and **angiotensin II receptor blockers**.
- If discontinued, therapy should be restarted if blood pressure exceeds 150 to 160 mm Hg systolic or 100 to 110 mm Hg diastolic or if target-organ damage is present.
- **Diuretic** use is acceptable for chronic hypertension.
- No evidence exists for the superior efficacy of one antihypertensive agent versus another. For women with severe hypertension (diastolic blood pressure greater than or equal to 100 mm Hg), the benefit of drug therapy may outweigh the risks.

## DEPRESSION

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- If antidepressants are used, the lowest possible dose should be used for the shortest possible time to minimize adverse fetal and maternal pregnancy outcomes.
- Pregnant women who stopped taking antidepressants were five times more likely to have a relapse than women who completed treatment.
- The **selective serotonin reuptake inhibitors (SSRIs)** are widely used by pregnant women. About one or two babies per 1,000 exposed to SSRIs in utero develop persistent pulmonary hypertension. The risk was six times greater in infants born to women who took SSRIs after week 20 of pregnancy. Another risk of using SSRIs late in pregnancy is a withdrawal reaction in the infant (e.g., irritability, difficulty feeding and breathing). An epidemiologic study suggests that first-trimester use of **paroxetine** may be associated with an increased risk for cardiac defects in the infant.
- When tricyclic antidepressants are withdrawn during pregnancy, they should be tapered gradually to avoid withdrawal symptoms. If possible, drug tapering is usually begun 5 to 10 days before the estimated date of confinement.

## LABOR AND DELIVERY

### PRETERM LABOR

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- Preterm labor is labor that occurs before 37 weeks of gestation.

### Tocolytic Therapy

- The goal of tocolytic therapy is to postpone delivery long enough to allow for administration of antenatal corticosteroids to improve pulmonary maturity and for transportation of the mother to a facility equipped to deal with high-risk deliveries.
- Drugs most commonly used for acute tocolysis include **magnesium sulfate**,  **$\beta$ -adrenergic agonists**, **NSAIDs**, and **calcium channel blockers**.
- Recommended doses of **terbutaline** are 250 to 500 mcg subcutaneously every 3 to 4 hours. Its use is associated with a higher incidence of maternal side effects (e.g., hyperkalemia, arrhythmias, hyperglycemia, hypotension, and pulmonary edema) than the other drugs.
- **Nifedipine** is associated with fewer side effects than magnesium or  $\beta$ -agonist therapy. Five to 10 mg nifedipine may be administered sublingually every 15 to 20 minutes for three doses. Once stabilized, 10 to 20 mg may be administered by mouth every 4 to 6 hours for preterm contractions.

### Antenatal Glucocorticoids

- A Cochrane metaanalysis shows the benefit of antenatal **corticosteroids** for fetal lung maturation to prevent respiratory distress syndrome, intraventricular hemorrhage, and death in infants delivered prematurely.
- Current recommendations are to administer **betamethasone**, 12 mg IM every 24 hours for two doses, or **dexamethasone**, 6 mg IM every 12 hours for four doses, to pregnant women between 26 and 34 weeks' gestation who are at risk for preterm delivery within the next 7 days. Benefits from

antenatal glucocorticoid administration are believed to begin within 24 hours. Repeat administration of antenatal glucocorticoids does not improve fetal outcomes.

## GROUP B *STREPTOCOCCUS* INFECTION

- The Centers for Disease Control and Prevention recommends prenatal screening (vaginal/rectal cultures) for group B *Streptococcus* colonization of all pregnant women at 35 to 37 weeks' gestation. If cultures are positive, and if the woman had a previous infant with invasive group B *Streptococcus* disease, or if the woman had group B *Streptococcus* bacteriuria, antibiotics are given.
- The currently recommended regimen for group B *Streptococcus* disease is **penicillin G**, 5 million units IV, followed by 2.5 million units IV every 4 hours until delivery. Alternatives include **ampicillin**, 2 g IV, followed by 1 g IV every 4 hours; **cefazolin** 2 g IV, followed by 1 g every 8 hours; **clindamycin**, 900 mg IV every 8 hours; or **erythromycin**, 500 mg IV every 6 hours. In women who are penicillin-allergic, and in whom sensitivity testing shows the organism to be resistant to clindamycin and erythromycin, **vancomycin** 1 g IV every 12 hours until delivery can be used.

## CERVICAL RIPENING AND LABOR INDUCTION

- Prostaglandin E<sub>2</sub> analogs (e.g., **dinoprostone [Prepidil and Cervidil]**) are the most commonly used pharmacologic agents for cervical ripening. Fetal heart rate monitoring is required when Cervidil is used. **Misoprostol**, a prostaglandin E<sub>1</sub> analog, is an effective and inexpensive drug used for cervical ripening and labor induction, but it is not approved for cervical ripening and has been associated with uterine rupture.
- **Oxytocin** is the most commonly used agent for labor induction after cervical ripening.

## LABOR ANALGESIA

- The IV or IM administration of parenteral narcotics (**meperidine, morphine, fentanyl**) is commonly used to treat the pain associated with labor. Compared to epidural analgesia, parenteral opioids are associated with lower rates of oxytocin augmentation, shorter stages of labor, and fewer instrumental deliveries.
- Epidural analgesia involves administering an opioid and/or an anesthetic (e.g., fentanyl and/or bupivacaine) through a catheter into the epidural space to provide pain relief. Epidural analgesia is associated with longer stages of labor and more instrumental deliveries than parenteral narcotic analgesia.
- Other options for labor analgesia include spinal analgesia and nerve blocks.

## POSTPARTUM ISSUES

### DRUG USE DURING LACTATION

- Medications enter breast milk via passive diffusion of nonionized and non-protein-bound medication. Drugs with high molecular weights,

lower lipid solubility, and higher protein binding are less likely to cross into breast milk or transfer more slowly or in smaller amounts. The higher the serum concentration of drug in the mother's serum, the higher the concentration will be in the breast milk. Drugs with longer half-lives are more likely to maintain higher levels in breast milk. The timing and frequency of feedings and amount of milk ingested by the infant are important considerations.

- Strategies for reducing risk to the infant from drug transferred through breast milk include selection of medications for the mother that would be considered safe for use in the infant; choosing medications with shorter half-lives; selecting those that are more protein bound, have lower bioavailability, and have lower lipid solubility.

## MASTITIS

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- Mastitis is usually caused by *Staphylococcus aureus*, *E. coli*, and *Streptococcus*.
- Treatment includes 10 to 14 days of antibiotic therapy for the mother (**cloxacillin**, **dicloxacillin**, **oxacillin**, or **cephalexin**), bedrest, adequate oral fluid intake, analgesia, and frequent evacuation of breast milk.

## POSTPARTUM DEPRESSION

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- Nondrug therapies include emotional support from family and friends, education about the condition, and psychotherapy.
- Drug therapies include **tricyclic antidepressants** and **SSRIs**. Treatment should be continued for at least 29 weeks. **Nortriptyline**, **amitriptyline**, **clomipramine**, **desipramine**, **fluvoxamine**, and **bupropion** have been used successfully.

## RELACTATION

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- Recommended pharmacologic therapy for relactation is **metoclopramide**, 10 mg three times daily for 7 to 14 days. It should be used only if nondrug therapy is ineffective.

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*See Chap. 81, Pregnancy and Lactation: Therapeutic Considerations, authored by Denise L. Walbrandt Pigarelli, Connie K. Kraus, and Beth E. Potter, for a more detailed discussion of this topic.*

## DEFINITION

- Anemias are a group of diseases characterized by a decrease in hemoglobin (Hb) or red blood cells (RBCs), resulting in decreased oxygen-carrying capacity of blood.

## PATHOPHYSIOLOGY

- Anemias can be classified on the basis of RBC morphology, etiology, or pathophysiology (Table 33-1). The most common anemias are included in this chapter.
- Morphologic classifications are based on cell size. Macrocytic cells are larger than normal and are associated with deficiencies of vitamin B<sub>12</sub> or folate. Microcytic cells are smaller than normal and are associated with iron deficiency whereas normocytic anemia may be associated with recent blood loss or chronic disease.
- Iron-deficiency anemia can be caused by inadequate dietary intake, inadequate GI absorption, increased iron demand (e.g., pregnancy), blood loss, and chronic diseases.
- Vitamin B<sub>12</sub>- and folate-deficiency anemias can be caused by inadequate dietary intake, decreased absorption, and inadequate utilization. Deficiency of intrinsic factor can cause decreased absorption of vitamin B<sub>12</sub> (i.e., pernicious anemia). Folate-deficiency anemia can be caused by hyperutilization due to pregnancy, hemolytic anemia, myelofibrosis, malignancy, chronic inflammatory disorders, long-term dialysis, or growth spurt. Drugs can cause anemia by reducing absorption of folate (e.g., **phenytoin**) or by interfering with corresponding metabolic pathways (e.g., **methotrexate**).
- Anemia of chronic disease is a hypoproliferative anemia associated with chronic infectious or inflammatory processes, tissue injury, or conditions that release proinflammatory cytokines. The pathogenesis is based on shortened RBC survival, impaired marrow response, and disturbance of iron metabolism. For information on anemia of chronic kidney disease, see Chap. 76.
- In anemia of critical illness, the mechanism for RBC replenishment and homeostasis is altered by, for example, blood loss or cytokines, which can blunt the erythropoietic response and inhibit RBC production.
- Age-related reductions in bone marrow reserve can render the elderly patient more susceptible to anemia that is caused by multiple minor and often unrecognized diseases (e.g., nutritional deficiencies) that negatively affect erythropoiesis.

**TABLE 33-1** Classification Systems for Anemias

<b>I. Morphology</b>	Gastritis
Macrocytic anemias	Hemorrhoids
Megaloblastic anemias	Chronic hemorrhage
Vitamin B <sub>12</sub> deficiency	Vaginal bleeding
Folic acid deficiency anemia	Peptic ulcer
Microcytic hypochromic anemias	Intestinal parasites
Iron-deficiency anemia	Aspirin and other nonsteroidal antiinflammatory agents
Genetic anomaly	Excessive RBC destruction
Sickle cell anemia	Extracorporeal (outside the cell) factors
Thalassemia	RBC antibodies
Other hemoglobinopathies (abnormal hemoglobins)	Drugs
Normocytic anemias	Physical trauma to RBC (artificial valves)
Recent blood loss	Excessive sequestration in the spleen
Hemolysis	Intracorporeal factors
Bone marrow failure	Heredity
Anemia of chronic disease	Disorders of hemoglobin synthesis
Renal failure	Inadequate production of mature RBCs
Endocrine disorders	Deficiency of nutrients (B <sub>12</sub> , folic acid, iron, protein)
Myelodysplastic anemias	Deficiency of erythroblasts
<b>II. Etiology</b>	Aplastic anemia
Deficiency	Isolated (often transient) erythroblastopenia
Iron	Folic acid antagonists
Vitamin B <sub>12</sub>	Antibodies
Folic acid	Conditions with infiltration of bone marrow
Pyridoxine	Lymphoma
Central, caused by impaired bone marrow function	Leukemia
Anemia of chronic disease	Myelofibrosis
Anemia of the elderly	Carcinoma
Malignant bone marrow disorders	Endocrine abnormalities
Peripheral	Hypothyroidism
Bleeding (hemorrhage)	Adrenal insufficiency
Hemolysis (hemolytic anemias)	Pituitary insufficiency
<b>III. Pathophysiology</b>	Chronic renal disease
Excessive blood loss	Chronic inflammatory disease
Recent hemorrhage	Granulomatous diseases
Trauma	Collagen vascular diseases
Peptic ulcer	Hepatic disease

RBC, red blood cell.

- Anemias in children are often due to a primary hematologic abnormality. The risk of iron-deficiency anemia is increased by rapid growth spurts and dietary deficiency.
- Hemolytic anemia results from decreased RBC survival time due to destruction in the spleen or circulation. The most common etiologies are RBC membrane defects (e.g., hereditary spherocytosis), altered Hb solubility or stability (e.g., sickle cell anemia [see Chap. 34] and thalassemias), and changes in intracellular metabolism (e.g., glucose-6-phosphate dehydrogenase deficiency). Some drugs cause direct oxidative damage to RBCs (see Appendix 3).

## CLINICAL PRESENTATION

- Signs and symptoms depend on the rate of development and the age and cardiovascular status of the patient. Acute-onset anemia is characterized by cardiorespiratory symptoms such as tachycardia, lightheadedness, and breathlessness. Chronic anemia is characterized by weakness, fatigue, headache, vertigo, faintness, cold sensitivity, pallor, and loss of skin tone.
- Iron-deficiency anemia is characterized by glossal pain, smooth tongue, reduced salivary flow, pica (compulsive eating of nonfood items), and pagophagia (compulsive eating of ice). These symptoms are not usually seen until the Hb concentration is less than 9 g/dL.
- Vitamin B<sub>12</sub>- and folate-deficiency anemias are characterized by pallor, icterus, and gastric mucosal atrophy. Vitamin B<sub>12</sub> anemia is distinguished by neuropsychiatric abnormalities (e.g., numbness, paresthesias, irritability), which are absent in patients with folate-deficiency anemia.

## DIAGNOSIS

- Rapid diagnosis is essential because anemia is often a sign of underlying pathology.
- Initial evaluation of anemia involves a complete blood cell count (Table 33-2), reticulocyte index, and examination of the stool for occult blood.

**TABLE 33-2** Normal Hematologic Values

Test	Reference Range (years)			
	2-6	6-12	12-18	18-49
Hemoglobin (g/dL)	11.5-15.5	11.5-15.5	M 13.0-16.0 F 12.0-16.0	M 13.5-17.5 F 12.0-16.0
Hematocrit (%)	34-40	35-45	M 37-49 F 36-46	M 41-53 F 36-46
MCV (fL)	75-87	77-95	M 78-98 F 78-102	80-100
MCHC (%)	—	31-37	31-37	31-37
MCH (pg)	24-30	25-33	25-35	26-34
RBC (million/mm <sup>3</sup> )	3.9-5.3	4.0-5.2	M 4.5-5.3	M 4.5-5.9
Reticulocyte count, absolute (%)				0.5-1.5
Serum iron (mcg/dL)		50-120	50-120	M 50-160 F 40-150
TIBC (mcg/dL)	250-400	250-400	250-400	250-400
RDW (%)				11-16
Ferritin (ng/mL)	7-140	7-140	7-140	M 15-200 F 12-150
Folate (ng/mL)				1.8-16.0 <sup>a</sup>
Vitamin B <sub>12</sub> (pg/mL)				100-900 <sup>a</sup>
Erythropoietin (milliunits/mL)				0-19

F, female; M, male; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RBC, red blood cell; RDW, red blood cell distribution; TIBC, total iron-binding capacity.

<sup>a</sup>Varies by assay method.

- The earliest and most sensitive laboratory change for iron-deficiency anemia is decreased serum ferritin (storage iron), which should be interpreted in conjunction with decreased transferrin saturation and increased total iron-binding capacity (TIBC). Hb, hematocrit, and RBC indices usually remain normal until later stages of iron-deficiency anemia.
- Macrocytic anemias are characterized by increased mean corpuscular volume (110 to 140 fL). One of the earliest and most specific indications of macrocytic anemia is hypersegmented polymorphonuclear leukocytes on the peripheral blood smear. Vitamin B<sub>12</sub> and folate concentrations can be measured to differentiate between the two deficiency anemias. A vitamin B<sub>12</sub> value of less than 150 pg/mL, together with appropriate peripheral smear and clinical symptoms, is diagnostic of vitamin B<sub>12</sub>-deficiency anemia. A decreased RBC folate concentration (less than 150 ng/mL) appears to be a better indicator of folate-deficiency anemia than a decreased serum folate concentration (less than 3 ng/mL).
- Diagnosis of anemia of chronic disease is usually one of exclusion, with consideration of coexisting iron and folate deficiencies. Serum iron is usually decreased but, unlike iron-deficiency anemia, serum ferritin is normal or increased and TIBC is decreased. The bone marrow reveals an abundance of iron; the peripheral smear reveals normocytic anemia.
- Laboratory findings of anemia of critical illness disease are similar to those of anemia of chronic disease.
- Elderly patients with symptoms of anemia should undergo a complete blood cell count with peripheral smear and reticulocyte count, and other laboratory studies as needed to determine the etiology of anemia.
- Diagnosis of anemia in pediatric populations requires the use of age- and sex-adjusted norms for laboratory values.
- Hemolytic anemias tend to be normocytic and normochromic and to have increased levels of reticulocytes, lactic dehydrogenase, and indirect bilirubin.

## DESIRED OUTCOME

- The ultimate goals of treatment in the anemic patient are to alleviate signs and symptoms, correct the underlying etiology (e.g., restore substrates needed for RBC production), and prevent recurrence of anemia.

## TREATMENT

### IRON-DEFICIENCY ANEMIA

- **Oral iron** therapy with soluble ferrous iron salts, which are not enteric coated and not slow- or sustained-release, is recommended at a daily dosage of 200 mg elemental iron in two or three divided doses (Table 33-3).
- Diet plays a significant role because iron is poorly absorbed from vegetables, grain products, dairy products, and eggs; iron is best absorbed from meat, fish, and poultry. Administration of iron therapy with a meal decreases absorption by more than 50% but may be needed to improve tolerability.
- **Parenteral iron** may be required for patients with iron malabsorption, intolerance of oral iron therapy, or noncompliance. Parenteral administra-

**TABLE 33-3** Oral Iron Products

Salt	Elemental Iron (%)	Elemental Iron Provided
Ferrous sulfate	20	60–65 mg/324–325 mg tablet 18 mg iron/5 mL syrup 44 mg iron/5 mL elixir 15 mg iron/0.6 mL drop
Ferrous sulfate (exsiccated)	30	65 mg/200 mg tablet 60 mg/187 mg tablet 50 mg/160 mg tablet
Ferrous gluconate	12	36 mg/325 mg tablet 27 mg/240 mg tablet
Ferrous fumarate	33	33 mg/100 mg tablet 63–66 mg/200 mg tablet 106 mg/324–325 mg tablet 15 mg/0.6 mL drop 33 mg/5 mL suspension
Polysaccharide iron complex	100	150 mg capsule 50 mg tablet 100 mg/5 mL elixir
Carbonyl iron	100	50 mg caplet

tion, however, does not hasten the onset of hematologic response. The replacement dose depends on etiology of anemia and Hb concentration (Table 33-4).

- Available parenteral iron preparations have similar efficacy but different pharmacologic, pharmacokinetic, and safety profiles (Table 33-5). The newer products, **sodium ferric gluconate** and **iron sucrose**, appear to be better tolerated than **iron dextran**.

### VITAMIN B<sub>12</sub>-DEFICIENCY ANEMIA

- Oral vitamin B<sub>12</sub> supplementation appears to be as effective as parenteral, even in patients with pernicious anemia, because the alternate vitamin B<sub>12</sub> absorption pathway is independent of intrinsic factor. Oral **cobalamin** is initiated at 1 to 2 mg daily for 1 to 2 weeks, followed by 1 mg daily.
- Parenteral therapy is more rapid acting than oral therapy and should be used if neurologic symptoms are present. A popular regimen is **cyanocobalamin** 1,000 mcg daily for 1 week, then weekly for 1 month, and then monthly. When symptoms resolve, daily oral administration can be initiated.
- Adverse events are rare with vitamin B<sub>12</sub> therapy.

### FOLATE-DEFICIENCY ANEMIA

- Oral **folate** 1 mg daily for 4 months is usually sufficient for treatment of folate-deficiency anemia, unless the etiology cannot be corrected. If malabsorption is present, the daily dose should be increased to 5 mg.

### ANEMIA OF CHRONIC DISEASE

- Treatment of anemia of chronic disease is less specific than that of other anemias and should focus on correcting reversible causes. Iron therapy is

**TABLE 33-4** Equations for Calculating Doses of Parenteral Iron**In patients with iron-deficiency anemia:**

Adults + children over 15 kg

$$\text{Dose (mL)} = 0.0442 (\text{desired Hb} - \text{observed Hb}) \times \text{LBW} + (0.26 \times \text{LBW})$$

$$\text{LBW males} = 50 \text{ kg} + (2.3 \times \text{inches over 5 ft})$$

$$\text{LBW females} = 45.5 \text{ kg} + (2.3 \times \text{inches over 5 ft})$$

Children 5–15 kg

$$\text{Dose (mL)} = 0.0442 (\text{desired Hb} - \text{observed Hb}) \times W + (0.26 \times W)$$

**In patients with anemia secondary to blood loss (hemorrhagic diathesis or long-term dialysis):**

$$\text{mg of iron} = \text{blood loss} \times \text{hematocrit}$$

where blood loss is in milliliters and hematocrit is expressed as a decimal fraction.

Hb, hemoglobin; LBW, lean body weight; W, weight.

**TABLE 33-5** Parenteral Iron Preparations

	<b>Sodium Ferric Gluconate</b>	<b>Iron Dextran</b>	<b>Iron Sucrose</b>
Elemental iron	62.5 mg iron/5 mL	50 mg iron/mL	20 mg iron/mL
Molecular weight	Ferlecit: 289,000–444,000 d	InFeD: 165,000 d DexFerrum: 267,000 d	Venofer: 34,000–60,000 d
Composition	Ferric oxide hydrate bonded to sucrose chelates with gluconate in a molar rate of two iron molecules to one gluconate molecule	Complex of ferric hydroxide and dextran	Complex of polynuclear iron hydroxide in sucrose
Preservative	Benzyl alcohol 9 mg/5 mL 20% (975 mg in 62.5 mg iron)	None	None
Indication	Iron deficiency anemia in patients undergoing chronic hemodialysis who are receiving supplemental erythropoietin therapy	Patients with documented iron deficiency in whom oral therapy is unsatisfactory or impossible	Iron deficiency anemia in patients undergoing chronic hemodialysis and receiving supplemental epoetin alfa therapy
Warning	No black box warning; hypersensitivity reactions	Black box warning: anaphylactic-type reactions	Black box warning: anaphylactic-type reactions
Intramuscular injection	No	Yes	No
Usual dose	125 mg (10 mL) diluted in 100 mL normal saline, infused over 60 minutes; or as a slow IV injection (rate of 12.5 mg/min)	100 mg undiluted at a rate not to exceed 50 mg (1 mL) per minute	100 mg into the dialysis line at a rate of 1 mL (20 mg of iron) undiluted solution per minute
Treatment	8 doses $\times$ 125 mg = 1,000 mg	10 doses $\times$ 100 mg = 1,000 mg	Up to 10 doses $\times$ 100 mg = 1,000 mg
Common adverse effects	Cramps, nausea and vomiting, flushing, hypotension, rash, pruritus	Pain and brown staining at injection site, flushing, hypotension, fever, chills, myalgia, anaphylaxis	Leg cramps, hypotension

d, daltons.

not effective when inflammation is present. RBC transfusions are effective but should be limited to episodes of inadequate oxygen transport and Hb of 8 to 10 g/dL.

- **Epoetin alfa** can be considered, especially if cardiovascular status is compromised, but the response can be impaired in patients with anemia of chronic disease (off-label use). The initial dosage is 50 to 100 units/kg three times weekly. If Hb does not increase after 6 to 8 weeks, the dosage can be increased to 150 units/kg three times weekly.
- Epoetin alfa is usually well tolerated. The hypertension seen in patients with end-stage kidney disease is less common in patients with acquired immune deficiency syndrome.

## OTHER TYPES OF ANEMIAS

- Patients with other types of anemias require appropriate supplementation depending on the etiology of anemia.
- In patients with anemia of critical illness, parenteral iron is often utilized but is associated with a theoretical risk of infection. Routine use of epoetin alfa or RBC transfusions is not supported by clinical studies.
- Anemia of prematurity is usually treated with RBC transfusions. The use of epoetin alfa is controversial.
- In the pediatric population, the daily dose of elemental iron, administered as iron sulfate, is 3 mg/kg for infants and 6 mg/kg for older children for 4 weeks. If response is seen, iron should be continued for 2 to 3 months to replace storage iron pools. The dose and schedule of vitamin B<sub>12</sub> should be titrated according to clinical and laboratory response. The daily dose of folate is 1 to 3 mg.
- Treatment of hemolytic anemia should focus on correcting the underlying cause. There is no specific therapy for glucose-6-phosphate dehydrogenase deficiency, so treatment consists of avoiding oxidant medications and chemicals. Steroids, other immunosuppressants, and even splenectomy can be indicated to reduce RBC destruction.

## EVALUATION OF THERAPEUTIC OUTCOMES

- In iron-deficiency anemia, **iron** therapy should cause reticulocytosis in 5 to 7 days and raise Hb by 2 to 4 g/dL every 3 weeks. The patient should be reevaluated if reticulocytosis does not occur or if Hb does not increase by 2 g/dL within 3 weeks. Iron therapy is continued until iron stores are replenished, which usually requires at least 3 to 6 months.
- In megaloblastic anemia, signs and symptoms usually improve within a few days after starting **vitamin B<sub>12</sub>** or **folate** therapy. Neurologic symptoms can take longer to improve or can be irreversible, but they should not progress during therapy. Reticulocytosis should occur within 2 to 5 days. A week after starting vitamin B<sub>12</sub> therapy, Hb should rise and leukocyte and platelet counts should normalize. Hematocrit should rise 2 weeks after starting folate therapy.
- In anemia of chronic disease, reticulocytosis should occur a few days after starting **epoetin alfa** therapy. Iron, TIBC, transferrin saturation, or ferritin

levels should be monitored at baseline and periodically because iron depletion is a major reason for treatment failure. The optimal form and schedule of iron supplementation are unknown. If clinical response does not occur by 8 weeks, epoetin alfa should be discontinued.

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*See Chap. 104, Anemias, authored by Beata Ineck, Barbara J. Mason, and William Lyons, for a more detailed discussion of this topic.*

## DEFINITION

- Sickle cell syndromes are hereditary disorders characterized by the presence of sickle hemoglobin (HbS) in red blood cells (RBCs).

## PATHOPHYSIOLOGY

- The most common abnormal hemoglobin in the United States is hemoglobin S (HbS). Two genes for HbS result in sickle cell disease (SCD) or sickle cell anemia, which occurs in 0.3% of African Americans. One gene for HbS results in sickle cell trait, which occurs in 8% of African Americans. Hemoglobin C, another abnormality, occurs in 2% to 3% of African Americans.
- Clinical manifestations of SCD are attributable to impaired circulation, RBC destruction, and stasis of blood flow. These problems are attributable to disturbances in RBC polymerization and to membrane damage.
- Polymerization allows deoxygenated hemoglobin to exist as a semisolid gel that protrudes into the cell membrane, distorting RBCs into sickle shapes. Sickle-shaped RBCs increase blood viscosity and encourage sludging in the capillaries and small vessels. Such obstructive events lead to local tissue hypoxia and accentuate the pathologic process.
- Repeated cycles of sickling, upon deoxygenation, and unsickling, upon oxygenation, damage the RBC membrane and cause irreversible sickling. Rigid, sickled RBCs are easily trapped, shortening their circulatory survival and resulting in chronic hemolysis.
- Additional contributing factors include functional asplenia (and increased risk of bacterial infection), deficient opsonization, and coagulation abnormalities.

## CLINICAL PRESENTATION

- SCD involves many organ systems. Clinical manifestations depend on the genotype (Table 34-1).
- Feature presentations of SCD are hemolytic anemia and vasoocclusion. Symptoms are delayed until 4 to 6 months of age when HbS replaces fetal hemoglobin (HbF). Common findings include pain with fever, pneumonia, splenomegaly and, in infants, pain and swelling of the hands and feet (e.g., hand-and-foot syndrome or dactylitis).
- Usual clinical signs and symptoms of SCD are chronic anemia; fever; pallor; arthralgia; scleral icterus; abdominal pain; weakness; anorexia; fatigue; enlarged liver, spleen, and heart; and hematuria.
- Children experience delayed growth and sexual maturation, and characteristic physical findings such as protuberant abdomen and exaggerated lumbar lordosis.
- Acute complications of SCD include fever and infection (e.g., sepsis caused by encapsulated pathogens such as *Streptococcus pneumoniae*), stroke, acute

**TABLE 34-1** Clinical Features of Sickle Cell Trait and Common Types of Sickle Cell Disease

Type	Clinical Features
Sickle cell trait	Rare painless hematuria; normal Hb level; heavy exercise under extreme conditions may provoke gross hematuria and complications
Sickle cell anemia	Pain crises, microvascular disruption of organs (spleen, liver, bone marrow, kidney, brain, and lung), gallstone, priapism, leg ulcers, anemia (Hb 7–10 g/dL)
Sickle cell hemoglobin C	Painless hematuria and rare aseptic necrosis of bone; vasoocclusive crises are less common and occur later in life; other complications are ocular disease and pregnancy-related problems; mild anemia (Hb 10–12 g/dL)
Sickle cell $\beta^+$ -thalassemia	Rare crises; milder severity than sickle cell disease because of production of HbA; Hb 10–14 g/dL with microcytosis
Sickle cell $\beta^0$ -thalassemia	No HbA production; severity similar to sickle cell anemia; Hb 7–10 g/dL with microcytosis

Hb, hemoglobin; HbA, hemoglobin A.

chest syndrome, and priapism. Acute chest syndrome is characterized by pulmonary infiltration, respiratory symptoms, and equivocal response to antibiotic therapy.

- Sickle cell crisis can be precipitated by fever, infection, dehydration, hypoxia, acidosis, sudden temperature change, or a combination of factors. The most common type is vasoocclusive or infarctive crisis, which is manifested by pain over the involved areas without change in hemoglobin. Aplastic crisis is characterized by decreased reticulocyte count and rapidly developing severe anemia, with or without pain. Splenic sequestration crisis is a massive enlargement of the spleen leading to hypotension, shock, and sudden death in young children. Repeated infarctions lead to autosplenectomy as the disease progresses, therefore, incidence declines as adolescence approaches.
- Chronic complications involve many organs and include pulmonary hypertension, bone and joint destruction, ocular problems, cholelithiasis, cardiovascular abnormalities, and hematuria and other renal complications.
- Patients with sickle cell trait are usually asymptomatic, except for rare painless hematuria.

## DIAGNOSIS

- SCD is usually identified by routine neonatal screening programs using isoelectric focusing.
- Laboratory findings include low hemoglobin; increased reticulocyte, platelet, and white blood cell counts; and sickle forms on the peripheral smear.

## DESIRED OUTCOME

- The goal of treatment is to reduce hospitalizations, complications, and mortality.

## TREATMENT

### GENERAL PRINCIPLES

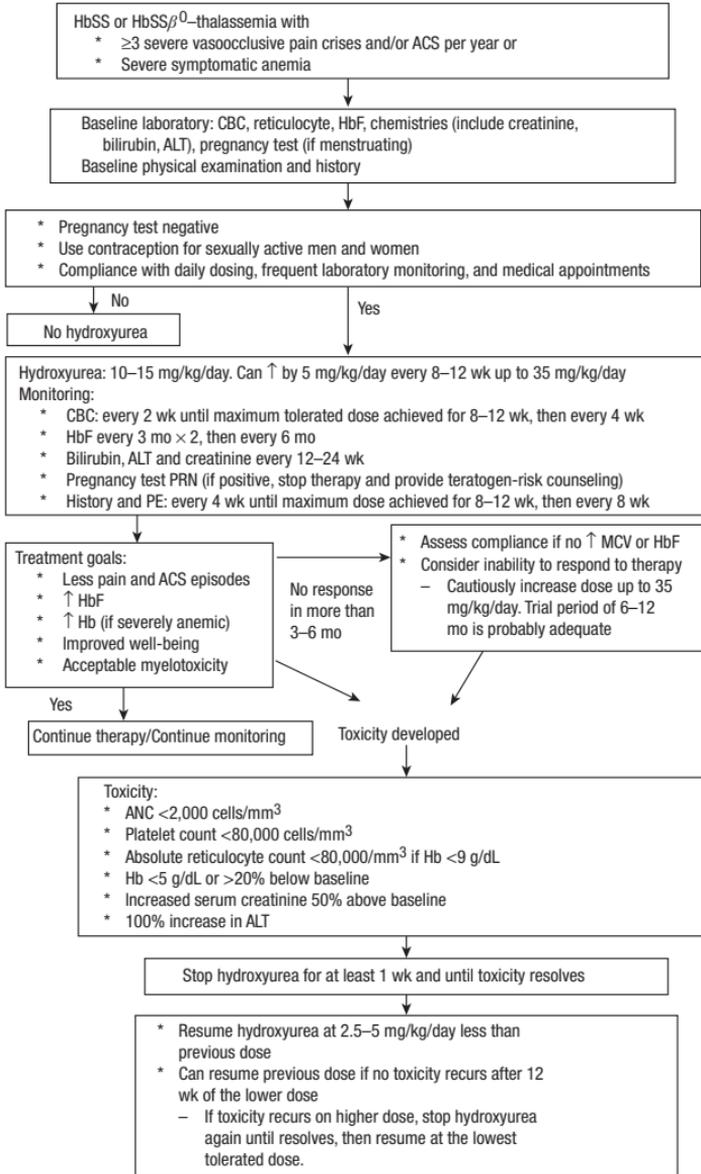
- Patients with SCD require lifelong multidisciplinary care. Interventions include general measures, preventive strategies, and treatment of complications and acute crises.
- Patients with SCD should receive routine immunizations plus influenza, meningococcal, and pneumococcal vaccinations.
- Prophylactic **penicillin** is recommended for children with SCD until they are 5 years old. Beginning at age 2 months or earlier, the dosage is penicillin V potassium, 125 mg orally twice daily until 3 years of age and then 250 mg twice daily until age 5 years, or benzathine penicillin, 600,000 units intramuscularly every 4 weeks from age 6 months to 6 years.
- **Folic acid**, 1 mg daily, is recommended in adult patients, pregnant women, and patients of all ages with chronic hemolysis.

### FETAL HEMOGLOBIN INDUCERS

- HbF directly effects polymer formation. Increases in HbF correlate with decreased RBC sickling and adhesion. Patients with low HbF levels have more frequent crises and higher mortality.
- **Hydroxyurea**, a chemotherapeutic agent, has many effects on blood cells, including the stimulation of HbF production. It is indicated for patients with frequent painful episodes, severe symptomatic anemia, acute chest syndrome, or other severe vasoocclusive complications. The dosage should be individualized based on response and toxicity (Fig. 34-1).
- Strategies being investigated to induce HbF include **butyrate** and **5-aza-2-deoxycytidine (decitabine)**.
- Chronic transfusion is indicated to prevent stroke and stroke recurrence in children. Transfusion frequency is usually every 3 to 4 weeks and should be adjusted to maintain HbS of less than 30% of total hemoglobin. The optimal duration is unknown. Risks include alloimmunization, hyperviscosity, viral transmission (requiring hepatitis A and B vaccination), volume and iron overload, and transfusion reactions.
- Allogeneic hematopoietic stem cell transplantation is the only therapy that is curative. The best candidates are younger than 16 years of age, have severe complications, and have human leukocyte antigen–matched donors. Risks must be carefully considered and include mortality, graft rejection, and secondary malignancies.

### TREATMENT OF COMPLICATIONS

- Patients should be educated to recognize conditions that require urgent evaluation. To avoid exacerbation during acute illness, patients should maintain balanced fluid status and oxygen saturation of at least 92%.
- RBC transfusions are indicated for acute exacerbation of baseline anemia (e.g., aplastic crisis, hepatic or splenic sequestration, severe hemolysis), severe vasoocclusive episodes, and procedures requiring general anesthesia or ionic contrast. Transfusions might be beneficial in patients with compli-



**FIGURE 34-1.** Hydroxyurea use in sickle cell disease. (ACS, acute chest syndrome; ALT, alanine aminotransferase; ANC, absolute neutrophil count; CBC, complete blood cell count; Hb, hemoglobin; HbF, fetal hemoglobin; HbSS, homozygous sickle cell hemoglobin; HbSS $\beta^0$ , sickle cell  $\beta^0$ -thalassemia; MCV, mean corpuscular volume; PE, physical examination; PRN, as needed; RBC, red blood cell.) (From Stuart MJ, Nagel RL. Sickle-cell disease. *Lancet* 2004;364:1343–1360; Sickle Cell Disease Care Consortium. *Sickle Cell Disease in Children and Adolescents: Diagnosis, Guidelines for Comprehensive Care, and Care Paths and Protocols for Management of Acute and Chronic Complications*. 2001, <http://www.tdh.texas.gov/newborn/sedona02.htm>; and Halsey C, Roberts IA. The role of hydroxyurea in sickle cell disease. *British J Hematol* 2003;120:177–186.)

cated obstetric problems, refractory leg ulcers, refractory and protracted painful episodes, and severe priapism.

- Fever of 38.5°C (101.3°F) or higher should be evaluated promptly. A low threshold for empiric antibiotic therapy with coverage against encapsulated organisms is recommended (e.g., **ceftriaxone** for outpatients and **cefotaxime** for inpatients).
- Patients with acute chest syndrome should receive incentive spirometry; appropriate fluid therapy; broad-spectrum antibiotics including a **macrolide** or **quinolone**; and, for hypoxia or acute distress, oxygen therapy. Steroids and nitric oxide are being evaluated.
- Priapism has been treated with analgesics, anti-anxiety agents, and vasoconstrictors to force blood out of the corpus cavernosum (e.g., **phenylephrine**, **epinephrine**), and vasodilators to relax smooth muscle (e.g., **terbutaline**, **hydralazine**).

## TREATMENT OF SICKLE CELL CRISIS

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- Treatment of *aplastic crisis* is primarily supportive. Blood transfusions may be indicated for severe or symptomatic anemia. Antibiotic therapy is not warranted because the most common etiology is viral, not bacterial, infection.
- Treatment options for *splenic sequestration* include observation alone, especially for adults because they tend to have milder episodes; chronic transfusion to delay splenectomy; and splenectomy after a life-threatening crisis, after repetitive episodes, or for chronic hypersplenism.
- Hydration and analgesics are the mainstays of treatment for *vasoocclusive (painful) crisis*. Fluid replacement should be 1.5 times the maintenance requirement, can be administered IV or orally, and should be monitored to avoid volume overload. An infectious etiology should be considered; if appropriate, empiric therapy should be initiated.
- Analgesic therapy should be tailored to the individual because of the variable frequency and severity of pain. Pain scales should be used to quantify the degree of pain.
- Mild to moderate pain should be treated with nonsteroidal antiinflammatory drugs or acetaminophen.
- Severe pain should be treated aggressively with an opioid, such as **morphine**, **hydromorphone**, **fentanyl**, and **methadone**. Moderate pain should be treated with a weak opioid, such as **codeine** or **hydrocodone**. **Meperidine** should be avoided because accumulation of the normeperidine metabolite can cause neurotoxicity, especially in patients with impaired renal function.
- Severe pain should be treated with an IV opioid titrated to pain relief and then administered on a scheduled basis with as-needed dosing for breakthrough pain. Patient-controlled analgesia is commonly utilized.
- Suspicion of addiction commonly leads to suboptimal pain control. Factors that minimize dependence include aggressive pain control, frequent monitoring, and tapering medication according to response.
- **Poloxamer 188** (Flocor) is being evaluated for vasoocclusive crisis. This surfactant returns RBCs to a nonadhesive state and blocks RBC aggregation to enhance blood flow in ischemic areas.

## EVALUATION OF THERAPEUTIC OUTCOMES

- All patients should be evaluated regularly to establish baseline, monitor changes, and provide age-appropriate education.
- Laboratory evaluations include complete blood cell and reticulocyte counts and HbF level. Renal, hepatobiliary, and pulmonary function should be evaluated. Patients should be screened for retinopathy.
- The efficacy of hydroxyurea can be assessed by monitoring the number, severity, and duration of sickle cell crises.

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*See Chap. 106, Sickle Cell Disease, authored by C. Y. Jennifer Chan and Reginald Moore, for a more detailed discussion of this topic.*

## INTRODUCTION

- A systematic approach to the selection and evaluation of an antimicrobial regimen is shown in Table 35-1. An “empiric” antimicrobial regimen is begun before the offending organism is identified and sometimes prior to the documentation of the presence of infection, while a “definitive” regimen is instituted when the causative organism is known.

## CONFIRMING THE PRESENCE OF INFECTION

### FEVER

- Fever is defined as a controlled elevation of body temperature above the normal range of 36.7 to 37.0°C (98.1 to 98.6°F) (measured orally). Fever is a manifestation of many disease states other than infection.
- Many drugs have been identified as causes of fever. Drug-induced fever is defined as persistent fever in the absence of infection or other underlying condition. The fever must coincide temporally with the administration of the offending agent and disappear promptly upon its withdrawal, after which the temperature remains normal.

## SIGNS AND SYMPTOMS

### White Blood Cell Count

- Most infections result in elevated white blood cell (WBC) counts (leukocytosis) because of the mobilization of granulocytes and/or lymphocytes to destroy invading microbes. The generally accepted range of normal values for WBC counts is between 4,000 and 10,000/mm<sup>3</sup>.
- Bacterial infections are associated with elevated granulocyte counts (neutrophils, basophils), often with increased numbers of immature forms (band neutrophils) seen in peripheral blood smears (left-shift). With infection, peripheral leukocyte counts may be very high, but are rarely higher than 30,000 to 40,000/mm<sup>3</sup>. Low neutrophil counts (neutropenia) after the onset of infection indicate an abnormal response and are generally associated with a poor prognosis for bacterial infection.
- Relative lymphocytosis, even with normal or slightly elevated total WBC counts, is generally associated with tuberculosis and viral or fungal infections. Many types of infections, however, may be accompanied by a completely normal WBC count and differential.

**TABLE 35-1** Systematic Approach for Selection of Antimicrobials

Confirm the presence of infection
Careful history and physical
Signs and symptoms
Predisposing factors
Identification of the pathogen
Collection of infected material
Stains
Serologies
Culture and sensitivity
Selection of presumptive therapy considering every infected site
Host factors
Drug factors
Monitor therapeutic response
Clinical assessment
Laboratory tests
Assessment of therapeutic failure

### Pain and Inflammation

- Pain and inflammation may accompany infection and are sometimes manifested by swelling, erythema, tenderness, and purulent drainage. Unfortunately, these signs may be apparent only if the infection is superficial or in a bone or joint.
- The manifestations of inflammation with deep-seated infections such as meningitis, pneumonia, endocarditis, and urinary tract infection must be ascertained by examining tissues or fluids. For example, the presence of polymorphonuclear leukocytes (neutrophils) in spinal fluid, lung secretions (sputum), and urine is highly suggestive of bacterial infection.

### IDENTIFICATION OF THE PATHOGEN

- Infected body materials must be sampled, if at all possible or practical, before the institution of antimicrobial therapy, for two reasons. First, a Gram stain of the material may reveal bacteria, or an acid-fast stain may detect mycobacteria or actinomycetes. Second, a delay in obtaining infected fluids or tissues until after therapy is started may result in false-negative culture results or alterations in the cellular and chemical composition of infected fluids.
- Blood cultures should be performed in the acutely ill, febrile patient. Less accessible fluids or tissues are obtained when needed to assess localized signs or symptoms (e.g., spinal fluid in meningitis, joint fluid in arthritis). Abscesses and cellulitic areas should also be aspirated.
- Caution must be used in the evaluation of positive culture results from normally sterile sites (e.g., blood, cerebrospinal fluid, joint fluid). The recovery of bacteria normally found on the skin in large quantities (e.g., coagulase-negative staphylococci, diphtheroids) from one of these sites may be a result of contamination of the specimen rather than a true infection.

## SELECTION OF PRESUMPTIVE THERAPY

- To select rational antimicrobial therapy for a given infection, a variety of factors must be considered, including the severity and acuity of the disease, host factors, factors related to the drugs used, and the necessity for use of multiple agents.
- There are generally accepted drugs of choice for the treatment of most pathogens (Table 35-2). The drugs of choice are compiled from a variety of sources and are intended as guidelines rather than specific rules for antimicrobial use.
- When selecting antimicrobial regimens, local susceptibility data should be considered whenever possible rather than information published by other institutions or national compilations.

## HOST FACTORS

- When evaluating a patient for initial or empiric therapy, the following factors should be considered:
  - ✓ Allergy or history of adverse drug reactions
  - ✓ Age of patient
  - ✓ Pregnancy
  - ✓ Metabolic abnormalities
  - ✓ Renal and hepatic function
  - ✓ Concomitant drug therapy
- Concomitant disease states. A list of selected drug interactions involving antimicrobials is provided in Table 35-3.
- Patients with diminished renal and/or hepatic function will accumulate certain drugs unless dosage is adjusted. Any concomitant therapy the patient is receiving may influence the selection of drug therapy, the dose, and monitoring.

## DRUG FACTORS

- Integration of both pharmacokinetic and pharmacodynamic properties of an agent is important when choosing antimicrobial therapy to ensure efficacy and prevent resistance. Antibiotics may demonstrate concentration-dependent (aminoglycosides and fluoroquinolones) or time-dependent ( $\beta$ -lactams) bactericidal effects.
- The importance of tissue penetration varies with the site of infection. The CNS is one body site where the importance of antimicrobial penetration is relatively well defined and correlations with clinical outcomes are established. Drugs that do not reach significant concentrations in cerebrospinal fluid should either be avoided or instilled directly when treating meningitis.
- Apart from the bloodstream, other body fluids where drug concentration data are clinically relevant include urine, synovial fluid, and peritoneal fluid.
- Pharmacokinetic parameters such as area under the concentration-time curve (AUC) and maximal plasma concentration can be predictive of treatment outcome when specific ratios of AUC or maximal plasma concentration to the minimum inhibitory concentration (MIC) are achieved. For

**TABLE 35-2** Drugs of Choice, First Choice, Alternative(s)**Gram-positive cocci***Enterococcus faecalis* (generally not as resistant to antibiotics as *Enterococcus faecium*)

Serious infection (endocarditis, meningitis, pyelonephritis with bacteremia)

Ampicillin (or penicillin G) + (gentamicin or streptomycin)

Vancomycin + (gentamicin or streptomycin), linezolid, daptomycin, tigecycline

Urinary tract infection (UTI)

Ampicillin, amoxicillin

Fosfomycin or nitrofurantoin

*E. faecium* (generally more resistant to antibiotics than *E. faecalis*)

Recommend consultation with infectious disease specialist.

Linezolid, quinupristin/dalfopristin, daptomycin, tigecycline

*Staphylococcus aureus*/*Staphylococcus epidermidis*

Methicillin (oxacillin)-sensitive

PRP<sup>a</sup>FGC,<sup>b,c</sup> trimethoprim-sulfamethoxazole, clindamycin,<sup>d</sup> ampicillin-sulbactam, or amoxicillin-clavulanate

Methicillin (oxacillin)-resistant

Vancomycin ± (gentamicin or rifampin)

Trimethoprim-sulfamethoxazole, doxycycline,<sup>e</sup> or clindamycin<sup>d</sup>; linezolid, quinupristin-dalfopristin, daptomycin, or tigecycline*Streptococcus* (groups A, B, C, G, and *Streptococcus bovis*)Penicillin G<sup>f</sup> or V<sup>g</sup> or ampicillinFGC,<sup>b,c</sup> erythromycin, azithromycin, clarithromycin<sup>h</sup>*Streptococcus pneumoniae*

Penicillin-sensitive (MIC &lt;0.1 mcg/mL)

Penicillin G or V or ampicillin

Erythromycin, FGC,<sup>b,c</sup> doxycycline, azithromycin, clarithromycin<sup>h</sup>

Penicillin intermediate (MIC 0.1–1.0 mcg/mL)

High-dose penicillin (12 million units/day for adults) or ceftriaxone<sup>c</sup> or cefotaxime<sup>c</sup>Levofloxacin,<sup>i</sup> moxifloxacin,<sup>i</sup> gemifloxacin,<sup>i</sup> telithromycin, or vancomycin

Penicillin-resistant (MIC ≥1.0 mcg/mL)

Recommend consultation with infectious disease specialist.

Vancomycin ± rifampin

Per sensitivities: TGC,<sup>c,j</sup> telithromycin, levofloxacin,<sup>i</sup> moxifloxacin,<sup>i</sup> or gemifloxacin<sup>i</sup>*Streptococcus, viridans* groupPenicillin G ± gentamicin<sup>k</sup>TGC,<sup>c,j</sup> erythromycin, azithromycin, clarithromycin,<sup>h</sup> or vancomycin ± gentamicin**Gram-negative cocci***Moraxella (Branhamella) catarrhalis*

Amoxicillin-clavulanate, ampicillin-sulbactam

Trimethoprim-sulfamethoxazole, erythromycin, azithromycin, clarithromycin,<sup>h</sup> doxycycline,<sup>e</sup> SGC,<sup>c,l</sup>TGC,<sup>c,j</sup> or TGC po<sup>c,m</sup>*Neisseria gonorrhoeae* (also give concomitant treatment for *Chlamydia trachomatis*)

Disseminated gonococcal infection

Ceftriaxone<sup>c</sup> or cefotaxime<sup>c</sup>Oral followup: Cefpodoxime,<sup>c</sup> ciprofloxacin,<sup>i</sup> or levofloxacin<sup>i</sup>

Uncomplicated infection

Ceftriaxone<sup>c</sup> or cefotaxime,<sup>c</sup> or cefpodoxime<sup>c</sup>Ciprofloxacin<sup>i</sup> or levofloxacin<sup>i</sup>*Neisseria meningitidis*

Penicillin G

TGC<sup>c,j</sup>**Gram-positive bacilli***Clostridium perfringens*

Penicillin G ± clindamycin

Metronidazole, clindamycin, doxycycline,<sup>e</sup> ceftazolin,<sup>c</sup> imipenem,<sup>n</sup> meropenem,<sup>n</sup> or ertapenem<sup>n</sup>

(continued)

**TABLE 35-2** Drugs of Choice, First Choice, Alternative(s) (Continued)

<i>Clostridium difficile</i>
Oral metronidazole
Oral vancomycin
<b>Gram-negative bacilli</b>
<i>Acinetobacter</i> spp.
Imipenem or meropenem ± aminoglycoside <sup>o</sup> (amikacin usually most effective)
Ciprofloxacin, <sup>i</sup> ampicillin-sulbactam, colistin, or tigecycline
<i>Bacteroides fragilis</i> (and others)
Metronidazole
BLIC, <sup>p</sup> clindamycin, cephamycins, <sup>c,q</sup> or carbapenem <sup>n</sup>
<i>Enterobacter</i> spp.
Imipenem, meropenem, ertapenem, or ceftipime ± aminoglycoside <sup>p</sup>
Ciprofloxacin, <sup>i</sup> levofloxacin, <sup>i</sup> piperacillin-tazobactam, ticarcillin-clavulanate, or tigecycline
<i>Escherichia coli</i>
Meningitis
TGC <sup>c,j</sup> or meropenem
Systemic infection
TGC <sup>c,j</sup>
Ampicillin-sulbactam, FGC, <sup>b,c</sup> BL/BLI, <sup>p</sup> fluoroquinolone, <sup>i,n,r</sup> imipenem, <sup>n</sup> meropenem <sup>n</sup>
UTI
Most oral agents: check sensitivities
Ampicillin, amoxicillin-clavulanate, doxycycline, <sup>e</sup> or cephalexin <sup>c</sup>
Aminoglycoside, <sup>p</sup> FGC, <sup>b,c</sup> nitrofurantoin, fluoroquinolone <sup>i,n,r</sup>
<i>Gardnerella vaginalis</i>
Metronidazole
Clindamycin
<i>Haemophilus influenzae</i>
Meningitis
Cefotaxime <sup>c</sup> or ceftriaxone <sup>c</sup>
Meropenem <sup>n</sup> or chloramphenicol <sup>s</sup>
Other infections
BLIC, <sup>p</sup> or if β-lactamase-negative, ampicillin or amoxicillin
Trimethoprim-sulfamethoxazole, cefuroxime, <sup>c</sup> azithromycin, clarithromycin, <sup>h</sup> or fluoroquinolone <sup>i,n,r</sup>
<i>Klebsiella pneumoniae</i>
TGC <sup>e,k</sup> (if UTI only: aminoglycoside <sup>p</sup> )
Cefuroxime, <sup>e</sup> fluoroquinolone, <sup>b,r</sup> BLIC, <sup>g</sup> imipenem, <sup>o</sup> meropenem, <sup>o</sup> or ertapenem
<i>Legionella</i> spp.
Erythromycin ± rifampin or fluoroquinolone <sup>i,r</sup>
Trimethoprim-sulfamethoxazole, clarithromycin, <sup>h</sup> azithromycin, or doxycycline <sup>e</sup>
<i>Pasteurella multocida</i>
Penicillin G, ampicillin, amoxicillin
Doxycycline, <sup>e</sup> BLIC, <sup>p</sup> trimethoprim-sulfamethoxazole, or ceftriaxone <sup>c,j</sup>
<i>Proteus mirabilis</i>
Ampicillin
Trimethoprim-sulfamethoxazole, most antibiotics except PRP <sup>a</sup>
<i>Proteus</i> (indole-positive) (including <i>Providencia rettgeri</i> , <i>Morganella morganii</i> , and <i>Proteus vulgaris</i> )
TGC <sup>c,h</sup> or fluoroquinolone <sup>i,r</sup>
BLIC, <sup>p</sup> aztreonam, <sup>t</sup> imipenem, <sup>n</sup> or TGC po <sup>c,m</sup>
<i>Providencia stuartii</i>
TGC <sup>c,i</sup> or fluoroquinolone <sup>i,r</sup>
Trimethoprim-sulfamethoxazole, aztreonam, <sup>t</sup> imipenem, <sup>n</sup> meropenem, <sup>n</sup> or ertapenem
<i>Pseudomonas aeruginosa</i>
Ceftipime, <sup>c</sup> ceftazidime, <sup>c</sup> piperacillin-tazobactam, or ticarcillin-clavulanate plus aminoglycoside <sup>e</sup>
Ciprofloxacin, <sup>i</sup> levofloxacin, <sup>i</sup> aztreonam, <sup>t</sup> imipenem, <sup>n</sup> meropenem, <sup>n</sup> or colistin

(continued)

**TABLE 35-2** Drugs of Choice, First Choice, Alternative(s) (Continued)*Pseudomonas aeruginosa* cont.

UTI only: aminoglycoside<sup>g</sup>  
 Ciprofloxacin,<sup>i</sup> levofloxacin<sup>i</sup>

*Salmonella typhi*

Ciprofloxacin,<sup>i</sup> levofloxacin,<sup>i</sup> ceftriaxone,<sup>c</sup> or cefotaxime<sup>e</sup>  
 Trimethoprim-sulfamethoxazole

*Serratia marcescens*

Piperacillin-tazobactam, ticarcillin-clavulanate, or TGC<sup>c,j</sup> ± gentamicin  
 Trimethoprim-sulfamethoxazole, ciprofloxacin,<sup>i</sup> levofloxacin,<sup>i</sup> aztreonam,<sup>t</sup> imipenem,<sup>n</sup> meropenem,<sup>n</sup> or ertapenem

*Stenotrophomonas (Xanthomonas) maltophilia*

Trimethoprim-sulfamethoxazole  
 Generally very resistant to all antimicrobials; check sensitivities to ceftazidime,<sup>e</sup> ticarcillin-clavulanate, doxycycline,<sup>e</sup> and minocycline<sup>e</sup>

**Miscellaneous microorganisms***Chlamydia pneumoniae*

Doxycycline<sup>e</sup>  
 Erythromycin, azithromycin, clarithromycin,<sup>h</sup> telithromycin, or fluoroquinolone<sup>f,t</sup>

*C. trachomatis*

Doxycycline<sup>e</sup> or azithromycin  
 Levofloxacin<sup>i</sup> or ofloxacin<sup>i</sup>

*Mycoplasma pneumoniae*

Erythromycin, azithromycin, clarithromycin<sup>h</sup>  
 Doxycycline<sup>e</sup> or fluoroquinolone<sup>f,t</sup>

**Spirochetes***Treponema pallidum*

Neurosyphilis  
 Penicillin G  
 Ceftriaxone<sup>c</sup>  
 Primary or secondary  
 Benzathine penicillin G  
 Doxycycline<sup>e</sup> or ceftriaxone<sup>c</sup>

*Borrelia burgdorferi* (choice depends on stage of disease)

Ceftriaxone<sup>c</sup> or cefuroxime axetil,<sup>c</sup> doxycycline,<sup>e</sup> amoxicillin  
 High-dose penicillin, cefotaxime,<sup>c</sup> or azithromycin

BLIC,  $\beta$ -lactamase inhibitor combination; BL/BLI,  $\beta$ -lactamase/ $\beta$ -lactamase inhibitor; FGC, first-generation cephalosporin; MIC, minimal inhibitory concentration; PRP, penicillinase-resistant penicillin; SGC, second-generation cephalosporin; TGC, third-generation cephalosporin.

<sup>a</sup>Penicillinase-resistant penicillin: nafcillin or oxacillin.

<sup>b</sup>First-generation cephalosporins—IV: cefazolin; po: cephalexin, cephhradine, or cefadroxil.

<sup>c</sup>Some penicillin-allergic patients may react to cephalosporins.

<sup>d</sup>Not reliably bactericidal; should not be used for endocarditis.

<sup>e</sup>Not for use in pregnant patients or children younger than 8 years old.

<sup>f</sup>Either aqueous penicillin G or benzathine penicillin G (pharyngitis only).

<sup>g</sup>Only for soft-tissue infections or upper respiratory infections (pharyngitis, otitis media).

<sup>h</sup>Do not use in pregnant patients.

<sup>i</sup>Not for use in pregnant patients or children younger than 18 years old.

<sup>j</sup>Third-generation cephalosporins—IV: cefotaxime, ceftriaxone.

<sup>k</sup>Gentamicin should be added if tolerance or moderately susceptible (MIC >0.1 g/mL) organisms are encountered; streptomycin is used but can be more toxic.

<sup>l</sup>Second-generation cephalosporins—IV: cefuroxime; po: cefaclor, cefditoren, cefprozil, cefuroxime axetil, and loracarbef.

<sup>m</sup>Third-generation cephalosporins—po: cefdinir, cefixime, cefetamet, cefpodoxime proxetil, and cefbutenol.

<sup>n</sup>Reserve for serious infection.

<sup>o</sup>Aminoglycosides: gentamicin, tobramycin, and amikacin; use per sensitivities.

<sup>p</sup> $\beta$ -Lactamase inhibitor combination—IV: ampicillin-sulbactam, piperacillin-tazobactam, ticarcillin-clavulanate; po: amoxicillin-clavulanate.

<sup>q</sup>Cefoxitin.

<sup>r</sup>IV/po: ciprofloxacin, levofloxacin, and moxifloxacin.

<sup>s</sup>Reserve for serious infection when less toxic drugs are not effective.

<sup>t</sup>Generally reserved for patients with hypersensitivity reactions to penicillin.

**TABLE 35-3 Major Drug Interactions with Antimicrobials**

Antimicrobial	Other Agent(s)	Mechanism of Action/Effect	Clinical Management
Aminoglycosides	Neuromuscular blocking agents Nephrotoxins (N) or ototoxins (O) (e.g., amphotericin B (N), cisplatin (N/O), cyclosporine (N), furosemide (O), NSAIDs (N), radio contrast (N), vancomycin (N))	Additive adverse effects Additive adverse effects	Avoid Monitor aminoglycoside SDC and renal function
Amphotericin B	Nephrotoxins (e.g., aminoglycosides, cidofovir, cyclosporine, foscarnet, pentamidine)	Additive adverse effects	Monitor renal function
Azoles	See Chap. 125 in <i>Pharmacotherapy: A Pathophysiologic Approach</i> , seventh edition, page 1998.		
Chloramphenicol	Phenytoin, tolbutamide, ethanol	Decreased metabolism of other agents	Monitor phenytoin SDC, blood glucose
Foscarnet	Pentamidine IV	Increased risk of severe nephrotoxicity/hypocalcemia	Monitor renal function/serum calcium
Isoniazid	Carbamazepine, phenytoin	Decreased metabolism of other agents (nausea, vomiting, nystagmus, ataxia)	Monitor drug SDC
Macrolides/azalides	Digoxin Theophylline	Decreased digoxin bioavailability and metabolism Decreased metabolism of theophylline	Monitor digoxin SDC; avoid if possible Monitor theophylline SDC
Metronidazole	Ethanol (drugs containing ethanol)	Disulfiram-like reaction	Avoid
Penicillins and cephalosporins	Probenecid, aspirin	Blocked excretion of $\beta$ -lactams	Use if prolonged high concentration of $\beta$ -lactam desirable
Ciprofloxacin/norfloxacin	Theophylline	Decreased metabolism of theophylline	Monitor theophylline
Quinolones	Class Ia and III antiarrhythmics Multivalent cations (antacids, iron, sucralfate, zinc, vitamins, dairy, citric acid) didanosine	Increased Q-T interval Decreased absorption of quinolone	Avoid Separate by 2 hours
Rifampin	Azoles, cyclosporine, methadone propranolol, PIs, oral contraceptives, tacrolimus, warfarin	Increased metabolism of other agent	Avoid if possible
Sulfonamides	Sulfonylureas, phenytoin, warfarin	Decreased metabolism of other agent	Monitor blood glucose, SDC, PT
Tetracyclines	Antacids, iron, calcium, sucralfate Digoxin	Decreased absorption of tetracycline Decreased digoxin bioavailability and metabolism	Separate by 2 hours Monitor digoxin SDC; avoid if possible

NSAIDs, nonsteroidal antiinflammatory drugs; PI, protease inhibitor; PT, prothrombin time; SDC, serum drug concentrations.

Azalides: azithromycin; Azoles: fluconazole, itraconazole, ketoconazole, and voriconazole; Macrolides: erythromycin, clarithromycin; Protease inhibitors: amprenavir, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, and saquinavir; Quinolones: ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin.

some agents, the ratio of AUC to MIC, peak-to-MIC ratio, or the time that the drug concentration is above the MIC may predict efficacy.

- The most important pharmacodynamic relationship for antimicrobials that display time-dependent bactericidal effects is the duration that drug concentrations exceed the MIC.

## COMBINATION ANTIMICROBIAL THERAPY

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- Combinations of antimicrobials are generally used to broaden the spectrum of coverage for empiric therapy, achieve synergistic activity against the infecting organism, and prevent the emergence of resistance.
- Increasing the coverage of antimicrobial therapy is generally necessary in mixed infections where multiple organisms are likely to be present, such as intraabdominal and female pelvic infections in which a variety of aerobic and anaerobic bacteria may produce disease. Another clinical situation in which increased spectrum of activity is desirable is with nosocomial infection.

### Synergism

- The achievement of synergistic antimicrobial activity is advantageous for infections caused by gram-negative bacilli in immunosuppressed patients.
- Traditionally, combinations of aminoglycosides and  $\beta$ -lactams have been used since these drugs together generally act synergistically against a wide variety of bacteria. However, the data supporting superior efficacy of synergistic over nonsynergistic combinations are weak.
- Synergistic combinations may produce better results in infections caused by *Pseudomonas aeruginosa*, in certain infections caused by *Enterococcus* spp.
- The use of combinations to prevent the emergence of resistance is widely applied but not often realized. The only circumstance where this has been clearly effective is in the treatment of tuberculosis.

### Disadvantages of Combination Therapy

- Although there are potentially beneficial effects from combining drugs, there are also potential disadvantages, including increased cost, greater risk of drug toxicity, and superinfection with even more resistant bacteria.
- Some combinations of antimicrobials are potentially antagonistic. For example, agents that are capable of inducing  $\beta$ -lactamase production in bacteria (such as ceftiofur) may antagonize the effects of enzyme-labile drugs such as penicillins or imipenem.

## MONITORING THERAPEUTIC RESPONSE

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- After antimicrobial therapy has been instituted, the patient must be monitored carefully for a therapeutic response. Culture and sensitivity reports from specimens collected must be reviewed.
- Use of agents with the narrowest spectrum of activity against identified pathogens is recommended.
- Patient monitoring should include a variety of parameters, including white blood cell count, temperature, signs and symptoms of infection, appetite, radiologic studies as appropriate, and determination of antimicrobial concentrations in body fluids.

- As the patient improves the route of antibiotic administration should be reevaluated. Switch to oral therapy is an accepted practice for many infections. Criteria favoring switch to oral therapy include:
  - ✓ Overall clinical improvement
  - ✓ Lack of fever for 8 to 24 hours
  - ✓ Decreased WBC
  - ✓ A functioning GI tract

## FAILURE OF ANTIMICROBIAL THERAPY

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- A variety of factors may be responsible for apparent lack of response to therapy. It is possible that the disease is not infectious or nonbacterial in origin, or there is an undetected pathogen. Other factors include those directly related to drug selection, the host, or the pathogen. Laboratory error in identification and/or susceptibility testing errors are rare.

### Failures Caused by Drug Selection

- Factors directly related to the drug selection include an inappropriate selection of drug, dosage, or route of administration. Malabsorption of a drug product because of GI disease (e.g., short-bowel syndrome) or a drug interaction (e.g., complexation of fluoroquinolones with multivalent cations resulting in reduced absorption) may lead to potentially subtherapeutic serum concentrations.
- Accelerated drug elimination is also a possible reason for failure and may occur in patients with cystic fibrosis or during pregnancy, when more rapid clearance or larger volumes of distribution may result in low serum concentrations, particularly for aminoglycosides.
- A common cause of failure of therapy is poor penetration into the site of infection. This is especially true for the so-called privileged sites such as the CNS, the eye, and the prostate gland.

### Failures Caused by Host Factors

- Patients who are immunosuppressed (e.g., granulocytopenia from chemotherapy, acquired immune deficiency syndrome) may respond poorly to therapy because their own defenses are inadequate to eradicate the infection despite seemingly adequate drug regimens.
- Other host factors are related to the necessity for surgical drainage of abscesses or removal of foreign bodies and/or necrotic tissue. If these situations are not corrected, they result in persistent infection and, occasionally, bacteremia, despite adequate antimicrobial therapy.

### Failures Caused by Microorganisms

- Factors related to the pathogen include the development of drug resistance during therapy. Primary resistance refers to the intrinsic resistance of the pathogens producing the infection. However, acquisition of resistance during treatment has become a major problem as well.
- The increase in resistance among pathogenic organisms is believed to be due, in large part, to continued overuse of antimicrobials in the commu-

nity, as well as in hospitals, and the increasing prevalence of immunosuppressed patients receiving long-term suppressive antimicrobials for the prevention of infections.

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*See Chap. 109, Antimicrobial Regimen Selection, authored by David S. Burgess, for a more detailed discussion of this topic.*

## DEFINITION

- CNS infections include a wide variety of clinical conditions and etiologies: meningitis, meningoencephalitis, encephalitis, brain and meningeal abscesses, and shunt infections. The focus of this chapter is meningitis.

## PATHOPHYSIOLOGY

- Infections are the result of hematogenous spread from a primary infection site, seeding from a parameningeal focus, reactivation from a latent site, trauma, or congenital defects in the CNS.
- Passive and active exposure to cigarette smoke and the presence of a cochlear implant that includes a positioner both increase the risk of bacterial meningitis.
- CNS infections may be caused by a variety of bacteria, fungi, viruses, and parasites. The most common causes of bacterial meningitis include *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Listeria monocytogenes*, and *Haemophilus influenzae*.
- The critical first step in the acquisition of acute bacterial meningitis is nasopharyngeal colonization of the host by the bacterial pathogen. The bacteria first attach themselves to nasopharyngeal epithelial cells and are then phagocytized into the host's bloodstream.
- A common characteristic of most CNS bacterial pathogens (e.g., *H. influenzae*, *Escherichia coli*, and *N. meningitidis*) is the presence of an extensive polysaccharide capsule that is resistant to neutrophil phagocytosis and complement opsonization.
- Bacterial cell death causes the release of cell wall components such as lipopolysaccharide, lipid A (endotoxin), lipoteichoic acid, teichoic acid, and peptidoglycan depending on whether the pathogen is gram-positive or gram-negative. These cell wall components cause capillary endothelial cells and CNS macrophages to release cytokines (interleukin-1, tumor necrosis factor, and other inflammatory mediators). Proteolytic products and toxic oxygen radicals cause an alteration of the blood-brain barrier while platelet-activating factor activates coagulation and arachidonic acid metabolites stimulate vasodilation. These events lead to cerebral edema, elevated intracranial pressure, cerebrospinal fluid (CSF) pleocytosis, decreased cerebral blood flow, cerebral ischemia, and death.

## CLINICAL PRESENTATION

## GENERAL

- Meningitis causes CSF fluid changes, and these changes can be used as diagnostic markers of infection (Table 36-1).

**TABLE 36-1** Mean Values of the Components of Normal and Abnormal Cerebrospinal Fluid

Type	Normal	Bacterial	Viral	Fungal	Tuberculosis
WBC (cells/mm <sup>3</sup> )	<5	1,000–5,000	100–1,000	40–400	100–500
Differential (%)	>90 <sup>a</sup>	≥80 PMNs	50 <sup>b,c</sup>	>50 <sup>b</sup>	>80 <sup>b,c</sup>
Protein (mg/dL)	<50	100–500	30–150	40–150	≤40–150
Glucose (mg/dL)	50–66% simultaneous serum value	<40 (<60% simultaneous serum value)	<30–70	<30–70	<30–70

<sup>a</sup>Monocytes.<sup>b</sup>Lymphocytes.<sup>c</sup>Initial cerebrospinal fluid, white blood cell (WBC) count may reveal a predominance of polymorphonuclear neutrophils (PMNs).

- Clinical presentation varies with age, and, generally, the younger the patient, the more atypical and the less pronounced is the clinical picture.
- Up to 50% of patients may receive antibiotics before a diagnosis of meningitis is made, delaying presentation to the hospital. Prior antibiotic therapy may cause the Gram stain and CSF culture to be negative, but the antibiotic therapy rarely affects CSF protein or glucose.
- Classic signs and symptoms include fever, nuchal rigidity, altered mental status, chills, vomiting, photophobia, and severe headache. Kernig's and Brudzinski's signs may be present but are poorly sensitive and frequently absent in children. Other signs and symptoms include irritability, delirium, drowsiness, lethargy, and coma.
- Clinical signs and symptoms in young children may include bulging fontanelle, apneas, purpuric rash, and convulsions in addition to those just mentioned.
- Seizures occur more commonly in children (20% to 30%) than in adults (0% to 12%).

## DIFFERENTIAL SIGNS AND SYMPTOMS

- Purpuric and petechial skin lesions typically indicate meningococcal involvement, although the lesions may be present with *H. influenzae* meningitis. Rashes rarely occur with pneumococcal meningitis.
- *H. influenzae* meningitis and meningococcal meningitis both can cause involvement of the joints during the illness.
- A history of head trauma with or without skull fracture or presence of a chronically draining ear is associated with pneumococcal involvement.

## LABORATORY TESTS

- Several tubes of CSF are collected via lumbar puncture for chemistry, microbiology, and hematology tests. Theoretically, the first tube has a higher likelihood of being contaminated with both blood and bacteria during the puncture, although the total volume is more important in practice than the tube cultured. CSF should not be refrigerated or stored on ice.
- Analysis of CSF chemistries typically includes measurement of glucose and total protein concentrations. An elevated CSF protein of 100 mg/dL or greater

and a CSF glucose concentration of less than 50% of the simultaneously obtained peripheral value suggest bacterial meningitis (see Table 36-1).

- The values for CSF glucose, protein, and WBC concentrations found with bacterial meningitis overlap significantly with those for viral, tuberculous, and fungal meningitis (see Table 36-1). Therefore, CSF white blood cell (WBC) counts and CSF glucose and protein concentrations cannot always distinguish the different etiologies of meningitis.

## OTHER DIAGNOSTIC TESTS

- Blood and other specimens should be cultured according to clinical judgment because meningitis frequently can arise via hematogenous dissemination or can be associated with infections at other sites. A minimum of 20 mL of blood in each of two to three separate cultures per each 24-hour period is necessary for the detection of most bacteremias.
- Gram stain and culture of the CSF are the most important laboratory tests performed for bacterial meningitis. When performed before antibiotic therapy is initiated, Gram stain is both rapid and sensitive and can confirm the diagnosis of bacterial meningitis in 75% to 90% of cases.
- Polymerase chain reaction (PCR) techniques can be used to diagnose meningitis caused by *N. meningitidis*, *S. pneumoniae*, and *H. influenzae* type b (Hib). PCR is considered to be highly sensitive and specific. PCR testing of the CSF is the preferred method of diagnosing most viral meningitis infections.
- Latex fixation, latex coagglutination, and enzyme immunoassay tests provide for the rapid identification of several bacterial causes of meningitis, including *S. pneumoniae*, *N. meningitidis*, and Hib. The rapid antigen tests should be used in situations in which the Gram stain is negative.
- Diagnosis of tuberculosis meningitis employs acid-fast staining, culture, and PCR of the CSF.

## DESIRED OUTCOME

- The goals of treatment include eradication of infection with amelioration of signs and symptoms, and prevention of neurologic sequelae, such as seizures, deafness, coma, and death.

## TREATMENT

### GENERAL PRINCIPLES

- The administration of fluids, electrolytes, antipyretics, analgesia, and other supportive measures are particularly important for patients presenting with acute bacterial meningitis.
- Antibiotic dosages for treatment of CNS infections must be maximized to optimize penetration to the site of infection.
- Meningitis caused by *S. pneumoniae* is successfully treated with 10 to 14 days of antibiotic therapy. Meningitis caused by *N. meningitidis* usually can be treated with a 7-day course. A longer course,  $\geq 21$  days, is recommended

**TABLE 36-2** Bacterial Meningitis: Most Likely Pathogens and Empirical Therapy by Age Group

Age Commonly Affected	Most Likely Organisms	Empirical Therapy	Risk Factors for All Age Groups
Newborn–1 month	Group B <i>Streptococcus</i> Gram-negative enterics <sup>a</sup> <i>Listeria monocytogenes</i>	Ampicillin plus cefotaxime or ceftriaxone or aminoglycoside	Respiratory tract infection Otitis media Mastoiditis
1 month–4 years	<i>S. pneumoniae</i> <i>N. meningitidis</i> <i>H. influenzae</i>	Vancomycin <sup>b</sup> and cefotaxime or ceftriaxone	Head trauma Alcoholism High-dose steroids
5–29 years	<i>N. meningitidis</i> <i>S. pneumoniae</i> <i>H. influenzae</i>	Vancomycin <sup>b</sup> and cefotaxime or ceftriaxone	Splenectomy Sickle cell disease Immunoglobulin deficiency
30–60 years	<i>S. pneumoniae</i> <i>N. meningitidis</i> <i>S. pneumoniae</i>	Vancomycin <sup>b</sup> and cefotaxime or ceftriaxone	Immunosuppression
>60 years	Gram-negative enterics <i>L. monocytogenes</i>	Vancomycin <sup>b</sup> plus ampicillin plus cefotaxime or ceftriaxone	

<sup>a</sup>*Escherichia coli*, *Klebsiella* species, *Enterobacter* species common.

<sup>b</sup>Vancomycin use should be based on local incidence of penicillin-resistant *S. pneumoniae* and until cefotaxime or ceftriaxone minimum inhibitory concentration results are available.

for patients infected with *L. monocytogenes*. Therapy should be individualized, and some patients may require longer courses.

## PHARMACOLOGIC TREATMENT

- Empiric antimicrobial therapy should be instituted as soon as possible to eradicate the causative organism (Table 36-2). Antimicrobial therapy should last at least 48 to 72 hours or until the diagnosis of bacterial meningitis can be ruled out. Continued therapy should be based on the assessment of clinical improvement, cultures, and susceptibility testing results. Once a pathogen is identified, antibiotic therapy should be tailored to the specific pathogen.
- With increased meningeal inflammation, there will be greater antibiotic penetration (Table 36-3). Problems of CSF penetration may be overcome by direct instillation of antibiotics by intrathecal, intracisternal, or intraventricular routes of administration (Table 36-4).

### Dexamethasone as an Adjunctive Treatment for Meningitis

- In addition to antibiotics, **dexamethasone** is a commonly used therapy for the treatment of pediatric meningitis. Several studies have shown that dexamethasone causes a significant improvement in CSF concentrations of proinflammatory cytokines, glucose, protein, and lactate as well as a significantly lower incidence of neurologic sequelae commonly associated with bacterial meningitis. However, there are conflicting results.

**TABLE 36-3** Penetration of Antimicrobial Agents into the Cerebrospinal Fluid (CSF)**Therapeutic levels in CSF with or without inflammation**

Chloramphenicol	Pyrazinamide
Cycloserine	Rifampin
Ethionamide	Sulfonamides
Isoniazid	Trimethoprim
Metronidazole	

**Therapeutic levels in CSF with inflammation of meninges**

Acyclovir	Ganciclovir
Ampicillin ± sulbactam	Imipenem
Aztreonam	Levofloxacin
Carbenicillin	Linezolid
Cefotaxime	Meropenem
Ceftazidime	Mezlocillin
Ceftizoxime	Moxifloxacin
Ceftriaxone	Nafcillin
Cefuroxime	Ofloxacin
Ciprofloxacin	Penicillin G
Colistin	Piperacillin
Daptomycin	Pyrimethamine
Ethambutol	Quinupristin/dalfopristin
Fluconazole	Ticarillin ± clavulanic acid
Flucytosine	Vancomycin
Foscarnet	Vidarabine

**Nontherapeutic levels in CSF with or without inflammation**

Aminoglycosides	Cephalosporins (second-generation) <sup>a</sup>
Amphotericin B	Clindamycin <sup>b</sup>
Cefoperazone	Itraconazole <sup>c</sup>
Cephalosporins (first-generation)	Ketoconazole

<sup>a</sup>Cefuroxime is an exception.<sup>b</sup>Achieves therapeutic brain tissue concentrations.<sup>c</sup>Achieves therapeutic concentrations for *Cryptococcus neoformans* therapy.

- The American Academy of Pediatrics suggests that the use of dexamethasone be considered for infants and children aged 2 months or older with pneumococcal meningitis and that it be given to those with *H. influenzae* meningitis. The commonly used IV dexamethasone dose is 0.15 mg/kg every 6 hours for 4 days. Alternatively, dexamethasone given 0.15 mg/kg every 6 hours for 2 days or 0.4 mg/kg every 12 hours for 2 days is equally effective and a potentially less toxic regimen.
- Dexamethasone should be administered prior to the first antibiotic dose and not after antibiotics have already been started. Serum hemoglobin and stool guaiac should be monitored for evidence of GI bleeding.

***Neisseria meningitidis* (Meningococcus)**

- *N. meningitidis* meningitis is the leading cause of bacterial meningitis in children and young adults in the United States. Most cases usually occur in the winter or spring, at a time when viral meningitis is relatively uncommon.

**TABLE 36-4** Intraventricular and Intrathecal Antibiotic Dosage Recommendation

Antibiotic	Dose (mg)	Expected CSF Concentration <sup>a</sup> (mg/L)
Ampicillin	10–50	60–300
Methicillin	25–100	160–600
Nafcillin	75	500
Cephalothin	25–100	160–600
Chloramphenicol	25–100	160–600
Gentamicin	1–10	6–60
Quinupristin/dalfopristin	1–2	7–13
Tobramycin	1–10	6–60
Vancomycin	5	30
Amphotericin B	0.05–0.25 mg/day to 0.05–1 mg 1–3 times weekly	–

CSF, cerebrospinal fluid.

<sup>a</sup>Assumes adult CSF volume = 150 mL.

### Clinical Presentation

- Approximately 10 to 14 days after the onset of the disease and despite successful treatment, the patient develops a characteristic immunologic reaction of fever, arthritis (usually involving large joints), and pericarditis.
- The synovial fluid is characterized by a large number of polymorphonuclear cells, elevated protein concentrations, normal glucose concentrations, and sterile cultures.
- Deafness unilaterally, or more commonly bilaterally, may develop early or late in the disease course.
- Approximately 50% of patients with meningococcal meningitis have purpuric lesions, petechiae, or both. Patients may have an obvious or subclinical picture of disseminated intravascular coagulation, which may progress to infarction of the adrenal glands and renal cortex and cause widespread thrombosis.

### Treatment and Prevention

- Aggressive, early intervention with **high-dose IV crystalline penicillin G**, 50,000 units/kg every 4 hours, is usually recommended for treatment of *N. meningitidis* meningitis.
- **Chloramphenicol** may be used in place of penicillin G. Several third-generation cephalosporins (e.g., **cefotaxime**, **ceftizoxime**, **ceftriaxone**, and **cefuroxime**) approved for the treatment of meningitis are acceptable alternatives to penicillin G (Table 36-5). Meropenem and fluoroquinolones are suitable alternatives for treatment of penicillin-nonsusceptible meningococci.
- Close contacts of patients contracting *N. meningitidis* meningitis are at an increased risk of developing meningitis. Prophylaxis of contacts should be started only after consultation with the local health department.
- Adult patients should receive 600 mg of *rifampin* orally every 12 hours for four doses. Children 1 month to 12 years of age should receive 10 mg/kg of rifampin orally every 12 hours for four doses, and children younger than 1 month should receive 5 mg/kg orally every 12 hours for four doses.

**TABLE 36-5** Antimicrobial Agents of First Choice and Alternative Choice for Treatment of Meningitis Caused by Gram-Positive and Gram-Negative Microorganisms

<b>Organism</b>	<b>Antibiotic of First Choice</b>	<b>Alternative Antibiotics</b>	<b>Recommended Duration of Therapy</b>
<b>Gram-positive</b>			
<i>Streptococcus pneumoniae</i>			10–14 days
Penicillin susceptible	Penicillin G or ampicillin (A-III)	Cefotaxime (A-III), ceftriaxone (A-III), chloramphenicol (A-III)	
Penicillin intermediate	Cefotaxime or ceftriaxone (A-III)	Cefepime (B-II), meropenem (B-II), moxifloxacin (B-II), linezolid (C-III)	
Penicillin resistant	Vancomycin <sup>a</sup> plus cefotaxime or ceftriaxone (A-III)	Cefepime (B-II), meropenem (B-II), moxifloxacin (B-II), linezolid (C-III)	
Group B <i>Streptococcus</i>	Penicillin G or ampicillin ± gentamicin <sup>a</sup> (A-III)	Cefotaxime (B-III), ceftriaxone (B-III), chloramphenicol (B-III)	14–21 days
<i>Staphylococcus aureus</i>			14–21 days <sup>e</sup>
Methicillin susceptible	Nafcillin or oxacillin (A-III)	Vancomycin <sup>a</sup> (A-III), meropenem (B-III)	
Methicillin resistant	Vancomycin <sup>a</sup> (A-III)	Trimethoprim–sulfamethoxazole (A-III), linezolid (B-III)	
<i>Staphylococcus epidermidis</i>	Vancomycin <sup>a</sup> (A-III)	Linezolid (B-III)	14–21 days <sup>e</sup>
<i>Listeria monocytogenes</i>	Penicillin G or ampicillin ± gentamicin <sup>a</sup> (A-III)	Trimethoprim–sulfamethoxazole (A-III), meropenem (B-III)	≥21 days

*(continued)*

**TABLE 36-5** Antimicrobial Agents of First Choice and Alternative Choice for Treatment of Meningitis Caused by Gram-Positive and Gram-Negative Microorganisms (Continued)

Organism	Antibiotic of First Choice	Alternative Antibiotics	Recommended Duration of Therapy
<b>Gram-negative</b>			
<i>Neisseria meningitidis</i>			7 days
Penicillin susceptible	Penicillin G or ampicillin (A-III)	Cefotaxime (A-III), ceftriaxone (A-III), chloramphenicol (A-III)	
Penicillin resistant	Cefotaxime or ceftriaxone (A-III)	Chloramphenicol (A-III), meropenem (A-III), fluoroquinolone (A-III)	
<i>Haemophilus influenzae</i>			7 days
$\beta$ -Lactamase negative	Ampicillin (A-III)	Cefotaxime (A-III), ceftriaxone (A-III), chloramphenicol (A-III), cefepime (A-III), fluoroquinolone (A-III)	
$\beta$ -Lactamase positive	Cefotaxime or ceftriaxone (A-I)	Cefepime (A-I), fluoroquinolone (A-III), chloramphenicol (A-III)	
<i>Enterobacteriaceae</i> <sup>d</sup>	Cefotaxime or ceftriaxone (A-II)	Cefepime (A-III), fluoroquinolone (A-III), meropenem (A-II), aztreonam (A-III)	21 days
<i>Pseudomonas aeruginosa</i>	Cefepime or ceftazidime (A-II) $\pm$ tobramycin <sup>a,b</sup> (A-III)	Ciprofloxacin (A-III), meropenem (A-III), piperacillin plus tobramycin <sup>a,b</sup> (A-III), colistin sulfomethate <sup>a,c</sup> (B-III), aztreonam (A-III)	21 days

Strength of recommendation: A, good evidence to support a recommendation for use; should always be offered; B, moderate evidence to support a recommendation for use; should generally be offered.

Quality of evidence: I, evidence from  $\geq 1$  properly randomized, controlled trial; II, evidence from  $\leq 1$  well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from  $>1$  center) or from multiple time-series; III, evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

<sup>a</sup>Monitor drug levels in serum.

<sup>b</sup>Direct central nervous system administration may be added; see Table 110-6, in *Pharmacotherapy: A Pathophysiologic Approach*, seventh edition, for dosage.

<sup>c</sup>Should be reserved for multidrug-resistant pseudomonal or *Acinetobacter* infections for which all other therapeutic options have been exhausted.

<sup>d</sup>Includes *Escherichia coli* and *Klebsiella* species.

<sup>e</sup>Based on clinical experience; no clear recommendations.

***Streptococcus pneumoniae* (Pneumococcus or Diplococcus)**

- *S. pneumoniae* is the leading cause of meningitis in adults. Pneumococcal meningitis occurs in the very young (less than 2 years of age) and the very old.
- Neurologic complications, such as coma and seizures, are common.

**Treatment**

(See Tables 36-5 and 36-6.)

**TABLE 36-6** Dosing of Antimicrobial Agents by Age Group

Antimicrobial Agent	Infants and Children	Adults
<b>Antibacterials</b>		
Ampicillin	75 mg/kg every 6 hours	2 g every 4 hours
Aztreonam		2 g every 6–8 hours
Cefepime	50 mg/kg every 8 hours	2 g every 8 hours
Cefotaxime	75 mg/kg every 6–8 hours	2 g every 4–6 hours
Ceftazidime	50 mg/kg every 8 hours	2 g every 8 hours
Ceftriaxone	100 mg/kg once daily	2 g every 12–24 hours
Chloramphenicol	25 mg/kg every 6 hours	1–1.5 g every 6 hours
Ciprofloxacin	10 mg/kg every 8 hours	400 mg every 8–12 hours
Colistin <sup>a,c</sup>	5 mg/kg once daily	5 mg/kg once daily
Gentamicin <sup>a,b</sup>	2.5 mg/kg every 8 hours	2 mg/kg every 8 hours
Linezolid	10 mg/kg every 8 hours	600 mg every 12 hours
Meropenem	40 mg/kg every 8 hours	2 mg every 8 hours
Moxifloxacin		400 mg once daily
Oxacillin/nafticillin	50 mg/kg every 6 hours	2 mg every 4 hours
Penicillin G	0.05 million units/kg every 4–6 hours	4 million units every 4 hours
Piperacillin	50 mg/kg every 4–6 hours	3 g every 4–6 hours
Tobramycin <sup>a,b</sup>	2.5 mg/kg every 8 hours	2 mg/kg every 8 hours
Trimethoprim–sulfamethoxazole <sup>d</sup>	5 mg/kg every 6–12 hours	5 mg/kg every 6–12 hours
Vancomycin <sup>d</sup>	15 mg/kg every 6 hours	15 mg/kg every 8–12 hours
<b>Antimycobacterials</b>		
Isoniazide	10–15 mg/kg once daily	5 mg/kg once daily
Rifampin	10–20 mg/kg once daily	600 mg once daily
Pyrazinamide	15–30 mg/kg once daily	15–30 mg/kg once daily
Ethambutol	15–25 mg/kg once daily	15–25 mg/kg once daily
<b>Antifungals</b>		
Amphotericin B		0.7–1 mg/kg once daily
Lipid amphotericin B		4 mg/kg once daily
Flucytosine		25 mg/kg every 6 hours
Fluconazole		400–800 mg once daily
Voriconazole		6 mg/kg every 12 hours × 2 doses, then 4 mg/kg every 12 hours
<b>Antivirals</b>		
Acyclovir	20 mg/kg every 8 hours	10 mg/kg every 8 hours
Foscarnet		60 mg/kg every 8–12 hours

<sup>a</sup>Monitor drug levels in serum.<sup>b</sup>Direct CNS administration may be added; see Table 110-6, in *Pharmacotherapy: A Pathophysiologic Approach*, seventh edition, for dosage.<sup>c</sup>Should be reserved for multidrug-resistant pseudomonal or *Acinetobacter* infections for which all other therapeutic options have been exhausted.<sup>d</sup>Dosing based on trimethoprim component.<sup>e</sup>Supplemental pyridoxine hydrochloride (vitamin B<sub>6</sub>) 50 mg/day is recommended.

- The treatment of choice until susceptibility of the organism is known as the combination of **vancomycin** plus **ceftriaxone**. Penicillin may be used for drug-susceptible isolates with minimum inhibitory concentrations of 0.06 mcg/mL or less, but for intermediate isolates ceftriaxone is used, and for highly drug-resistant isolates a combination of ceftriaxone and vancomycin should be used. A high percent of *S. pneumoniae* is either intermediately or highly resistant to penicillin.
- Virtually all serotypes of *S. pneumoniae* exhibiting intermediate or complete resistance to penicillin are found in the current 23 serotype pneumococcal vaccine. A heptavalent conjugate vaccine is available for use in infants between 2 months and 9 years of age. Current recommendations are for all healthy infants younger than 2 years of age to be immunized with the heptavalent vaccine at 2, 4, 6, and 12 to 15 months.

### ***Haemophilus influenzae***

- In the past, *H. influenzae* was the most common cause of meningitis in children 6 months to 3 years of age, but this has declined dramatically since the introduction of effective vaccines.
- Approximately 30% to 40% of *H. influenzae* are ampicillin resistant. For this reason, many clinicians use a third-generation cephalosporin (**cefotaxime** or **ceftriaxone**) for initial antimicrobial therapy. Once bacterial susceptibilities are available, ampicillin may be used if the isolate proves ampicillin sensitive. Cefepime and fluoroquinolones are suitable alternatives regardless of  $\beta$ -lactamase activity.
- Secondary cases may occur within 30 days of the index case, and so treatment of close contacts (household members, individuals sharing sleeping quarters, crowded confined populations, daycare attendees, and nursing home residents) of patients is usually recommended. The goal of prophylaxis is to eliminate nasopharyngeal and oropharyngeal carriage of *H. influenzae*.
- Prophylaxis of close contacts should be started only after consultation with the local health department and the Centers for Disease Control and Prevention. In general, children should receive 20 mg/kg (maximum 600 mg) and adults 600 mg daily in one dose for 4 days. Fully vaccinated individuals should not receive prophylaxis.
- Vaccination with Hib conjugate vaccines is usually begun in children at 2 months.
- The vaccine should be considered in patients older than 5 years with sickle cell disease, asplenia, or immunocompromising diseases.

### ***Listeria monocytogenes***

- *L. monocytogenes* is a gram-positive, diphtheroid-like organism and is responsible for 8% of all reported cases of meningitis. The disease affects primarily neonates, alcoholics, immunocompromised patients, and the elderly.
- The combination of **penicillin G** or **ampicillin** with an aminoglycoside results in a bactericidal effect. Patients should be treated for 2 to 3 weeks after defervescence to prevent the possibility of relapse. Combination therapy is given for at least 10 days with the remainder completed with penicillin G or ampicillin alone.

- **Trimethoprim-sulfamethoxazole** may be an effective alternative because adequate CSF penetration is achieved with these agents.

### Gram-Negative Bacillary Meningitis

- Currently, gram-negative bacteria (excluding *H. influenzae*) are the fourth leading cause of meningitis.

#### Treatment

(See Table 36-5.)

- Optimal antibiotic therapies for gram-negative bacillary meningitis have not been fully defined. Meningitis caused by *Pseudomonas aeruginosa* is initially treated with **ceftazidime** or **cefepime**, **piperacillin + tazobactam**, or **meropenem** plus an aminoglycoside, usually **tobramycin**.
- If the pseudomonad is suspected to be antibiotic resistant or becomes resistant during therapy, an intraventricular aminoglycoside (preservative-free) should be considered along with IV aminoglycoside. Intraventricular aminoglycoside dosages are adjusted to the estimated CSF volume (0.03 mg of tobramycin or **gentamicin** per mL of CSF and 0.1 mg of **amikacin** per mL of CSF every 24 hours). Ventricular levels of aminoglycoside are monitored every 2 or 3 days, just prior to the next intraventricular dose, and “trough levels” should approximate 2 to 10 mg/L. Intraventricular administration of aminoglycosides to infants is not recommended.
- Gram-negative organisms, other than *P. aeruginosa*, that cause meningitis can be treated with a third-generation or fourth-generation cephalosporin such as **cefotaxime**, **ceftriaxone**, **ceftazidime**, or **cefepime**. In adults, daily doses of 8 to 12 g/day of these third-generation cephalosporins or 2 g of ceftriaxone twice daily should produce CSF concentrations of 5 to 20 mg/L.
- Therapy for gram-negative meningitis is continued for a minimum of 21 days. CSF cultures may remain positive for several days or more on a regimen that will eventually be curative.

### *Mycobacterium tuberculosis*

- *Mycobacterium tuberculosis* var. *hominis* is the primary cause of tuberculous meningitis. Tuberculous meningitis may exist in the absence of disease in the lung or extrapulmonary sites. Upon initial examination, CSF usually contains 100 to 1,000 WBC/mm<sup>3</sup>, which may be 75% to 80% polymorphonuclear cells. Over time, the pattern of WBCs in the CSF will shift to lymphocytes and monocytes.
- The Centers for Disease Control and Prevention recommends a regimen of four drugs for empiric treatment of *M. tuberculosis*. This regimen should consist of **isoniazid**, **rifampin**, **pyrazinamide**, and **ethambutol**, 15 to 20 mg/kg/day (maximum 1.6 g/day) for the first 2 months generally followed by isoniazid plus rifampin for the duration of therapy.
- **Isoniazid** is the mainstay in virtually any regimen to treat *M. tuberculosis*. In children, the usual dose of isoniazid is 10 to 15 mg/kg/day (maximum 300 mg/day). Adults usually receive 5 mg/kg/day or a daily dose of 300 mg.
- Supplemental doses of **pyridoxine hydrochloride (vitamin B<sub>6</sub>)**, 50 mg/day, are recommended to prevent the peripheral neuropathy associated with isoniazid administration.

- Concurrent administration of rifampin is recommended at doses of 10 to 20 mg/kg/day (maximum 600 mg/day) for children and 600 mg/day for adults. The addition of pyrazinamide (children and adults, 15 to 30 mg/kg/day; maximum in both, 2 g/day) to the regimen of isoniazid and rifampin is now recommended. The duration of concomitant pyrazinamide therapy should be limited to 2 months to avoid hepatotoxicity.
- Patients with *M. tuberculosis* meningitis should be treated for a duration of 9 months or longer with multiple-drug therapy, and patients with rifampin-resistant strains should receive 18 to 24 months of therapy.
- The use of glucocorticoids for tuberculous meningitis remains controversial. The administration of steroids such as oral **prednisone**, 60 to 80 mg/day (1 to 2 mg/kg/day in children), or 0.2 mg/kg/day of IV **dexamethasone**, tapered over 4 to 8 weeks, improves neurologic sequelae and survival in adults and decrease mortality, long-term neurologic complications, and permanent sequelae in children.

### ***Cryptococcus neoformans***

- In the United States, cryptococcal meningitis is the most common form of fungal meningitis and is a major cause of morbidity and mortality in immunosuppressed patients.
- Fever and a history of headaches are the most common symptoms of cryptococcal meningitis, although altered mentation and evidence of focal neurologic deficits may be present. Diagnosis is based on the presence of a positive CSF, blood, sputum, or urine culture for *Cryptococcus neoformans*.
- CSF cultures are positive in greater than 90% of cases.
- **Amphotericin B** is the drug of choice for treatment of acute *C. neoformans* meningitis. Amphotericin B, 0.5 to 1 mg/kg/day, combined with **flucytosine**, 100 mg/kg/day, is more effective than amphotericin alone. In the acquired immune deficiency syndrome (AIDS) population, flucytosine is often poorly tolerated, causing bone marrow suppression and GI distress.
- Due to the high relapse rate following acute therapy for *C. neoformans*, AIDS patients require lifelong maintenance or suppressive therapy. The standard of care for AIDS-associated cryptococcal meningitis is primary therapy, generally using amphotericin B with or without flucytosine followed by maintenance therapy with fluconazole for the life of the patient.

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See Chap. 110, *Central Nervous System Infections*, authored by Isaac F. Mitropoulos, Elizabeth D. Hermsen, Jeremy A. Schafer, and John C. Rotschafer, for a more detailed discussion of this topic.

## DEFINITION

- Endocarditis is an inflammation of the endocardium, the membrane lining the chambers of the heart and covering the cusps of the heart valves. *Infective endocarditis* (IE) refers to infection of the heart valves by microorganisms, primarily bacteria.
- Endocarditis is often referred to as either acute or subacute depending on the clinical presentation. Acute bacterial endocarditis is a fulminating infection associated with high fevers, systemic toxicity, and death within days to weeks if untreated. Subacute infectious endocarditis is a more indolent infection, usually occurring in a setting of prior valvular heart disease.

## PATHOPHYSIOLOGY

- Most patients with IE have risk factors, such as preexisting cardiac valve abnormalities.
- Most types of structural heart disease resulting in turbulence of blood flow will increase the risk for IE. Some of the most important risk factors include:
  - ✓ Presence of a prosthetic valve (highest risk)
  - ✓ Previous endocarditis (highest risk)
  - ✓ Complex cyanotic congenital heart disease (e.g., single ventricle states)
  - ✓ Surgically constructed systemic pulmonary shunts or conduits
  - ✓ Acquired valvular dysfunction (e.g., rheumatic heart disease)
  - ✓ Hypertrophic cardiomyopathy
  - ✓ Mitral valve prolapse with regurgitation
  - ✓ IV drug abuse
- Three groups of organisms cause most cases of IE: streptococci (60% to 80%), staphylococci (20% to 35%), and enterococci (5% to 18%) (Table 37-1).

## CLINICAL PRESENTATION

- The clinical presentation of patients with IE is highly variable and nonspecific (Table 37-2). Fever is the most common finding.
- Important clinical signs, especially prevalent in subacute illness, may include the following peripheral manifestations (“stigmata”) of endocarditis:
  - ✓ Osler’s nodes
  - ✓ Janeway lesions
  - ✓ Splinter hemorrhages
  - ✓ Petechiae
  - ✓ Clubbing of the fingers
  - ✓ Roth’s spots
  - ✓ Emboli
- Without appropriate antimicrobial therapy and surgery, IE is usually fatal. With proper management, recovery can be expected in most patients.

**TABLE 37-1** Etiologic Organisms in Infective Endocarditis

Agent	Percentage of Cases (%)
Streptococci	60–80
Viridans streptococci	30–40
Other streptococci	15–25
Staphylococci	20–35
Coagulase positive	10–27
Coagulase negative	1–3
Enterococci	5–18
Gram-negative aerobic bacilli	1.5–13
Fungi	2–4
Miscellaneous bacteria	<5
Mixed infections	1–2
“Culture negative”	<5–24

Adapted from Fowler G, Scheld WM, Bayer AJ. Endocarditis and intravascular infection. In Mandell GL, Bennett JE, Dolin R, eds., *Principles and Practice of Infectious Diseases*, 6th Ed. New York: Churchill-Livingstone, 2005, 975–1022.

- Factors associated with increased mortality include the following:
  - ✓ Congestive heart failure
  - ✓ Culture-negative endocarditis
  - ✓ Endocarditis caused by resistant organisms such as fungi and gram-negative bacteria
  - ✓ Left-sided endocarditis caused by *Staphylococcus aureus*
  - ✓ Prosthetic valve endocarditis (PVE)

## LABORATORY AND DIAGNOSTIC FINDINGS

- More than 95% of patients with IE have a positive blood culture when three samples are obtained during a 24-hour period.
- Transesophageal echocardiography is important in identifying and localizing valvular lesions in patients suspected of having IE. Transesophageal

**TABLE 37-2** Clinical Presentation of Infective Endocarditis

<b>Symptoms</b>	The patient may complain of fever, chills, weakness, dyspnea, night sweats, weight loss, and/or malaise.
<b>Signs</b>	Fever is common as well as a heart murmur (sometimes new or changing). The patient may or may not have embolic phenomenon, splenomegaly, or skin manifestations (e.g., Osler's nodes, Janeway lesions).
<b>Laboratory tests</b>	The patient's white blood cell count may be normal or only slightly elevated. Nonspecific findings include anemia (normocytic, normochromic), thrombocytopenia, an elevated erythrocyte sedimentation rate or C-reactive protein, and altered urinary analysis (proteinuria/microscopic hematuria). The hallmark laboratory finding is continuous bacteremia; three sets of blood cultures should be collected over 24 hours.
<b>Other diagnostic tests</b>	An electrocardiogram, chest radiograph, and echocardiogram are commonly performed. Echocardiography to determine the presence of valvular vegetations plays a key role in the diagnosis of infective endocarditis; it should be performed in all suspected cases.

echocardiography is more sensitive for detecting vegetations (90% to 100%), compared to transthoracic echocardiography (58% to 63%).

- The Modified Duke criteria, encompassing major findings of persistent bacteremia and echocardiographic findings and other minor findings, are used to categorize patients as “definite IE” or “possible IE.”

## DESIRED OUTCOME

- Relieve the signs and symptoms of disease.
- Decrease morbidity and mortality associated with infection.
- Eradicate the causative organism with minimal drug exposure.
- Provide cost-effective antimicrobial therapy.
- Prevent IE in high-risk patients with appropriate prophylactic antimicrobials.

## TREATMENT

### GENERAL PRINCIPLES

- The most important approach to treatment of IE includes isolation of the infecting pathogen and determination of antimicrobial susceptibilities, followed by high-dose, bactericidal antibiotics for an extended period.
- Treatment usually is started in the hospital, but in selected patients, it may be completed in the outpatient setting.
- Large doses of parenteral antimicrobials usually are necessary to achieve bactericidal concentrations within vegetations.
- An extended duration of therapy is required, even for susceptible pathogens, because microorganisms are enclosed within valvular vegetations and fibrin deposits.

### NONPHARMACOLOGIC THERAPY

- Surgery is an important adjunct to management of endocarditis in certain patients. In most cases, valvectomy and valve replacement are performed to remove infected tissues and restore hemodynamic function. The most important indications for surgical intervention in the past have been heart failure in left-sided IE and persistent infections in right-sided IE.

### STREPTOCOCCAL ENDOCARDITIS

- Streptococci are a common cause of IE, with most isolates being viridans streptococci.
- Most viridans streptococci are exquisitely sensitive to penicillin G with minimal inhibitory concentrations (MICs) less than or equal to 0.12 mcg/mL. The MIC should be determined for all viridans streptococci and the results used to guide therapy. Approximately 10% to 20% are moderately susceptible (MIC 0.12 to 0.5 mcg/mL).
- Recommended therapy in the uncomplicated case caused by fully susceptible strains is 4 weeks of either high-dose **penicillin G** or **ceftriaxone**, or 2 weeks of combined therapy with high-dose penicillin G plus **gentamicin** (Table 37-3).

**TABLE 37-3** Therapy of Native Valve Endocarditis Caused by Highly Penicillin-Susceptible Viridans Group Streptococci and *Streptococcus bovis*

Regimen	Dosage <sup>a</sup> and Route	Duration (weeks)	Strength of Recommendation	Comments
Aqueous crystalline penicillin G sodium	12–18 million units/24 hours IV either continuously or in four or six equally divided doses	4	I A	Preferred in most patients older than age 65 years or patients with impairment of 8th cranial nerve function or renal function
<b>or</b>				
Ceftriaxone sodium	2 g/24 h IV/IM in one dose <i>Pediatric dose<sup>b</sup></i> : penicillin 200,000 units/kg per 24 hours IV in four to six equally divided doses; ceftriaxone 100 mg/kg per 24 hours IV/IM in one dose	4	I A	
Aqueous crystalline penicillin G sodium	12–18 million units/24 h IV either continuously or in six equally divided doses	2	I B	2-week regimen not intended for patients with known cardiac or extracardiac abscess or for those with creatinine clearance of less than 20 mL/min, impaired 8th cranial nerve function, or <i>Abiotrophia</i> , <i>Granulicatella</i> , or <i>Gemella</i> spp. infection; gentamicin dosage should be adjusted to achieve peak serum concentration of 3–4 mcg/mL and trough serum concentration of less than 1 mcg/mL when three divided doses are used (second option to single daily dose)
<b>or</b>				
Ceftriaxone sodium	2 g/24 hours IV/IM in one dose	2	I B	
<b>plus</b>				
Gentamicin sulfate <sup>c</sup>	3 mg/kg per 24 hours IV/IM in one dose <i>Pediatric dose</i> : penicillin 200,000 units/kg per 24 hours IV in four to six equally divided doses; ceftriaxone 100 mg/kg per 24 hours IV/IM in one dose; gentamicin 3 mg/kg per 24 hours IV/IM in one dose or three equally divided doses <sup>d</sup>	2		
Vancomycin hydrochloride <sup>e</sup>	30 mg/kg per 24 hours IV in two equally divided doses not to exceed 2 g/24 hours unless concentrations are inappropriately low <i>Pediatric dose</i> : 40 mg/kg per 24 hours IV in two to three equally divided doses	4	I B	Vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone; vancomycin dosage should be adjusted to obtain peak (1 hour after infusion completed) serum concentration of 30–45 mcg/mL and a trough concentration range of 10–15 mcg/mL

Minimum inhibitory concentration less than 0.12 mcg/mL.

<sup>a</sup>Dosages recommended are for patients with normal renal function.

<sup>b</sup>Pediatric dose should not exceed that of a normal adult.

<sup>c</sup>Other potentially nephrotoxic drugs (e.g., nonsteroidal antiinflammatory drugs) should be used with caution in patients receiving gentamicin therapy.

<sup>d</sup>Data for once-daily dosing of aminoglycosides for children exist, but no data for treatment of infective endocarditis exist.

<sup>e</sup>Vancomycin dosages should be infused during course of at least 1 hour to reduce risk of histamine-release “red man” syndrome.

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- The following conditions should all be present to consider a 2-week treatment regimen:
  - ✓ The isolate is penicillin sensitive (MIC less than or equal to 0.1 mcg/mL).
  - ✓ There are no cardiovascular risk factors such as heart failure, aortic insufficiency, or conduction abnormalities.
  - ✓ No evidence of thrombotic disease.
  - ✓ Native valve infection.
  - ✓ No vegetation greater than 5 mm diameter.
  - ✓ Clinical response is evident within 7 days.
- Vancomycin is effective and is the drug of choice for the patient with a history of immediate-type hypersensitivity reaction to penicillin. When vancomycin is used, the addition of gentamicin is not recommended.
- For patients with complicated infection (e.g., extracardiac foci) or when the organism is relatively resistant (MIC = 0.12 to 0.5 mcg/mL), combination therapy with an aminoglycoside and penicillin (higher dose) or ceftriaxone for the first 2 weeks is recommended (Table 37-4).
- In patients with endocarditis of prosthetic valves or other prosthetic material caused by viridans streptococci and *Streptococcus bovis*, treatment courses are extended to 6 weeks (Table 37-5).

## STAPHYLOCOCCAL ENDOCARDITIS

- *S. aureus* has become more prevalent as a cause of endocarditis because of increased IV drug abuse, frequent use of peripheral and central venous catheters, and valve-replacement surgery. Coagulase-negative staphylococci (CNST, usually *S. epidermidis*) are prominent causes of PVE.
- The recommended therapy for patients with left-sided IE caused by methicillin-sensitive *S. aureus* (MSSA) is 4 to 6 weeks of **nafcillin** or **oxacillin**, often combined with a short course of gentamicin (Table 37-6).
- If a patient has a mild, delayed allergy to penicillin, **first-generation cephalosporins** are effective alternatives but should be avoided in patients with an immediate-type hypersensitivity reaction.
- In a patient with a positive penicillin skin test or a history of immediate hypersensitivity to penicillin, **vancomycin** is the agent of choice. Vancomycin, however, kills *S. aureus* slowly and is generally regarded as inferior to penicillinase-resistant penicillins for MSSA. Penicillin-allergic patients who fail on vancomycin therapy should be considered for penicillin desensitization.
- **Vancomycin** is the drug of choice for methicillin-resistant staphylococci since most methicillin-resistant *S. aureus* and most CNST are susceptible.

### Treatment of *Staphylococcus* Endocarditis in IV Drug Abusers

- IE in IV drug abusers is most frequently (60% to 70%) caused by *S. aureus*, although other organisms may be more common in certain geographic locations.
- Standard treatment for MSSA consists of 4 weeks of therapy with a **penicillinase-resistant penicillin** (see Table 37-6).
- A 2-week course of **nafcillin** or **oxacillin** plus an aminoglycoside may be effective.

**TABLE 37-4** Therapy of Native Valve Endocarditis Caused by Strains of Viridans Group Streptococci and *Streptococcus bovis* Relatively Resistant to Penicillin

Regimen	Dosage <sup>a</sup> and Route	Duration (weeks)	Strength of Recommendation	Comments
Aqueous crystalline penicillin G sodium	24 million units/24 hours IV either continuously or in four to six equally divided doses	4	I B	Patients with endocarditis caused by penicillin-resistant (MIC greater than 0.5 mcg/mL) strains should be treated with regimen recommended for enterococcal endocarditis (see Table 37-8)
<b>or</b> Ceftriaxone sodium	2 g/24 hours IV/IM in one dose	4	I B	
<b>plus</b> Gentamicin sulfate <sup>b</sup>	3 mg/kg per 24 hours IM/IV in one dose <i>Pediatric dose</i> <sup>c</sup> : penicillin 300,000 units/24 hours IV in four to six equally divided doses; ceftriaxone 100 mg/kg per 24 hours IV/IM in one dose; gentamicin 3 mg/kg per 24 hours IV/IM in one dose or three equally divided doses	2		Although it is preferred that gentamicin (3 mg/kg) be given as a single daily dose to adult patients, as a second option, gentamicin can be administered daily in three equally divided doses
Vancomycin hydrochloride <sup>c</sup>	30 mg/kg per 24 hours IV in two equally divided doses not to exceed 2 g/24 hours unless serum concentrations are inappropriately low <i>Pediatric dose</i> : 40 mg/kg 24 hours in two or three equally divided doses	4	I B	Vancomycin <sup>d</sup> therapy recommended only for patients unable to tolerate penicillin or ceftriaxone therapy

Minimum inhibitory concentration (MIC) greater than 0.12 mcg/mL to less than or equal to 0.5 mcg/mL.

<sup>a</sup>Dosages recommended are for patients with normal renal function.

<sup>b</sup>See Table 37-3 for appropriate dosage of gentamicin.

<sup>c</sup>Pediatric dose should not exceed that of a normal adult.

<sup>d</sup>See Table 37-3 for appropriate dosage of vancomycin.

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**TABLE 37-5** Therapy for Endocarditis of Prosthetic Valves or Other Prosthetic Material Caused by Viridans Group Streptococci and *Streptococcus bovis*

Regimen	Dosage <sup>a</sup> and Route	Duration (weeks)	Strength of Recommendation	Comments	
<b>Penicillin-susceptible strain (minimum inhibitory concentration ≤0.12 mcg/mL)</b>					
Aqueous crystalline penicillin G sodium <b>or</b> Ceftriaxone sodium <b>with or without</b> Gentamicin sulfate <sup>b</sup>	24 million units/24 hours IV either continuously or in four to six equally divided doses  2 g/24 hours IV/IM in one dose  3 mg/kg per 24 hours IM/IV in one dose <i>Pediatric dose<sup>c</sup>:</i> penicillin 300,000 units/24 hours IV in four to six equally divided doses; ceftriaxone 100 mg/kg per 24 hours IV/IM in one dose; gentamicin 3 mg/kg per 24 hours IV/IM in one dose or three equally divided doses	6  6  2	I B  I B	Penicillin or ceftriaxone together with gentamicin has not demonstrated superior cure rates compared with monotherapy with penicillin or ceftriaxone for patients with highly susceptible strain; gentamicin therapy should not be administered to patients with creatinine clearance of less than 30 mL/min	
Vancomycin hydrochloride <sup>d</sup>	30 mg/kg per 24 hours IV in two equally divided doses <i>Pediatric dose:</i> 40 mg/kg 24 hours in two or three equally divided doses	6	I B		Vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone therapy
<b>Penicillin relatively or fully resistant strain (minimum inhibitory concentration &gt;0.12 mcg/mL)</b>					
Aqueous crystalline penicillin sodium <b>or</b> Ceftriaxone <b>plus</b> Gentamicin sulfate	24 million units/24 hours IV either continuously or in four to six equally divided doses  2 g/24 h IV/IM in one dose  3 mg/kg per 24 hours IV/IM in one dose <i>Pediatric dose:</i> penicillin 300,000 units/kg per 24 hours IV in four to six equally divided doses	6  6  6	I B  I B	Vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone therapy	
Vancomycin hydrochloride	30 mg/kg per 24 hours IV in two equally divided doses <i>Pediatric dose:</i> 40 mg/kg per 24 hours IV in two or three equally divided doses	6	I B		

<sup>a</sup>Dosages recommended are for patients with normal renal function.

<sup>b</sup>See Table 37-3 for appropriate dosage of gentamicin.

<sup>c</sup>Pediatric dose should not exceed that of a normal adult.

<sup>d</sup>See text and Table 37-3 for appropriate dosage of vancomycin.

From Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis diagnosis, antimicrobial therapy, and management of complications. *Circulation* 2005;111:e394-e433, with permission. Copyright 2005, American Medical Association.

**TABLE 37-6** Therapy for Endocarditis Caused by Staphylococci in the Absence of Prosthetic Materials

Regimen	Dosage <sup>a</sup> and Route	Duration	Strength of Recommendation	Comments
<b>Oxacillin-susceptible strains</b>				
Nafcillin or oxacillin <sup>b</sup> <b>with</b>	12 g/24 hours IV in four to six equally divided doses	6 weeks	I A	For complicated right-sided infective endocarditis and for left-sided infective endocarditis; for uncomplicated right-sided infective endocarditis, 2 weeks
Optional addition of gentamicin sulfate <sup>c</sup>	3 mg/kg per 24 hours IV/IM in two or three equally divided doses	3–5 days		Clinical benefit of aminoglycosides has not been established
For penicillin-allergic (nonanaphylactoid type) patients: <b>with</b>				Consider skin testing for oxacillin-susceptible staphylococci and questionable history of immediate-type hypersensitivity to penicillin
Cefazolin	6 g/24 hours IV in three equally divided doses	6 weeks	I B	Cephalosporins should be avoided in patients with anaphylactoid-type hypersensitivity to $\beta$ -lactams; vancomycin should be used in these cases <sup>d</sup>
Optional addition of gentamicin sulfate	3 mg/kg per 24 hours IV/IM in two or three equally divided doses <i>Pediatric dose:</i> cefazolin 100 mg/kg per 24 hours IV in three equally divided doses; gentamicin 3 mg/kg per 24 hours IV/IM in three equally divided doses	3–5 days		Clinical benefit of aminoglycosides has not been established
<b>Oxacillin-resistant strains</b>				
Vancomycin <sup>e</sup>	30 mg/kg per 24 hours IV in two equally divided doses <i>Pediatric dose:</i> 40 mg/kg per 24 hours IV in two or three equally divided doses	6 weeks	I B	Adjust vancomycin dosage to achieve 1-hour serum concentration of 30–45 mcg/mL and trough concentration of 10–15 mcg/mL

<sup>a</sup>Dosages recommended are for patients with normal renal function.

<sup>b</sup>Penicillin G 24 million units/24 h IV in four to six equally divided doses may be used in place of nafcillin or oxacillin if strain is penicillin susceptible (minimum inhibitory concentration  $\leq 0.1$  mcg/mL) and does not produce  $\beta$ -lactamase.

<sup>c</sup>Gentamicin should be administered in close temporal proximity to vancomycin, nafcillin, or oxacillin dosing. See Table 37-3 for appropriate dosage of gentamicin.

<sup>d</sup>Pediatric dose should not exceed that of a normal adult.

<sup>e</sup>For specific dosing adjustment and issues concerning vancomycin, see Table 37-3 footnotes.

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- Short-course vancomycin, in place of nafcillin or oxacillin, appears to be ineffective.

### Treatment of Staphylococcal Prosthetic Valve Endocarditis

- PVE that occurs within 2 months of cardiac surgery is usually caused by staphylococci implanted at the time of surgery. Methicillin-resistant organisms are common. Vancomycin is the cornerstone of therapy.
- Because of the high morbidity and mortality associated with PVE and refractoriness to therapy, combinations of antimicrobials are usually recommended.
- For methicillin-resistant staphylococci (both methicillin-resistant *S. aureus* and CNST), **vancomycin** is used with rifampin for 6 weeks or more (Table 37-7). An **aminoglycoside** is added for the first 2 weeks if the organism is susceptible.
- For methicillin-susceptible staphylococci, a **penicillinase-stable penicillin** is used in place of vancomycin. If an organism is identified other than staphylococci, the treatment regimen should be guided by susceptibilities and should be at least 6 weeks in duration.

## ENTEROCOCCAL ENDOCARDITIS

- Enterococci cause 5% to 18% of endocarditis cases and are noteworthy for the following reasons: (1) no single antibiotic is bactericidal; (2) MICs to penicillin are relatively high (1 to 25 mcg/mL); (3) they are intrinsically resistant to all cephalosporins and relatively resistant to aminoglycosides (i.e., “low-level” aminoglycoside resistance); (4) combinations of a cell wall-active agent, such as a penicillin or vancomycin, plus an aminoglycoside are necessary for killing; (5) resistance to all available drugs is increasing.
- Enterococcal endocarditis ordinarily requires 4 to 6 weeks of high-dose **penicillin G** or **ampicillin**, plus **gentamicin** for cure (Table 37-8). A 6-week course is recommended for patients with symptoms lasting longer than 3 months and those with PVE.
- In addition to isolates with high-level aminoglycoside resistance,  $\beta$ -lactamase-producing enterococci (especially *Enterococcus faecium*) are increasingly reported. If these organisms are discovered, use of vancomycin or ampicillin-sulbactam in combination with gentamicin should be considered.
- Vancomycin-resistant enterococci, particularly *E. faecium*, are becoming more common.

## EVALUATION OF THERAPEUTIC OUTCOMES

- The evaluation of patients treated for IE includes assessment of signs and symptoms, blood cultures, microbiologic tests (e.g., MIC, minimum bactericidal concentration [MBC], or serum bactericidal titers), serum drug concentrations, and other tests to evaluate organ function.
- Persistence of fever beyond 1 week may indicate ineffective antimicrobial therapy, emboli, infections of intravascular catheters, or drug reactions. In some patients, low-grade fever may persist even with appropriate antimicrobial therapy.

**TABLE 37-7** Therapy for Prosthetic Valve Endocarditis Caused by Staphylococci

Regimen	Dosage <sup>a</sup> and Route	Duration (weeks)	Strength of Recommendation	Comments
<b>Oxacillin-susceptible strains</b>				
Nafcillin or oxacillin	12 g/24 hours IV in four to six equally divided doses	≥6	I B	Penicillin G 24 million units/24 h IV in four to six equally divided doses may be used in place of nafcillin or oxacillin if strain is penicillin susceptible (minimum inhibitory concentration ≤0.1 mcg/mL) and does not produce β-lactamase; vancomycin should be used in patients with immediate-type hypersensitivity reactions to beta-lactam antibiotics (see Table 37-3 for dosing guidelines); cefazolin may be substituted for nafcillin or oxacillin in patients with non-immediate-type hypersensitivity reactions to penicillins
<b>plus</b> Rifampin	900 mg per 24 hours IV/orally in three equally divided doses	≥6		
<b>plus</b> Gentamicin <sup>b</sup>	3 mg/kg per 24 hours IV/IM in two or three equally divided doses <i>Pediatric dose<sup>c</sup>:</i> nafcillin or oxacillin 200 mg/kg per 24 hours IV in four to six equally divided doses; rifampin 20 mg/kg per 24 hours IV/orally in three equally divided doses; gentamicin 3 mg/kg per 24 hours IV/IM in three equally divided doses	2		
<b>Oxacillin-resistant strains</b>				
Vancomycin	30 mg/kg 24 hours in two equally divided doses	≥6	I B	Adjust vancomycin to achieve 1-hour serum concentration of 30–45 mcg/mL and trough concentration of 10–15 mcg/mL
<b>plus</b> Rifampin	900 mg/24 hours IV/orally in three equally divided doses	≥6		
<b>plus</b> Gentamicin	3 mg/kg per 24 hours IV/IM in two or three equally divided doses <i>Pediatric dose:</i> vancomycin 40 mg/kg per 24 hours IV in two or three equally divided doses; rifampin 20 mg/kg per 24 hours IV/orally in three equally divided doses (up to adult dose); gentamicin 3 mg/kg per 24 hours IV or IM in three equally divided doses	2		

<sup>a</sup>Dosages recommended are for patients with normal renal function.

<sup>b</sup>Gentamicin should be administered in close proximity to vancomycin, nafcillin, or oxacillin dosing. See Table 37–3 for appropriate dosage of gentamicin.

<sup>c</sup>Pediatric dose should not exceed that of a normal adult.

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**TABLE 37-8** Therapy for Native Valve or Prosthetic Valve Enterococcal Endocarditis Caused by Strains Susceptible to Penicillin, Gentamicin, and Vancomycin

Regimen	Dosage <sup>a</sup> and Route	Duration (weeks)	Strength of Recommendation	Comments
Ampicillin sodium <b>or</b>	12 g/24 hours IV in six equally divided doses	4–6	I A	Native valve: 4-week therapy recommended for patients with symptoms of illness less than 3 months; 6-week therapy recommended for patients with symptoms greater than 3 months
Aqueous crystalline penicillin G sodium	18–30 million units/24 hours IV either continuously or in six equally divided doses	4–6	I A	
<b>plus</b>				Prosthetic valve or other prosthetic cardiac material: minimum of 6 weeks of therapy recommended
Gentamicin sulfate <sup>b</sup>	3 mg/kg per 24 hours IV/IM in three equally divided doses	4–6		
Vancomycin hydrochloride <sup>d</sup>	30 mg/kg per 24 hours IV in 2 equally divided doses	6	I B	Vancomycin therapy recommended only for patients unable to tolerate penicillin or ampicillin
<b>plus</b>				
Gentamicin sulfate	3 mg/kg per 24 hours IV/IM in three equally divided doses <i>Pediatric dose<sup>c</sup>:</i> vancomycin 40 mg/kg per 24 hours IV in two or three equally divided doses; gentamicin 3 mg/kg per 24 hours IV/IM in three equally divided doses	6		6 weeks of vancomycin therapy recommended because of decreased activity against enterococci

<sup>a</sup>Dosages recommended are for patients with normal renal function.

<sup>b</sup>Dosage of gentamicin should be adjusted to achieve peak serum concentration of 3–4 mcg/mL and a trough concentration of less than 1 mcg/mL. See Table 37-3 for appropriate dosage of gentamicin.

<sup>c</sup>Pediatric dose should not exceed that of a normal adult.

<sup>d</sup>See text and Table 37-3 for appropriate dosing of vancomycin.

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- With effective therapy, blood cultures should be negative within a few days, although microbiologic response to vancomycin may be unusually slower.
- After the initiation of therapy, blood cultures should be rechecked until they are negative. During the remainder of the therapy, frequent blood culturing is not necessary.
- If bacteria continue to be isolated from blood beyond the first few days of therapy, it may indicate that the antimicrobials are inactive against the pathogen or that the doses are not producing adequate concentrations at the site of infection.
- For all isolates from blood cultures, MICs (not MBCs) should be determined.
- When aminoglycosides are used for endocarditis caused by gram-positive cocci with a traditional three-times daily regimen, peak serum concentrations are recommended to be on the low side of the traditional ranges (3 to 4 mcg/mL for gentamicin).
- Serum bactericidal titers may be useful only when the causative organisms are moderately susceptible to antimicrobials, when less well-established regimens are used, or when response to therapy is suboptimal and dosage escalation is considered.
- Serum concentrations of the antimicrobial should generally exceed the MBC of the organism; however, in practice this principle is usually not helpful in monitoring patients with endocarditis.

## PREVENTION OF ENDOCARDITIS

- Antimicrobial prophylaxis is used to prevent IE in patients believed to be at high risk.
- The use of antimicrobials for this purpose requires consideration of the types of patients who are at risk; the procedures causing bacteremia; the organisms that are likely to cause endocarditis; and the pharmacokinetics, spectrum, cost, and ease of administration of available agents. The objective

**TABLE 37-9** Cardiac Conditions Associated with the Highest Risk of Adverse Outcome from Endocarditis for Which Prophylaxis with Dental Procedures Is Recommended

Prosthetic cardiac valves
Previous infective endocarditis
Congenital heart disease (CHD) <sup>a</sup>
Unrepaired cyanotic CHD, including palliative shunts and conduits
Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure <sup>b</sup>
Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)
Cardiac transplantation recipients who develop cardiac valvulopathy

<sup>a</sup>Except for the conditions listed above, antibiotic prophylaxis is no longer recommended for any other form of CHD.

<sup>b</sup>Prophylaxis is recommended because endothelialization of prosthetic material occurs within 6 months after the procedure.

From Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis. *Circulation* 2007;116:1736–1754 with permission. Copyright 2007, American Medical Association.

**TABLE 37-10** Antibiotic Regimens for a Dental Procedure

Situation	Agent	Regimen: Single Dose 30 to 60 Minutes Before Procedure	
		Adult	Children
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral medication	Ampicillin <i>or</i>	2 g IM or IV	50 mg/kg IM or IV
Allergic to penicillins or ampicillin—oral	Cefazolin or ceftriazone	1 g IM or IV	50 mg/kg IM or IV
	Cephalexin <sup>a,b</sup>	2 g	50 mg/kg
	<i>or</i> Clindamycin	600 mg	20 mg/kg
	<i>or</i> Azithromycin or clarithromycin	500 mg	15 mg/kg
Allergic to penicillins or ampicillin and unable to take oral medication	Cefazolin or ceftriazone <sup>b</sup>	1 g IM or IV	50 mg/kg IM or IV
	<i>or</i> Clindamycin	600 mg IM or IV	20 mg/kg IM or IV

<sup>a</sup>Or other first- or second-generation oral cephalosporin in equivalent adult or pediatric dosage.

<sup>b</sup>Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticaria with penicillins or ampicillin.

From Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis. *Circulation* 2007;116:1736–1754 with permission. Copyright 2007, American Medical Association.

of prophylaxis is to diminish the likelihood of IE in high-risk individuals who are undergoing procedures that cause transient bacteremia. Cardiac conditions associated with the highest risk of adverse outcome from endocarditis are listed in Table 37-9.

- Endocarditis prophylaxis is recommended for all dental procedures that involve manipulation of the gingival tissue of the periapical region of teeth or perforation of the oral mucosa.
- Antibiotic regimens for a dental procedure are given in Table 37-10.
- When antibiotic prophylaxis is appropriate, a single 2-g dose of amoxicillin for adult patients at risk, given 30 to 60 minutes before undergoing procedures associated with bacteremia.

See Chap. 115, *Infective Endocarditis*, authored by Michael A. Crouch and Angie Veverka, for a more detailed discussion of this topic.

## INTRODUCTION

- Systemic mycoses, such as histoplasmosis, coccidioidomycosis, cryptococcosis, blastomycosis, paracoccidioidomycosis, and sporotrichosis, are caused by primary or “pathogenic” fungi that can cause disease in both healthy and immunocompromised individuals. In contrast, mycoses caused by opportunistic fungi such as *Candida albicans*, *Aspergillus* spp., *Trichosporon*, *Torulopsis (Candida) glabrata*, *Fusarium*, *Alternaria*, and *Mucor* are generally found only in the immunocompromised host. Advances in medical technology, including organ and bone marrow transplantation, cytotoxic chemotherapy, the widespread use of indwelling IV catheters, and the increased use of potent, broad-spectrum antimicrobial agents, have all contributed to the dramatic increase in the incidence of fungal infections worldwide.

## SPECIFIC FUNGAL INFECTIONS

### HISTOPLASMOSIS

- Histoplasmosis is caused by inhalation of dust-borne microconidia of the dimorphic fungus *Histoplasma capsulatum*.
- In the United States, most disease is localized along the Ohio and Mississippi river valleys.

#### Clinical Presentation and Diagnosis

- In the vast majority of patients, low-inoculum exposure to *H. capsulatum* results in mild or asymptomatic pulmonary histoplasmosis. The course of disease is generally benign, and symptoms usually abate within a few weeks of onset. Patients exposed to a higher inoculum during a primary infection or reinfection may experience an acute, self-limited illness with flu-like pulmonary symptoms, including fever, chills, headache, myalgia, and non-productive cough.
- Chronic pulmonary histoplasmosis generally presents as an opportunistic infection imposed on a preexisting structural abnormality such as lesions resulting from emphysema. Patients demonstrate chronic pulmonary symptoms and apical lung lesions that progress with inflammation, calcified granulomas, and fibrosis. Progression of disease over a period of years, seen in 25% to 30% of patients, is associated with cavitation, bronchopleural fistulas, extension to the other lung, pulmonary insufficiency, and often death.
- In patients exposed to a large inoculum and in immunocompromised hosts, progressive illness, disseminated histoplasmosis, occurs. The clinical severity of the diverse forms of disseminated histoplasmosis (Table 38-1) generally parallels the degree of macrophage parasitization observed.
- Acute (infantile) disseminated histoplasmosis is seen in infants and young children and (rarely) in adults with Hodgkin’s disease or other lympho-

**TABLE 38-1** Clinical Manifestations and Therapy of Histoplasmosis

Type of Disease and Common Clinical Manifestations	Approximate Frequency (%) <sup>a</sup>	Therapy/Comments
<b>Nonimmunosuppressed host</b>		
<i>Acute pulmonary histoplasmosis</i>		
Asymptomatic or mild disease	50–99	<i>Asymptomatic, mild, or symptoms &lt;4 weeks:</i> No therapy generally required <i>Symptoms &gt;4 weeks:</i> Itraconazole 200 mg once daily × 6–12 weeks <sup>b</sup>
Self-limited disease	1–50	<i>Self-limited disease:</i> Amphotericin B <sup>c</sup> 0.3–0.5 mg/kg/day × 2–4 weeks (total dose 500 mg) or ketoconazole 400 mg orally daily × 3–6 months can be beneficial in patients with severe hypoxia following inhalation of large inocula
Mediastinal granulomas	1–50	Antifungal therapy generally not useful for arthritis or pericarditis; NSAIDs or corticosteroids can be useful in some cases Most lesions resolve spontaneously; surgery or antifungal therapy with amphotericin B 40–50 mg/day × 2–3 weeks or itraconazole 400 mg/day orally × 6–12 months can be beneficial in some severe cases; mild to moderate disease can be treated with itraconazole for 6–12 months
Severe diffuse pulmonary disease		Amphotericin B 0.7 mg/kg/day, for a total dose of ≤35 mg/kg (or 3 mg/kg/day of one of the lipid preparations) + prednisone 60 mg daily tapered over 2 weeks, <sup>d</sup> followed by itraconazole 200 mg twice daily for 6–12 weeks; in patients who do not require hospitalization, itraconazole 200 mg once or twice daily for 6–12 weeks can be used
Inflammatory/fibrotic disease	0.02	<i>Fibrosing mediastinitis:</i> The benefit of antifungal therapy (itraconazole 200 mg twice daily × 3 months) is controversial but should be considered, especially in patients with elevated ESR or CF titers ≥1:32; surgery can be of benefit if disease is detected early; late disease cannot respond to therapy <i>Sarcoid-like:</i> NSAIDs or corticosteroids can be of benefit for some patients <i>Pericarditis:</i> Severe disease: corticosteroids 1 mg/kg/day or pericardial drainage procedure
<i>Chronic pulmonary histoplasmosis</i>		
	0.05	Antifungal therapy generally recommended for all patients to halt further lung destruction and reduce mortality <i>Mild–moderate disease:</i> Itraconazole 200–400 mg PO daily × 6–24 months is the treatment of choice Itraconazole and ketoconazole (200–800 mg/day orally for 1 year) are effective in 74% to 86% of cases, but relapses are common; fluconazole 200–400 mg daily is less effective (64%) than ketoconazole or itraconazole, and relapses are seen in 29% of responders <i>Severe disease:</i> Amphotericin B 0.7 mg/kg/day for a minimum total dose of 35 mg/kg is effective in 59% to 100% of cases and should be used in patients who require hospitalization or are unable to take itraconazole because of drug interactions, allergies, failure to absorb drug, or failure to improve clinically after a minimum of 12 weeks of itraconazole therapy

(continued)

**TABLE 38-1** Clinical Manifestations and Therapy of Histoplasmosis (Continued)

Type of Disease and Common Clinical Manifestations	Approximate Frequency (%) <sup>a</sup>	Therapy/Comments
<b>Immunosuppressed host</b>		
<i>Disseminated histoplasmosis</i> Acute (Infantile) Subacute	0.02–0.05	<i>Disseminated histoplasmosis:</i> Untreated mortality 83% to 93%; relapse 5% to 23% in non-AIDS patients; therapy is recommended for all patients <i>Nonimmunosuppressed patients:</i> Ketoconazole 400 mg/day orally × 6–12 months or amphotericin B 35 mg/kg IV <i>Immunosuppressed patients (non-AIDS) or endocarditis or CNS disease:</i> Amphotericin B >35 mg/kg × 3 months followed by fluconazole or itraconazole 200 mg orally twice daily × 12 months
Progressive histoplasmosis (immuno-competent patients and immunosuppressed patients without AIDS)		<i>Life-threatening disease:</i> Amphotericin B 0.7–1 mg/kg/day IV for a total dosage of 35 mg/kg over 2–4 months; once the patient is afebrile, able to take oral medications, and no longer requires blood pressure or ventilatory support, therapy can be changed to itraconazole 200 mg orally twice daily for 6–18 months <i>Non-life-threatening disease:</i> Itraconazole 200–400 mg orally daily for 6–18 months; fluconazole therapy 400–800 mg daily should be reserved for patients intolerant to itraconazole, and the development of resistance can lead to relapses
<i>Progressive disease of AIDS</i>	25–50 <sup>e</sup>	Amphotericin B 15–30 mg/kg (1–2 g over 4–10 weeks) <sup>f</sup> or itraconazole 200 mg three times daily for 3 days then twice daily for 12 weeks, followed by lifelong suppressive therapy with itraconazole 200–400 mg orally daily. Although patients receiving secondary prophylaxis (chronic maintenance therapy) might be at low risk for recurrence of systemic mycosis when their CD4+ T-lymphocyte counts increase to >100 cells/microliter in response to HAART, the number of patients who have been evaluated is insufficient to warrant a recommendation to discontinue prophylaxis.

AIDS, acquired immune deficiency syndrome; CF, complement fixation; ESR, erythrocyte sedimentation rate; HAART, highly active antiretroviral therapy; NSAIDs, nonsteroidal antiinflammatory drugs.

<sup>a</sup>As a percentage of all patients presenting with histoplasmosis.

<sup>b</sup>Itraconazole plasma concentrations should be measured during the second week of therapy to ensure that detectable concentrations have been achieved. If the concentration is below 1 mcg/mL, the dose may be insufficient or drug interactions can be impairing absorption or accelerating metabolism, requiring a change in dosage. If plasma concentrations are greater than 10 mcg/mL, the dosage can be reduced.

<sup>c</sup>Desoxycholate amphotericin B.

<sup>d</sup>Effectiveness of corticosteroids is controversial.

<sup>e</sup>As a percentage of AIDS patients presenting with histoplasmosis as the initial manifestation of their disease.

<sup>f</sup>Liposomal amphotericin B (AmBisome) may be more appropriate for disseminated disease.

Data from Deepe GS. *Histoplasma capsulatum*. In: Mandell GL, Bennett JE, Dolin R, eds. *Principles and Practice of Infectious Diseases*, 6th ed. Philadelphia, PA: Churchill Livingstone, 2005:3012–3026; Wheat J, Sarosi G, McKinsey D, et al. *Practice guidelines for the management of patients with histoplasmosis*. *Clin Infect Dis* 2000;30:688–695; Wheat LJ, Kauffman CA. *Histoplasmosis*. *Infect Dis Clin North Am* 2003;17(1):1–19.

proliferative disorders. It is characterized by unrelenting fever; anemia; leukopenia or thrombocytopenia; enlargement of the liver, spleen, and visceral lymph nodes; and GI symptoms, particularly nausea, vomiting, and diarrhea. Untreated disease is uniformly fatal in 1 to 2 months.

- Most adults with disseminated histoplasmosis demonstrate a mild, chronic form of the disease. Untreated patients are often ill for 10 to 20 years, with long asymptomatic periods interrupted by relapses characterized by weight loss, weakness, and fatigue.
- Adult patients with acquired immune deficiency syndrome (AIDS) demonstrate an acute form of disseminated disease that resembles the syndrome seen in infants and children.
- Identification of mycelial isolates from clinical cultures can be made by conversion of the mycelium to the yeast form (requires 3 to 6 weeks) or by the more rapid (2-hour) and 100% sensitive DNA probe that recognizes ribosomal DNA.
- In most patients, serologic evidence remains the primary method in the diagnosis of histoplasmosis. Results obtained from complement fixation, immunodiffusion, and latex antigen agglutination antibody tests are used alone or in combination.
- In the AIDS patient with progressive disseminated histoplasmosis, the diagnosis is best established by bone marrow biopsy and culture, which yield positive cultures in 90% of patients.

### Treatment

- Recommended therapy for the treatment of histoplasmosis is summarized in Table 38-1.
- Asymptomatic or mildly ill patients and patients with sarcoid-like disease generally do not benefit from antifungal therapy. Therapy may be helpful in symptomatic patients whose conditions have not improved during the first month of infection.
- Patients with mild, self-limited disease, chronic disseminated disease, or chronic pulmonary histoplasmosis who have no underlying immunosuppression can usually be treated with either oral ketoconazole or IV amphotericin B.
- In AIDS patients, intensive 12-week primary (induction and consolidation therapy) antifungal therapy is followed by lifelong suppressive (maintenance) therapy with **itraconazole**.
- In AIDS patients, **amphotericin B** should be administered in patients who require hospitalization. Itraconazole 200 mg twice daily may be used to complete a 12-week course or for a full 12-week course in patients who do not require hospitalization.
- Response to therapy should be measured by resolution of radiologic, serologic, and microbiologic parameters and improvement in signs and symptoms of infection.
- Once the initial course of therapy for histoplasmosis is completed, lifelong suppressive therapy with oral azoles or **amphotericin B** (1 to 1.5 mg/kg weekly or biweekly) is recommended, because of the frequent recurrence of infection.
- Relapse rates in AIDS patients not receiving preventive maintenance are 50% to 90%.

## BLASTOMYCOSIS

- North American blastomycosis is a systemic fungal infection caused by *Blastomyces dermatitidis*.
- Pulmonary disease probably occurs by inhalation conidia, which convert to the yeast forms in the lungs. It may be acute or chronic and can mimic infection with tuberculosis, pyogenic bacteria, other fungi, or malignancy.
- Blastomycosis can disseminate to virtually every other body organ, including skin, bones, and joints, or the genitourinary tract, without any evidence of pulmonary disease.

### Clinical Presentation and Diagnosis

- Acute pulmonary blastomycosis is generally an asymptomatic or self-limited disease characterized by fever, shaking chills, and a productive, purulent cough, with or without hemoptysis in immunocompetent individuals.
- Sporadic pulmonary blastomycosis may present as a more chronic or subacute disease, with low-grade fever, night sweats, weight loss, and a productive cough resembling that of tuberculosis rather than bacterial pneumonia. Chronic pulmonary blastomycosis is characterized by fever, malaise, weight loss, night sweats, and cough.
- The simplest and most successful method of diagnosing blastomycosis is by direct microscopic visualization of the large, multinucleated yeast with single, broad-based buds in sputum or other respiratory specimens, following digestion of cells and debris with 10% potassium hydroxide.
- Histopathologic examination of tissue biopsies and culture of secretions should be used to identify *B. dermatitidis*.

### Treatment

- In patients with mild pulmonary blastomycosis, the clinical presentation of the patient, the immune competence of the patient, and the toxicity of the antifungal agents are the main determinants of whether or not to administer antifungal therapy. All immunocompromised patients and patients with progressive disease or with extrapulmonary disease should be treated (Table 38-2).
- Some authors recommend **ketoconazole** therapy for the treatment of self-limited pulmonary disease, with the hope of preventing late extrapulmonary disease.
- **Itraconazole**, 200 to 400 mg/day, is effective as a first-line agent in the treatment of non-life-threatening, non-CNS blastomycosis.
- All patients with disseminated blastomycosis and those with extrapulmonary disease require therapy (**ketoconazole**, 400 mg/day orally for 6 months). CNS disease should be treated with **amphotericin B** for a total cumulative dose greater than 1 g.
- Patients who fail or are unable to tolerate itraconazole therapy, or who develop CNS disease, should be treated with amphotericin B for a total cumulative dose of 1.5 to 2.5 g.
- HIV-infected patients should receive induction therapy with **amphotericin B** and chronic suppressive therapy with an oral azole antifungal. Itraconazole is the drug of choice for non-life-threatening histoplasmosis.

**TABLE 38-2** Therapy of Blastomycosis

Type of Disease	Preferred Treatment	Comments
<b>Pulmonary<sup>a</sup></b>		
Life-threatening	Amphotericin B <sup>b</sup> IV 0.7–1 mg/kg/day IV (total dose 1.5–2.5 g)	Patients may be initiated on amphotericin B and changed to oral itraconazole 200–400 mg orally daily once patient is clinically stabilized and a minimum dose of 500 mg of amphotericin B has been administered.
Mild to moderate	Itraconazole 200 mg orally twice daily × ≥6 months <sup>c</sup>	Alternative therapy: Ketoconazole 400–800 mg orally daily × ≥6 months or fluconazole 400–800 mg orally daily × ≥6 months. <sup>d</sup> <i>In patients intolerant of azoles or in whom disease progresses during azole therapy:</i> Amphotericin B 0.5–0.7 mg/kg/day IV (total dose 1.5–2.5 g).
<b>Disseminated or extrapulmonary</b>		
CNS	Amphotericin B 0.7–1 mg/kg/day IV (total dose 1.5–2.5 g)	For patients unable to tolerate a full course of amphotericin B, consider lipid formulations of amphotericin B or fluconazole ≥800 mg orally daily.
Non-CNS life-threatening	Amphotericin B 0.7–1 mg/kg/day IV (total dose 1.5–2.5 g)	Patients may be initiated on amphotericin B and changed to oral itraconazole 200–400 mg orally daily once stabilized.
Mild to moderate	Itraconazole 200–400 mg orally daily × ≥6 months	Ketoconazole 400–800 mg orally daily or fluconazole 400–800 mg orally daily × ≥6 months. <i>In patients intolerant of azoles or in whom disease progresses during azole therapy:</i> Amphotericin B 0.5–0.7 mg/kg/day IV (total dose 1.5–2.5 g). <i>Bone disease:</i> Therapy with azoles should be continued for 12 months.
<b>Immunocompromised host (including patients with acquired immune deficiency syndrome, transplants, or receiving chronic glucocorticoid therapy)</b>		
Acute disease	Amphotericin B 0.7–1 mg/kg/day IV (total dose 1.5–2.5 g)	Patients without CNS infection may be switched to itraconazole once clinically stabilized and a minimum dose of 1 g of amphotericin B has been administered; long-term suppressive therapy with an azole is advised.
Suppressive therapy	Itraconazole 200–400 mg orally daily	For patients with CNS disease or those intolerant of itraconazole, consider fluconazole 800 mg orally daily.

<sup>a</sup>Some patients with acute pulmonary infection may have a spontaneous cure. Patients with progressive pulmonary disease should be treated.

<sup>b</sup>Desoxycholate amphotericin B.

<sup>c</sup>In patients not responding to 400 mg, dosage should be increased by 200 mg increments every 4 weeks to a maximum of 800 mg daily.

<sup>d</sup>Therapy with ketoconazole is associated with relapses, and fluconazole therapy achieves a lower response rate than itraconazole.

## COCCIDIOIDOMYCOSIS

- Coccidioidomycosis is caused by infection with *Coccidioides immitis*. The endemic regions encompass the semi-arid regions of the southwestern United States from California to Texas, known as the Lower Sonoran Zone. It encompasses a spectrum of illnesses ranging from primary uncomplicated respiratory tract infection that resolves spontaneously to progressive pulmonary or disseminated infection.

### Clinical Presentation and Diagnosis

- Most of those infected are asymptomatic or have nonspecific symptoms that are often indistinguishable from those of ordinary upper respiratory infec-

tions, including fever, cough, headache, sore throat, myalgias, and fatigue. A fine, diffuse rash may appear during the first few days of illness. Chronic, persistent pneumonia or persistent pulmonary coccidioidomycosis (primary disease lasting more than 6 weeks) is complicated by hemoptysis, pulmonary scarring, and the formation of cavities or bronchopleural fistulas.

- “Valley fever” is a syndrome characterized by erythema nodosum and erythema multiforme of the upper trunk and extremities in association with diffuse joint aches or fever. Valley fever occurs in approximately 25% of infected persons, although, more commonly, a diffuse mild erythroderma or maculopapular rash is observed.
- Disseminated infection occurs in less than 1% of infected patients. Dissemination may occur to the skin, lymph nodes, bone, meninges, spleen, liver, kidney, and adrenal gland. CNS infection occurs in approximately 16% of patients with disseminated infection.
- Most patients develop a positive skin test within 3 weeks of the onset of symptoms.
- Infection is characterized by the development of immunoglobulin M to *C. immitis*, which peaks within 2 to 3 weeks of infection and then declines rapidly, and immunoglobulin G, which peaks in 4 to 12 weeks and declines over months to years.
- Recovery of *C. immitis* from infected tissues or secretions for direct examination and culture provides an accurate and rapid method of diagnosis.

### Treatment

- Therapy of coccidioidomycosis is difficult, and the results are unpredictable. Only 5% of infected persons require therapy. Candidates for therapy include those with severe primary pulmonary infection or concurrent risk factors (e.g., human immunodeficiency virus infection, organ transplant, or high doses of glucocorticoids), particularly patients with high complement fixation antibody titers in whom dissemination is likely.
- Specific antifungals (and their usual dosages) for the treatment of coccidioidomycosis include **amphotericin B** IV (0.5 to 1.5 mg/kg/day), **ketoconazole** (400 mg orally daily), IV or oral **fluconazole** (usually 400 to 800 mg daily, although dosages as high as 1,200 mg/day have been utilized without complications), and **itraconazole** (200 to 300 mg orally twice daily as either capsules or solution). If itraconazole is used, measurement of serum concentrations may be helpful to ascertain whether oral bioavailability is adequate.
- Amphotericin B is generally preferred as initial therapy in patients with rapidly progressive disease, whereas azoles are generally preferred in patients with subacute or chronic presentations. Lipid formulations of amphotericin B have not been extensively studied for coccidioidomycosis but can offer a means of giving more drug with less toxicity. Treatments for primary respiratory disease (mainly symptomatic patients) are 3- to 6-month courses of therapy.
- Patients with disease outside the lungs should be treated with 400 mg/day of an oral azole. For meningeal disease, fluconazole 400 mg/day orally should be used; however, some clinicians initiate therapy with 800 mg or 1,000 mg/day and itraconazole doses of 400 to 600 mg/day are comparable.

## CRYPTOCOCCOSIS

- Cryptococcosis is a noncontagious, systemic mycotic infection caused by the ubiquitous encapsulated soil yeast *Cryptococcus neoformans*.

### Clinical Presentation and Diagnosis

- Primary cryptococcosis in humans almost always occurs in the lungs. Symptomatic infections are usually manifested by cough, rales, and shortness of breath that generally resolve spontaneously.
- Disease may remain localized in the lungs or disseminate to other tissues, particularly the CNS, although the skin can also be affected.
- In the non-AIDS patient, the symptoms of cryptococcal meningitis are nonspecific. Headache, fever, nausea, vomiting, mental status changes, and neck stiffness are generally observed. In AIDS patients, fever and headache are common, but meningismus and photophobia are much less common than in non-AIDS patients.
- Examination of cerebrospinal fluid (CSF) in patients with cryptococcal meningitis generally reveals an elevated opening pressure, CSF pleocytosis (usually lymphocytes), leukocytosis, a decreased CSF glucose, an elevated CSF protein, and a positive cryptococcal antigen.
- Antigens to *C. neoformans* can be detected by latex agglutination. *C. neoformans* can be detected in approximately 60% of patients by India ink smear of CSF and cultured in more than 96% of patients.

### Treatment

- Treatment of cryptococcosis is detailed in Table 38-3. For asymptomatic, immunocompetent persons with isolated pulmonary disease and no evidence of CNS disease, careful observation may be warranted. With symptomatic infection, **fluconazole** or **amphotericin B** is warranted.
- The combination of **amphotericin B** with **flucytosine** for 6 weeks is often used for treatment of cryptococcal meningitis. An alternative is amphotericin B for 2 weeks followed by **fluconazole** for an additional 8 to 10 weeks. Suppressive therapy with fluconazole 200 mg/day for 6 to 12 months is optional.
- The use of intrathecal **amphotericin B** is not recommended for the treatment of cryptococcal meningitis except in very ill patients or in those with recurrent or progressive disease despite aggressive IV amphotericin B therapy. The dosage of amphotericin B employed is usually 0.5 mg administered via the lumbar, cisternal, or intraventricular (via an Ommaya reservoir) route two or three times weekly.
- **Amphotericin B** with **flucytosine** is the initial treatment of choice for acute therapy of cryptococcal meningitis in AIDS patients. Many clinicians will initiate therapy with amphotericin B, 0.7 mg/kg/day IV (with flucytosine, 100 mg/kg/day). After 2 weeks, consolidation therapy with either itraconazole 400 mg/day orally or **fluconazole** 400 mg/day orally can be administered for 8 weeks or until CSF cultures are negative. Lifelong therapy with fluconazole is then recommended.
- Relapse of *C. neoformans* meningitis occurs in approximately 50% of AIDS patients after completion of primary therapy. **Fluconazole** (200 mg daily)

**TABLE 38-3** Therapy of Cryptococcosis<sup>a,b</sup>**Type of Disease and Common Clinical Manifestations****Nonimmunocompromised host**

Isolated pulmonary disease (without evidence of CNS infection)

Cryptococemia with positive serum antigen titer (>1:8), cutaneous infection, a positive urine culture, or prostatic disease

Recurrent or progressive disease not responsive to amphotericin B

Isolated pulmonary disease (without evidence of CNS infection)

CNS disease acute (induction/consolidation therapy) (follow all regimens with suppressive therapy)

CNS disease

**Therapy/Comments**

Comparative trials for amphotericin B<sup>c</sup> versus azoles not available

*Asymptomatic disease:* Drug therapy generally not required; observe carefully or fluconazole 400 mg orally daily × 3–6 months

*Mild to moderate symptoms:* Fluconazole 200–400 mg orally daily × 3–6 months; severe disease or inability to take azoles: amphotericin B 0.4–0.7 mg/kg/day (total dose of 1–2 g)

Clinician must decide whether to follow the pulmonary therapeutic regimen or the CNS (disseminated) regimen

Amphotericin B<sup>d</sup> IV 0.5–0.75 mg/kg/day ± intrathecal amphotericin B 0.5 mg 2–3 times weekly

*Mild to moderate symptoms or asymptomatic with a positive pulmonary specimen:* Fluconazole 200–400 mg orally daily × lifelong

or

Itraconazole 200–400 mg orally daily × lifelong

or

Fluconazole 400 mg orally daily + flucytosine 100–150 mg/kg/day orally × 10 weeks

*Severe disease:* Amphotericin B until symptoms are controlled, followed by fluconazole

Amphotericin B<sup>d</sup> IV 0.7–1 mg/kg/day orally × ≥2 weeks, then fluconazole 400 mg orally daily × ≥8 weeks<sup>e</sup>

or

Amphotericin B<sup>d</sup> IV 0.7–1 mg/kg/day + flucytosine 100 mg/kg/day orally × 6–10 weeks<sup>e</sup>

or

Amphotericin B<sup>d</sup> IV 0.7–1 mg/kg/day × 6–10 weeks<sup>e</sup>

or

Fluconazole 400–800 mg orally daily × 10–12 weeks

or

Itraconazole 400–800 mg orally daily × 10–12 weeks

or

Fluconazole 400–800 mg orally daily + flucytosine 100–150 mg/kg/day orally × 6 weeks<sup>e</sup>

or

Lipid formulation of amphotericin B IV 3–6 mg/kg/day × 6–10 weeks (*Note:* Induction therapy with azoles alone is discouraged.)

Amphotericin B<sup>d</sup> IV 0.7–1 mg/kg/day + flucytosine 100 mg/kg/day orally × 2 wk, followed by fluconazole 400 mg orally daily for a minimum of 10 weeks (in patients intolerant to fluconazole, substitute itraconazole 200–400 mg orally daily)

or

Amphotericin B<sup>d</sup> IV 0.7–1 mg/kg/day + 5-flucytosine 100 mg/kg/day orally × 6–10 weeks

or

Amphotericin B<sup>d</sup> IV 0.7–1 mg/kg/day × 10 weeks

Refractory disease: Intrathecal or intraventricular amphotericin B

(continued)

**TABLE 38-3** Therapy of Cryptococcosis<sup>a,b</sup> (Continued)

Type of Disease and Common Clinical Manifestations	Therapy/Comments
<b>Immunocompromised patients</b>	
Non-CNS pulmonary and extrapulmonary disease	Same as nonimmunocompromised patients with CNS disease
CNS disease	Amphotericin B <sup>d</sup> IV 0.7–1 mg/kg/day × 2 weeks, followed by fluconazole 400–800 mg orally daily 8–10 weeks, followed by fluconazole 200 mg orally daily × 6–12 months (in patients intolerant to fluconazole, substitute itraconazole 200–400 mg orally daily) <i>Refractory disease:</i> Intrathecal or intraventricular amphotericin B
<b>HIV-infected patients</b>	
Suppressive/maintenance therapy	Fluconazole 200–400 mg orally daily × lifelong <i>or</i> Itraconazole 200 mg orally twice daily × lifelong <i>or</i> Amphotericin B IV 1 mg/kg 1–3 times weekly × lifelong

HIV, human immunodeficiency virus.

<sup>a</sup>When more than one therapy is listed, they are listed in order of preference.

<sup>b</sup>See text for definitions of induction, consolidation, suppressive/maintenance therapy, and prophylactic therapy.

<sup>c</sup>Deoxycholate amphotericin B.

<sup>d</sup>In patients with significant renal disease, lipid formulations of amphotericin B can be substituted for deoxycholate amphotericin B during the induction.

<sup>e</sup>Or until cerebrospinal fluid cultures are negative.

is currently recommended for chronic suppressive therapy of cryptococcal meningitis in AIDS patients.

## CANDIDA INFECTIONS

- Eight species of *Candida* are regarded as clinically important pathogens in human disease: *C. albicans*, *C. tropicalis*, *C. parapsilosis*, *C. krusei*, *C. stellatoidea*, *C. guilliermondii*, *C. lusitaniae*, and *C. glabrata*.

## HEMATOGENOUS CANDIDIASIS

- Hematogenous candidiasis describes the clinical circumstances in which hematogenous seeding to deep organs such as the eye, brain, heart, and kidney occurs.
- *Candida* is generally acquired via the GI tract, although organisms may also enter the bloodstream via indwelling IV catheters. Immunosuppressed patients, including those with lymphoreticular or hematologic malignancies, diabetes, immunodeficiency diseases, or those receiving immunosuppressive therapy with high-dose corticosteroids, immunosuppressants, antineoplastic agents, or broad-spectrum antimicrobial agents are at high risk for invasive fungal infections. Major risk factors include the use of central venous catheters, total parenteral nutrition, receipt of multiple antibiotics, extensive surgery and burns, renal failure and hemodialysis, mechanical ventilation, and prior fungal colonization.
- Three distinct presentations of disseminated *C. albicans* have been recognized: (1) the acute onset of fever, tachycardia, tachypnea, and occasionally

- chills or hypotension (similar to bacterial sepsis); (2) intermittent fevers; (3) progressive deterioration with or without fever; and (4) hepatosplenic candidiasis manifested only as fever while the patient is neutropenic.
- No test has demonstrated reliable accuracy in the clinical setting for diagnosis of disseminated *Candida* infection. Blood cultures are positive in only 25% to 45% of neutropenic patients with disseminated candidiasis. Fluorescence in situ hybridization has excellent sensitivity and specificity in the identification of *C. albicans* from blood.
  - Treatment of candidiasis is presented in Table 38-4. Amphotericin B may be switched to fluconazole (IV or oral) for completion of therapy. Azoles and deoxycholate amphotericin B are similarly effective; however, fewer adverse effects are observed with azoles. Echinocandins are at least as effective as amphotericin B or fluconazole in nonneutropenic adult patients with candidemia.
  - In patients with an intact immune system, removal of all existing central venous catheters should be considered.
  - Lipid-associated formulations of amphotericin B, liposomal amphotericin B (AmBisome) and amphotericin B lipid complex (Abelcet) have been approved for use in proven cases of candidiasis; however, patients with invasive candidiasis have also been treated successfully with amphotericin B colloid dispersion (Amphotec or Amphocil). The lipid-associated formulations are less toxic but as effective as amphotericin B deoxycholate.
  - Many clinicians advocate early institution of empiric IV **amphotericin B** in patients with neutropenia and persistent fever (more than 5 to 7 days). Suggested criteria for the empiric use of amphotericin B include (1) fever of 5 to 7 days' duration that is unresponsive to antibacterial agents, (2) neutropenia of more than 7 days' duration, (3) no other obvious cause for fever, (4) progressive debilitation, (5) chronic adrenal corticosteroid therapy, and (6) indwelling intravascular catheters.

## ASPERGILLUS INFECTIONS

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- Of more than 300 species of *Aspergillus*, three are most commonly pathogenic: *A. fumigatus*, *A. flavus*, and *A. niger*.
- Aspergillosis is generally acquired by inhalation of airborne conidia that are small enough (2.5 to 3 μm) to reach the alveoli or the paranasal sinuses.

### Superficial Infection

- Superficial or locally invasive infections of the ear, skin, or appendages can often be managed with topical antifungal therapy.

### Allergic Bronchopulmonary Aspergillosis

- Allergic manifestations of *Aspergillus* range in severity from mild asthma to allergic bronchopulmonary aspergillosis characterized by severe asthma with wheezing, fever, malaise, weight loss, chest pain, and a cough productive of blood-streaked sputum.
- Therapy is aimed at minimizing the quantity of antigenic material released in the tracheobronchial tree.
- Antifungal therapy is generally not indicated in the management of allergic manifestations of aspergillosis, although some patients have demonstrated a

**TABLE 38-4** Therapy of Invasive Candidiasis

Type of Disease and Common Clinical Manifestations	Therapy/Comments
<b>Prophylaxis of candidemia</b>	
Nonneutropenic patients <sup>a</sup>	Not recommended except for severely ill/high-risk patients in whom fluconazole IV/po 400 mg daily should be used
Neutropenic patients <sup>a</sup>	The optimal duration of therapy is unclear but at a minimum should include the period at risk for neutropenia: Fluconazole IV/po 400 mg daily or Itraconazole solution 2.5 mg/kg every 12 hours po or Micafungin 50 mg (1 mg/kg in patients under 50 kg) IV daily
Solid-organ transplantation	<i>Patients with two or more key risk factors<sup>b</sup>:</i>
Liver transplantation	Amphotericin B IV 10–20 mg daily or Liposomal amphotericin B (AmBisome) 1 mg/kg/day or fluconazole 400 mg orally daily
<b>Empirical antifungal therapy (unknown <i>Candida</i> species)</b>	
Suspected disseminated candidiasis in febrile nonneutropenic patients	None recommended; data are lacking defining subsets of patients who are appropriate for therapy
Febrile neutropenic patients with prolonged fever despite 4–6 days of empirical antibacterial therapy	<i>Treatment duration:</i> Until resolution of neutropenia Amphotericin B IV 0.5–0.7 mg/kg/day or Liposomal amphotericin B (AmBisome) IV 3 mg/kg/day or Itraconazole 200 mg IV every 12 hours × 2 days, then 200 mg/day × 12 days, then 400 mg po (solution) daily or Voriconazole 6 mg/kg IV loading dose every 12 hours × 2 doses, then 3 mg/kg every 12 hours (restrict to allogeneic bone marrow transplant and relapsed leukemia patients) or Fluconazole 400 mg/day IV/po (restrict to patients with a low risk for invasive aspergillosis or azole-resistant strains of <i>Candida</i> in patients with no previous azole exposure or signs and symptoms suggesting aspergillosis)
<b>Treatment of candidemia and acute hematogenously disseminated candidiasis</b>	
Nonimmunocompromised host <sup>c</sup>	<i>Treatment duration:</i> 2 weeks after the last positive blood culture and resolution of signs and symptoms of infection Remove existing central venous catheters when feasible, plus: Amphotericin B IV 0.6 mg/kg/day or Fluconazole IV/po 6 mg/kg/day or An echinocandin <sup>d</sup> or Amphotericin B IV 0.7 mg/kg/day plus fluconazole IV/po 800 mg/day
<i>Candida albicans</i> , <i>C. tropicalis</i> , <i>C. parapsilosis</i>	<i>Patients intolerant or refractory to other therapy<sup>e</sup>:</i> Amphotericin B lipid complex IV 5 mg/kg/day Liposomal amphotericin B IV 3–5 mg/kg/day Amphotericin B colloid dispersion IV 2–6 mg/kg/day

(continued)

**TABLE 38-4** Therapy of Invasive Candidiasis (Continued)

Type of Disease and Common Clinical Manifestations	Therapy/Comments
<i>C. krusei</i>	Amphotericin B IV $\geq 1$ mg/kg/day or An echinocandin <sup>d</sup>
<i>C. lusitanae</i>	Fluconazole IV/po 6 mg/kg/day
<i>C. glabrata</i>	Amphotericin B IV $\geq 0.7$ mg/kg/day or Fluconazole IV/po 6–12 mg/kg/day (400–800 mg/day in a 70-kg patient) or An echinocandin <sup>d</sup>
Neutropenic host <sup>f</sup>	<i>Treatment duration:</i> Until resolution of neutropenia Remove existing central venous catheters when feasible, plus: Amphotericin B IV 0.7–1 mg/kg/day (total dosages 0.5–1 g) or <i>Patients failing therapy with traditional amphotericin B:</i> Lipid formulation of amphotericin B IV 3–5 mg/kg/day
<b>Chronic disseminated candidiasis (hepatosplenic candidiasis)</b>	<i>Treatment duration:</i> Until calcification or resolution of lesions <i>Stable patients:</i> Fluconazole IV/po 6 mg/kg/day <i>Acutely ill or refractory patients:</i> Amphotericin B IV 0.6–0.7 mg/kg/day <i>Asymptomatic disease:</i> Generally no therapy is required
<b>Urinary candidiasis</b>	<i>Symptomatic or high-risk patients<sup>g</sup>:</i> Removal of urinary tract instruments, stents, and Foley catheters) plus 7–14 days therapy with fluconazole 200 mg orally daily or amphotericin B IV 0.3–1 mg/kg/day

<sup>a</sup>Patients at significant risk for invasive candidiasis include those receiving standard chemotherapy for acute myelogenous leukemia, allogeneic bone marrow transplants, or high-risk autologous bone marrow transplants. However, among these populations, chemotherapy or bone marrow transplant protocols do not all produce equivalent risk, and local experience should be used to determine the relevance of prophylaxis.

<sup>b</sup>Risk factors include retransplantation, creatinine of more than 2 mg/dL, choledochojejunostomy, intraoperative use of 40 units or more of blood products, fungal colonization detected within the first 3 days after transplantation.

<sup>c</sup>Therapy is generally the same for acquired immune deficiency syndrome/non-acquired immune deficiency syndrome patients except where indicated and should be continued for 2 weeks after the last positive blood culture and resolution of signs and symptoms of infection. All patients should receive an ophthalmologic examination. Amphotericin B may be switched to fluconazole (intravenous or oral) for the completion of therapy. Susceptibility testing of the infecting isolate is a useful adjunct to species identification during selection of a therapeutic approach because it can be used to identify isolates that are unlikely to respond to fluconazole or amphotericin B. However, this is not currently available at most institutions.

<sup>d</sup>Echinocandin = caspofungin 70 mg loading dose, then 50 mg IV daily maintenance dose, or micafungin 100 mg daily, or anidulafungin 200 mg loading dose, then 100 mg daily maintenance dose.

<sup>e</sup>Often defined as failure of  $\geq 500$  mg amphotericin B, initial renal insufficiency (creatinine  $\geq 2.5$  mg/dL or creatinine clearance  $< 25$  mL/min), a significant increase in creatinine (to 2.5 mg/dL for adults or 1.5 mg/dL for children) or severe acute administration-related toxicity.

<sup>f</sup>Patients who are neutropenic at the time of developing candidemia should receive a recombinant cytokine (granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor) that accelerates recovery from neutropenia.

<sup>g</sup>Patients at high risk for dissemination include neutropenic patients, low-birth-weight infants, patients with renal allografts, and patients who will undergo urologic manipulation.

decrease in their glucocorticoid dose following therapy with itraconazole. Itraconazole 200 mg twice daily for 16 weeks resulted in reduced corticosteroid dose and improvement in exercise tolerance and pulmonary function.

## Aspergilloma

- In the nonimmunocompromised host, *Aspergillus* infections of the sinuses most commonly occur as saprophytic colonization (aspergillomas, or

“fungus balls”) of previously abnormal sinus tissue. Treatment consists of removal of the aspergilloma. Therapy with glucocorticoids and surgery is generally successful.

- Although IV amphotericin B is generally not useful in eradicating aspergillomas, intracavitary instillation of amphotericin B has been employed successfully in a limited number of patients. Hemoptysis generally ceases when the aspergilloma is eradicated.

### **Invasive Aspergillosis**

- Patients often present with classic signs and symptoms of acute pulmonary embolus: pleuritic chest pain, fever, hemoptysis, a friction rub, and a wedge-shaped infiltrate on chest radiographs.
- Demonstration of *Aspergillus* by repeated culture and microscopic examination of tissue provides the most firm diagnosis.
- In the immunocompromised host, aspergillosis is characterized by vascular invasion leading to thrombosis, infarction, and necrosis of tissue.

### **Treatment**

- Antifungal therapy should be instituted in any of the following conditions: (1) persistent fever or progressive sinusitis unresponsive to antimicrobial therapy; (2) an eschar over the nose, sinuses, or palate; (3) the presence of characteristic radiographic findings, including wedge-shaped infarcts, nodular densities, or new cavitary lesions; or (4) any clinical manifestation suggestive of orbital or cavernous sinus disease or an acute vascular event associated with fever. Isolation of *Aspergillus* spp. from nasal or respiratory tract secretions should be considered confirmatory evidence in any of the previously mentioned clinical settings.
- Voriconazole is the drug of choice for primary therapy of most patients with aspergillosis since it provided improved survival and fewer side effects.
- In patients who cannot tolerate voriconazole, amphotericin B can be used. Full doses (1 to 1.5 mg/kg/day) are generally recommended, with response measured by defervescence and radiographic clearing. The lipid-based formulations may be preferred as initial therapy in patients with marginal renal function or in patients receiving other nephrotoxic drugs. The optimal duration of treatment is unknown.
- **Caspofungin** is indicated for treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies such as amphotericin B.
- The use of prophylactic antifungal therapy to prevent primary infection or reactivation of aspergillosis during subsequent courses of chemotherapy is controversial.

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See Chap. 125, *Invasive Fungal Infections*, authored by Peggy L. Carver, for a more detailed discussion of this topic.

## INTRODUCTION

- GI infections are among the more common causes of morbidity and mortality around the world. Most are caused by viruses, and some are caused by bacteria or other organisms. In underdeveloped and developing countries, acute gastroenteritis involving diarrhea is the leading cause of mortality in infants and children younger than 5 years of age. In the United States, there are approximately 211 million episodes of acute gastroenteritis each year, causing over 900,000 hospitalizations and over 6,000 deaths.

## REHYDRATION THERAPY

- Fluid replacement is the cornerstone of therapy for diarrhea regardless of etiology.
- Initial assessment of fluid loss is essential for rehydration. Weight loss is the most reliable means of determining the extent of water loss. Clinical signs such as changes in skin turgor, sunken eyes, dry mucous membranes, decreased tearing, decreased urine output, altered mentation, and changes in vital signs can be helpful in determining approximate deficits (Table 39-1).
- The necessary components of oral rehydration therapy (ORT) solutions include glucose, sodium, potassium, chloride, and water (Table 39-2). The American Academy of Pediatrics recommends rehydration with an electrolyte-concentrated rehydration phase followed by a maintenance phase using dilute electrolyte solutions and larger volumes.
- The maintenance phase should not exceed 100 to 150 mL/kg/day and is generally adjusted to equal stool losses.
- Weight loss of 9% to 10% is considered severe and requires IV fluid replacement with Ringer's lactate or 0.9% sodium chloride. IV therapy is also indicated in patients with uncontrolled vomiting, the presence of paralytic ileus, stool output greater than 10 mL/kg/hour, shock, or loss of consciousness.
- Early refeeding as tolerated is recommended. Age-appropriate diet may be resumed as soon as dehydration is corrected. Early initiation of feeding shortens the course of diarrhea. Initially, easily digested foods, such as bananas, applesauce, and cereal, may be added as tolerated. Foods high in fiber, sodium, and sugar should be avoided.

## BACTERIAL INFECTIONS

- The bacterial species most commonly associated with GI infection and infectious diarrhea in the United States are *Shigella* spp., *Salmonella* spp., *Campylobacter* spp., *Yersinia* spp., *Escherichia* spp., *Clostridium* spp., and *Staphylococcus* spp.
- Antibiotics are not essential in the treatment of most mild diarrheas, and empirical therapy for acute GI infections may result in unnecessary

**TABLE 39-1** Clinical Assessment of Degree of Dehydration in Children Based on Percentage of Body Weight Loss<sup>a</sup>

Variable	Mild, 3–5%	Moderate, 6–9%	Severe, ≥10%
Blood pressure	Normal	Normal	Normal to reduced
Quality of pulses	Normal	Normal or slightly decreased	Moderately decreased
Heart rate	Normal	Increased	Increased (bradycardia in severe cases)
Skin turgor	Normal	Decreased	Decreased
Fontanelle	Normal	Sunken	Sunken
Mucous membranes	Slightly dry	Dry	Dry
Eyes	Normal	Sunken orbits/ decreased tears	Deeply sunken orbits/decreased tears
Extremities	Warm, normal capillary refill	Delayed capillary refill	Cool, mottled
Mental status	Normal	Normal to listless	Normal to lethargic or comatose
Urine output	Slightly decreased	<1 mL/kg/hour	<1 mL/kg/hour
Thirst	Slightly increased	Moderately increased	Very thirsty or too lethargic to indicate
Fluid replacement	ORT 50 mL/kg over 2–4 hours Replace ongoing losses with low-sodium ORT (40–60 mEq/L Na <sup>+</sup> ) at 10 mL/kg per stool or emesis	ORT 100 mL/kg over 2–4 hours Replace ongoing losses with low-sodium ORT (40–60 mEq/L Na <sup>+</sup> ) at 10 mL/kg per stool or emesis	Ringer's lactate 40 mL/kg in 15–30 minutes, then 20–40 mL/kg if skin turgor, alertness, and pulse have not returned to normal <i>or</i> Ringer's lactate or normal saline 20 mL/kg, repeat if necessary, and then replace water and electrolyte deficits over 1–2 days Followed by ORT 100 mL/kg over 4 hours. Replace ongoing losses with low-sodium ORT (40–60 mEq/L Na <sup>+</sup> ) at 10 mL/kg per stool or emesis

ORT, oral rehydration therapy.

<sup>a</sup>Percentages vary among authors for each dehydration category; hemodynamic and perfusion status is most important; when unsure of category, therapy for more severe category is recommended.

antibiotic courses. Antibiotic choices for bacterial infections are given in Table 39-3.

## ENTEROTOXIGENIC (CHOLERA-LIKE) DIARRHEA

### Cholera (*Vibrio cholerae*)

- *Vibrio cholerae* 01 is the serogroup that most often causes human epidemics and pandemics. Four mechanisms for transmission have been proposed: Animal reservoirs, chronic carriers, asymptomatic or mild disease victims, or water reservoirs.
- Most pathology of cholera is thought to result from an enterotoxin that increases cyclic adenosine monophosphate–mediated secretion of chloride ion into the intestinal lumen, which results in isotonic secretion (primarily in the small intestine) exceeding the absorptive capacity of the intestinal tract (primarily the colon).

**TABLE 39-2** Comparison of Common Solutions Used in Oral Rehydration and Maintenance

Product	Na (mEq/L)	K (mEq/L)	Base (mEq/L)	Carbohydrate (mmol/L)	Osmolality (mOsm/L)
Naturalyte (unlimited beverage)	45	20	48	140	265
Pediatric electrolyte (NutraMax)	45	20	30	140	250
Pedialyte (Ross)	45	20	30	140	250
Infalyte (formerly Ricelyte; Mead Johnson)	50	25	30	70	200
Rehydralyte (Ross)	75	20	30	140	310
World Health Organization/ United Nations Children's Fund oral rehydration salts	90	20	30	111	310
Cola	2	0	13	700	750
Apple juice	5	32	0	690	730
Chicken broth	250	8	0	0	500
Sports beverage	20	3	3	255	330

- The incubation period of *V. cholerae* is 1 to 3 days.
- Cholera is characterized by a spectrum from the asymptomatic state to the most severe typical cholera syndrome. Patients may lose up to 1 L of isotonic fluid every hour. The onset of diarrhea is abrupt and is followed rapidly or sometimes preceded by vomiting. Fever occurs in less than 5% of patients. In the most severe state, this disease can progress to death in a matter of 2 to 4 hours if not treated.

### Treatment

- The mainstay of treatment for cholera consists of fluid and electrolyte replacement with ORT to restore fluid and electrolyte losses. Rice-based rehydration formulations are the preferred ORT for cholera patients. In patients who cannot tolerate ORT, IV therapy with Ringer's lactate can be used.
- Antibiotics shorten the duration of diarrhea, decrease the volume of fluid lost, and shorten the duration of the carrier state (see Table 39-3). A single dose of oral doxycycline is the preferred agent. In children younger than 7 years of age, **trimethoprim-sulfamethoxazole**, **erythromycin**, and **furazolidone** can be used. In areas of high tetracycline resistance, fluoroquinolones are effective.

### ESCHERICHIA COLI

- *Escherichia coli* GI disease may be caused by enterotoxigenic *E. coli* (ETEC), enteroinvasive *E. coli*, enteropathogenic *E. coli*, enteroadhesive *E. coli*, and enterohemorrhagic *E. coli*. ETEC is now incriminated as being the most common cause of traveler's diarrhea.
- ETEC is capable of producing two plasmid-mediated enterotoxins: heat-labile toxin and heat-stable toxin. The net effect of either toxin on the mucosa is production of a cholera-like secretory diarrhea.
- Nausea and watery stools, with or without abdominal cramping, are characteristic of the disease caused by ETEC. Most ETEC diarrhea is typically abrupt in onset and resolves within 24 to 48 hours without complication.

**TABLE 39-3** Recommendations for Antibiotic Therapy

Pathogen	First-Line Agents	Alternative Agents
<b>Enterotoxigenic (cholera-like) diarrhea</b>		
<i>Vibrio cholerae</i> O1 or O139	Doxycycline 300 mg oral single dose; tetracycline 500 mg orally four times daily × 3 days; or trimethoprim-sulfamethoxazole DS tablet twice daily × 3 days; norfloxacin 400 mg orally twice daily × 3 days; or ciprofloxacin 500 mg orally twice daily × 3 days or 1 g orally single dose	Chloramphenicol 50 mg/kg IV every 6 hours, erythromycin 250–500 mg orally every 6–8 hours, and furazolidone
Enterotoxigenic <i>Escherichia coli</i>	Norfloxacin 400 mg or ciprofloxacin 500 mg orally twice daily × 3 days	Trimethoprim-sulfamethoxazole DS tablet every 12 hours
<i>Clostridium difficile</i>	Metronidazole 250 mg four times daily to 500 mg three times daily × 10 days	Vancomycin 125 mg orally four times daily × 10 days; bacitracin 20,000–25,000 units four times daily × 7–10 days
<b>Invasive (dysentery-like) diarrhea</b>		
<i>Shigella</i> species <sup>a</sup>	Trimethoprim-sulfamethoxazole DS twice daily × 3–5 days	Ofloxacin 300 mg, norfloxacin 400 mg, or ciprofloxacin 500 mg twice daily × 3 days, or nalidixic acid 1 g/day × 5 days; azithromycin 500 mg orally × 1 day, then 250 mg orally daily × 4 days
<i>Salmonella</i>		
Nontyphoidal <sup>a</sup>	Trimethoprim-sulfamethoxazole DS twice daily; ofloxacin 300 mg, norfloxacin 400 mg, or ciprofloxacin 500 mg twice daily × 5 days; or ceftriaxone 2 g IV daily or cefotaxime 2 g IV three times daily × 5 days	Azithromycin 1,000 mg orally × 1 day, followed by 500 mg orally once daily × 6 days
Enteric fever	Ciprofloxacin 500 mg orally twice daily × 3–14 days (ofloxacin and pefloxacin equally efficacious)	Azithromycin 1,000 mg orally × 1 day, followed by 500 mg daily × 5 days; or cefixime, cefotaxime, and cefuroxime; or chloramphenicol 500 mg four times daily orally or IV × 14 days
<i>Campylobacter</i> <sup>a</sup>	Erythromycin 500 mg orally twice daily × 5 days; azithromycin 1,000 mg orally × 1 day, followed by 500 mg daily or clarithromycin 500 mg orally twice daily	Ciprofloxacin 500 mg or norfloxacin 400 mg orally twice daily × 5 days
<i>Yersinia</i> species <sup>a</sup>	A combination therapy with doxycycline, aminoglycosides, trimethoprim-sulfamethoxazole, or fluoroquinolones	
<b>Traveler's diarrhea</b>		
Prophylaxis <sup>a</sup>	Norfloxacin 400 mg or ciprofloxacin 500 mg orally daily (in Asia, Africa, and South America); trimethoprim-sulfamethoxazole DS tablet orally daily (in Mexico)	Rifaximin 200 mg one to three times daily × 2 weeks
Treatment	Norfloxacin 400 mg or ciprofloxacin 500 mg orally twice daily × 3 days, or trimethoprim-sulfamethoxazole DS tablet orally twice daily × 3 days (in Mexico), or azithromycin 500 mg orally once daily × 3 days (only in areas of high prevalence of quinolone-resistant <i>Campylobacter</i> species, such as Thailand)	Rifaximin 200 mg three times a day or 400 mg twice a day × 3 days

DS, dilute strength.

<sup>a</sup>For high-risk patients only. See the preceding text for the high-risk patients in each infection.

- Most cases respond readily to ORT, and although antibiotic therapy is seldom necessary, prophylaxis has been shown to effectively prevent the development of ETEC diarrhea.
- Fluid and electrolyte replacement should be initiated at the onset of diarrhea.
- Antibiotics used for treatment are found in Table 39-3.
- Loperamide should not be used in patients with fever or dysentery.
- Effective prophylaxis of ETEC diarrhea can be accomplished with **doxycycline**, **trimethoprim-sulfamethoxazole**, or a **fluoroquinolone**, but this approach is not routinely recommended.

### **PSEUDOMEMBRANOUS COLITIS (*CLOSTRIDIUM DIFFICILE*)**

- Pseudomembranous colitis (PMC) results from toxins produced by *Clostridium difficile*. It occurs most often in epidemic fashion and affects high-risk groups such as the elderly, debilitated patients, cancer patients, surgical patients, any patient receiving antibiotics, patients with nasogastric tubes, or those who frequently use laxatives.
- PMC has been associated most often with broad-spectrum antimicrobials, including clindamycin, ampicillin, or third-generation cephalosporins.
- PMC may result in a spectrum of disease from mild diarrhea to enterocolitis. In colitis without pseudomembranes, patients present with malaise, abdominal pain, nausea, anorexia, watery diarrhea, low-grade fever, and leukocytosis. With pseudomembranes, there is more severe illness with severe abdominal pain, profuse diarrhea, high fever, and marked leukocytosis. Symptoms can start a few days after the start of antibiotic therapy to several weeks after antibiotics have been stopped.
- Diagnosis is made by colonoscopic visualization of pseudomembranes, finding cytotoxins A or B in stools, or stool culture for *C. difficile*.
- Initial therapy of PMC should include discontinuation of the offending agent. The patient should be supported with fluid and electrolyte replacement.
- Both vancomycin and metronidazole are effective, but **metronidazole** 250 mg orally four times daily is the drug of choice. Oral **vancomycin**, 125 mg orally four times daily, is second-line therapy. It should be reserved for patients not responding to metronidazole, organisms resistant to metronidazole, patients allergic or intolerant to metronidazole, other treatments that include alcohol-containing solutions, patients who are pregnant or younger than 10 years, critically ill patients, or those with diarrhea that is caused by *Staphylococcus aureus*. Bacitracin is the third-line agent.
- Drugs that inhibit peristalsis, such as **diphenoxylate**, are contraindicated.
- Relapse can occur in 20% to 25% of patients and may be treated with metronidazole or vancomycin for 10 to 14 days.

### **INVASIVE (DYSENTERY-LIKE) DIARRHEA**

#### **BACILLARY DYSENTERY (SHIGELLOSIS)**

- Four species of *Shigella* are most often associated with disease: *S. dysenteriae* type I, *S. flexneri*, *S. boydii*, and *S. sonnei*.

- Poor sanitation, poor personal hygiene, inadequate water supply, malnutrition, and increased population density are associated with increased risk of *Shigella* gastroenteritis epidemics, even in developed countries. The majority of cases are thought to result from fecal–oral transmission.
- *Shigella* spp. cause dysentery upon penetrating the epithelial cells lining the colon. Microabscesses may eventually coalesce, forming larger abscesses. Some *Shigella* species produce a cytotoxin, or shigatoxin, the pathogenic role of which is unclear, although it is thought to damage endothelial cells of the lamina propria, resulting in microangiopathic changes that can progress to hemolytic uremic syndrome. Watery diarrhea commonly precedes the dysentery and may be a result of these toxins.
- Initial signs and symptoms include abdominal pain, cramping, and fever followed by frequent watery stools. Within a few days, patients experience a decrease in fever, severe abdominal pain, and tenderness prior to the development of bloody diarrhea and other signs of dysentery.
- If untreated, bacillary dysentery usually lasts about 1 week (range 1 to 30 days).
- Shigellosis is usually a self-limiting disease. Most patients recover in 4 to 7 days. Treatment of bacillary dysentery generally includes correction of fluid and electrolyte disturbances and, occasionally, antimicrobials.
- Antimicrobials are indicated in the infirm, those who are immunocompromised, children in daycare centers, the elderly, malnourished children, and healthcare workers. Antimicrobials may shorten the period of fecal shedding and attenuate the clinical illness.
- The agent of choice depends on location. **Trimethoprim–sulfamethoxazole** is used for infections acquired in the United States. For infections acquired outside the United States, the agents of choice are **ciprofloxacin**, **norfloxacin**, and **azithromycin**. Fluoroquinolones are generally contraindicated in children and adolescents.
- Fluid and electrolyte losses can generally be replaced with oral therapy, as dysentery is generally not associated with significant fluid loss. IV replacement is necessary only for children or the elderly.
- Antimotility agents such as diphenoxylate are not recommended because they can worsen dysentery.

## SALMONELLOSIS

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- Human disease caused by *Salmonella* generally falls into four categories: acute gastroenteritis (enterocolitis), bacteremia, extraintestinal localized infection, and enteric fever (typhoid and paratyphoid fever), and a chronic carrier state. *S. typhimurium* is the most common cause of salmonellosis. Salmonellosis is a disease primarily of infants, children, and adolescents.
- Conditions which predispose to infection include those which decrease gastric acidity, antibiotic use, malnutrition, and immunodeficiency states. Contaminated food or water is implicated in most cases.
- With enterocolitis, patients often complain of nausea and vomiting within 72 hours of ingestion followed by crampy abdominal pain, fever, and diarrhea, although the actual presentation is quite variable.

- Stool cultures inevitably yield the causative organism, if obtained early. However, recovery of organisms continues to decrease with time so that by 3 to 4 weeks, only 5% to 15% of adult patients are passing *Salmonella*.
- Some patients may continue to shed *Salmonella* for 1 year or longer. These “chronic-carrier” states are rare for serotypes other than *S. typhi*.
- *Salmonella* can produce bacteremia without classic enterocolitis or enteric fever. The clinical syndrome is characterized by persistent bacteremia and prolonged intermittent fever with chills. Stool cultures are frequently negative.
- Extraluminal infection and/or abscess formation can occur at any site after any of the other syndromes or may be the primary presentation. Metastatic infections have been reported to involve bone, cysts, heart, kidney, liver, lungs, pericardium, spleen, and tumors.
- Enteric fever caused by *S. typhi* is called typhoid fever. If caused by any other serotype, it is referred to as paratyphoid fever. The onset of symptoms is gradual. Nonspecific symptoms of fever, dull headache, malaise, anorexia, and myalgias are most common. Initially, fever tends to be remittent but gradually progresses over the first week to temperatures that are often sustained over 40°C (104°F). Other frequently encountered symptoms include chills, nausea, vomiting, cough, weakness, and sore throat.
- About 80% of patients with enteric fever have positive blood cultures. Bacteremia persists in about one-third of patients for several weeks if not treated. Diagnostic tests other than culture are unreliable.

### Treatment

- Most patients with enterocolitis require no therapeutic intervention. The most important part of therapy for *Salmonella* enterocolitis is fluid and electrolyte replacement. Antimotility drugs should be avoided because they increase the risk of mucosal invasion and complications.
- Antibiotics have no effect on the duration of fever or diarrhea, and their frequent use increases the likelihood of resistance and the duration of fecal shedding. Antibiotics should be used in neonates or infants younger than 6 months, patients with primary or secondary immunodeficiency, severely symptomatic patients with fever and bloody diarrhea, and patients after splenectomy.
- Recommended antibiotics with adult doses include:
  - ✓ Fluoroquinolones, trimethoprim–sulfamethoxazole, ampicillin, third-generation cephalosporins
- For bacteremia, life-threatening treatment should include the combination of a third-generation cephalosporin (ceftriaxone 2 g IV daily) and ciprofloxacin 500 mg orally twice daily. The duration of antibiotic therapy is dictated by the site.
- Fluoroquinolones such as **ciprofloxacin** (500 mg orally twice daily for 10 days in adults) are the drugs of choice for enteric fever, particularly in areas where multidrug resistance is common. A short course of 3 to 5 days is effective but a minimum of 10 days is recommended in severe cases.
- The drug of choice for chronic carriers of *Salmonella* is **norfloxacin**, 400 mg orally twice daily for 28 days.

- Vaccines are recommended for high-risk groups. Live oral attenuated vaccine Ty21a and parenteral polysaccharide vaccine have been shown to confer 42% to 77% efficacy for a duration of 3 to 5 years.

## CAMPYLOBACTERIOSIS

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- *Campylobacter* species are thought to be a major cause of diarrhea. Transmission of infection occurs primarily by ingestion of contaminated food or water.
- Incubation usually averages 2 to 4 days. The most common symptoms include diarrhea of varying consistency and severity, abdominal pain, and fever. Nausea, vomiting, headache, myalgias, and malaise may also occur. Bowel movements may be numerous, bloody (dysentery-like), foul smelling, and melanic and range from loose to watery (dysentery-like).
- The disease is self-limiting, and signs and symptoms usually resolve in about 1 week but may persist longer in 10% to 20% of patients.
- As with other acute diarrheal illnesses, fluid and electrolyte support is a mainstay of therapy, mainly with ORT.
- Antibiotics are not useful unless started within 4 days of the start of illness, as they do not shorten the duration or severity of diarrhea.
- Antibiotics are warranted in patients who present with high fevers, severe bloody diarrhea, prolonged illness (greater than 1 week), pregnancy, and immunocompromised states, including human immunodeficiency virus infection.
- Erythromycin is considered the drug of choice for treatment. Clarithromycin or azithromycin is equally effective. Antimotility drugs are contraindicated.

## YERSINIOSIS

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- *Yersinia enterocolitica* and *Y. pseudotuberculosis* are associated with intestinal infection. The organisms have been isolated from a variety of food sources, including raw goat and cow milk.
- These bacteria cause a wide spectrum of clinical syndromes. The majority of cases present with enterocolitis that is mild and self-limiting. Symptoms, generally lasting 1 to 3 weeks, include vomiting, abdominal pain, diarrhea, and fever. A clinical syndrome seen in older children may resemble appendicitis.
- Many patients develop a reactive arthritis 1 to 2 weeks after recovery from enteritis.
- These diseases are generally self-limiting and are easily managed with oral rehydration solutions.
- Antibiotics should be used in high-risk patients who develop bacteremia (i.e., infants younger than 3 months and patients with cirrhosis or iron overload) or in patients with bone and joint infections.
- Drugs of choice are not yet identified. *Y. enterocolitica* is generally susceptible to **fluoroquinolones**, alone or in combination with **third-generation cephalosporins** or **aminoglycosides**. Alternative agents include **chloramphenicol**, **tetracycline**, and **trimethoprim-sulfamethoxazole**.
- Suggested antibiotics of choice are given in Table 39-3.

## ACUTE VIRAL GASTROENTERITIS

### ROTAVIRUSES

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- The highest frequency of rotavirus-associated diarrhea appears in children less than 5 years of age. The incubation period is typically 1 to 3 days.
- Clinical manifestations of rotavirus infections vary from asymptomatic (which is common in adults) to severe nausea, vomiting, and diarrhea with dehydration. Symptoms are characterized initially by nausea and vomiting. The symptoms begin abruptly, with vomiting often preceding the onset of diarrhea. Other signs and symptoms include fever, respiratory symptoms, irritability, lethargy, pharyngeal erythema, rhinitis, red tympanic membranes, and palpable cervical lymph nodes. Dehydration and electrolyte disturbances occur more frequently in children.
- Oral fluid and electrolyte replacement is the cornerstone of treatment. Oral Lactobacillus therapy may reduce the duration of diarrhea and or viral excretion. There is no role for antibiotics.
- Antimotility agents are not recommended.

### CALICIVIRUSES

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- Caliciviruses include Norovirus (including Norwalk virus) and Sapovirus. Calicivirus gastroenteritis is characterized by sudden onset of abdominal cramps with nausea and/or vomiting. Although adults frequently experience nonbloody diarrhea, children experience vomiting more often. Other frequent complaints are myalgias, headache, and malaise, which are accompanied by fever in about 50% of cases. Signs and symptoms generally last only 12 to 48 hours.
- The disease is generally self-limiting and does not require therapy. On occasion, oral rehydration may be required. Rarely is parenteral hydration necessary.

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See Chap. 117, *Gastrointestinal Infections and Enterotoxigenic Poisonings*, authored by Steven Martin and Rose Jung, for a more detailed discussion of this topic.

## INTRODUCTION

- Tables 40-1 and 40-2 present the revised classification systems for adult and child HIV infection.

## PATHOGENESIS

## TRANSMISSION OF HUMAN IMMUNODEFICIENCY VIRUS

- Infection with human immunodeficiency virus (HIV) occurs through three primary modes: sexual, parenteral, and perinatal. Sexual intercourse, primarily receptive anal and vaginal intercourse, is the most common vehicle for transmission. The probability of HIV transmission from receptive anorectal intercourse is 0.1% to 3% per sexual contact and 0.1% to 0.2% per sexual contact for receptive vaginal intercourse. Condom use reduces the risk of transmission by approximately 20-fold. Individuals with genital ulcers or sexually transmitted diseases, such as syphilis, chancroid, herpes, gonorrhea, *Chlamydia*, and trichomoniasis, are at great risk for contracting HIV.
- The use of contaminated needles or other injection-related paraphernalia by drug abusers has been the main cause of parenteral transmissions of HIV.
- Healthcare workers have a small risk of occupationally acquiring HIV, mostly through accidental injury, most often, percutaneous needlestick injury.
- Perinatal infection, or vertical transmission, is the most common cause of pediatric HIV infection. The risk of mother-to-child transmission is approximately 25% in the absence of breast-feeding or antiretroviral therapy. Breast-feeding can also transmit HIV.

## CLINICAL PRESENTATION

- Clinical presentations of primary HIV infection vary, but patients often have a viral syndrome or mononucleosis-like illness with fever, pharyngitis, and adenopathy (Table 40-3). Symptoms may last for 2 weeks.
- Probability of progression to acquired immune deficiency syndrome (AIDS) is related to RNA viral load; in one study, 5-year progression rates to AIDS were 8% and 62% for RNA copies per milliliter of less than 4,530 and greater than 36,270, respectively. The mortality rates were 5% and 49%, respectively.
- The classification scheme of the Centers for Disease Control and Prevention divides HIV infection into a matrix of nine categories based on the CD4 cell count (see Diagnosis below) and clinical conditions (see Table 40-1).
- Most children born with HIV are asymptomatic. On physical examination, they often present with unexplained physical signs such as lymphadenopathy, hepatomegaly, splenomegaly, failure to thrive, and weight loss or unexplained low birth weight, and fever of unknown origin. Laboratory

**TABLE 40-1** Centers for Disease Control and Prevention 1993 Revised Classification System for HIV Infection in Adults and AIDS Surveillance Case Definition

<b>CD4<sup>+</sup> T-Cell Categories (Absolute Number and Percentage)</b>	<b>(A) Asymptomatic, Acute (Primary) HIV or PGL</b>	<b>(B) Symptomatic, not (A) or (C) Conditions</b>	<b>(C) AIDS-Indicator Conditions</b>
≥500/μL or ≥29%	A1	B1	C1
200–499/μL or 14–28%	A2	B2	C2
<200/μL or <14%	A3	B3	C3
<b>AIDS-Indicator Conditions</b>			
Candidiasis of bronchi, trachea, or lungs		Lymphoma, Burkitt's	
Candidiasis, esophageal		Lymphoma, immunoblastic	
Cervical cancer, invasive		Lymphoma, primary, or brain	
Coccidioidomycosis, disseminated or extrapulmonary		<i>Mycobacterium avium</i> complex or <i>M. kansasii</i> , disseminated or extrapulmonary	
Cryptococcosis, extrapulmonary		<i>M. tuberculosis</i> , any site (pulmonary or extrapulmonary)	
Cryptosporidiosis, chronic intestinal (duration >1 month)		<i>Mycobacterium</i> , other species or unidentified species, disseminated or extrapulmonary	
Cytomegalovirus disease (other than liver, spleen, or nodes)		<i>Pneumocystis carinii</i> pneumonia	
Cytomegalovirus retinitis (with loss of vision)		Pneumonia, recurrent	
Encephalopathy, HIV-related		Progressive multifocal leukoencephalopathy	
Herpes simplex: chronic ulcer(s) (duration >1 month); or bronchitis, pneumonitis, or esophagitis		<i>Salmonella</i> septicemia, recurrent	
Histoplasmosis, disseminated or extrapulmonary		Toxoplasmosis of brain	
Isosporiasis, chronic intestinal (duration >1 month)		Wasting syndrome due to HIV	
Kaposi's sarcoma			

AIDS, acquired immune deficiency syndrome; HIV, human immunodeficiency virus; PGL, persistent generalized lymphadenopathy.

**TABLE 40-2** Centers for Disease Control and Prevention 1994 Revised Classification System for HIV Infection in Children Younger Than 13 Years

<b>Immunologic Categories</b>	<b>12 Months cells/μL (%)<sup>a</sup></b>	<b>1–5 Years cells/μL (%)<sup>a</sup></b>	<b>6–12 Years cells/μL (%)<sup>a</sup></b>	
1. No evidence of suppression	≥1,500 (≥25%)	≥1,000 (≥25%)	≥500 (≥25%)	
2. Evidence of moderate suppression	750–1,499 (15–24%)	500–999 (15–24%)	200–499 (15–24%)	
3. Severe suppression	<750 (<15%)	<500 (<15%)	<200 (<15%)	
<b>Immunologic Categories</b>	<b>N: No Signs/Symptoms</b>	<b>A: Mild Signs/Symptoms</b>	<b>B: Moderate Signs/Symptoms</b>	<b>C: Severe Signs/Symptoms</b>
1. No evidence of suppression	N1	A1	B1	C1
2. Evidence of moderate suppression	N2	A2	B2	C2
3. Severe suppression	N3	A3	B3	C3

AIDS, acquired immune deficiency syndrome; HIV, human immunodeficiency virus.

<sup>a</sup>Percentage of total lymphocytes.

**TABLE 40-3** Clinical Presentation of Primary HIV Infection in Adults**Symptoms**

Fever, sore throat, fatigue, weight loss, and myalgia  
 40–80% of patients will also exhibit a morbilliform or maculopapular rash usually involving the trunk  
 Diarrhea, nausea, and vomiting  
 Lymphadenopathy, night sweats  
 Aseptic meningitis (fever, headache, photophobia, and stiff neck) may be present in a one-fourth of presenting cases

**Other**

High viral load (exceeding 50,000 copies/mL in the adult or 500,000 copies/mL in the child)  
 Persistent decrease in CD4 lymphocytes

HIV, human immunodeficiency virus.

findings include anemia, hypergammaglobulinemia, altered mononuclear cell function, and altered T-cell subset ratios. The normal range for CD4 cell counts in children is much different than for adults (see Table 40-2).

- Clinical presentations of the opportunistic infections are presented in Infectious Complications of HIV below.

**DIAGNOSIS**

- The most commonly used screening method for HIV is an enzyme-linked immunosorbent assay, which detects antibodies against HIV-1 and is both highly sensitive and specific. False positives can occur in multiparous women; in recent recipients of hepatitis B, HIV, influenza, or rabies vaccine; following multiple blood transfusions; and in those with liver disease or renal failure, or undergoing chronic hemodialysis. False negatives may occur if the patient is newly infected and the test is performed before antibody production is adequate. The minimum time to develop antibodies is 3 to 4 weeks from initial exposure.
- Positive enzyme-linked immunosorbent assays are repeated in duplicate and if one or both tests are reactive, a confirmatory test is performed for final diagnosis. Western blot assay is the most commonly used confirmatory test, although an indirect immunofluorescence assay is available.
- The viral load test quantifies viremia by measuring the amount of viral RNA. There are several methods used for determining the amount of HIV RNA: reverse transcriptase-coupled polymerase chain reaction, branched DNA, and nucleic acid sequence-based assay. Each assay has its own lower limit of sensitivity, and results can vary from one assay method to the other; therefore, it is recommended that the same assay method be used consistently within patients.
- Viral load can be used as a prognostic factor to monitor disease progression and the effects of treatment.
- The number of CD4 lymphocytes in the blood is a surrogate marker of disease progression. The normal adult CD4 lymphocyte count ranges between 500 and 1,600 cells/ $\mu\text{L}$ , or 40% to 70% of all lymphocytes.

## TREATMENT

- The central goal of antiretroviral therapy is to decrease morbidity and mortality through maximum suppression of HIV replication (HIV RNA level that is undetectable). Secondary goals include an increase in CD4 lymphocytes.

### GENERAL APPROACH TO TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS INFECTION

- Regular, periodic measurement of plasma HIV RNA levels and CD4 cell counts is necessary to determine the risk of disease progression in an HIV-infected individual and to determine when to initiate or modify antiretroviral treatment regimens.
- Treatment decisions should be individualized by level of risk indicated by plasma HIV RNA levels and CD4 counts.
- The use of potent combination antiretroviral therapy to suppress HIV replication to below the levels of detection of sensitive plasma HIV RNA assays limits the potential for selection of antiretroviral-resistant HIV variants, the major factor limiting the ability of antiretroviral drugs to inhibit virus replication and delay disease progression.
- The most effective means to accomplish durable suppression of HIV replication is the simultaneous initiation of combinations of effective anti-HIV drugs with which the patient has not been previously treated and that are not cross resistant with antiretroviral agents with which the patient has been treated previously.
- Each of the antiretroviral drugs used in combination therapy regimens should always be used according to optimum schedules and dosages.
- Women should receive optimal antiretroviral therapy regardless of pregnancy status.
- The same principles of antiretroviral therapy apply to both HIV-infected children and adults, although the treatment of HIV-infected children involves unique pharmacologic, virologic, and immunologic considerations.
- Persons with acute primary HIV infections should be treated with combination antiretroviral therapy to suppress virus replication to levels below the limit of detection of sensitive plasma HIV RNA assays.
- HIV-infected persons, even those with viral loads below detectable limits, should be considered infectious and should be counseled to avoid sexual and drug-use behaviors that are associated with transmission or acquisition of HIV and other infectious pathogens.
- An excellent source for information on treatment guidelines can be found at <http://aidsinfo.nih.gov/>.
- Treatment is recommended for all HIV-infected persons with an AIDS-defining event, symptomatic disease, or a CD4 lymphocyte count below 200 cells/mm<sup>3</sup> should be offered therapy. Treatment is generally not recommended in persons with CD4 counts above 350 cells/mm<sup>3</sup>. Those between 201 and 350 cells/mm<sup>3</sup> should be offered therapy (Table 40-4).

**TABLE 40-4** Treatment of Human Immunodeficiency Virus Infection: Antiretroviral Regimens Recommended in Antiretroviral-Naive Persons

	<b>Agents</b>	<b>Limitation</b>
<b>Nonnucleoside reverse transcriptase inhibitor (NNRTI) for combination with dual NRTIs (strength of recommendation in parentheses)</b>		
Preferred	Efavirenz (All)	Efavirenz is not recommended in pregnant women or in women without adequate contraception
Alternative	Nevirapine (BII)	Nevirapine should not be initiated in women with CD4 <sup>+</sup> T-cell count >250 cells/ $\mu$ L or in men with CD4 <sup>+</sup> T-cell count >400 cells/ $\mu$ L because of increased risk of symptomatic hepatic events in these patients
<b>Protease inhibitor (PI)-based regimens</b>		
Preferred	Atazanavir + ritonavir (All)	Drug interaction with proton pump inhibitors, unconjugated hyperbilirubinemia
	<i>or</i> Fosamprenavir + ritonavir (twice daily) (All)	
Alternatives	<i>or</i> Lopinavir/ritonavir (twice daily) (coformulated) (All)	Twice-daily dosing, lipids
	Atazanavir (BII)	Twice-daily dosing, lipids
	<i>or</i> Fosamprenavir (BII)	See above (ritonavir recommended when given with tenofovir)
	<i>or</i> Fosamprenavir + ritonavir (once daily) (BII)	Fewer head-to-head data with once-daily fosamprenavir-ritonavir and lopinavir-ritonavir, as well as saquinavir (Invirase) + ritonavir
	<i>or</i> Lopinavir/ritonavir (once daily) (coformulated) (BII)	
	<i>or</i> Saquinavir (Invirase) + ritonavir (CII)	

*(continued)*

**TABLE 40-4** Treatment of Human Immunodeficiency Virus Infection: Antiretroviral Regimens Recommended in Antiretroviral-Naive Persons (Continued)

	<b>Agents</b>	<b>Limitation</b>
<b>Dual nucleoside (nucleotide) reverse transcriptase inhibitor (NtRTI) backbones</b>		
Preferred	Lamivudine <sup>a</sup> <i>plus</i> zidovudine (coformulated) (AII) <i>or</i> Tenofovir <i>plus</i> emtricitabine <sup>a</sup> (coformulated) (AII)	Twice daily, nausea and anemia with zidovudine  Potential tenofovir nephrotoxicity in susceptible patients
Alternative	Abacavir <i>plus</i> lamivudine <sup>a</sup> (coformulated) (BII) <i>or</i> Didanosine <i>plus</i> lamivudine <sup>a</sup> (BII)	Abacavir hypersensitivity in ~5% of patients  Didanosine-associated pancreatitis and peripheral neuropathy
<b>Triple nucleoside (nucleotide) reverse transcriptase inhibitor (NtRTI) regimens</b>		
(Only as an alternative to NNRTI- or PI-based regimens when these cannot be used as preferred therapy)		
Alternative	Abacavir <i>plus</i> lamivudine <i>plus</i> zidovudine (CII)	See above

NRTI, nucleoside reverse transcriptase inhibitor.

**Evidence-Based Rating Definition**

Rating Strength of Recommendation:

- A, Both strong evidence for efficacy and substantial clinical benefit support recommendation for use; should always be offered.
- B, Moderate evidence for efficacy or strong evidence for efficacy but only limited clinical benefit, supports recommendation for use; should usually be offered.
- C, Evidence for efficacy is insufficient to support a recommendation for or against use, or evidence for efficacy might not outweigh adverse consequences (e.g., drug toxicity, drug interactions) or cost of treatment under consideration; use is optional.
- D, Moderate evidence for lack of efficacy or for adverse outcome supports recommendation against use; should usually not be offered.
- E, Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use; should never be offered.

Rating Quality of Evidence Supporting the Recommendation

- I, Evidence from at least one correctly randomized, controlled trial.
- II, Evidence from at least one well-designed clinical trial without randomization and with laboratory results, from cohort or case-controlled analytic studies (preferably from more than one center), or from multiple time-series studies, or dramatic results from uncontrolled experiments.
- III, Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of consulting committees.

<sup>a</sup>Lamivudine and emtricitabine are considered interchangeable.

From Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. October 10, 2006, <http://AIDSinfo.NIH.gov>.

## PHARMACOLOGIC THERAPY

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### Antiretroviral Agents

- Inhibiting viral replication with combination of potent antiretroviral therapy has been the most clinically successful strategy in the treatment of HIV infection. There have been three primary groups of drugs used: **nucleoside and nonnucleoside reverse transcriptase inhibitors** and **protease inhibitors** (PIs) (Table 40-5).
- Reverse transcriptase inhibitors are of two types: those that are derivatives of purine- and pyrimidine-based nucleosides and nucleotides (NtRTIs) and those that are not nucleoside or nucleotide based (NNRTIs).
- Current recommendations for treating HIV infection advocate a minimum of three antiretroviral agents. The typical regimen consists of two NtRTIs and either a ritonavir-boosted PI or NNRTI. The dual NtRTI backbone should include tenofovir plus emtricitabine (coformulated as Truvada) or zidovudine plus lamivudine (coformulated as Combivir). Abacavir plus lamivudine is an alternative. Recommended initial NtRTIs include atazanavir-ritonavir, lopinavir-ritonavir, or fosamprenavir-ritonavir. Efavirenz is the recommended NNRTI except for women who plan to become pregnant or who do not have adequate contraception.
- Significant drug interactions can occur with many antiretroviral agents:
  - ✓ The latest information on drug interactions of antiretroviral drugs should be consulted.
  - ✓ **Ritonavir** is a potent inhibitor of cytochrome P<sub>450</sub> enzyme 3A and is used to reduce clearance of other PIs.
  - ✓ Two NtRTIs, **zidovudine** and **stavudine**, antagonize each other's metabolism and should not be given together.
  - ✓ Rifampin may substantially reduce the concentrations of PIs and is contraindicated with use of most PIs.
  - ✓ Saint John's wort is a potent inducer of metabolism and is contraindicated with PIs and NNRTIs.

### TREATMENT DURING PREGNANCY

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- Therapy during pregnancy is warranted, particularly in light of the dramatic reduction in transmission seen with **zidovudine** monotherapy. In general, pregnant women should be treated similar to nonpregnant adults; if possible, zidovudine should be used for both mother and infant. Efavirenz should not be used, particularly in the first trimester, because of the risk of teratogenicity.

### POSTEXPOSURE PROPHYLAXIS

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- Postexposure prophylaxis with a triple-drug regimen consisting of two NtRTIs and a boosted-PI is recommended for percutaneous blood exposure involving significant risk (i.e., large-bore needle or large volume of blood or blood from patients with advanced AIDS).
- Two NtRTIs may be offered to healthcare workers with lower risk of exposure such as that involving either the mucous membrane or skin. Treatment is not necessary if the source of exposure is urine or saliva.

**TABLE 40-5** Pharmacologic Characteristics of Antiretroviral Compounds

Drug	F (%)	t <sub>1/2</sub> (hour) <sup>a</sup>	Adult Dose <sup>b</sup> (doses/day)	Plasma C <sub>max</sub> /C <sub>min</sub> (μM)	Distinguishing Adverse Effect
<b>Nucleoside (Nucleotide) reverse transcriptase inhibitors (NtRTIs)</b>					
Abacavir	83	1.5/20	300 mg (2) or 600 mg (1)	5.2/0.03 7.4 <sup>c</sup>	Hypersensitivity
Didanosine	42	1.4/24	200 mg (2) or 400 mg (1)	2.8/0.03 5.6 <sup>c</sup>	Peripheral neuropathy, pancreatitis
Emtricitabine	93	10/39	200 mg (1)	7.3/0.04	Pigmentation on soles and palms in non-whites
Lamivudine	86	5/22	150 mg (2) or 300 mg (1)	6.3/1.6 10.5/0.5	Headache, pancreatitis (children)
Stavudine	86	1.4/7	40 mg (2)	2.4/0.04	Lipoatrophy, peripheral neuropathy
Tenofovir	40	17/60	300 mg (1)	1.04/0.4	Renal toxicity (proximal tubule)
Zalcitabine	85	2/3.5	0.75 mg (3)	0.05/0.001	Oral ulcers, peripheral neuropathy
Zidovudine	64	1.1/7	200 mg (3) or 300 mg (2)	2/0.2 3 <sup>c</sup>	Anemia, neutropenia, myopathy
<b>Nonnucleoside reverse transcriptase inhibitors (NNRTIs)</b>					
Delavirdine	85	5.8	400 mg (3) or 600 mg (2)	35/14	Rash, elevated liver function tests
Efavirenz	43	48	600 mg (1)	12.9/5.6	CNS disturbances and teratogenicity
Nevirapine	93	25	200 mg (2) <sup>d</sup>	22/14	Potentially serious rash and hepatotoxicity
<b>Protease inhibitors (PIs)</b>					
Amprenavir <sup>e</sup> or Forsamprenavir <sup>e</sup>	?	9	1,400 mg (2) <sup>e</sup> or 1,400 mg (1) <sup>e,f</sup>	9.5/0.7 14.3/2.9	Rash
Atazanavir	68	7	400 mg (1) or 300 mg (1) <sup>f</sup>	3.3/0.23 6.2/0.9	Unconjugated hyperbilirubinemia
Darunavir	82	15	600 mg (2) <sup>f</sup>	11.9/6.5	Hyperlipidemia, rash
Indinavir	60	1.5	800 mg (3) or 400–800 mg (2) <sup>f</sup>	13/0.25 13.6/7.5	Nephrolithiasis
Lopinavir <sup>g</sup>	?	5.5	400 mg (2)	5.3/1.76	Hyperlipidemia
Nelfinavir	?	2.6	750 mg (3) or 1,250 mg (2)	7/1.2	Diarrhea
Ritonavir	60	3–5	600 mg (2) <sup>d</sup> or “Boosting doses”	16/5	GI intolerance

(continued)

**TABLE 40-5** Pharmacologic Characteristics of Antiretroviral Compounds (Continued)

Drug	F (%)	t <sub>1/2</sub> (hour) <sup>a</sup>	Adult Dose <sup>b</sup> (doses/day)	Plasma C <sub>max</sub> /C <sub>min</sub> (μM)	Distinguishing Adverse Effect
Saquinavir	4	3	1,000 mg (2) <sup>f</sup>	3.9/0.55	Mild nausea, bloating
Tipranavir	?	6	500 mg (2) <sup>f</sup>	77.6/35.6	Hepatotoxicity, intracranial hemorrhage
<b>Entry inhibitors</b>					
Enfuvirtide	84	3.8	90 mg (2)	1.1/0.73	Injection-site reactions

C<sub>max</sub>, maximum plasma concentration; C<sub>min</sub>, minimum plasma concentration; F, bioavailability; t<sub>1/2</sub>, elimination half-life.

<sup>a</sup>NRTIs: Plasma NRTI t<sub>1/2</sub>/intracellular (peripheral blood mononuclear cells) NRTI-triphosphate t<sub>1/2</sub>; plasma t<sub>1/2</sub> only for other classes.

<sup>b</sup>Dose adjustment may be required for weight, renal, or hepatic disease, and drug interactions.

<sup>c</sup>C<sub>min</sub> concentration typically below the limit of quantification.

<sup>d</sup>Initial dose escalation recommended to minimize side effects.

<sup>e</sup>Fosamprenavir is a tablet phosphate prodrug of amprenavir. Amprenavir is available only as oral solution.

<sup>f</sup>Must be boosted with low doses of ritonavir (100–200 mg).

<sup>g</sup>Available as coformulation 4:1 lopinavir to ritonavir.

Data from Panel on Clinical Practices for the Treatment of HIV Infection. Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents. 2006. <http://www.AIDSinfo.NIH.gov>; Anderson PL, Kakuda TN, Lichtenstein KA. The cellular pharmacology of nucleoside- and nucleotide-analogue reverse-transcriptase inhibitors and its relationship to clinical toxicities. *Clin Infect Dis* 2004;38:743–753; and product information for agents.

- The optimal duration of treatment is unknown, but at least 4 weeks of therapy is advocated. Ideally, treatment should be initiated within 1 to 2 hours of exposure, but treatment is recommended for up to 72 hours post-exposure.

## EVALUATION OF THERAPEUTIC OUTCOMES

- Following the initiation of therapy, patients are usually monitored at 3-month intervals with immunologic (i.e., CD4 count), virologic (HIV RNA), and clinical assessments.
- There are two general indications to change therapy: significant toxicity or treatment failure.
- Specific criteria to indicate treatment failure have not been established through controlled clinical trials. As a general guide, the following events should prompt consideration for changing therapy:
  - ✓ Less than a 1 log<sub>10</sub> reduction in HIV RNA 1 to 4 weeks after the initiation of therapy, or a failure to achieve less than 400 copies/mL by 24 weeks or less than 50 copies/mL by 48 weeks.
  - ✓ After HIV RNA suppression, repeated detection of HIV-RNA.
  - ✓ Failure to achieve a rise in CD4 of 25 to 50 cells/mm<sup>3</sup> by 48 weeks.
  - ✓ Clinical disease progression, usually the development of a new opportunistic infection.

## THERAPEUTIC FAILURE

- Therapeutic failure may be the result of nonadherence to medication, development of drug resistance, intolerance to one or more medications, adverse drug–drug interactions, or pharmacokinetic–pharmacodynamic variability.

- In general, patients failing their first regimens should be treated with at least one new drug representing a new class. Therapy should be changed to at least two new antiretroviral drugs that are not cross resistant with the agents the patient previously received.

## INFECTIOUS COMPLICATIONS OF HUMAN IMMUNODEFICIENCY VIRUS

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- The development of certain opportunistic infections is directly or indirectly related to the level of CD4 lymphocytes.
- The most common opportunistic diseases and their frequencies found before death in patients with AIDS between 1990 and 1994 were *Pneumocystis carinii* pneumonia (PCP), *Mycobacterium avium* complex, and cytomegalovirus disease.
- The spectrum of infectious diseases observed in HIV-infected individuals and recommended first-line therapies are shown in Table 40-6.

### ***Pneumocystis carinii* (*Pneumocystis jiroveci*)**

- *P. jiroveci* pneumonia is the most common life-threatening opportunistic infection in patients with AIDS. The taxonomy of the organism is unclear, having been classified as both protozoan and fungal.

#### **Clinical Presentation**

- Characteristic symptoms include fever and dyspnea; clinical signs are tachypnea, with or without rales or rhonchi, and a nonproductive or mildly productive cough. Chest radiographs may show florid or subtle infiltrates or may occasionally be normal, although infiltrates are usually interstitial and bilateral. Arterial blood gases may show minimal hypoxia (PaO<sub>2</sub> 80 to 95 mm Hg) but in more advanced disease may be markedly abnormal.
- The onset of PCP is often insidious, occurring over a period of weeks. Clinical signs are tachypnea with or without rales or rhonchi and a nonproductive or mildly productive cough occurring over a period of weeks, although more fulminant presentations can occur.

#### **Treatment**

- Treatment with **trimethoprim–sulfamethoxazole** or parenteral pentamidine is associated with a 60% to 100% response rate. Trimethoprim–sulfamethoxazole is the regimen of choice for treatment and subsequent prophylaxis of PCP in patients with and without HIV.
- Trimethoprim–sulfamethoxazole is given in doses of 15 to 20 mg/kg/day (based on the trimethoprim component) as three to four divided doses for the treatment of PCP. Treatment duration is typically 21 days but must be based on clinical response.
- Trimethoprim–sulfamethoxazole is usually initiated by the IV route, although oral therapy (as oral absorption is high) may suffice in mildly ill and reliable patients or to complete a course of therapy after a response has been achieved with IV administration.
- The more common adverse reactions seen with trimethoprim–sulfamethoxazole are rash, fever, leukopenia, elevated serum transaminases, and

**TABLE 40-6 Therapies for Common Opportunistic Pathogens in HIV-Infected Individuals**

Clinical Disease	Selected Initial Therapies for Acute Infection in Adults (strength of recommendation in parentheses)	Common Drug- or Dose-Limiting Adverse Reactions
<b>Fungi</b>		
Candidiasis, oral	Fluconazole 100 mg orally for 7–14 days (AI) <i>or</i>	Elevated liver function tests, hepatotoxicity, nausea and vomiting
Candidiasis, esophageal	Nystatin 500,000 units oral swish (~5 mL) four times daily for 7–14 days (BII) Fluconazole 100–400 mg orally or IV on the first day, then 100 mg/day for 14–21 days (AI) <i>or</i>	Taste, patient acceptance Same as above
<i>Pneumocystis jiroveci</i> pneumonia	Itraconazole 200 mg/day orally for 14–21 days (AI) Trimethoprim–sulfamethoxazole IV or orally 15–20 mg/kg/day as trimethoprim component in 3–4 divided doses for 21 days <sup>a</sup> (AI) <i>or</i> Pentamidine IV 4 mg/kg/day for 21 days <sup>a</sup> (AI)	Elevated liver function tests, hepatotoxicity, nausea and vomiting Skin rash, fever, leukopenia Thrombocytopenia
Cryptococcal meningitis	<i>Mild episodes</i> Atovaquone suspension 750 mg (5 mL) orally twice daily with meals for 21 days <sup>a</sup> (BI) Amphotericin B 0.7 mg/kg/day IV for a minimum of 2 weeks <i>with</i> or <i>without</i> flucytosine 100 mg/kg/day orally in four divided doses (AI) <i>followed by</i>	Rash, elevated liver enzymes, diarrhea Nephrotoxicity, hypokalemia, anemia, fever, chills Bone marrow suppression Elevated liver enzymes
Histoplasmosis	Fluconazole 400 mg/day, orally for 8 weeks or until CSF cultures are negative (AI) <sup>a</sup> Amphotericin B 0.7 mg/kg/day IV for 3 to 10 days (AI) <i>followed by</i>	Same as above Same as above
Coccidioidomycosis	Itraconazole 200 mg twice daily, orally for 12 weeks (AII) <sup>a</sup> Amphotericin B 0.5–1 mg/kg/day IV until clinical improvement (usually after 500–1,000 mg) (AII) <sup>a</sup> <i>or</i> Fluconazole 400–800 mg once daily (meningeal disease) (AII) <sup>a</sup>	Same as above Same as above

*(continued)*

**TABLE 40-6** Therapies for Common Opportunistic Pathogens in HIV-Infected Individuals (Continued)

Clinical Disease	Selected Initial Therapies for Acute Infection in Adults (strength of recommendation in parentheses)	Common Drug- or Dose-Limiting Adverse Reactions
<b>Protozoa</b>		
Toxoplasmic encephalitis	Pyrimethamine 200 mg orally once, then 50–75 mg/day <i>plus</i> Sulfadiazine 1–1.5 g orally four times daily <i>and</i> Leucovorin 10–20 mg orally daily for 6 weeks (AI) <sup>a</sup>	Bone marrow suppression  Allergy, rash, drug fever
Isosporiasis	Trimethoprim and sulfamethoxazole: 160 mg trimethoprim and 800 mg sulfamethoxazole orally or IV four times daily for 10 days (AII) <sup>a</sup>	Same as above
<b>Bacteria</b>		
<i>Mycobacterium avium</i> complex	Clarithromycin 500 mg orally twice daily, <i>plus</i> ethambutol 15 mg/kg/day orally (AI), <i>and</i> For advanced disease, rifabutin 300 mg/day (dose may need adjustment with ART) (AI) <sup>a</sup>	GI intolerance, optic neuritis, peripheral neuritis Rash, GI intolerance Neutropenia, discolored urine, uveitis
<i>Salmonella</i> enterocolitis or bacteremia	Ciprofloxacin 500–750 mg orally twice daily for 14 days (longer duration for bacteremia or advanced HIV) (AIII)	GI intolerance
<i>Campylobacter</i> enterocolitis	Ciprofloxacin 500 mg orally twice daily for 7 days (or 14 days with bacteremia) (BIII)	Same as above
<i>Shigella</i> enterocolitis	Ciprofloxacin 500 mg orally twice daily for 5 days (or 14 days for bacteremia) (AIII)	Same as above
<b>Viruses</b>		
Mucocutaneous herpes simplex	Acyclovir 5 mg/kg IV every 8 hours until lesions regress, then acyclovir 400 mg orally three times daily until complete healing (famciclovir or valacyclovir is alternative) (AII)	GI intolerance, crystalluria
Primary varicella-zoster	Acyclovir 30 mg/kg/day IV in 3 divided doses for 7–10 days, then switch to oral acyclovir 800 mg four times daily after defervescence (famciclovir or valacyclovir is alternative) (AIII)	Obstructive nephropathy, central nervous system symptomatology
Cytomegalovirus (retinitis)	Ganciclovir intraocular implant <i>plus</i> valganciclovir 900 mg once daily until immune recovery from ART (AI) <sup>a</sup>	Neutropenia, thrombocytopenia
Cytomegalovirus esophagitis or colitis	Ganciclovir 5 mg/kg IV every 12 hours or foscarnet 180 mg/kg/day in two or three divided doses IV for 21 to 28 days (BII)	Same as above Nephrotoxicity, hypophosphatemia, hypophosphatemia, anemia

ART, antiretroviral therapy; CSF, cerebrospinal fluid; HIV, human immunodeficiency virus.

<sup>a</sup>Maintenance therapy is recommended.

See Table 40-4 for levels of evidence-based recommendations.

From Panel on Clinical Practices for the Treatment of HIV Infection. *Treating Opportunistic Infections among HIV-Infected Adults and Adolescents: recommendations from Center for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association/Infectious Diseases Society of America. December 17, 2004, <http://www.AIDSinfo.NIH.gov>.*

**TABLE 40-7 Therapies for Prophylaxis of First-Episode Opportunistic Diseases in Adults and Adolescents**

Pathogen	Indication	First Choice (strength of recommendation in parentheses)
<b>I. Standard of care</b>		
<i>Pneumocystis jirovecii</i>	CD4 <sup>+</sup> count <200/ $\mu\text{L}$ or oropharyngeal candidiasis	Trimethoprim-sulfamethoxazole, one double-strength tablet orally once daily (AI) or 1 single-strength tablet orally once daily (AI)
<i>Mycobacterium tuberculosis</i> Isoniazid-sensitive	TST reaction $\geq 5$ mm or prior positive TST result without treatment or contact with case of active tuberculosis	Isoniazid 300 mg orally plus pyridoxine, 50 mg orally once daily for 9 months (AII) or Isoniazid 900 mg orally plus pyridoxine 100 mg orally twice weekly for 9 months (BII)
Isoniazid-resistant	Same as isoniazid-sensitive; high probability of exposure to isoniazid-resistant tuberculosis	Rifampin 600 mg orally once daily (AIII) or rifabutin 300 mg orally once daily (BIII) for 4 months
<i>Toxoplasma gondii</i>	Immunoglobulin G antibody to <i>Toxoplasma</i> and CD4 <sup>+</sup> count <100/ $\mu\text{L}$ <sup>3</sup>	Trimethoprim-sulfamethoxazole one double-strength tablet orally once daily (AII)
<i>Mycobacterium avium</i> complex	CD4 <sup>+</sup> count <50/ $\mu\text{L}$ <sup>3</sup>	Azithromycin 1,200 mg orally once weekly (AI) or clarithromycin 500 mg orally twice daily (AI)
Varicella zoster virus (VZV)	Significant exposure to chicken pox or shingles for patients who have no history of either condition or, if available, negative antibody to VZV	Varicella-zoster immune globulin, five vials (1.25 mL each) intramuscularly administered ideally within 48 hours of exposure but $\leq 96$ hours (AIII)
<b>II. Usually recommended</b>		
<i>Streptococcus pneumoniae</i>	CD4 count $\geq 200$ cells/ $\mu\text{L}$ <sup>3</sup>	23-valent polysaccharide vaccine, 0.5 mL intramuscularly (BII)
Hepatitis B virus	All susceptible (antihepatitis B core antigen negative) patients	Hepatitis B vaccine, three doses (BII)
Influenza virus	All patients (annually, before influenza season)	Inactivated trivalent influenza virus vaccine (annual): 0.5 mL intramuscularly (BII)
Hepatitis A virus	All susceptible (anti-hepatitis A virus-negative) patients at increased risk for hepatitis A infection (e.g., illegal drug users, men who have sex with men, hemophiliacs) or patients with chronic liver disease including chronic hepatitis B or C	Hepatitis A vaccine: two doses (BIII)

*(continued)*

**TABLE 40-7** Therapies for Prophylaxis of First-Episode Opportunistic Diseases in Adults and Adolescents (Continued)

Pathogen	Indication	First Choice (strength of recommendation in parentheses)
<b>III. Indicated for use only in selected circumstances</b>		
Bacteria	Neutropenia	Granulocyte colony-stimulating factor (G-CSF), 5–10 mcg/kg subcutaneously once daily for 2–4 weeks; or granulocyte-macrophage colony-stimulating factor (GM-CSF), 250 mcg/m <sup>2</sup> subcutaneously for 2–4 weeks (CI)
<i>Cryptococcus neoformans</i>	CD4 <sup>+</sup> count <50/ $\mu\text{L}^3$	Fluconazole 100–200 mg orally once daily (CI)
<i>Histoplasma capsulatum</i>	CD4 <sup>+</sup> count < 100/ $\mu\text{L}^3$ , endemic geographic area	Itraconazole capsule, 200 mg orally once daily (CI)
Cytomegalovirus	CD4 <sup>+</sup> count <50/ $\mu\text{L}^3$ and cytomegalovirus antibody positivity	Oral ganciclovir, 1 g orally three times daily (valganciclovir should be used in place of ganciclovir due to better bioavailability) (CI)

TST, tuberculin skin test.

See Table 40-4 for levels of evidence-based recommendations.

From Kaplan JE, Masur H, Holmes KK. Guidelines for preventing opportunistic infections among HIV-infected persons-2002: recommendations of the U.S. Public Health Service and the Infectious Diseases Society of America. *MMWR Recomm Rep* 2002;51(RR-8):1–52.

thrombocytopenia. The incidence of these adverse reactions is higher in HIV-infected individuals than in those not infected with HIV.

- For pentamidine, side effects include hypotension, tachycardia, nausea, vomiting, severe hypoglycemia or hyperglycemia, pancreatitis, irreversible diabetes mellitus, elevated transaminases, nephrotoxicity, leukopenia, and cardiac arrhythmias.
- The early addition of adjunctive glucocorticoid therapy to anti-PCP regimens has been shown to decrease the risk of respiratory failure and improve survival in patients with AIDS and moderate to severe PCP ( $\text{PaO}_2 \leq 70$  mm Hg or [alveolar–arterial] gradient  $\geq 35$  mm Hg).

### **Prophylaxis**

(Table 40-7)

- Currently, PCP prophylaxis is recommended for all HIV-infected individuals who have already had previous PCP. Prophylaxis is also recommended for all HIV-infected persons who have a CD4 lymphocyte count of less than  $200 \text{ cells/mm}^3$  (i.e., their CD4 cells are less than 20% of total lymphocytes) or a history of oropharyngeal candidiasis.
- Trimethoprim–sulfamethoxazole is the preferred therapy for both primary and secondary prophylaxis of PCP in adults and adolescents. The recommended dose in adults and adolescents is one double-strength tablet daily.

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*See Chap. 129, Human Immunodeficiency Virus Infection, authored by Peter L. Anderson, Thomas N. KaKuda, and Courtney V. Fletcher, for a more detailed discussion of this topic.*

## DEFINITION

- Influenza is a viral illness associated with high mortality and high hospitalization rates among persons younger than age 65 years. Seasonal influenza epidemics result in 25 to 50 million influenza cases, approximately 200,000 hospitalizations, and more than 30,000 deaths each year in the United States. Overall, more people die of influenza than of any other vaccine-preventable illness.

## PATHOPHYSIOLOGY

- The route of influenza transmission is person-to-person via inhalation of respiratory droplets, which can occur when an infected person coughs or sneezes. The incubation period for influenza ranges between 1 and 4 days, with an average incubation of 2 days. Adults are considered infectious from the day before their symptoms begin through the fifth day after the onset of illness, while children can be infectious for longer than 10 days after the onset of illness. Viral shedding can persist for weeks to months in severely immunocompromised people.

## CLINICAL PRESENTATION

### GENERAL

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- The presentation of influenza is similar to a number of other respiratory illnesses.
- The clinical course and outcome are affected by age, immunocompetence, viral characteristics, smoking, comorbidities, pregnancy, and the degree of preexisting immunity.
- Complications of influenza may include exacerbation of underlying comorbidities, primary viral pneumonia, secondary bacterial pneumonia or other respiratory illnesses (e.g., sinusitis, bronchitis, otitis), encephalopathy, transverse myelitis, myositis, myocarditis, pericarditis, and Reye's syndrome.

### SIGNS AND SYMPTOMS

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- Classic signs and symptoms of influenza include rapid onset of fever, myalgia, headache, malaise, nonproductive cough, sore throat, and rhinitis.
- Nausea, vomiting, and otitis media are also commonly reported in children.
- Signs and symptoms typically resolve in approximately 3 to 7 days, although cough and malaise may persist for more than 2 weeks.

### LABORATORY TESTS

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- The gold standard for diagnosis of influenza is viral culture.

- Rapid antigen and point-of-care tests, direct fluorescence antibody test, and the reverse-transcription polymerase chain reaction assay may be used for rapid detection of virus.
- Chest radiograph should be obtained if pneumonia is suspected.
- Rapid tests have allowed for prompt diagnosis and initiation of antiviral therapy and decreased inappropriate use of antibiotics.

## PREVENTION

- The best means to decrease the morbidity and mortality associated with influenza is to prevent infection through vaccination. Appropriate infection control measures, such as hand hygiene, basic respiratory etiquette (cover your cough, throw tissues away), and contact avoidance, are also important in preventing the spread of influenza.
- Annual vaccination is recommended for those at high risk for complications and severe disease, such as:
  - ✓ Children between 6 and 59 months old.
  - ✓ Pregnant women.
  - ✓ People older than age 50 years.
  - ✓ Children between 6 months and 18 years old who are receiving long-term aspirin therapy, placing them at risk for Reye's syndrome following influenza.
  - ✓ People of any age with chronic pulmonary or cardiovascular disorders, including asthma but not including hypertension.
  - ✓ People of any age who have required regular medical follow-up or hospitalization in the prior year because of chronic metabolic diseases, including diabetes, renal dysfunction, hemoglobinopathies, or immunodeficiency, including medication-induced immunosuppression and human immunodeficiency virus.
  - ✓ People of any age who have any condition that may compromise respiratory function or increase the risk of aspiration (e.g., cognitive dysfunction, spinal cord injuries, or epilepsy).
  - ✓ Residents of long-term care facilities.
- Vaccination is also recommended for those who live with and/or care for people who are at high risk, including household contacts and healthcare workers.
  - ✓ The ideal time for vaccination is during October or November to allow for the development and maintenance of immunity during the peak of the influenza season.
  - ✓ The two vaccines currently available for prevention of influenza are the trivalent influenza vaccine (TIV) and the live-attenuated influenza vaccine (LAIV). The specific strains included in the vaccine each year change based on antigenic drift.
  - ✓ TIV is FDA approved for use in people over 6 months of age, regardless of their immune status. Of note, several commercial products are available and are approved for different age groups (Table 41-1).
  - ✓ Adults older than the age of 65 years benefit from influenza vaccination, including prevention of complications and decreased risk of influenza-

**TABLE 41-1** Approved Influenza Vaccines for Different Age Groups—United States, 2006–2007 Season

Vaccine	Trade Name	Manufacturer	Dose/ Presentation	Thimerosal Mercury Content (mcg Hg/0.5 mL dose)	Age Group	Number of Doses
TIV	Fluzone	Sanofi Pasteur	0.25 mL pre-filled syringe	0	6–35 months	1 or 2 <sup>a</sup>
			0.5 mL prefilled syringe	0	≥36 months	1 or 2 <sup>a</sup>
			0.5 mL vial	0	≥36 months	1 or 2 <sup>a</sup>
			5 mL multidose vial	25	≥6 months	1 or 2 <sup>a</sup>
TIV	Fluvirin	Novartis Vaccine	0.5 mL prefilled syringe	<1	≥4 years	1 or 2 <sup>a</sup>
			5 mL multidose vial	24.5	≥4 years	1 or 2 <sup>a</sup>
TIV	Fluarix	GlaxoSmith-Kline	0.5 mL prefilled syringe	<1.25	≥18 years	1
LAIV	FluMist	MedImmune	0.5 mL sprayer	0	5–49 years	1 or 2 <sup>b</sup>

LAIV, live-attenuated influenza vaccine; TIV, trivalent influenza vaccine.

<sup>a</sup>Two doses administered at least 1 month apart are recommended for children ages 6 months to less than 9 years who are receiving influenza vaccine for the first time.

<sup>b</sup>Two doses administered at least 6 weeks apart are recommended for children ages 5 to 9 years who are receiving influenza vaccine for the first time.

From Smith NM, Bresee JS, Shay DK, et al. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2006;55(RR-10):1–42.

related hospitalization and death. However, people in this population may not generate a strong antibody response to the vaccine and may remain susceptible to infection.

- ✓ The most frequent adverse effect associated with TIV is soreness at the injection site that lasts for less than 48 hours. TIV may cause fever and malaise in those who have not previously been exposed to the viral antigens in the vaccine. Allergic-type reactions (hives, systemic anaphylaxis) rarely occur after influenza vaccination and are likely a result of a reaction to residual egg protein in the vaccine.
- ✓ Vaccination should be avoided in persons who are not at high risk for influenza complications and who have experienced Guillain-Barré syndrome within 6 weeks of receiving a previous influenza vaccine.
- ✓ LAIV is made with live, attenuated viruses and is approved for intranasal administration in healthy people between 5 and 49 years of age (Table 41-2). Advantages of LAIV include its ease of administration, intranasal rather than intramuscular administration, and the potential induction of broad mucosal and systemic immune response.
- ✓ LAIV is only approved for children over the age of 5 years in part because of data showing an increase in asthma or reactive airway disease in those younger than 5 years old.
- ✓ The adverse effects typically associated with LAIV administration included runny nose, congestion, sore throat, and headache.

**TABLE 41-2** Comparison of Trivalent (TIV) and Live-Attenuated Influenza Vaccine (LAIV)

Characteristic	TIV	LAIV
Age groups approved for use	>6 months	5 to 49 years
Immune status requirements	Immunocompetent or immunocompromised	Immunocompetent
Viral properties	Inactivated (killed) influenza A (H3N2), A (H1N1), and B viruses	Live-attenuated influenza A (H3N2), A (H1N1), and B viruses
Route of administration	Intramuscular	Intranasal
Immune system response	High serum IgG antibody response	Lower IgG response and high serum IgA mucosal response

Ig, immunoglobulin.

- ✓ LAIV should not be given to immunosuppressed patients or given by healthcare workers who are severely immunocompromised.

## POSTEXPOSURE PROPHYLAXIS

- Antiviral drugs available for prophylaxis of influenza should be considered adjuncts but are not replacements for annual vaccination.
- The adamantanes, amantadine and rimantadine, are currently not recommended for prophylaxis or treatment in the United States because 92% of the circulating influenza A viruses are resistant to these agents.
- The neuraminidase inhibitors, oseltamivir and zanamivir, are effective prophylactic agents against influenza in terms of preventing laboratory-confirmed influenza when used for seasonal prophylaxis and preventing influenza illness among persons exposed to a household contact who was diagnosed with influenza. Table 41-3 gives dosing recommendations.
- In those patients who did not receive the influenza vaccination and are receiving an antiviral drug for prevention of disease during the influenza season, the medication should optimally be taken for the entire duration of influenza activity in the community.
- Prophylaxis should be considered during influenza season for the following groups of patients:
  - ✓ Persons at high risk of serious illness and/or complications who cannot be vaccinated.
  - ✓ Persons at high risk of serious illness and/or complications who are vaccinated after influenza activity has begun in their community because the development of sufficient antibody titers after vaccination takes approximately 2 weeks.
  - ✓ Unvaccinated persons who have frequent contact with those at high risk.
  - ✓ Persons who may have an inadequate response to vaccination (e.g., advanced human immunodeficiency virus disease).
  - ✓ Long-term care facility residents, regardless of vaccination status, when an outbreak has occurred in the institution.
  - ✓ Unvaccinated household contacts of someone who was diagnosed with influenza.

**TABLE 41-3** Recommended Daily Dosage of Influenza Antiviral Medications for Treatment and Prophylaxis—United States

Antiviral Agent	Age Group (years)				
	1–6	7–9	10–12	13–64	At Least 65
<b>Zanamivir</b>					
Treatment	N/A	10 mg twice daily	10 mg twice daily	10 mg twice daily	10 mg twice daily
Prophylaxis	Ages 1–4, N/A	Ages 5–9, 10 mg once daily	10 mg once daily	10 mg once daily	10 mg once daily
<b>Oseltamivir</b>					
Treatment <sup>a</sup>	According to weight <sup>b</sup>	According to weight <sup>b</sup>	According to weight <sup>b</sup>	75 mg twice daily	75 mg twice daily
Prophylaxis <sup>d</sup>	According to weight <sup>c</sup>	According to weight <sup>c</sup>	According to weight <sup>c</sup>	75 mg once daily	75 mg once daily

N/A, not applicable.

<sup>a</sup>Dose reduction recommended in those with creatinine clearance less than 30 mL/min.

<sup>b</sup>Treatment dosing of oseltamivir for children weighing  $\leq 15$  kg is 30 mg twice daily; for those  $>15$  kg to 23 kg, the dose is 45 mg twice daily; for those weighing  $>23$  kg to 40 kg, the dose is 60 mg twice daily; and for those  $>40$  kg, the dose is 75 mg twice daily.

<sup>c</sup>The prophylactic dosing of oseltamivir for children weighing  $\leq 15$  kg is 30 mg once daily; for those  $>15$  kg to 23 kg, the dose is 45 mg once daily; for those weighing  $>23$  kg up to 40 kg, the dose is 60 mg once daily; and for those  $>40$  kg, the dose is 75 mg once daily.

From Smith NM, Bresee JS, Shay DK, et al. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2006;55(RR-10):1–42.

- LAIV should not be administered until 48 hours after influenza antiviral therapy has stopped, and influenza antiviral drugs should not be administered for 2 weeks after the administration of LAIV because the antiviral drugs inhibit influenza virus replication.
- Pregnant women, regardless of trimester, should receive annual influenza vaccination with TIV but not with LAIV.
- The adamantanes and neuraminidase inhibitors are not recommended during pregnancy because of concerns regarding the effects of the drugs on the fetus.
- Immunocompromised hosts should receive annual influenza vaccination with TIV but not LAIV.

## TREATMENT

### GOALS OF THERAPY

- The four primary goals of therapy of influenza are as follows:
  1. Control symptoms
  2. Prevent complications
  3. Decrease work and/or school absenteeism
  4. Prevent the spread of infection
- In the era of pandemic preparedness and increasing resistance, early and definitive diagnosis of influenza is crucial. The currently available antiviral drugs are most effective if started within 48 hours of the onset of illness. Adjunct agents, such as acetaminophen for fever or an antihistamine for rhinitis, may be used concomitantly with the antiviral drugs.

## NONPHARMACOLOGIC THERAPY

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- Patients suffering from influenza should get adequate sleep and maintain a low level of activity. They should stay home from work and/or school in order to rest and prevent the spread of infection. Appropriate fluid intake should be maintained. Cough/throat lozenges, warm tea, or soup may help with symptom control (cough, sore throat).

## PHARMACOLOGIC THERAPY

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- The two classes of antiviral drugs available for treatment of influenza are the same as those available for prophylaxis and include the adamantanes, amantadine and rimantadine, and the neuraminidase inhibitors, oseltamivir and zanamivir. Because of widespread resistance to the adamantanes among influenza A viruses in the United States, amantadine and rimantadine are not recommended for treatment of influenza until susceptibility can be reestablished.
- Oseltamivir and zanamivir are neuraminidase inhibitors that have activity against both influenza A and influenza B viruses. When administered within 48 hours of the onset of illness, oseltamivir and zanamivir may reduce the duration of illness by approximately 1 day versus placebo.
- Oseltamivir is approved for treatment in those older than the age of 1 year, while zanamivir is approved for treatment in those older than the age of 7 years. The recommended dosages vary by agent and age (see Table 41-3), and the recommended duration of treatment for both agents is 5 days.
- The FDA has received 103 reports, occurring between August 29, 2005, and July 6, 2006, of delirium, hallucinations, and self-injury in pediatric patients (mostly from Japan) following treatment with oseltamivir.
- No clinical studies have been conducted evaluating the safety and efficacy of the adamantanes or the neuraminidase inhibitors during pregnancy, and all of the drugs are Pregnancy Category C. Both the adamantanes and the neuraminidase inhibitors are excreted in breast milk and should be avoided by mothers who are breast-feeding their infants. More studies are needed in these populations who are at high risk for serious disease and complications from influenza.

## EVALUATION OF THERAPEUTIC OUTCOMES

- Patients should be monitored daily for resolution of signs and symptoms associated with influenza, such as fever, myalgia, headache, malaise, nonproductive cough, sore throat, and rhinitis. These signs and symptoms will typically resolve within approximately 1 week. If the patient continues to exhibit signs and symptoms of illness beyond 10 days or a worsening of symptoms after 7 days, a physician visit is warranted as this may be an indication of a secondary bacterial infection.

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See Chap. 113, *Influenza*, authored by Elizabeth D. Hermsen and Mark E. Rupp, for a more detailed discussion of this topic.

## DEFINITION

- Intraabdominal infections are those contained within the peritoneum or retroperitoneal space. Two general types of intraabdominal infections are discussed throughout this chapter: peritonitis and abscess.
- Peritonitis is defined as the acute, inflammatory response of peritoneal lining to microorganisms, chemicals, irradiation, or foreign body injury. Peritonitis may be classified as either primary or secondary. With primary peritonitis, an intraabdominal focus of disease may not be evident. In secondary peritonitis, a focal disease process is evident within the abdomen.
- An abscess is a purulent collection of fluid separated from surrounding tissue by a wall consisting of inflammatory cells and adjacent organs. It usually contains necrotic debris, bacteria, and inflammatory cells.

## PATHOPHYSIOLOGY

- Table 42-1 summarizes many of the potential causes of bacterial peritonitis. The causes of intraabdominal abscess somewhat overlap those of peritonitis and, in fact, both may occur sequentially or simultaneously. Appendicitis is the most frequent cause of abscess. Intraabdominal infection results from entry of bacteria into the peritoneal or retroperitoneal spaces or from bacterial collections within intraabdominal organs. When peritonitis results from peritoneal dialysis, skin surface flora are introduced via the peritoneal catheter.
- In primary peritonitis, bacteria may enter the abdomen via the bloodstream or the lymphatic system, by transmigration through the bowel wall, through an indwelling peritoneal dialysis catheter, or via the fallopian tubes in females.
- In secondary peritonitis, bacteria most often enter the peritoneum or retroperitoneum as a result of disruption of the integrity of the GI tract caused by diseases or traumatic injuries.
- When bacteria become dispersed throughout the peritoneum, the inflammatory process involves the majority of the peritoneal lining. Fluid and protein shift into the abdomen (called “third spacing”) may decrease circulating blood volume and cause shock.
- Peritonitis often results in death because of the effects on major organ systems. Fluid shifts and endotoxins may cause hypotension and shock.
- An abscess begins by the combined action of inflammatory cells (such as neutrophils), bacteria, fibrin, and other inflammatory components. Within the abscess, oxygen tension is low, and anaerobic bacteria thrive.

## MICROBIOLOGY

- Primary bacterial peritonitis is often caused by a single organism. In children, the pathogen is usually Group A *Streptococcus*, *Streptococcus*

**TABLE 42-1** Causes of Bacterial Peritonitis**Primary bacterial peritonitis**

Peritoneal dialysis  
 Cirrhosis with ascites  
 Nephrotic syndrome

**Secondary bacterial peritonitis**

Miscellaneous causes  
 Diverticulitis  
 Appendicitis  
 Inflammatory bowel diseases  
 Salpingitis  
 Biliary tract infections  
 Necrotizing pancreatitis  
 Neoplasms  
 Intestinal obstruction  
 Perforation  
 Mechanical GI problems  
 Any cause of small bowel obstruction (adhesions, hernia)  
 Vascular causes  
 Mesenteric arterial or venous occlusion (atrial fibrillation)  
 Mesenteric ischemia without occlusion  
 Trauma  
 Blunt abdominal trauma with rupture of intestine  
 Penetrating abdominal trauma  
 Iatrogenic intestinal perforation (endoscopy)  
 Intraoperative events  
 Peritoneal contamination during abdominal operation  
 Leakage from gastrointestinal anastomosis

*pneumoniae*, *Escherichia coli*, or *Bacteroides* species. When peritonitis occurs in association with cirrhotic ascites, *E. coli* is isolated most frequently.

- Peritonitis in patients undergoing peritoneal dialysis is most often caused by common skin organisms: *Staphylococcus epidermidis*, *S. aureus*, streptococci, and diphtheroids.
- Secondary intraabdominal infections are often polymicrobial. The mean number of isolates of microorganisms from infected intraabdominal sites has ranged from 2.9 to 3.7, including an average of 1.3 to 1.6 aerobes and 1.7 to 2.1 anaerobes. The frequencies with which specific bacteria were isolated in intraabdominal infections are given in Table 42-2.
- The combination of aerobic and anaerobic organisms appears to greatly increase pathogenicity. In intraabdominal infections, facultative bacteria may provide an environment conducive to the growth of anaerobic bacteria.
- Aerobic enteric bacteria and anaerobic bacteria are both pathogens in intraabdominal infection. Aerobic bacteria, particularly *E. coli*, appear responsible for the early mortality from peritonitis, whereas anaerobic bacteria are major pathogens in abscesses, with *Bacteroides fragilis* predominating.
- The role of *Enterococcus* as a pathogen is not clear. Enterococcal infection occurs more commonly in postoperative peritonitis, in the presence of specific risk factors indicating failure of the host defenses, or with the use of broad-spectrum antibiotics.

**TABLE 42-2** Pathogens Isolated from Patients with Secondary Peritonitis

<b>Gram-negative bacteria</b>	
<i>Escherichia coli</i>	32–61%
<i>Enterobacter</i>	8–26%
<i>Klebsiella</i>	6–26%
<i>Proteus</i>	4–23%
<b>Gram-positive bacteria</b>	
Enterococci	18–24%
Streptococci	6–55%
Staphylococci	6–16%
<b>Anaerobic bacteria</b>	
<i>Bacteroides</i>	25–80%
<i>Clostridium</i>	5–18%
<b>Fungi</b>	2–5%

## CLINICAL PRESENTATION

- Intraabdominal infections have a wide spectrum of clinical features often depending on the specific disease process, the location and the magnitude of bacterial contamination, and concurrent host factors. Patients with primary and secondary peritonitis present quite differently (Table 42-3).
- If peritonitis continues untreated, the patient may experience hypovolemic shock from fluid loss into the peritoneum, bowel wall, and lumen. This may be accompanied by generalized sepsis. Intraabdominal abscess may pose a diagnostic challenge as the symptoms are neither specific nor dramatic.
- The overall outcome from intraabdominal infection depends on five key factors: inoculum size, virulence of the organisms, the presence of adjuvants within the peritoneal cavity that facilitate infection, the adequacy of host defenses, and the adequacy of initial treatment.

## DESIRED OUTCOME

- The goals of treatment are the correction of intraabdominal disease processes or injuries that have caused infection and the drainage of collections of purulent material (e.g., abscess).
- A secondary objective is to achieve resolution of infection without major organ system complications or adverse treatment effects.

## TREATMENT

### GENERAL PRINCIPLES

- The three major modalities for the treatment of intraabdominal infection are prompt surgical drainage, support of vital functions, and appropriate antimicrobial therapy to treat infection not removed by surgery.
- Antimicrobials are an important adjunct to drainage procedures in the treatment of intraabdominal infections; however, the use of antimicrobial agents without surgical intervention is usually inadequate. For some specific situations (e.g., most cases of primary peritonitis), drainage procedures

**TABLE 42-3** Clinical Presentation of Peritonitis**Primary Peritonitis**

The patient may not be in acute distress, particularly with peritoneal dialysis.

**Signs and symptoms**

The patient may complain of nausea, vomiting (sometimes with diarrhea), and abdominal tenderness.

Temperature may be only mildly elevated or not elevated in patients undergoing peritoneal dialysis.

Bowel sounds are hypoactive.

The cirrhotic patient may have worsening encephalopathy.

Cloudy dialysate fluid with peritoneal dialysis.

**Laboratory tests**

The patient's WBC count may be only mildly elevated.

Ascitic fluid usually contains  $>300$  leukocytes/ $\text{mm}^3$ , and bacteria may be evident on Gram stain of a centrifuged specimen.

In 60–80% of patients with cirrhotic ascites, the Gram stain is negative.

**Other diagnostic tests**

Culture of peritoneal dialysate or ascitic fluid should be positive.

**Secondary Peritonitis****Signs and symptoms**

Generalized abdominal pain.

Tachypnea.

Tachycardia.

Nausea and vomiting.

Temperature normal initially then increasing to  $37.7$ – $38.8^\circ\text{C}$  ( $100$ – $102^\circ\text{F}$ ) within the first few hours and may continue to rise for the next several hours.

Hypotension and shock if volume is not restored.

Decreased urine output due to dehydration.

**Physical examination**

Voluntary abdominal guarding changing to involuntary guarding and a “board-like abdomen.” Abdominal tenderness and distension.

Faint bowel sounds that cease over time.

**Laboratory tests**

Leukocytosis ( $15,000$ – $20,000$  WBC/ $\text{mm}^3$ ), with neutrophils predominating and an elevated percentage of immature neutrophils (bands).

Elevated hematocrit and blood urea nitrogen because of dehydration.

Patient progresses from early alkalosis because of hyperventilation and vomiting to acidosis and lactic acidemia.

**Other diagnostic tests**

Abdominal radiographs may be useful because free air in the abdomen (indicating intestinal perforation) or distension of the small or large bowel is often evident.

Ultrasound, CT scan, or magnetic resonance imaging may be used to locate an abscess.

CT, computed tomography; WBC, white blood cell.

may not be required, and antimicrobial agents become the mainstay of therapy.

- With generalized peritonitis, large volumes of IV fluids are required to restore vascular volume, to improve cardiovascular function, and to maintain adequate tissue perfusion and oxygenation.

## NONPHARMACOLOGIC TREATMENT

- Secondary peritonitis is treated surgically, and this is called “source control,” which refers to the physical measures undertaken to eradicate the

focus of infection. Abdominal laparotomy may be used to correct the cause of peritonitis.

- Aggressive fluid repletion and management are required for the purposes of achieving or maintaining proper intravascular volume to ensure adequate cardiac output, tissue perfusion, and correction of acidosis.
- In the initial hour of treatment, a large volume of IV solution (lactated Ringer's solution) may need to be administered to restore intravascular volume. This may be followed by up to 1 L/hour until fluid balance is restored in a few hours.
- In patients with significant blood loss (hematocrit of 25% or less), blood should be given. This is generally in the form of packed red blood cells.
- Enteral or parenteral nutrition facilitates improved immune function and wound healing to ensure recovery.

## PHARMACOLOGIC THERAPY

- The goals of antimicrobial therapy are to control bacteremia and to establish the metastatic foci of infection, to reduce suppurative complications after bacterial contamination, and to prevent local spread of existing infection.
- An empiric antimicrobial regimen should be started as soon as the presence of intraabdominal infection is suspected on the basis of likely pathogens.

### Recommendations

- Table 42-4 presents recommended and alternative regimens for selected situations. These are general guidelines, not rules, because there are many factors that cannot be incorporated into such a table. Guidelines for initial antimicrobial treatment of specific intraabdominal infections are presented in Table 42-5.

**TABLE 42-4** Recommended Agents for the Treatment of Community-Acquired, Complicated Intraabdominal Infections

Agents Recommended for Mild to Moderate Infections	Agents Recommended for High-Severity Infections
<b><math>\beta</math>-Lactamase inhibitor combinations</b>	
Ampicillin-sulbactam	Piperacillin-tazobactam
Ticarcillin-clavulanate	
<b>Carbapenems</b>	
Ertapenem	Imipenem-cilastatin
	Meropenem
<b>Combination regimens</b>	
Cefazolin or cefuroxime plus metronidazole	Third- or fourth-generation cephalosporins (cefotaxime, ceftriaxone, ceftizoxime, ceftazidime, cefepime) plus metronidazole
Ciprofloxacin, levofloxacin, moxifloxacin, or gatifloxacin in combination with metronidazole	Ciprofloxacin in combination with metronidazole Aztreonam plus metronidazole

From Solomkin JS, Mazuski JE, Baron EJ, et al. Guidelines for the selection of anti-infective agents for complicated intraabdominal infections. *Clin Infect Dis* 2003;37:997-1005; Mazuski JE, Sawyer RC, Nathens AB, et al. The Surgical Infection Society guidelines on antimicrobial therapy for intraabdominal infections: an executive summary. *Surg Infect (Larchmt)* 2002;3:161-174; and Mazuski JE, Sawyer RC, Nathens AB, et al. The Surgical Infection Society guidelines on antimicrobial therapy for intraabdominal infections: evidence for recommendations. *Surg Infect (Larchmt)* 2002;3:175-234.

**TABLE 42-5** Guidelines for Initial Antimicrobial Agents for Intraabdominal Infections

	Primary Agents	Alternatives
<b>Primary bacterial peritonitis</b>		
Cirrhosis	Cefotaxime	<ol style="list-style-type: none"> <li>1. Add clindamycin or metronidazole if anaerobes are suspected</li> <li>2. Other third-generation cephalosporins, extended-spectrum penicillins, aztreonam, and imipenem as alternatives</li> <li>3. Aminoglycoside with antipseudomonal penicillin</li> </ol>
Peritoneal dialysis	Initial empiric regimens	<ol style="list-style-type: none"> <li>1. An aminoglycoside may be used in place of ceftazidime or cefepime</li> <li>2. Imipenem-cilastatin or cefepime may be used alone</li> <li>3. Quinolones may be used in place of ceftazidime or cefepime if local susceptibilities allow</li> </ol>
	Cefazolin or cephalothin plus ceftazidime or cefepime	<ol style="list-style-type: none"> <li>1. Alternative for methicillin resistant staphylococci is vancomycin</li> <li>2. For vancomycin-resistant <i>Staphylococcus aureus</i>, linezolid, daptomycin, or quinupristin-dalfopristin must be used</li> </ol>
	1. <i>Staphylococcus</i> : penicillinase-resistant penicillin or first-generation cephalosporin	<ol style="list-style-type: none"> <li>1. An aminoglycoside may be added for enterococcal peritonitis</li> <li>2. Linezolid or quinupristin-dalfopristin should be used to treat vancomycin-resistant enterococcus not susceptible to ampicillin</li> </ol>
	2. <i>Streptococcus</i> or <i>Enterococcus</i> : ampicillin	<ol style="list-style-type: none"> <li>1. The regimen should be based on in vitro sensitivity tests</li> </ol>
	3. Aerobic gram-negative bacilli: ceftazidime or cefepime	
	4. <i>Pseudomonas aeruginosa</i> : two agents with differing mechanisms of actions, such as an oral quinolone plus ceftazidime, cefepime, tobramycin, or piperacillin	
<b>Secondary bacterial peritonitis</b>		
Perforated peptic ulcer	First-generation cephalosporins	<ol style="list-style-type: none"> <li>1. Antianaerobic cephalosporins<sup>a</sup></li> <li>2. Possibly add aminoglycoside if patient condition is poor</li> <li>3. Aminoglycoside with clindamycin or metronidazole; add ampicillin if patient is immunocompromised or if biliary tract origin of infection</li> </ol>
Other	Imipenem-cilastatin, meropenem, ertapenem, or extended-spectrum penicillins with $\beta$ -lactamase inhibitor	<ol style="list-style-type: none"> <li>1. Ciprofloxacin with metronidazole</li> <li>2. Aztreonam with clindamycin or metronidazole</li> <li>3. Antianaerobic cephalosporins<sup>a</sup></li> </ol>
<b>Abscess</b>		
General	Imipenem-cilastatin, meropenem, ertapenem, or extended-spectrum penicillins with $\beta$ -lactamase inhibitor	<ol style="list-style-type: none"> <li>1. Aztreonam with clindamycin or metronidazole</li> <li>2. Ciprofloxacin with metronidazole</li> <li>3. Aminoglycoside with clindamycin or metronidazole</li> </ol>

(continued)

**TABLE 42-5** Guidelines for Initial Antimicrobial Agents for Intraabdominal Infections (Continued)

	<b>Primary Agents</b>	<b>Alternatives</b>
Liver	As above but add a first-generation cephalosporin	Use metronidazole if amoebic liver abscess is suspected
Spleen	Aminoglycoside plus penicillinase-resistant penicillin	Alternatives for penicillinase-resistant penicillin are first-generation cephalosporins or vancomycin
<b>Appendicitis</b>		
Normal or inflamed	Antianaerobic cephalosporins <sup>a</sup> (discontinued immediately post-operation)	1. Ampicillin-sulbactam
Gangrenous or perforated	Imipenem-cilastatin, meropenem, ertapenem, antianaerobic cephalosporins, or extended-spectrum penicillins with $\beta$ -lactamase inhibitor	1. Aztreonam with clindamycin or metronidazole 2. Ciprofloxacin with metronidazole 3. Aminoglycoside with clindamycin or metronidazole
<b>Acute cholecystitis</b>	First-generation cephalosporin	Aminoglycoside plus ampicillin if severe infection
<b>Cholangitis</b>	Aminoglycoside with ampicillin with or without clindamycin or metronidazole	Use vancomycin instead of ampicillin if patient is allergic to penicillin
<b>Acute contamination from abdominal trauma</b>	Antianaerobic cephalosporins <sup>a</sup> or ampicillin-sulbactam	1. A carbapenem 2. Ciprofloxacin plus metronidazole
<b>Pelvic inflammatory disease</b>	Cefotetan or cefoxitin with doxycycline	1. Clindamycin with gentamicin 2. Ampicillin-sulbactam with doxycycline 3. Ciprofloxacin with doxycycline and metronidazole

<sup>a</sup>Cefoxitin, cefotetan, and ceftizoxime.

- Evidence-based treatment principles for complicated intraabdominal infections are given in Table 42-6.
- The selection of a specific agent or combination should be based on culture and susceptibility data for peritonitis that occurs from chronic peritoneal dialysis. If microbiologic data are unavailable, empiric therapy should be initiated.
- For established intraabdominal infections, most patients are adequately treated with 5 to 7 days of antimicrobial therapy.
- Intraperitoneal administration of antibiotics is preferred over IV therapy in the treatment of peritonitis that occurs in patients undergoing continuous ambulatory peritoneal dialysis. Initial antibiotic regimens should be effective against both gram-positive and gram-negative organisms.
- Suitable antibiotics for initial empiric treatment of continuous ambulatory peritoneal dialysis-associated peritonitis are: cefazolin (loading dose 500 mg/L, maintenance dose 125 mg/L in the dialysis solution) or cefepime (500 mg/L loading dose and 125 mg/L maintenance dose) or an aminoglycoside (gentamicin/tobramycin 8 mg/L loading dose and 4 mg/L maintenance dose). If the patient is allergic to cephalosporins, vancomycin (1 g/L loading dose and 25 mg/L maintenance dose) or an aminoglycoside should be substituted.

**TABLE 42-6** Evidence-Based Recommendations for Treatment of Complicated Intraabdominal Infections

	<b>Grade of Recommendation<sup>a</sup></b>
<b>Acute contamination as a result of trauma</b>	
Bowel injuries caused by penetrating, blunt, or iatrogenic trauma that are repaired within 12 hours and intraoperative contamination of the operative field by enteric contents under other circumstances should be treated with antibiotics $\leq 24$ hours.	A-1
<b>Acute appendicitis</b>	
Acute appendicitis without evidence of gangrene, perforation, abscess, or peritonitis requires only prophylactic administration of inexpensive regimens active against facultative and obligate anaerobes.	A-1
<b>Community-acquired infections</b>	
Antibiotics used for empirical treatment of community-acquired intraabdominal infections should be active against empiric gram-negative aerobic and facultative bacilli and $\beta$ -lactam-susceptible gram-positive cocci.	A-1
For patients with mild-to-moderate community-acquired infections, agents that have a narrower spectrum of activity, such as ampicillin-sulbactam, cefazolin, or cefuroxime-metronidazole, ticarcillin-clavulanate, and ertapenem are preferable to more-costly agents that have broader coverage against gram-negative organisms and/or greater risk of toxicity.	A-1
<b>Anaerobic coverage</b>	A-1
Coverage against obligate anaerobic bacilli should be provided for distal small-bowel and colon-derived infections and for more-proximal gastrointestinal perforations when obstruction is present.	
<b>Nosocomial infections</b>	
Agents used to treat nosocomial infections in the intensive care unit (e.g., expanded gram-negative bacterial spectrum) should not be routinely used to treat community-acquired infections.	B-2
If a patient with diagnosed infection has previously been treated with an antibiotic, that patient should be treated as if he or she has had a healthcare-associated (nosocomial) infection.	B-3
<b>Aminoglycosides</b>	
Aminoglycosides are not recommended for routine use in community-acquired intraabdominal infections.	A-1
<b>Oral completion therapy</b>	
Completion of the antimicrobial course with oral forms of a quinolone plus metronidazole,	A-1
or with amoxicillin-clavulanic acid is acceptable for patients who are able to tolerate an oral diet.	B-3
<b>Suspected fungal infection</b>	
Antiinfective therapy for <i>Candida</i> should be withheld until the infecting species is identified.	C-3
<b>Enterococcal infection</b>	
Routine coverage against <i>Enterococcus</i> is not necessary for patients with community-acquired intraabdominal infections.	A-1

<sup>a</sup>Strength of recommendations: A, B, C = good, moderate, and poor evidence to support recommendation, respectively. Quality of evidence: 1 = Evidence from >1 properly randomized, controlled trial. 2 = Evidence from >1 well-designed clinical trial with randomization, from cohort or case-controlled analytic studies; from multiple time series, or from dramatic results from uncontrolled experiments. 3 = Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert communities.

From Solomkin JS, Mazuski JE, Baron EJ, et al. Guidelines for the selection of anti-infective agents for complicated intraabdominal infections. *Clin Infect Dis* 2003;37:997-1005; Mazuski JE, Sawyer RG, Nathens AB, et al. The Surgical Infection Society guidelines on antimicrobial therapy for intraabdominal infections: an executive summary. *Surg Infect (Larchmt)* 2002;3:161-174; and Mazuski JE, Sawyer RG, Nathens AB, et al. The Surgical Infection Society guidelines on antimicrobial therapy for intraabdominal infections: evidence for recommendations. *Surg Infect (Larchmt)* 2002;3:175-234.

- Antimicrobial therapy should be continued for at least 1 week after the dialysate fluid is clear and for a total of at least 14 days.
- Antianaerobic cephalosporins or extended-spectrum penicillins are effective in preventing most infectious complications after acute bacterial contamination, such as with abdominal trauma where GI contents enter the peritoneum, and when the patient is seen soon after injury (within 2 hours) and surgical measures are instituted promptly.
- Acute intraabdominal contamination, such as after a traumatic injury, may be treated with a short course (24 hours). For established infections (peritonitis or intraabdominal abscess), an antimicrobial course of at least 7 days is justified.

## EVALUATION OF THERAPEUTIC OUTCOMES

- The patient should be continually reassessed to determine the success or failure of therapies.
- Once antimicrobials are initiated and other important therapies described earlier in the Treatment section are used, most patients should show improvement within 2 to 3 days. Usually, temperature will return to near normal, vital signs should stabilize, and the patient should not appear in distress, with the exception of recognized discomfort and pain from incisions, drains, and nasogastric tube.
- At 24 to 48 hours, aerobic bacterial culture results should return. If a suspected pathogen is not sensitive to the antimicrobial agents being given, the regimen should be changed if the patient has not shown sufficient improvement.
- If the isolated pathogen is extremely sensitive to one antimicrobial, and the patient is progressing well, concurrent antimicrobial therapy may often be discontinued.
- With present anaerobic culturing techniques and the slow growth of these organisms, anaerobes are often not identified until 4 to 7 days after culture, and sensitivity information is difficult to obtain. For this reason, there are usually few data with which to alter the antianaerobic component of the antimicrobial regimen.
- Superinfection in patients being treated for intraabdominal infection is often due to *Candida*, however enterococci or opportunistic gram-negative bacilli such as *Pseudomonas* or *Serratia* may be involved.
- Treatment regimens for intraabdominal infection can be judged successful if the patient recovers from the infection without recurrent peritonitis or intraabdominal abscess and without the need for additional antimicrobials. A regimen can be considered unsuccessful if a significant adverse drug reaction occurs, if reoperation is necessary, or if patient improvement is delayed beyond 1 or 2 weeks.

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See Chap. 118, *Intraabdominal Infections*, authored by Joseph T. DiPiro and Thomas R. Howdieshell, for a more detailed discussion of this topic.

## DEFINITION

- Lower respiratory tract infections include infectious processes of the lungs and bronchi, pneumonia, bronchitis, bronchiolitis, and lung abscess.

## BRONCHITIS

## ACUTE BRONCHITIS

- *Bronchitis* refers to an inflammatory condition of the large elements of the tracheobronchial tree that is usually associated with a generalized respiratory infection. The inflammatory process does not extend to include the alveoli. The disease entity is frequently classified as either acute or chronic. Acute bronchitis occurs in all ages, whereas chronic bronchitis primarily affects adults.
- Acute bronchitis most commonly occurs during the winter months. Cold, damp climates and/or the presence of high concentrations of irritating substances such as air pollution or cigarette smoke may precipitate attacks.

## Pathophysiology

- Respiratory viruses are by far the most common infectious agents associated with acute bronchitis. The common cold viruses, rhinovirus and coronavirus, and lower respiratory tract pathogens, including influenza virus, adenovirus, and respiratory syncytial virus, account for the majority of cases. *Mycoplasma pneumoniae* also appears to be a frequent cause of acute bronchitis. Other bacterial causes include *Chlamydia pneumoniae* and *Bordetella pertussis*.
- Infection of the trachea and bronchi causes hyperemic and edematous mucous membranes and an increase in bronchial secretions. Destruction of respiratory epithelium can range from mild to extensive and may affect bronchial mucociliary function. In addition, the increase in bronchial secretions, which can become thick and tenacious, further impairs mucociliary activity. Recurrent acute respiratory infections may be associated with increased airway hyperreactivity and possibly the pathogenesis of chronic obstructive lung disease.

## Clinical Presentation

- Bronchitis is primarily a self-limiting illness and rarely a cause of death. Acute bronchitis usually begins as an upper respiratory infection. The patient typically has nonspecific complaints such as malaise and headache, coryza, and sore throat.
- Cough is the hallmark of acute bronchitis. It occurs early and will persist despite the resolution of nasal or nasopharyngeal complaints. Frequently, the cough is initially nonproductive but progresses, yielding mucopurulent sputum.
- Chest examination may reveal rhonchi and coarse, moist rales bilaterally. Chest radiographs, when performed, are usually normal.

- Bacterial cultures of expectorated sputum are generally of limited utility because of the inability to avoid normal nasopharyngeal flora by the sampling technique. Viral antigen detection tests can be used when a specific diagnosis is necessary. Cultures or serologic diagnosis of *M. pneumoniae* and culture or direct fluorescent antibody detection for *B. pertussis* should be obtained in prolonged or severe cases when epidemiologic considerations would suggest their involvement.

### Desired Outcome

- The goals of therapy are to provide comfort to the patient and, in the unusually severe case, to treat associated dehydration and respiratory compromise.

### Treatment

- The treatment of acute bronchitis is symptomatic and supportive in nature. Reassurance and antipyretics alone are often sufficient. Bedrest and mild analgesic-antipyretic therapy are often helpful in relieving the associated lethargy, malaise, and fever. Patients should be encouraged to drink fluids to prevent dehydration and possibly decrease the viscosity of respiratory secretions.
- **Aspirin** or **acetaminophen** (650 mg in adults or 10 to 15 mg/kg per dose in children with a maximum daily adult dose of 4 g and 60 mg/kg for children) or **ibuprofen** (200 to 800 mg in adults or 10 mg/kg per dose in children with a maximum daily dose of 3.2 g for adults and 40 mg/kg for children) is administered every 4 to 6 hours.
- In children, aspirin should be avoided and acetaminophen used as the preferred agent because of the possible association between aspirin use and the development of Reye's syndrome.
- Mist therapy and/or the use of a vaporizer may further promote the thinning and loosening of respiratory secretions.
- Persistent, mild cough, which may be bothersome, may be treated with **dextromethorphan**; more severe coughs may require intermittent **codeine** or other similar agents.
- Routine use of antibiotics in the treatment of acute bronchitis is discouraged; however, in patients who exhibit persistent fever or respiratory symptomatology for more than 4 to 6 days, the possibility of a concurrent bacterial infection should be suspected.
- When possible, antibiotic therapy is directed toward anticipated respiratory pathogen(s) (i.e., *Streptococcus pneumoniae*, *Haemophilus influenzae*) and/or those demonstrating a predominant growth upon throat culture.
- *M. pneumoniae*, if suspected by history or positive cold agglutinins (titers greater than or equal to 1:32) or if confirmed by culture or serology, may be treated with **azithromycin**. Also, a fluoroquinolone with activity against these pathogens (**levofloxacin**) may be used in adults.
- During known epidemics involving the influenza A virus, **amantadine** or **rimantadine** may be effective in minimizing associated symptomatology if administered early in the course of the disease.

## CHRONIC BRONCHITIS

### Pathophysiology

- Chronic bronchitis is a result of several contributing factors, including cigarette smoking; exposure to occupational dusts, fumes, and environmental pollution; and bacterial (and possibly viral) infection.
- In chronic bronchitis, the bronchial wall is thickened and the number of mucus-secreting goblet cells in the surface epithelium of both larger and smaller bronchi is markedly increased. Hypertrophy of the mucus glands and dilatation of the mucus gland ducts are also observed. As a result of these changes, patients with chronic bronchitis have substantially more mucus in their peripheral airways, further impairing normal lung defenses and causing mucus plugging of the smaller airways.
- Continued progression of this pathology can result in residual scarring of small bronchi, augmenting airway obstruction and the weakening of bronchial walls.

### Clinical Presentation

- The hallmark of chronic bronchitis is cough that may range from a mild “smoker’s” cough to severe incessant coughing productive of purulent sputum. Expectoration of the largest quantity of sputum usually occurs upon arising in the morning, although many patients expectorate sputum throughout the day. The expectorated sputum is usually tenacious and can vary in color from white to yellow-green.
- The diagnosis of chronic bronchitis is based primarily on clinical assessment and history. By definition, any patient who reports coughing up sputum on most days for at least 3 consecutive months each year for 2 consecutive years suffers from chronic bronchitis. Table 43-1 presents a classification and treatment scheme for chronic bronchitis.
- With the exception of pulmonary findings, the physical examination of patients with mild to moderate chronic bronchitis is usually unremarkable (Table 43-2).
- An increased number of polymorphonuclear granulocytes in sputum often suggests continual bronchial irritation, whereas an increased number of eosinophils may suggest an allergic component. The most common bacterial isolates (expressed in percentages of total cultures) identified from sputum culture in patients experiencing an acute exacerbation of chronic bronchitis are as follows:

<i>Haemophilus influenzae</i> <sup>a</sup>	45%
<i>Moraxella catarrhalis</i> <sup>a</sup>	30%
<i>Streptococcus pneumoniae</i> <sup>b</sup>	20%
<i>Escherichia coli</i> , <i>Enterobacter</i> species, <i>Klebsiella</i> , <i>Pseudomonas aeruginosa</i>	5%

<sup>a</sup>Often  $\beta$ -lactamase positive.

<sup>b</sup>As many as 25% of strains may have intermediate or high resistance to penicillin.

### Desired Outcome

- The goals of therapy for chronic bronchitis are to reduce the severity of symptoms, to ameliorate acute exacerbations, and to achieve prolonged infection-free intervals.

**TABLE 43-1** Classification System for Patients with Chronic Bronchitis and Initial Treatment Options

Baseline Status	Criteria or Risky Factors	Usual Pathogens	Initial Treatment Options
<b>Class I</b> Acute tracheo-bronchitis	No underlying structural disease	Usually a virus	1. None unless symptoms persist 2. Amoxicillin; amoxicillin-clavulanate; or a macrolide/azalide if bacterial infection is suspected/documented
<b>Class II</b> Chronic bronchitis	FEV <sub>1</sub> >50% predicted value, increased sputum volume and purulence	<i>Haemophilus influenzae</i> , <i>Haemophilus</i> spp., <i>Moraxella catarrhalis</i> , <i>Streptococcus pneumoniae</i> ( $\beta$ -lactam resistance possible)	1. Same as Class I, No. 2, or fluoroquinolone if prevalence of <i>H. influenzae</i> resistance to amoxicillin is >20% 2. Fluoroquinolone, amoxicillin-clavulanate, azithromycin, tetracycline, or trimethoprim-sulfamethoxazole
<b>Class III</b> Chronic bronchitis with complications	FEV <sub>1</sub> <50% predicted value, increased sputum volume and purulence, advanced age, at least four flares per year, or significant comorbidity	Same as class II; also <i>Escherichia coli</i> , <i>Klebsiella</i> , <i>Enterobacter</i> spp., <i>Pseudomonas aeruginosa</i> ( $\beta$ -lactam resistance common)	1. Fluoroquinolone 2. Expanded spectrum cephalosporin, amoxicillin-clavulanate, or azithromycin
<b>Class IV</b> Chronic bronchial infection	Same as for class III plus yearlong production of purulent sputum	Same as class III	1. Oral or parenteral fluoroquinolone, carbapenem, or expanded spectrum cephalosporin

1, Preferred therapy; 2, alternative treatment options.  
FEV<sub>1</sub>, forced expiratory volume in 1 second.

## Treatment

### General Principles

- A complete occupational/environmental history for the determination of exposure to noxious, irritating gases, as well as cigarette smoking, must be assessed. Exposure to bronchial irritants should be reduced.
- Attempts should be made with the patient to reduce or eliminate cigarette smoking.
- Humidification of inspired air may promote the hydration (liquefaction) of tenacious secretions, allowing for more effective sputum production. The use of mucolytic aerosols (e.g., *N*-acetylcysteine; deoxyribonuclease) is of questionable therapeutic value. Mucolytics may have the greatest benefit

**TABLE 43-2** Clinical Presentation of Chronic Bronchitis**Signs and symptoms**

- Cyanosis (advanced disease)
- Obesity

**Physical examination**

- Chest auscultation usually reveals inspiratory and expiratory rales, rhonchi, and mild wheezing with an expiratory phase that is frequently prolonged. There is hyperresonance on percussion with obliteration of the area of cardiac dullness.
- Normal vesicular breathing sounds are diminished.
- Clubbing of digits (advanced disease).

**Chest radiograph**

- Increase in the anteroposterior diameter of the thoracic cage (observed as a barrel chest)
- Depressed diaphragm with limited mobility

**Laboratory tests**

- Erythrocytosis (advanced disease)

**Pulmonary function tests**

- Decreased vital capacity
- Prolonged expiratory flow

in patients with moderate or severe chronic obstructive pulmonary disease who are not receiving inhaled corticosteroids.

- Postural drainage may assist in promoting clearance of pulmonary secretions.

**Pharmacologic Therapy**

- Oral or aerosolized bronchodilators (e.g., **albuterol** aerosol) may be of benefit to some patients during acute pulmonary exacerbations. For patients who consistently demonstrate limitations in airflow, a therapeutic change of bronchodilators should be considered.
- Long-term inhalation of ipratropium decreases the frequency of cough, severity of cough, and the volume of expectorated sputum.
- The use of antimicrobials has been controversial, although antibiotics are an important component of treatment. Agents should be selected that are effective against likely pathogens, have the lowest risk of drug interactions, and can be administered in a manner that promotes compliance (see Table 43-1).
- Selection of antibiotics should consider that up to 30% to 40% of *H. influenzae* and 95% of *M. pneumoniae* are  $\beta$ -lactamase producers, and up to 30% of *S. pneumoniae* are at least moderately penicillin resistant.
- Antibiotics commonly used in the treatment of these patients and their respective adult starting doses are outlined in Table 43-3. Duration of symptom-free periods may be enhanced by antibiotic regimens using the upper limit of the recommended daily dose for 5 to 7 days.
- In patients whose history suggests recurrent exacerbations of their disease that might be attributable to certain specific events (i.e., seasonal, winter months), a trial of prophylactic antibiotics might be beneficial. If no clinical improvement is noted over an appropriate period (e.g., 2 to 3 months per year for 2 to 3 years), prophylactic therapy could be discontinued.

**TABLE 43-3** Oral Antibiotics Commonly Used for the Treatment of Acute Respiratory Exacerbations in Chronic Bronchitis

Antibiotic	Usual Adult Dose (g)	Dose Schedule (doses/day)
<b>Preferred drugs</b>		
Ampicillin	0.25–0.5	4
Amoxicillin	0.5–0.875	3/2
Amoxicillin-clavulanate	0.5–0.875	3/2
Ciprofloxacin	0.5–0.75	2
Levofloxacin	0.5–0.75	1
Moxifloxacin	0.4	1
Doxycycline	0.1	2
Minocycline	0.1	2
Tetracycline HCl	0.5	4
Trimethoprim-sulfamethoxazole	1 DS <sup>a</sup>	2
<b>Supplemental drugs</b>		
Azithromycin	0.25–0.5	1
Erythromycin	0.5	4
Clarithromycin	0.25–0.5	2
Cephalexin	0.5	4

<sup>a</sup>DS, double-strength tablet (160 mg trimethoprim/800 mg sulfamethoxazole).

## BRONCHIOLITIS

- Bronchiolitis is an acute viral infection of the lower respiratory tract of infants that affects approximately 50% of children during the first year of life and 100% by 3 years.
- Respiratory syncytial virus is the most common cause of bronchiolitis, accounting for up to 70% of all cases. Parainfluenza viruses are the second most common cause. Bacteria serve as secondary pathogens in only a small minority of cases.

### Clinical Presentation

- The most common clinical signs of bronchiolitis are found in Table 43-4. A prodrome suggesting an upper respiratory tract infection, usually lasting from 2 to 8 days, precedes the onset of clinical symptoms.
- As a result of limited oral intake due to coughing combined with fever, vomiting, and diarrhea, infants are frequently dehydrated.
- The diagnosis of bronchiolitis is based primarily on history and clinical findings. The isolation of a viral pathogen in the respiratory secretions of a wheezing child establishes a presumptive diagnosis of infectious bronchiolitis.

### Treatment

- Bronchiolitis is a self-limiting illness and usually requires no therapy (other than reassurance and antipyretics) unless the infant is hypoxic or dehydrated. Otherwise healthy infants can be treated for fever, provided generous amounts of oral fluids, and observed closely.
- In severely affected children, the mainstays of therapy for bronchiolitis are oxygen therapy and IV fluids.

**TABLE 43-4** Clinical Presentation of Bronchiolitis**Signs and symptoms**

- Prodrome with irritability, restlessness, and mild fever
- Cough and coryza
- Vomiting, diarrhea, noisy breathing, and an increase in respiratory rate as symptoms progress
- Labored breathing with retractions of the chest wall, nasal flaring, and grunting

**Physical examination**

- Tachycardia and respiratory rate of 40–80/min in hospitalized infants
- Wheezing and inspiratory rales
- Mild conjunctivitis in one-third of patients
- Otitis media in 5–10% of patients

**Laboratory examinations**

- Peripheral white blood cell count normal or slightly elevated
- Abnormal arterial blood gases (hypoxemia and, rarely, hypercarbia)

- Aerosolized  $\beta$ -adrenergic therapy appears to offer little benefit for the majority of patients but may be useful in the child with a predisposition toward bronchospasm.
- Because bacteria do not represent primary pathogens in the etiology of bronchiolitis, antibiotics should not be routinely administered. However, many clinicians frequently administer antibiotics initially while awaiting culture results because the clinical and radiographic findings in bronchiolitis are often suggestive of a possible bacterial pneumonia.
- **Ribavirin** may be considered for bronchiolitis caused by respiratory syncytial virus in a subset of patients (those with underlying pulmonary or cardiac disease or with severe acute infection). Use of the drug requires special equipment (small-particle aerosol generator) and specifically trained personnel for administration via oxygen hood or mist tent.

**PNEUMONIA**

- Pneumonia is the most common infectious cause of death in the United States. It occurs in persons of all ages, although the clinical manifestations are most severe in the very young, the elderly, and the chronically ill.

**PATHOPHYSIOLOGY**

- Microorganisms gain access to the lower respiratory tract by three routes: they may be inhaled as aerosolized particles; they may enter the lung via the bloodstream from an extrapulmonary site of infection; or aspiration of oropharyngeal contents may occur.
- Lung infections with viruses suppress the bacterial clearing activity of the lung by impairing alveolar macrophage function and mucociliary clearance, thus setting the stage for secondary bacterial pneumonia.
- The vast majority of pneumonia cases acquired in the community by otherwise healthy adults are due to *S. pneumoniae* (pneumococcus) (up to 75% of all acute bacterial pneumonias in the United States). Other common bacterial causes include *M. pneumoniae*, *Legionella*, and *C. pneumoniae*, which are referred to as “atypical” pathogens. Community-acquired

pneumonias caused by *Staphylococcus aureus* and gram-negative rods are observed primarily in the elderly, especially those residing in nursing homes, and in association with alcoholism and other debilitating conditions.

- Gram-negative aerobic bacilli and *S. aureus* are also the leading causative agents in hospital-acquired pneumonia.
- Anaerobic bacteria are the most common etiologic agents in pneumonia that follows the gross aspiration of gastric or oropharyngeal contents.
- In the pediatric age group, most pneumonias are due to viruses, especially respiratory syncytial virus, parainfluenza, and adenovirus. Pneumococcus is the most common bacterial cause, followed by Group A *Streptococcus* and *S. aureus*.

## CLINICAL PRESENTATION

### Gram-Positive and Gram-Negative Bacterial Pneumonia

- The clinical presentation of pneumonia is found in Table 43-5.
- Infection with *Legionella pneumophila* is characterized by multisystem involvement, including rapidly progressive pneumonia. It has a gradual onset, with prominent constitutional symptoms such as malaise, lethargy, weakness, and anorexia occurring early in the course of the illness. A dry, nonproductive cough is initially present that over several days becomes productive of mucoid or purulent sputum. Fevers exceed 40°C (104°F) and are typically unremitting and associated with a relative bradycardia. Pleuritic chest pain and progressive dyspnea may be seen, and fine rales are found on lung examination, progressing to signs of frank consolidation later in the course of the illness. Extrapulmonary manifestations remain evident throughout the course of the illness and include diarrhea, nausea, vomiting, myalgias, and arthralgias.
- Substantial changes in a patient's mental status, often out of proportion to the degree of fever, are seen in approximately one-fourth of patients.

**TABLE 43-5** Clinical Presentation of Pneumonia

#### Signs and symptoms

- Abrupt onset of fever, chills, dyspnea, and productive cough
- Rust-colored sputum or hemoptysis
- Pleuritic chest pain

#### Physical examination

- Tachypnea and tachycardia
- Dullness to percussion
- Increased tactile fremitus, whispered pectoriloquy, and egophony
- Chest wall retractions and grunting respirations
- Diminished breath sounds over the affected area
- Inspiratory crackles during lung expansion

#### Chest radiograph

- Dense lobar or segmental infiltrate

#### Laboratory examination

- Leukocytosis with a predominance of polymorphonuclear cells
- Low oxygen saturation on arterial blood gas or pulse oximetry

Obtundation, hallucinations, grand mal seizures, and focal neurologic findings have also been associated with this illness.

- Laboratory findings include leukocytosis with predominance of mature and immature granulocytes in 50% to 75% of patients. Because *L. pneumophila* stains poorly with commonly used stains, routine microscopic examination of sputum is of little diagnostic value. Fluorescent antibody testing can be performed to diagnose Legionnaires' disease.

### **Anaerobic Pneumonia**

- The course of anaerobic pneumonia is typically indolent with cough, low-grade fever, and weight loss, although an acute presentation may occur. Putrid sputum, when present, is highly suggestive of the diagnosis. Chest radiographs reveal infiltrates typically located in dependent lung segments, and lung abscesses develop in 20% of patients 1 to 2 weeks into the course of the illness.

### ***Mycoplasma pneumoniae***

- *M. pneumoniae* pneumonia presents with a gradual onset of fever, headache, and malaise, with the appearance 3 to 5 days after the onset of illness of a persistent, hacking cough that initially is nonproductive. Sore throat, ear pain, and rhinorrhea are often present. Lung findings are generally limited to rales and rhonchi; findings of consolidation are rarely present.
- Nonpulmonary manifestations are extremely common and include nausea, vomiting, diarrhea, myalgias, arthralgias, polyarticular arthritis, skin rashes, myocarditis and pericarditis, hemolytic anemia, meningoencephalitis, cranial neuropathies, and Guillain-Barré syndrome. Systemic symptoms generally clear in 1 to 2 weeks, whereas respiratory symptoms may persist up to 4 weeks.
- Radiographic findings include patchy or interstitial infiltrates, which are most commonly seen in the lower lobes.
- Sputum Gram stain may reveal mononuclear or polymorphonuclear leukocytes, with no predominant organism. Although *M. pneumoniae* can be cultured from respiratory secretions using specialized medium, 2 to 3 weeks may be necessary for culture identification.

### **Viral Pneumonia**

- The clinical pictures produced by respiratory viruses are sufficiently variable and overlap to such a degree that an etiologic diagnosis cannot confidently be made on clinical grounds alone. Serologic tests for virus-specific antibodies are often used in the diagnosis of viral infections. The diagnostic fourfold rise in titer between acute and convalescent phase sera may require 2 to 3 weeks to develop; however, same-day diagnosis of viral infections is now possible through the use of indirect immunofluorescence tests on exfoliated cells from the respiratory tract.
- Radiographic findings are nonspecific and include bronchial wall thickening and perihilar and diffuse interstitial infiltrates.

### **Nosocomial Pneumonia**

- The strongest predisposing factor for nosocomial pneumonia is mechanical ventilation. Risk is increased by prior antibiotic use, use of H<sub>2</sub>-receptor antagonists, and severe illness.

- The diagnosis of nosocomial pneumonia is usually established by presence of a new infiltrate on chest radiograph, fever, worsening respiratory status, and the appearance of thick, neutrophil-laden respiratory secretions.

## DESIRED OUTCOME

- Eradication of the offending organism and complete clinical cure are the primary objectives. Associated morbidity should be minimized (e.g., renal, pulmonary, or hepatic dysfunction).

## TREATMENT

- The first priority on assessing the patient with pneumonia is to evaluate the adequacy of respiratory function and to determine whether there are signs of systemic illness, specifically dehydration or sepsis with resulting circulatory collapse.
- The supportive care of the patient with pneumonia includes the use of humidified oxygen for hypoxemia, fluid resuscitation, administration of bronchodilators when bronchospasm is present, and chest physiotherapy with postural drainage if there is evidence of retained secretions.

**TABLE 43-6** Empirical Antimicrobial Therapy for Pneumonia in Adults<sup>a</sup>

Clinical Setting	Usual Pathogen(s)	Presumptive Therapy
Previously healthy, ambulatory patient	Pneumococcus, <i>Mycoplasma pneumoniae</i>	Macrolide/azalide, <sup>b</sup> tetracycline <sup>c</sup>
Elderly	Pneumococcus, gram-negative bacilli (such as <i>Klebsiella pneumoniae</i> ); <i>Staphylococcus aureus</i> , <i>Haemophilus influenzae</i>	Piperacillin-tazobactam, cephalosporin <sup>d</sup> , carbapenem <sup>e</sup>
Chronic bronchitis	Pneumococcus, <i>H. influenzae</i> , <i>M. catarrhalis</i>	Amoxicillin, tetracycline, <sup>c</sup> trimethoprim-sulfamethoxazole, cefuroxime, amoxicillin-clavulanate, macrolide/azalide, <sup>b</sup> fluoroquinolone
Alcoholism	Pneumococcus, <i>K. pneumoniae</i> , <i>S. aureus</i> , <i>H. influenzae</i> , possibly mouth anaerobes	Ticarcillin-clavulanate, piperacillin-tazobactam, plus aminoglycoside; carbapenem, <sup>e</sup> fluoroquinolone <sup>f</sup>
Aspiration pneumonia		
Community	Mouth anaerobes	Penicillin or clindamycin
Hospital/residential care	Mouth anaerobes, <i>S. aureus</i> , gram-negative enterics	Clindamycin, ticarcillin-clavulanate, piperacillin-tazobactam, plus aminoglycoside
Nosocomial pneumonia	Gram-negative bacilli (such as <i>K. pneumoniae</i> , <i>Enterobacter</i> spp., <i>Pseudomonas aeruginosa</i> ), <i>S. aureus</i>	Piperacillin-tazobactam, carbapenem, <sup>e</sup> or extended-spectrum cephalosporin <sup>g</sup> plus aminoglycoside, fluoroquinolone <sup>f</sup>

<sup>a</sup>See section on treatment of bacterial pneumonia.

<sup>b</sup>Macrolide/azalide: erythromycin, clarithromycin, azithromycin.

<sup>c</sup>Tetracycline: tetracycline hydrochloride, doxycycline.

<sup>d</sup>Cephalosporin: cefuroxime, ceftriaxone, cefotaxime.

<sup>e</sup>Carbapenem: imipenem-cilastatin, meropenem.

<sup>f</sup>Fluoroquinolone: ciprofloxacin, gatifloxacin, or levofloxacin.

<sup>g</sup>Extended-spectrum cephalosporin: ceftazidime, cefepime.

**TABLE 43-7** Empirical Antimicrobial Therapy for Pneumonia in Pediatric Patients<sup>a</sup>

Age	Usual Pathogen(s)	Presumptive Therapy
1 month	Group B <i>Streptococcus</i> , <i>Haemophilus influenzae</i> (nontypable), <i>Escherichia coli</i> , <i>Staphylococcus aureus</i> , <i>Listeria</i> , CMV, RSV, adenovirus	Ampicillin-sulbactam, cephalosporin, <sup>b</sup> carbapenem, <sup>c</sup> ribavirin for RSV
1–3 months	<i>Chlamydia</i> , possibly <i>Ureaplasma</i> , CMV, <i>Pneumocystis carinii</i> (afebrile pneumonia syndrome) RSV <i>Pneumococcus</i> , <i>S. aureus</i>	Macrolide-azalide, <sup>d</sup> trimethoprim-sulfamethoxazole Ribavirin Semisynthetic penicillin <sup>e</sup> or cephalosporin <sup>f</sup>
3 months to 6 years	<i>Pneumococcus</i> , <i>H. influenzae</i> , RSV, adenovirus, parainfluenza	Amoxicillin or cephalosporin, <sup>f</sup> ampicillin-sulbactam, amoxicillin-clavulanate, ribavirin for RSV
>6 years	<i>Pneumococcus</i> , <i>Mycoplasma pneumoniae</i> , adenovirus	Macrolide/azalide, <sup>d</sup> cephalosporin, <sup>f</sup> amoxicillin-clavulanate

CMV, cytomegalovirus; RSV, respiratory syncytial virus.

<sup>a</sup>See section on treatment of bacterial pneumonia.

<sup>b</sup>Third-generation cephalosporin: ceftriaxone, cefotaxime, cefepime. Note that cephalosporins are not active against *Listeria*.

<sup>c</sup>Carbapenem: imipenem-clastatin, meropenem.

<sup>d</sup>Macrolide/azalide: erythromycin, clarithromycin-azithromycin.

<sup>e</sup>Semisynthetic penicillin: nafcillin, oxacillin.

<sup>f</sup>Second-generation cephalosporin: cefuroxime, cefprozil.

**TABLE 43-8** Antibiotic Doses for the Treatment of Bacterial Pneumonia

Antibiotic Class	Antibiotic	Daily Antibiotic Dose	
		Pediatric (mg/kg/day)	Adult (total dose/day)
Macrolide	Clarithromycin	15	0.5–1 g
	Erythromycin	30–50	1–2 g
Azalide	Azithromycin	10 mg/kg × 1 day, then 5 mg/kg/day × 4 days	500 mg day 1, then 250 mg/day × 4 days
Tetracycline <sup>a</sup>	Tetracycline hydrochloride	25–50	1–2 g
	Oxytetracycline	15–25	0.25–0.3 g
Penicillin	Ampicillin	100–200	2–6 g
	Amoxicillin/amoxicillin-clavulanate <sup>b</sup>	40–90	0.75–1 g
	Piperacillin-tazobactam	200–300	12 g
	Ampicillin-sulbactam	100–200	4–8 g
Extended-spectrum	Ceftriaxone	50–75	1–2 g
Cephalosporins	Ceftazidime	150	2–6 g
	Cefepime	100–150	2–4 g
Fluoroquinolones	Gatifloxacin <sup>c</sup>	10–20	0.4 g
	Levofloxacin	10–15	0.5–0.75 g
	Ciprofloxacin	20–30	0.5–1.5 g
Aminoglycosides	Gentamicin	7.5	3–6 mg/kg
	Tobramycin	7.5	3–6 mg/kg

Note: Doses may be increased for more severe disease and may require modification in patients with organ dysfunction.

<sup>a</sup>Tetracyclines are rarely used in pediatric patients, particularly in those younger than 8 years of age because of tetracycline-induced permanent tooth discoloration.

<sup>b</sup>Higher dose amoxicillin, amoxicillin-clavulanate (e.g., 90 mg/kg/day) is used for penicillin-resistant *Streptococcus pneumoniae*.

<sup>c</sup>Fluoroquinolones are avoided in pediatric patients because of the potential for cartilage damage; however, their use in pediatrics is emerging. Doses shown are extrapolated from adults and will require further study.

**TABLE 43-9** Empirical Treatment for Suspected Bacterial Community-Acquired Pneumonia (CAP)

Clinical Setting	Empirical Therapy
<b>Outpatient</b>	
Previously healthy	
No recent antibiotic therapy	A macrolide <sup>a</sup> or doxycycline
Recent antibiotic therapy <sup>b</sup>	A respiratory fluoroquinolone <sup>c</sup> alone, an advanced macrolide <sup>d</sup> plus high-dose amoxicillin, or an advanced macrolide plus high-dose amoxicillin-clavulanate
Comorbidities (chronic obstructive pulmonary disease, diabetes, renal or congestive heart failure, malignancy)	
No recent antibiotic therapy	An advanced macrolide <sup>d</sup> or a respiratory fluoroquinolone
Recent antibiotic therapy <sup>b</sup>	A respiratory fluoroquinolone <sup>c</sup> alone or an advanced macrolide plus a $\beta$ -lactam <sup>e</sup>
Suspected aspiration with infection	Amoxicillin-clavulanate or clindamycin
Influenza with bacterial superinfection	A $\beta$ -lactam <sup>e</sup> or a respiratory fluoroquinolone
<b>Inpatient</b>	
Medical ward	
No recent antibiotic therapy <sup>b</sup>	A respiratory fluoroquinolone alone or an advanced macrolide plus a $\beta$ -lactam <sup>f</sup>
Recent antibiotic therapy <sup>b</sup>	An advanced macrolide plus a $\beta$ -lactam or a respiratory fluoroquinolone alone (regimen selected will depend on nature of recent antibiotic therapy)
Intensive care unit (ICU)	
<i>Pseudomonas</i> infection is not an issue	A $\beta$ -lactam <sup>f</sup> plus either an advanced macrolide or a respiratory fluoroquinolone
<i>Pseudomonas</i> infection is not an issue but patient has a $\beta$ -lactam allergy	A respiratory fluoroquinolone, with or without clindamycin
<i>Pseudomonas</i> infection is an issue <sup>g</sup>	Either (a) an antipseudomonal agent <sup>h</sup> plus ciprofloxacin, or (b) an antipseudomonal agent plus an aminoglycoside plus a respiratory fluoroquinolone or a macrolide
<i>Pseudomonas</i> infection is an issue but the patient has a $\beta$ -lactam allergy	Either (a) aztreonam plus levofloxacin or (b) aztreonam plus moxifloxacin or gatifloxacin, with or without an aminoglycoside

<sup>a</sup>Erythromycin, azithromycin, or clarithromycin.

<sup>b</sup>The patient was given a course of antibiotic(s) for treatment of any infection within the past 3 months, excluding the current episode of infection. Such treatment is a risk factor for drug-resistant *Streptococcus pneumoniae* and possibly for infection with gram-negative bacilli. Depending on the class of antibiotics recently given, one or another of the suggested options may be selected. Recent use of a fluoroquinolone should dictate selection of a nonfluoroquinolone regimen, and vice versa.

<sup>c</sup>Moxifloxacin, gatifloxacin, levofloxacin, or gemifloxacin (oral).

<sup>d</sup>Azithromycin or clarithromycin.

<sup>e</sup>High-dose amoxicillin, high-dose amoxicillin-clavulanate, cefpodoxime, cefprozil, or cefuroxime.

<sup>f</sup>Cefotaxime, ceftriaxone, ampicillin-sulbactam, or ertapenem; ertapenem was recently approved for such use (in once-daily parenteral treatment) but little experience is available.

<sup>g</sup>The antipseudomonal agents chosen reflect this concern. Risk factors for *Pseudomonas* infection include severe structural lung disease (e.g., bronchiectasis), and recent antibiotic therapy or stay in hospital (especially in the ICU). For patients with CAP in the ICU, coverage for *Streptococcus pneumoniae* and *Legionella* species must always be assured. Piperacillin-tazobactam, imipenem, meropenem, and ceftipime are excellent  $\beta$ -lactams and are adequate for most *S. pneumoniae* and *Haemophilus influenzae* infections. They may be preferred when there is concern for relatively unusual CAP pathogens, such as *Pseudomonas aeruginosa*, *Klebsiella* species, and other gram-negative bacteria.

<sup>h</sup>Piperacillin, piperacillin-tazobactam, imipenem, meropenem, or ceftipime.

Data from Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007;44:S27-S72.

- Important therapeutic adjuncts include adequate hydration (by IV route if necessary), optimal nutritional support, and fever control.
- The treatment of bacterial pneumonia initially involves the empiric use of a relatively broad-spectrum antibiotic (or antibiotics) effective against probable pathogens after appropriate cultures and specimens for laboratory evaluation have been obtained. Therapy should be narrowed to cover specific pathogens once the results of cultures are known.
- Appropriate empiric choices for the treatment of bacterial pneumonias relative to a patient's underlying disease are shown in Table 43-6 for adults and Table 43-7 for children. Dosages for antibiotics to treat pneumonia are provided in Table 43-8.
- Antibiotic concentrations in respiratory secretions in excess of the pathogen minimum inhibitory concentration (MIC) are necessary for successful treatment of pulmonary infections.
- For treatment of bacterial pneumonia with concentration-independent antimicrobials (e.g.,  $\beta$ -lactams and carbapenems), a plasma drug concentration exceeding the pathogen MIC for more than 50% of the dosing interval correlates with bacteriologic cure. For concentration-dependent antimicrobials (e.g., aminoglycosides and fluoroquinolones) a peak drug concentration to pathogen MIC ratio  $>8$  to  $10$  or a ratio of pathogen MIC to antibiotic area under the curve  $>25$  to  $40$  for gram-positive pathogens and  $>100$  for gram-negative pathogens correlates with bacteriologic cure.
- Drugs recommended for empiric treatment of community-acquired pneumonia are presented in Table 43-9.
- The benefit of antibiotic aerosols or direct endotracheal instillation has not been consistently demonstrated.

## EVALUATION OF THERAPEUTIC OUTCOMES

- With community-acquired pneumonia, time for resolution of cough, sputum production, and presence of constitutional symptoms (e.g., malaise, nausea or vomiting, lethargy) should be assessed. Progress should be noted in the first 2 days, with complete resolution in 5 to 7 days.
- With nosocomial pneumonia, the above parameters should be assessed along with white blood cell counts, chest radiograph, and blood gas determinations.

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*See Chap. 111, Lower Respiratory Tract Infections, authored by Mark L. Glover and Michael D. Reed, for a more detailed discussion of this topic.*

## OTITIS MEDIA

## DEFINITION

- Otitis media is an inflammation of the middle ear. Acute otitis media involves the rapid onset of signs and symptoms of inflammation in the middle ear that manifests clinically as one or more of the following: otalgia (denoted by pulling of the ear in some infants), hearing loss, fever, or irritability. Otitis media with effusion (accumulation of liquid in the middle ear cavity) differs from acute otitis media in that signs and symptoms of an acute infection are absent.
- Otitis media is most common in infants and children.
- Risk factors contributing to increased incidence of otitis media include the winter season, attendance at a daycare center, non-breast-feeding in infants, aboriginal or Inuit origin, early age at first infection, and nasopharyngeal colonization with middle ear pathogens.

## PATHOPHYSIOLOGY

- Acute bacterial otitis media usually follows a viral upper respiratory tract infection that causes eustachian tube dysfunction and mucosal swelling in the middle ear.
- *Streptococcus pneumoniae* is the most common cause of acute otitis media (20% to 35%). Nontypable strains of *Haemophilus influenzae* and *Moraxella catarrhalis* are each responsible for 20% to 30% and 20% of cases, respectively. In 44% of cases, a viral etiology is found with or without concomitant bacteria.
- *S. pneumoniae* isolates are often intermediate resistant to penicillin (8% to 34%) and some are highly penicillin resistant (12% to 21%). Penicillin-resistant isolates are often resistant to multiple antibiotics.  $\beta$ -Lactam resistance occurs in about 23% to 35% of *H. influenzae* and in up to 100% of *M. catarrhalis*.

## CLINICAL PRESENTATION

- Acute otitis media presents as an acute onset of signs and symptoms of middle ear infection such as otalgia, irritability, and tugging on the ear, accompanied by signs such as a gray, bulging, nonmotile tympanic membrane. These often follow cold symptoms of runny nose, nasal congestion, or cough (Table 44-1).
- Resolution of acute otitis media occurs over 1 week. Pain and fever tend to resolve over 2 to 3 days, with most children becoming asymptomatic at 7 days. Effusions resolve slowly, 90% have disappeared by 3 months.

## DESIRED OUTCOME

- The goals of treatment include reduction in signs and symptoms, eradication of infection, and prevention of complications. Avoidance of unnecessary antibiotic use is another goal in view of *S. pneumoniae*.

**TABLE 44-1** Clinical Presentation of Acute Otitis Media**General**

The acute onset of signs and symptoms of middle ear infection following cold symptoms of runny nose, nasal congestion, or cough.

**Signs and symptoms**

Pain that can be severe (>75% of patients).

Children may be irritable, tug on the involved ear, and have difficulty sleeping.

Fever is present in less than 25% of patients and, when present, is more often in younger children.

Examination shows a discolored, thickened, bulging eardrum.

Pneumatic otoscopy or tympanometry demonstrates an immobile eardrum; 50% of cases are bilateral.

Draining middle ear fluid occurs (<3% of patients) that usually reveals a bacterial etiology.

**Laboratory tests**

Gram stain, culture, and sensitivities of draining fluid or aspirated fluid if tympanocentesis is performed.

**TREATMENT**

- Antimicrobial therapy is used to treat otitis media; however, a high percentage of children will be cured with symptomatic treatment alone. Antibiotic use reduces the duration of symptoms by about 1 day.
- Delayed antibiotic treatment (48 to 72 hours) may be considered in children 6 months to 2 years of age if symptoms are not severe, as it decreases antibiotic adverse effects and minimizes bacterial resistance.
- It is difficult to identify who will benefit from antimicrobial therapy. With or without treatment, about 60% of children who have acute otitis media are symptom-free within 24 hours.
- **Acetaminophen** or a nonsteroidal antiinflammatory agent, such as **ibuprofen**, can be used to relieve pain and malaise in acute otitis media. Decongestants, antihistamines, topical corticosteroids, or expectorants have not been proven effective for acute otitis media.
- Surgical insertion of tympanostomy tubes (T tubes) is an effective method for the prevention of recurrent otitis media.
- Amoxicillin is the drug of choice for acute otitis media. High-dose amoxicillin (80 to 90 mg/kg/day) is recommended. Treatment recommendations for acute otitis media are found in Table 44-2 and evidence-based recommendations are found in Table 44-3.
- If treatment failure occurs with amoxicillin, an agent should be chosen with activity against  $\beta$ -lactamase-producing *H. influenzae* and *M. catarrhalis* as well as drug-resistant *S. pneumoniae* (such as high-dose amoxicillin-clavulanate (recommended), or, cefuroxime, cefdinir, cefpodoxime, cefprozil, or intramuscular ceftriaxone).
- A metaanalysis reported no difference in cure rates with short (less than 7 days) and usual durations (at least 7 days) of antibiotic therapy in children. Five to 7 days of therapy may be used in children at least 6 years old who have mild to moderate acute otitis media.

**Antibiotic Prophylaxis of Recurrent Infections**

- Recurrent otitis media is defined as at least three episodes in 6 months or at least four episodes in 12 months. Recurrent infections are of concern because patients younger than 3 years of age are at high risk for hearing loss

**TABLE 44-2** Acute Otitis Media Treatment Recommendations

First Line	Penicillin Allergy	Treatment Failure
Amoxicillin high dose 80–90 mg/kg/day divided twice daily	Non-type I: Cefdinir 14 mg/kg/day once or twice daily Cefuroxime 30 mg/kg/day divided twice daily Cefpodoxime 10 mg/kg/day once daily Cefprozil 30 mg/kg/day divided twice daily	Amoxicillin-clavulanate <sup>d</sup>
	Type I: Azithromycin 10 mg/kg/day 1, then 5 mg/kg/day for days 2–5 Clarithromycin 15 mg/kg/day divided twice daily	Ceftriaxone 50 mg/kg/day IM/IV for 3 days
If severe symptoms (severe otalgia and temperature above 39°C [102.2°F])		Alternatives: Clindamycin 30–40 mg/kg/day in 3 divided doses
Amoxicillin-clavulanate <sup>d</sup>		Tympanocentesis

<sup>d</sup>Amoxicillin component 80–90 mg/kg/day divided twice daily; clavulanate component 6.4 mg/kg/day. Amoxicillin-clavulanate 90:6.4 or 14:1 ratio is available in the United States; 7:1 ratio is available in Canada (use amoxicillin 45 mg/kg for one dose, amoxicillin 45 mg/kg with clavulanate 6.4 mg/kg for second dose).

*American Academy of Pediatrics and American Academy of Family Physicians. Diagnosis and management of acute otitis media. Pediatrics 2004;113(5):1451–1465.*

and language and learning disabilities. Data from studies generally do not favor prophylaxis.

- Vaccination against influenza and pneumococcus may decrease risk of acute otitis media, especially in those with recurrent episodes. Immunization with the influenza vaccine reduces the incidence of acute otitis media by 36%.

**TABLE 44-3** Evidence-Based Principles for the Treatment of Acute Otitis Media

Recommendations	Rating
Properly diagnosed acute otitis media should be treated with antibiotics.	AI
Delayed therapy (observation) may be an option in nonsevere cases.	BI
Antimicrobial resistance should be considered before choosing an antibiotic.	AII-1
High-dose amoxicillin (80–90 mg/kg/day) is first line for uncomplicated infection.	AI-II-2
Short-course therapy may be considered in some instances.	AI
Ten-day courses are recommended for children older than age 2 years and in recurrent otitis media, or otitis media with perforated tympanic membrane.	AI-AIII
When episodes of acute otitis media are frequent, preventive measures are recommended, including handwashing and limiting exposure to daycare, pacifiers, and second-hand smoke.	BII-BIII
Influenza vaccine is recommended in children with chronic medical conditions.	AI
Pneumococcal conjugate vaccine is recommended for children ages 2 months to 2 years and in those with high-risk conditions and older than age 2.	AI

**Rating System:**

*Strength:* A, good evidence; B, fair evidence; C, conflicting evidence; D, evidence against; I, insufficient evidence.

*Level of evidence:* I, randomized controlled trials; II-1, controlled trials not randomized; II-2, cohort or case control studies; II-3, dramatic results from uncontrolled experiments; III, expert opinion.

## PHARYNGITIS

- Pharyngitis is an acute infection of the oropharynx or nasopharynx that results in 1% to 2% of all outpatient visits. While viral causes are most common, Group A  $\beta$ -hemolytic *Streptococcus*, or *Streptococcus pyogenes*, is the primary bacterial cause.
- Viruses (such as rhinovirus, coronavirus, and adenovirus) cause most of the cases of acute pharyngitis. A bacterial etiology for acute pharyngitis is far less likely. Of all of the bacterial causes, Group A *Streptococcus* is the most common (15% to 30% of persons of all ages with pharyngitis), and it is the only commonly occurring form of acute pharyngitis for which antimicrobial therapy is indicated.
- Nonsuppurative complications such as acute rheumatic fever, acute glomerulonephritis, and reactive arthritis may occur as a result of pharyngitis with Group A *Streptococcus*.

## CLINICAL PRESENTATION

- The incubation period is 2 to 5 days, and the illness often occurs in clusters. The clinical presentation of Group A streptococcal pharyngitis is presented in Table 44-4.
- Guidelines from the Infectious Disease Society of America, American Academy of Pediatrics, and the American Heart Association suggest that testing for Group A *Streptococcus* be done in all patients with signs and symptoms. Only those with a positive test for Group A *Streptococcus* require antibiotic treatment.

## TREATMENT

- The goals of treatment of pharyngitis are to improve clinical signs and symptoms, minimize adverse drug reactions, prevent transmission to close

**TABLE 44-4** Clinical Presentation and Diagnosis of Group A Streptococcal Pharyngitis

### General

A sore throat of sudden onset that is mostly self-limited.

Fever and constitutional symptoms resolving in about 3–5 days.

Clinical signs and symptoms are similar for viral causes as well as nonstreptococcal bacterial causes.

### Signs and symptoms

Sore throat.

Pain on swallowing.

Fever.

Headache, nausea, vomiting, and abdominal pain (especially children).

Erythema/inflammation of the tonsils and pharynx with or without patchy exudates.

Enlarged, tender lymph nodes.

Red swollen uvula, petechiae on the soft palate, and a scarlatiniform rash.

Several symptoms that are not suggestive of Group A *Streptococcus* are cough, conjunctivitis, coryza, and diarrhea.

### Laboratory tests

Throat swab and culture or rapid antigen detection testing.

- contacts, and prevent acute rheumatic fever and suppurative complications such as peritonsillar abscess, cervical lymphadenitis, and mastoiditis.
- Antimicrobial therapy should be limited to those who have clinical and epidemiologic features of Group A streptococcal pharyngitis with a positive laboratory test.
  - As pain is often the primary reason for visiting a physician, emphasis on analgesics such as acetaminophen and nonsteroidal antiinflammatory drugs to aid in pain relief is strongly recommended. However, acetaminophen is a better option because there is some concern that nonsteroidal antiinflammatory drugs may increase the risk for necrotizing fasciitis or toxic shock syndrome. Either systemic or topical analgesics can be used, as well as antipyretics and other supportive care including rest, fluids, lozenges, and saltwater gargles.
  - Antimicrobial treatment should be limited to those who have clinical and epidemiologic features of Group A streptococcal pharyngitis with a positive laboratory test. **Penicillin** is the drug of choice in the treatment of Group A streptococcal pharyngitis (Table 44-5). Table 44-6 presents dosing guidelines for recurrent infections. Table 44-7 presents evidence-based principles for diagnosis of Group A *Streptococcus* pharyngitis.
  - In patients allergic to penicillin, a macrolide such as **erythromycin** or a first-generation cephalosporin such as **cephalexin** (if the reaction is non-immunoglobulin E–mediated hypersensitivity) can be used. Newer macrolides such as azithromycin and clarithromycin are as effective as erythromycin and cause fewer GI adverse effects.
  - If patients are unable to take oral medications, intramuscular **benzathine penicillin** can be given although it is painful and no longer available in Canada.

**TABLE 44-5** Dosing Guidelines for Pharyngitis

Drug	Adult Dosage	Pediatric Dosage	Duration
Penicillin VK	250 mg three to four times daily or 500 mg twice daily	50 mg/kg/day divided in three doses	10 days
Penicillin benzathine	1.2 million units intramuscularly	0.6 million units for under 27 kg (50,000 units/kg)	One dose
Penicillin G procaine and benzathine mixture	Not recommended in adolescents and adults	1.2 million units (benzathine 0.9 million units, procaine 0.3 million units)	One dose
Amoxicillin	500 mg three times daily	40–50 mg/kg/day divided in three doses	10 days
Erythromycin			10 days
Estate	20–40 mg/kg/day divided two to four times daily (maximum: 1 g/day)	Same as adults	–
Stearate	1 g daily divided two to four times daily (adolescents, adults)	–	–
Ethylsuccinate	40 mg/kg/day divided two to four times daily (maximum: 1 g/day)	Same as adults	–
Cephalexin	250–500 mg orally four times daily	25–50 mg/kg/day divided in four doses	10 days

**TABLE 44-6** Antibiotics and Dosing for Recurrent Episodes of Pharyngitis

Drug	Adult Dosage	Pediatric Dosage
Clindamycin	600 mg orally divided in two to four doses	20 mg/kg/day in three divided doses (maximum: 1.8 g/day)
Amoxicillin-clavulanate	500 mg twice daily	40 mg/kg/day in three divided doses
Penicillin benzathine	1.2 million units intramuscularly for one dose	0.6 million units for under 27 kg (50,000 units/kg)
Penicillin benzathine with rifampin	As above Rifampin 20 mg/kg/day orally in two divided doses × last 4 days of treatment with penicillin	As above Rifampin dose same as adults

- The duration of therapy for Group A streptococcal pharyngitis is 10 days to maximize bacterial eradication.

## EVALUATION OF THERAPEUTIC OUTCOMES

- Most cases of pharyngitis are self-limited; however, antimicrobial therapy will hasten resolution when given early to proven cases of group A *Streptococcus*. Symptoms generally resolve by 3 to 4 days even without therapy. Children should be kept home from daycare or school until afebrile and for the first 24 hours after antimicrobial treatment is initiated,

**TABLE 44-7** Evidence-Based Principles for Diagnosis of Group A *Streptococcus*

Recommendations	Level
Selective use of diagnostic testing in only those with clinical features suggestive of Group A <i>Streptococcus</i> will increase the proportion of positive tests as well as results of those truly infected, not carriers.	A-II
Clinical diagnosis cannot be made with certainty even by the most experienced clinician; bacteriologic confirmation is required.	A-II
Throat culture remains the diagnostic standard, with a sensitivity of 90%–95% for detection of Group A <i>Streptococcus</i> if done correctly.	A-II
Rapid identification and treatment of patients with disease can reduce transmission, allow patients to return to work or school earlier, and reduce the acute morbidity of the disease.	A-II
The majority of rapid antigen-detection tests available have a specificity >95% (minimizes overprescription to those without disease), and a sensitivity of 80–90%, compared to culture.	A-II
Early initiation of antimicrobial therapy results in faster resolution of signs and symptoms. Delays in therapy (if awaiting cultures) can be made safely for up to 9 days after symptom onset and still prevent major complications such as rheumatic fever.	A-I

### Rating:

Strength of recommendation—A to E

Evidence to support use: A, good; B, moderate; C, poor

Evidence against use: D, moderate; E, good

Quality of evidence—I, II, or III

I: at least 1 randomized controlled trial

II: at least 1 well-designed clinical trial, not randomized, or a cohort or case-controlled analytical study, or from multiple time series, or from dramatic results of an uncontrolled trial

III: opinions of respected authorities

Data from Bisno AL, Gerber MA, Gwaltney JM, et al. Practice guidelines for the diagnosis and management of group A streptococcal pharyngitis (IDSA guidelines) *Clin Infect Dis* 2002;35:113–125.

after which time transmission is unlikely. Follow-up testing is generally not necessary for index cases or in asymptomatic contacts of the index patient.

## SINUSITIS

- Sinusitis is an inflammation and/or infection of the paranasal sinus mucosa. The term *rhinosinusitis* is used by some specialists, because sinusitis typically also involves the nasal mucosa. The majority of these infections are viral in origin. It is important to differentiate between viral and bacterial sinusitis to aid in optimizing treatment decisions.
- Bacterial sinusitis can be categorized into acute and chronic disease. Acute disease lasts less than 30 days with complete resolution of symptoms. Chronic sinusitis is defined as episodes of inflammation lasting more than 3 months with persistence of respiratory symptoms.
- Acute bacterial sinusitis is most often caused by the same bacteria implicated in acute otitis media: *S. pneumoniae* and *H. influenzae*. These organisms are responsible for about 70% of bacterial causes of acute sinusitis in both adults and children. Chronic sinusitis can be polymicrobial, with an increased prevalence of anaerobes as well as less common pathogens including gram-negative bacilli and fungi.

## CLINICAL PRESENTATION

- The typical clinical presentation of bacterial sinusitis is presented in Table 44-8.

## TREATMENT

- The goals of treatment of acute sinusitis are the reduction in signs and symptoms, achieving and maintaining patency of the ostia, limiting anti-

**TABLE 44-8** Clinical Presentation and Diagnosis of Bacterial Sinusitis

### General

A nonspecific upper respiratory tract infection that persists beyond 7–14 days.

### Signs and symptoms

#### Acute

##### Adults:

Nasal discharge/congestion.

Maxillary tooth pain, facial or sinus pain that may radiate (unilateral in particular) as well as deterioration after initial improvement.

Severe or persistent (beyond 7 days) signs and symptoms are most likely bacterial and should be treated with antimicrobials.

##### Children:

Nasal discharge and cough for greater than 10–14 days or severe signs and symptoms such as temperature 39°C (102.2°F) or facial swelling or pain are indications for antimicrobial therapy.

#### Chronic

Symptoms are similar to those of acute sinusitis but more nonspecific.

Rhinorrhea is associated with acute exacerbations.

Chronic unproductive cough, laryngitis, and headache may occur.

Chronic/recurrent infections occur three to four times a year and are unresponsive to steam and decongestants.

**TABLE 44-9** Approach to Treatment of Acute Bacterial Sinusitis

Uncomplicated Sinusitis	Amoxicillin
Uncomplicated sinusitis, penicillin-allergic patient	Immediate-type hypersensitivity: Clarithromycin or azithromycin or trimethoprim-sulfamethoxazole or doxycycline or respiratory fluoroquinolone (levofloxacin or gatifloxacin). Nonimmediate-type hypersensitivity: $\beta$ -Lactamase-stable cephalosporin.
Treatment failure or prior antibiotic therapy in past 4–6 weeks	High-dose amoxicillin with clavulanate or $\beta$ -lactamase-stable cephalosporin. Second choice: respiratory fluoroquinolone.
High suspicion of penicillin-resistant <i>Streptococcus pneumoniae</i>	High-dose amoxicillin or clindamycin. Second choice: respiratory fluoroquinolone.

crobial treatment to those who may benefit, eradication of bacterial infection with appropriate antimicrobial therapy, minimizing the duration of illness, prevention of complications, and prevention of progression from acute disease to chronic disease.

- Approximately 65% of patients with acute sinusitis will recover spontaneously (these are likely patients with viral sinusitis).

**TABLE 44-10** Dosing Guidelines for Acute Bacterial Sinusitis

Drug	Adult Dosage	Pediatric Dosage
Amoxicillin	500 mg three times daily High dose: 1 g three times daily	Low dose: 40–50 mg/kg/day divided in three doses High dose: 80–100 mg/kg/day divided in three doses
Amoxicillin-clavulanate	500/125 mg three times daily High dose: 2 g/125 mg twice daily	40–50 mg/kg/day divided in three doses High dose: Can add 40–50 mg/kg/day amoxicillin
Cefuroxime	250–500 mg twice daily	15 mg/kg/day divided in two doses
Cefaclor	250–500 mg three times daily	20 mg/kg/day divided in three doses
Cefixime	200–400 mg twice daily	8 mg/kg/day in one dose or divided in two doses
Cefdinir	600 mg daily or divided in two doses	14 mg/kg/day in one dose or divided in two doses
Cefpodoxime	200 mg twice daily	10 mg/kg/day in two divided doses (maximum: 400 mg daily)
Cefprozil	250–500 mg twice daily	15–30 mg/kg/day divided in two doses
Doxycycline	100 mg every 12 hours	N/A
Trimethoprim-sulfamethoxazole	160/800 mg every 12 hours	6–8 mg/kg/day trimethoprim, 30–40 mg/kg/day sulfamethoxazole divided in two doses
Clindamycin	150–450 mg every 6 hours	30–40 mg/kg/day divided in three doses
Clarithromycin	250–500 mg twice daily	15 mg/kg/day divided in two doses
Azithromycin	500 mg day 1, then 250 mg/day for days 2–5	10 mg/kg day 1, then 5 mg/kg/day for days 2–5
Levofloxacin	500 mg daily	N/A
Telithromycin	800 mg daily for 5 days	N/A
Ceftriaxone	1 g daily	50–75 mg/kg/day divided every 12–24 hours

N/A, not applicable.

- Nasal decongestant sprays such as **phenylephrine** and **oxymetazoline** that reduce inflammation by vasoconstriction are often used in sinusitis. Use should be limited to the recommended duration of the product to prevent rebound congestion. Oral decongestants may also aid in nasal or sinus patency. To reduce mucociliary function, irrigation of the nasal cavity with saline and steam inhalation may be used to increase mucosal moisture, and mucolytics (e.g., guaifenesin) may be used to decrease the viscosity of nasal secretions. Antihistamines should not be used for acute bacterial sinusitis in view of their anticholinergic effects that can dry mucosa and disturb clearance of mucosal secretions.
- Antimicrobial therapy is superior to placebo in reducing or eliminating symptoms, although the benefit is small.
- **Amoxicillin** is first-line treatment for acute bacterial sinusitis. It is cost effective in acute uncomplicated disease, and initial use of newer broad-spectrum agents is not justified. The approach to treating acute bacterial sinusitis is given in Table 44-9. Dosing guidelines are given in Table 44-10.
- The current recommendations are 10 to 14 days, or at least 7 days, of antimicrobial therapy after signs and symptoms are under control.

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*See Chap. 112, Upper Respiratory Tract Infections, authored by Yasmin Khaliq, Sarah Forgie, and George Zhanel, for a more detailed discussion of this topic.*

## DEFINITIONS

- Definitions of terms related to sepsis are given in Table 45-1. Physiologically similar systemic inflammatory response syndrome can be seen even in the absence of identifiable infection.

## PATHOPHYSIOLOGY

- The sites of infections that most frequently led to sepsis were the respiratory tract (21% to 68%), urinary tract (14% to 18%), and intraabdominal space (14% to 22%). Sepsis may be caused by gram-negative (38% of sepsis) or gram-positive bacteria (40%), as well as by fungi (17%) or other microorganisms.
- *Escherichia coli* and *Pseudomonas aeruginosa* are the most commonly isolated gram-negative pathogens in sepsis. Other common gram-negative pathogens include *Klebsiella* spp., *Serratia* spp., *Enterobacter* spp., and *Proteus* spp. *P. aeruginosa* is the most frequent cause of sepsis fatality. Common gram-positive pathogens include *Staphylococcus aureus*, *Streptococcus pneumoniae*, coagulase-negative staphylococci, and *Enterococcus* species.
- *Candida* species (particularly *Candida albicans*) are a common cause of sepsis in hospitalized patients.
- The pathophysiologic focus of gram-negative sepsis has been on the lipopolysaccharide (endotoxin) component of the gram-negative cell wall.
- Lipid A is a part of the endotoxin molecule from the gram-negative bacterial cell wall that is highly immunoreactive and is responsible for most of the toxic effects. Endotoxin first associates with a protein called lipopolysaccharide-binding protein in plasma. This complex then engages a specific receptor (CD14) on the surface of the macrophage, which activates it and causes release of inflammatory mediators.
- Sepsis involves a complex interaction of proinflammatory (e.g., tumor necrosis factor- $\alpha$  [TNF- $\alpha$ ]; interleukin [IL]-1, IL-6) and antiinflammatory mediators (e.g., IL-1 receptor antagonist, IL-4, and IL-10). IL-8, platelet-activating factor, and a variety of prostaglandins, leukotrienes, and thromboxanes are also important.
- TNF- $\alpha$  is considered the primary mediator of sepsis, and concentrations are elevated early in the inflammatory response during sepsis, and there is a correlation with severity of sepsis. TNF- $\alpha$  release leads to activation of other cytokines associated with cellular damage and it stimulates release of arachidonic acid metabolites that contribute to endothelial cell damage. IL-6 is a more consistent predictor of sepsis as it remains elevated for longer periods of time than does TNF- $\alpha$ .
- Antiinflammatory mediators including IL-1 receptor antagonist, IL-4, and IL-10 are also produced in sepsis and inhibit production of proinflammatory cytokines. The net effect can vary depending on the state of activation of the target cell, and the ability of the target cell to release mediators that

**TABLE 45-1** Definitions Related to Sepsis

Condition	Definition
Bacteremia (fungemia) Infection	Presence of viable bacteria (fungi) in the bloodstream. Inflammatory response to invasion of normally sterile host tissue by the microorganisms.
Systemic inflammatory response syndrome	Systemic inflammatory response to a variety of clinical insults that can be infection, but can be noninfectious etiology. The response is manifested by two or more of the following conditions: Temperature $>38^{\circ}\text{C}$ ( $100.4^{\circ}\text{F}$ ) or $<36^{\circ}\text{C}$ ( $96.8^{\circ}\text{F}$ ); heart rate $>90$ beats/min; respiratory rate $>20$ breaths/min or $\text{PaCO}_2 <32$ torr; white blood cell count $>12,000$ cells/ $\text{mm}^3$ , $<4,000$ cells/ $\text{mm}^3$ , or $>10\%$ immature (band) forms.
Sepsis	Systemic inflammatory response syndrome secondary to infection.
Severe sepsis	Sepsis associated with organ dysfunction, hypoperfusion, or hypotension. Hypoperfusion and perfusion abnormalities may include, but are not limited to, lactic acidosis, oliguria, or acute alteration in mental status.
Septic shock	Sepsis with hypotension, despite fluid resuscitation, along with the presence of perfusion abnormalities. Patients who are on inotropic or vasopressor agents may not be hypotensive at the time perfusion abnormalities are measured.
Multiple-organ dysfunction syndrome	Presence of altered organ function requiring intervention to maintain homeostasis.
Compensatory antiinflamma- tory response syndrome	Compensatory physiologic response to systemic inflammatory response syndrome that is considered secondary to the actions of antiinflammatory cytokine mediators.

can augment or inhibit the primary mediator. An excess of proinflammatory mediators can cause a systemic inflammatory response syndrome, followed by a compensatory antiinflammatory response syndrome.

- A primary mechanism of injury with sepsis is through endothelial cells. With inflammation, endothelial cells allow circulating cells (e.g., granulocytes) and plasma constituents to enter inflamed tissues, which may result in organ damage.
- Endotoxin activates complement, which then augments the inflammatory response through stimulation of leukocyte chemotaxis, phagocytosis and lysosomal enzyme release, increased platelet adhesion and aggregation, and production of toxic superoxide radicals.
- Proinflammatory mechanisms in sepsis are also procoagulant and antifibrinolytic. Levels of activated protein C, a fibrinolytic and antiinflammatory substance, are decreased in sepsis.
- Shock is the most ominous complication associated with gram-negative sepsis and causes death in about one-half of patients. Other important complications of sepsis are disseminated intravascular coagulation, which occurs in up to 50% of patients with gram-negative sepsis. Disseminated intravascular coagulation causes activation of the coagulation cascade and inhibition of fibrinolysis, which can result in coagulopathy and microthrombosis. Acute respiratory distress syndrome is a common complication of sepsis.
- The hallmark of the hemodynamic effect of sepsis is the hyperdynamic state characterized by high cardiac output and an abnormally low systemic vascular resistance.

**TABLE 45-2** Signs and Symptoms Associated with Sepsis

Early Sepsis	Late Sepsis
Fever or hypothermia	Lactic acidosis
Rigors, chills	Oliguria
Tachycardia	Leukopenia
Tachypnea	DIC
Nausea, vomiting	Myocardial depression
Hyperglycemia	Pulmonary edema
Myalgias	Hypotension (shock)
Lethargy, malaise	Hypoglycemia
Proteinuria	Azotemia
Hypoxia	Thrombocytopenia
Leukocytosis	ARDS
Hyperbilirubinemia	Gastrointestinal hemorrhage
	Coma

ARDS, acute respiratory distress syndrome; DIC, disseminated intravascular coagulation.

## CLINICAL PRESENTATION

- The signs and symptoms of early sepsis are quite variable and include fever, chills, and a change in mental status with lethargy and malaise. Hypothermia may occur instead of fever. Tachypnea and tachycardia are also evident. White blood cell count is usually elevated, as may be blood sugar. The patient may be hypoxic. Signs and symptoms of early and late sepsis are found in Table 45-2.
- Progression of uncontrolled sepsis leads to evidence of organ dysfunction, which may include oliguria, hemodynamic instability with hypotension or shock, lactic acidosis, hyperglycemia or hypoglycemia, possibly leukopenia, disseminated intravascular coagulation, thrombocytopenia, acute respiratory distress syndrome, GI hemorrhage, or coma.

## TREATMENT

- The primary goals for treatment of sepsis are as follows:
  1. Timely diagnosis and identification of the pathogen
  2. Rapid elimination of the source of infection
  3. Early initiation of aggressive antimicrobial therapy
  4. Interruption of the pathogenic sequence leading to septic shock
  5. Avoidance of organ failure
- An important overall approach for treatment of sepsis is “goal-directed” therapy. Mortality can be reduced by early placement and use of a central venous catheter, increased fluid volume administration, dobutamine therapy if needed, and red blood cell transfusion, to achieve specific physiologic goals in the first 6 hours. Evidence-based treatment recommendations for sepsis and septic shock from the *Surviving Sepsis* campaign are presented in Table 45-3.

**TABLE 45-3** Evidence-Based Treatment Recommendations for Sepsis and Septic Shock

Recommendations	Recommendation Grades <sup>a</sup>
<b>Antibiotic therapy</b>	
Use a broad initial empirical antibiotic regimen against all likely pathogens	D
There is no evidence of higher efficacy with combination therapy	E
<b>Fluid therapy</b>	
Immediate initial resuscitation of a patient in severe sepsis or sepsis-induced tissue hypoperfusion should be instituted to achieve central venous pressure 8–12 mm Hg, mean arterial pressure $\geq 65$ mm Hg, urine output $\geq 0.5$ mL/kg/hour, central venous or mixed venous oxygen saturation $\geq 70\%$	B
There is no clinical outcome difference between colloids and crystalloids	C
<b>Vasopressors</b>	
The advantages of norepinephrine and dopamine over epinephrine (potential tachycardia, possibly disadvantageous effects on splanchnic circulation) and phenylephrine (decrease in stroke volume) are not supported by the literature.	D
There is no support of low doses of dopamine to maintain or improve renal function	B
<b>Inotropic therapy</b>	
Dobutamine as the first-choice inotrope to increase cardiac output combined with norepinephrine in the presence of low blood pressure is not supported in the literature.	E
<b>Glucose control</b>	
There is minimal support for maintaining blood glucose $<150$ mg/dL to improve survival	D
<b>Steroids</b>	
The value of intravenous hydrocortisone 200–300 mg/day for 7 days in three or four divided doses in patients with septic shock is not clear.	C
The use of fludrocortisone 50 mcg orally per day is not supported	E
<b>Drotrecogin</b>	
Drotrecogin is effective in patients at high risk of death (Acute Physiology and Chronic Health Evaluation II $>25$ , sepsis-induced multiple organ failure, septic shock, or sepsis-induced acute respiratory distress syndrome)	B
<b>Deep vein thrombosis prophylaxis</b>	
Either low-dose unfractionated heparin or low-molecular weight heparin are effective in preventing deep vein thrombosis	A
<b>Stress ulcer prophylaxis</b>	
H <sub>2</sub> receptor inhibitors are more efficacious than sucralfate	A

<sup>a</sup>Grading of recommendations: A, B, C, D, E = at least two level I investigations, one level I investigation, level II investigations, at least one level III investigation, and level IV or V evidence to support recommendation, respectively. Quality of evidence: I = Large, randomized trials with clear-cut results; low risk of false-positive (alpha) error or false-negative (beta) error. II = Small, randomized trials with uncertain results; moderate-to-high risk of false-positive and/or false-negative error. III = Nonrandomized, contemporaneous controls. IV = Nonrandomized, historical controls and expert opinion. V = Case series, uncontrolled studies, and expert opinion. Data from Dellinger RP, Carlet JM, Masur H, et al. *Surviving sepsis campaign guidelines for management of severe sepsis and septic shock*. *Crit Care Med* 2004;32:858–873.

## ANTIMICROBIAL THERAPY

- Aggressive, early antimicrobial therapy is critical in the management of septic patients. The regimen selected should be based on the suspected site of infection, likely pathogens, and the local antibiotic susceptibility patterns, whether the organism was acquired from the community or a hospital, and the patient's immune status.
- The antibiotics that may be used for empiric treatment of sepsis are listed in Table 45-4. In the nonneutropenic patient with urinary tract infection, fluoroquinolones are generally recommended.

**TABLE 45-4** Empiric Antimicrobial Regimens in Sepsis

Infection (Site or Type)	Antimicrobial Regimen		
	Community-Acquired	Hospital-Acquired	
Urinary tract	Ciprofloxacin or levofloxacin	Ciprofloxacin, levofloxacin or ceftazidime, ceftriaxone	± gentamicin
Respiratory tract	Newer fluoroquinolone <sup>d</sup> or ceftriaxone + clarithromycin/azithromycin	Piperacillin, ceftazidime, or cefepime	+ gentamicin or ciprofloxacin
Intraabdominal	β-Lactamase inhibitor combo <sup>b</sup> or ciprofloxacin + metronidazole	Piperacillin/tazobactam or carbapenem	
Skin/soft tissue	Vancomycin or linezolid or daptomycin	β-Lactamase inhibitor combo <sup>b</sup> or clindamycin plus ciprofloxacin or carbapenem	
Catheter-related		Vancomycin	
Unknown		Piperacillin or ceftazidime/cefepime or imipenem/meropenem	+ gentamicin ± vancomycin

<sup>d</sup>Levofloxacin, moxifloxacin, gemifloxacin.

<sup>b</sup>Ampicillin/sulbactam, ticarcillin/clavulanic acid, piperacillin/tazobactam.

- If *P. aeruginosa* is suspected, or with sepsis from hospital-acquired infections, an antipseudomonal antibiotic, such as ceftazidime, is recommended.
- The antimicrobial regimen should be reassessed after 48 to 72 hours based on microbiological and clinical data.
- **Vancomycin** should be added whenever the risk of methicillin-resistant staphylococci is significant.
- The average duration of antimicrobial therapy in the normal host with sepsis is 10 to 14 days.
- Suspected systemic mycotic infection leading to sepsis in neutropenic and critically ill patients should be empirically treated with parenteral amphotericin B or caspofungin, especially if the patient is clinically unstable.

## HEMODYNAMIC SUPPORT

- Maintenance of adequate tissue oxygenation is important in the treatment of sepsis and is dependent on adequate perfusion and adequate oxygenation of the blood.
- Rapid fluid resuscitation is the best initial therapeutic intervention for treatment of hypotension in sepsis. The goal is to maximize cardiac output by increasing the left ventricular preload, which will ultimately restore tissue perfusion.
- Fluid administration should be titrated to clinical endpoints such as heart rate, urine output, blood pressure, and mental status. Isotonic crystalloids, such as 0.9% sodium chloride or lactated Ringer's solution, are commonly used for fluid resuscitation.
- Iso-oncotic colloid solutions (plasma and plasma protein fractions), such as 5% albumin and 6% hetastarch, offer the advantage of more rapid restoration of intravascular volume with less volume infused, but there is no significant clinical outcome differences compared with crystalloids.

**TABLE 45-5** Receptor Activity of Cardiovascular Agents Commonly Used in Septic Shock

Agent	$\alpha_1$	$\alpha_2$	$\beta_1$	$\beta_2$	Dopaminergic
Dopamine	++/+++	?	++++	++	++++
Dobutamine	+	+	++++	++	0
Norepinephrine	+++	+++	+++	+/++	0
Phenylephrine	++/+++	+	?	0	0
Epinephrine	++++	++++	++++	+++	0

$\alpha_1$ ,  $\alpha_1$ -adrenergic receptor;  $\alpha_2$ ,  $\alpha_2$ -adrenergic receptor;  $\beta_1$ ,  $\beta_1$ -adrenergic receptor;  $\beta_2$ ,  $\beta_2$ -adrenergic receptor; 0, no activity; +, maximal activity; ?, unknown activity.

Clinical outcome differences with the use of crystalloids or colloids have not been demonstrated, so crystalloids are generally recommended.

## INOTROPE AND VASOACTIVE DRUG SUPPORT

- When fluid resuscitation is insufficient to maintain tissue perfusion, the use of inotropes and vasoactive drugs is necessary. Selection and dosage are based on the pharmacologic properties of various catecholamines and how they influence hemodynamic parameters (Table 45-5).

### Suggested Protocol for the Use of Inotropes and Vasoactive Agents

- **Norepinephrine** is a potent  $\alpha$ -adrenergic agent (0.01 to 3 mcg/kg/min) that is useful as a vasopressor to restore adequate blood pressure after failure to restore adequate blood pressure and organ perfusion with appropriate fluid resuscitation.
- **Dopamine** in doses greater than 5 mcg/kg/min is used to support blood pressure and to increase cardiac index. Low dose dopamine (1 to 5 mcg/kg/min) is not effective to increase renal and mesenteric perfusion.
- **Dobutamine** (in doses of 2 to 20 mcg/kg/min) is an  $\alpha$ -adrenergic inotropic agent that many clinicians prefer for improving cardiac output and oxygen delivery. Dobutamine should be considered in severely septic patients with adequate filling pressures and blood pressure but low cardiac index.
- **Epinephrine**, in doses of 0.1 to 0.5 mcg/kg/min, increases cardiac index and produces peripheral vasoconstriction. It is reserved for patients who fail to respond to traditional therapies.
- Before administering vasoactive agents, aggressive appropriate fluid resuscitation should occur. Vasoactive agents should not be considered an acceptable alternative to volume resuscitation.
- Administration of activated protein C (**drotrecogin**) to promote fibrinolysis and associated antiinflammatory mechanisms may be beneficial in patients with an **APACHE II** (Acute Physiology and Chronic Health Evaluation II) score greater than 25. This agent reduced mortality in severe sepsis but poses an increased risk of serious bleeding.

See Chap. 123, *Sepsis and Septic Shock*, authored by S. Lena Kang-Birken and Joseph T. DiPiro, for a more detailed discussion of this topic.

## DEFINITION

- The spectrum of sexually transmitted diseases (STDs) includes the classic venereal diseases—gonorrhea, syphilis, chancroid, lymphogranuloma venereum, and granuloma inguinale—as well as a variety of other pathogens known to be spread by sexual contact (Table 46-1). Common clinical syndromes associated with STDs are listed in Table 46-2. The most current information on epidemiology, diagnosis, and treatment of STDs provided by the Centers for Disease Control and Prevention (CDC) can be found at <http://www.cdc.gov>.

## GONORRHEA

- *Neisseria gonorrhoeae* is a gram-negative diplococcus estimated to cause up to 600,000 infections per year in the United States. Humans are the only known host of this intracellular parasite.

## CLINICAL PRESENTATION

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- Infected individuals may be symptomatic or asymptomatic, have complicated or uncomplicated infections, and have infections involving several anatomic sites.
- The most common clinical features of gonococcal infections are presented in Table 46-3.
- Approximately 15% of women with gonorrhea develop pelvic inflammatory disease. Left untreated, pelvic inflammatory disease can be an indirect cause of infertility and ectopic pregnancies.
- In 0.5% to 3.0% of patients with gonorrhea, the gonococci invade the bloodstream and produce disseminated disease. The usual clinical manifestations of disseminated gonococcal infection are tender necrotic skin lesions, tenosynovitis, and monoarticular arthritis.

## DIAGNOSIS

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- Diagnosis of gonococcal infections can be made by gram-stained smears, culture (the most reliable method), or newer methods based on the detection of cellular components of the gonococcus (e.g., enzymes, antigens, DNA, or lipopolysaccharide) in clinical specimens.
- Although culture of infected fluids is not the most sensitive of diagnostic tests for gonorrhea, it is still the diagnostic test of choice because of the high specificity.
- Alternative methods of diagnosis include enzyme immunoassay, DNA probes, and nucleic acid amplification techniques.

**TABLE 46-1** Sexually Transmitted Diseases

Disease	Associated Pathogens
<b>Bacterial</b>	
Gonorrhea	<i>Neisseria gonorrhoeae</i>
Syphilis	<i>Treponema pallidum</i>
Chancroid	<i>Haemophilus ducreyi</i>
Granuloma inguinale	<i>Calymmatobacterium granulomatis</i>
Enteric disease	<i>Salmonella</i> spp., <i>Shigella</i> spp., <i>Campylobacter fetus</i>
<i>Campylobacter</i> infection	<i>C. jejuni</i>
Bacterial vaginosis	<i>Gardnerella vaginalis</i> , <i>Mycoplasma hominis</i> , <i>Bacteroides</i> spp., <i>Mobiluncus</i> spp.
Group B streptococcal infections	Group B <i>Streptococcus</i>
<b>Chlamydial</b>	
Nongonococcal urethritis	<i>Chlamydia trachomatis</i>
Lymphogranuloma venereum	<i>C. trachomatis</i> , type L
<b>Viral</b>	
Acquired immune deficiency syndrome	Human immunodeficiency virus
Herpes genitalis	Herpes simplex virus, types I and II
Viral hepatitis	Hepatitis A, B, C, and D viruses
Condylomata acuminata	Human papillomavirus
Molluscum contagiosum	Poxvirus
Cytomegalovirus infection	Cytomegalovirus
<b>Mycoplasmal</b>	
Nongonococcal urethritis	<i>Ureaplasma urealyticum</i>
<b>Protozoal</b>	
Trichomoniasis	<i>Trichomonas vaginalis</i>
Amebiasis	<i>Entamoeba histolytica</i>
Giardiasis	<i>Giardia lamblia</i>
<b>Fungal</b>	
Vaginal candidiasis	<i>Candida albicans</i>
<b>Parasitic</b>	
Scabies	<i>Sarcoptes scabiei</i>
Pediculosis pubis	<i>Phthirus pubis</i>
Enterobiasis	<i>Enterobius vermicularis</i>

## TREATMENT

- All currently recommended regimens are single-dose treatments with various oral or parenteral **cephalosporins** and **fluoroquinolones** (Table 46-4). **Ceftriaxone** is the only parenteral agent recommended by the CDC as a first-line agent for treatment of gonorrhea.
- Coexisting chlamydial infection, which is documented in up to 50% of women and 20% of men with gonorrhea, constitutes the major cause of postgonococcal urethritis, cervicitis, and salpingitis in patients treated for gonorrhea. As a result, concomitant treatment with **doxycycline** or **azithromycin** is recommended in all patients treated for gonorrhea. A single dose of azithromycin (2 g) is highly effective against chlamydia.
- Pregnant women infected with *N. gonorrhoeae* should be treated with either a **cephalosporin** or **spectinomycin**, because fluoroquinolones are contraindicated. **Azithromycin** or **amoxicillin** is the preferred treatment for presumed *Chlamydia trachomatis* infection.

**TABLE 46-2** Selected Syndromes Associated with Common Sexually Transmitted Pathogens

Syndrome	Commonly Implicated Pathogens	Common Clinical Manifestations <sup>a</sup>
Urethritis	<i>Chlamydia trachomatis</i> , herpes simplex virus, <i>Neisseria gonorrhoeae</i> , <i>Trichomonas vaginalis</i> , <i>Ureaplasma urealyticum</i>	Urethral discharge, dysuria
Epididymitis	<i>C. trachomatis</i> , <i>N. gonorrhoeae</i>	Scrotal pain, inguinal pain, flank pain, urethral discharge
Cervicitis/vulvovaginitis	<i>C. trachomatis</i> , <i>Gardnerella vaginalis</i> , herpes simplex virus, human papillomavirus, <i>N. gonorrhoeae</i> , <i>T. vaginalis</i>	Abnormal vaginal discharge, vulvar itching/irritation, dysuria, dyspareunia
Genital ulcers (painful)	<i>Haemophilus ducreyi</i> , herpes simplex virus	Usually multiple vesicular/pustular (herpes) or papular/pustular ( <i>H. ducreyi</i> ) lesions that may coalesce; painful, tender lymphadenopathy <sup>b</sup>
Genital ulcers (painless)	<i>Treponema pallidum</i>	Usually single papular lesion
Genital/anal warts	Human papillomavirus	Multiple lesions ranging in size from small papular warts to large exophytic condylomas
Pharyngitis	<i>C. trachomatis</i> (?), herpes simplex virus, <i>N. gonorrhoeae</i>	Symptoms of acute pharyngitis, cervical lymphadenopathy, fever <sup>c</sup>
Proctitis	<i>C. trachomatis</i> , herpes simplex virus, <i>N. gonorrhoeae</i> , <i>T. pallidum</i>	Constipation, anorectal discomfort, tenesmus, mucopurulent rectal discharge
Salpingitis	<i>C. trachomatis</i> , <i>N. gonorrhoeae</i>	Lower abdominal pain, purulent cervical or vaginal discharge, adnexal swelling, fever <sup>d</sup>

<sup>a</sup>For some syndromes, clinical manifestations may be minimal or absent.

<sup>b</sup>Recurrent herpes infection may manifest as a single lesion.

<sup>c</sup>Most cases of pharyngeal gonococcal infection are asymptomatic.

<sup>d</sup>Salpingitis increases the risk of subsequent ectopic pregnancy and infertility.

**TABLE 46-3** Presentation of Gonorrhea Infections

	<b>Males</b>	<b>Females</b>
General	Incubation period 1–14 days Symptom onset in 2–8 days	Incubation period 1–14 days Symptom onset in 10 days
Site of infection	Most common—urethra Others—rectum (usually due to rectal intercourse in men who have sex with men), oropharynx, eye	Most common—endocervical canal Others—urethra, rectum (usually due to perineal contamination), oropharynx, eye
Symptoms	May be asymptomatic or minimally symptomatic Urethral infection—dysuria and urinary frequency Anorectal infection—asymptomatic to severe rectal pain Pharyngeal infection asymptomatic to mild pharyngitis	May be asymptomatic or minimally symptomatic Endocervical infection—usually asymptomatic or mildly symptomatic Urethral infection—dysuria, urinary frequency Anorectal and pharyngeal infection—symptoms same as for men
Signs	Purulent urethral or rectal discharge can be scant to profuse Anorectal—pruritus, mucopurulent discharge, bleeding	Abnormal vaginal discharge or uterine bleeding; purulent urethral or rectal discharge can be scant to profuse
Complications	Rare (epididymitis, prostatitis, inguinal lymphadenopathy, urethral stricture)  Disseminated gonorrhea	Pelvic inflammatory disease and associated complications (i.e., ectopic pregnancy, infertility)  Disseminated gonorrhea (three times more common than in men)

- Treatment of gonorrhea during pregnancy is essential to prevent ophthalmia neonatorum. The CDC recommends that either **tetracycline** (1%) ophthalmic ointment or **erythromycin** (0.5%) ophthalmic ointment be instilled in each conjunctival sac immediately postpartum to prevent ophthalmia neonatorum.

## SYPHILIS

- The causative organism of syphilis is *Treponema pallidum*, a spirochete.
- Syphilis is usually acquired by sexual contact with infected mucous membranes or cutaneous lesions, although on rare occasions it can be acquired by nonsexual personal contact, accidental inoculation, or blood transfusion.

## CLINICAL PRESENTATION

- The clinical presentation of syphilis is varied, with progression through multiple stages possible in untreated or inadequately treated patients (Table 46-5).

### Primary Syphilis

- Primary syphilis is characterized by the appearance of a chancre on cutaneous or mucocutaneous tissue. Chancres persist only for 1 to 8 weeks before spontaneously disappearing.

**TABLE 46-4 Treatment of Gonorrhea**

Type of Infection	Recommended Regimens <sup>a</sup>	Alternative Regimens <sup>b</sup>
Uncomplicated infections of the cervix, urethra, and rectum in adults <sup>c,d</sup>	Ceftriaxone 125 mg IM once, <sup>e,f</sup> or cefixime 400 mg po once, <sup>f,g</sup> or ciprofloxacin 500 mg po once, <sup>e</sup> or ofloxacin 400 mg po once, <sup>e</sup> or levofloxacin 250 mg po once <i>plus</i> A treatment regimen for presumptive <i>C. trachomatis</i> coinfection if chlamydial infection has not been ruled out (see Table 121-8 in <i>Pharmacotherapy: A Pathophysiologic Approach</i> , seventh edition)	Spectinomycin 2 g IM once, or ceftizoxime 500 mg IM once, or cefotaxime 500 mg IM once, or cefoxitin 2 g IM once with probenecid 1 g po once, or gatifloxacin 400 mg po once, or lomefloxacin 400 mg po once, or norfloxacin 800 mg po once <i>plus</i> A treatment regimen for presumptive <i>C. trachomatis</i> coinfection if chlamydial infection has not been ruled out (see Table 121-8 in <i>Pharmacotherapy: A Pathophysiologic Approach</i> , seventh edition)
Gonococcal infections in pregnancy	Ceftriaxone 125 mg IM once, <sup>h,i</sup> or Cefixime 400 mg po once <i>plus</i> A recommended treatment regimen for presumptive <i>C. trachomatis</i> infection during pregnancy, <sup>i</sup> if chlamydial infection has not been ruled out (see Table 121-8 in <i>Pharmacotherapy: A Pathophysiologic Approach</i> , seventh edition)	Spectinomycin 2 g IM once, or ceftizoxime 500 mg IM once, or cefotaxime 500 mg IM once, or cefoxitin 2 g IM once with probenecid 1 g po once <i>plus</i> A recommended treatment regimen for presumptive <i>C. trachomatis</i> infection during pregnancy, <sup>i</sup> if chlamydial infection has not been ruled out (see Table 121-8 in <i>Pharmacotherapy: A Pathophysiologic Approach</i> , seventh edition)
Disseminated gonococcal infection in adults (>45 kg) <sup>ii,k,l</sup>	Ceftriaxone 1 g IM or IV every 24 hours <sup>l</sup>	Cefotaxime 1 g IV every 8 hours <sup>l</sup> or ceftizoxime 1 g IV every 8 hours, <sup>l</sup> or ciprofloxacin 400 mg IV every 12 hours, <sup>ll</sup> or ofloxacin 400 mg IV every 12 hours, <sup>ll</sup> or levofloxacin 250 mg IV every 24 hours, <sup>ll</sup> or spectinomycin 2 g IM every 12 hours <sup>l</sup> Spectinomycin 40 mg/kg IM once (not to exceed 2 g)
Uncomplicated infections of the cervix, urethra, and rectum in children (<45 kg)	Ceftriaxone 125 mg IM once <sup>m</sup>	

*(continued)*

**TABLE 46-4 Treatment of Gonorrhea (Continued)**

Type of Infection	Recommended Regimens <sup>a</sup>	Alternative Regimens <sup>b</sup>
Gonococcal conjunctivitis in adults	Ceftriaxone 1 g IM once <sup>d</sup>	
Ophthalmia neonatorum	Ceftriaxone 25–50 mg/kg IV or IM once (not to exceed 125 mg)	
Infants born to mothers with gonococcal infection (prophylaxis)	Erythromycin (0.5%) ophthalmic ointment in a single application <sup>e</sup> ; or Tetracycline (1%) ophthalmic ointment in a single application <sup>f</sup>	

CDC, Centers for Disease Control and Prevention; *C. trachomatis*, *Chlamydia trachomatis*; MSM, men who have sex with men.

<sup>a</sup>Recommendations are those of the CDC.

<sup>b</sup>A number of other antimicrobials have demonstrated efficacy in treating uncomplicated gonorrhea but are not included in the CDC guidelines.

<sup>c</sup>Treatment failures are usually caused by reinfection and necessitate patient education and sex-partner referral; additional treatment regimens for gonorrhea and chlamydia infections should be administered. Epididymitis should be treated for 10 days (see Table 121-8 in *Pharmacotherapy: A Pathophysiologic Approach*, seventh edition).

<sup>d</sup>Patients allergic to  $\beta$ -lactams should receive a quinolone. Persons unable to tolerate a  $\beta$ -lactam (penicillin or cephalosporin) or a quinolone should receive spectinomycin.

<sup>e</sup>Also recommended for the treatment of uncomplicated infections of the pharynx in combination with a treatment regimen for presumptive *C. trachomatis* infection, if chlamydial infection has not been ruled out.

<sup>f</sup>Fluoroquinolones are *not* recommended for treating infections in MSM or infections acquired in Hawaii, California, or other parts of the world where high-level resistance to fluoroquinolones is reported, or in heterosexuals with a history of recent foreign travel (including exposure from a partner with a history of recent foreign travel).

<sup>g</sup>In July 2002, Wyeth Pharmaceutical discontinued manufacturing cefixime; at the time of publication, Lupin, Ltd, which has FDA approval to market cefixime, had marketed only a suspension formulation of the drug and not the 400-mg tablet dosage form.

<sup>h</sup>Another recommended IM or po cephalosporin also can be used.

<sup>i</sup>The fluoroquinolones, doxycycline, and erythromycin ethylsuccinate are contraindicated during pregnancy.

<sup>j</sup>Patients treated with one of the recommended regimens should be treated with doxycycline or azithromycin for possible coexistent chlamydial infection.

<sup>k</sup>Patients with gonococcal meningitis should be treated for 10 to 14 days and those with endocarditis for at least 4 weeks with ceftriaxone 1–2 g IV every 12 hours.

<sup>l</sup>All treatment regimens should be continued for 24–48 hours after improvement begins; at this time therapy can be switched to one of the following oral regimens to complete a 7-day course of treatment: cefixime 400 mg po twice daily, or ciprofloxacin 500 mg po twice daily, or ofloxacin 400 mg po twice daily, or levofloxacin 500 mg po once daily; ciprofloxacin, ofloxacin, and levofloxacin are not recommended for treating infections in MSM or infections acquired in Hawaii, California, or other parts of the world where high-level resistance to fluoroquinolones is reported, or in heterosexuals with a history of recent foreign travel (including exposure from a partner with a history of recent foreign travel).

<sup>m</sup>Patients with bacteremia or arthritis should receive ceftriaxone 50 mg/kg (maximum 1 g) IM or IV once daily for 7 days.

<sup>n</sup>A single lavage of the infected eye should be considered.

<sup>o</sup>Efficacy in preventing chlamydial ophthalmia is unclear.

**TABLE 46-5** Presentation of Syphilis Infections**General**

Primary	Incubation period 10–90 days (mean, 21 days)
Secondary	Develops 2–8 weeks after initial infection in untreated or inadequately treated individuals
Latent	Develops 4–10 weeks after secondary stage in untreated or inadequately treated individuals
Tertiary	Develops in approximately 30% of untreated or inadequately treated individuals 10–30 years after initial infection

**Site of infection**

Primary	External genitalia, perianal region, mouth, and throat
Secondary	Multisystem involvement secondary to hematogenous and lymphatic spread
Latent	Potentially multisystem involvement (dormant)
Tertiary	CNS, heart, eyes, bones, and joints

**Signs and symptoms**

Primary	Single, painless, indurated lesion (chancre) that erodes, ulcerates, and eventually heals (typical); regional lymphadenopathy is common; multiple, painful, purulent lesions possible but uncommon
Secondary	Pruritic or nonpruritic rash, mucocutaneous lesions, flu-like symptoms, lymphadenopathy
Latent	Asymptomatic
Tertiary	Cardiovascular syphilis (aortitis or aortic insufficiency), neurosyphilis (meningitis, general paresis, dementia, tabes dorsalis, eighth cranial nerve deafness, blindness), gummatous lesions involving any organ or tissue

**Secondary Syphilis**

- The secondary stage of syphilis is characterized by a variety of mucocutaneous eruptions, resulting from widespread hematogenous and lymphatic spread of *T. pallidum*.
- Signs and symptoms of secondary syphilis disappear in 4 to 10 weeks; however, in untreated patients, lesions may recur at any time within 4 years.

**Latent Syphilis**

- Persons with a positive serologic test for syphilis but with no other evidence of disease have latent syphilis.
- Most untreated patients with latent syphilis have no further sequelae; however, approximately 25% to 30% progress to either neurosyphilis or late syphilis with clinical manifestations other than neurosyphilis.

**Tertiary Syphilis and Neurosyphilis**

- Forty percent of patients with primary or secondary syphilis exhibit CNS infection.

**DIAGNOSIS**

- Because *T. pallidum* is difficult to culture in vitro, diagnosis is based primarily on dark-field or direct fluorescent antibody microscopic examination of serous material from a suspected syphilitic lesion or on results from serologic testing.
- Serologic tests are the mainstay in the diagnosis of syphilis and are categorized as nontreponemal or treponemal. Commonly used nontreponemal tests include the Venereal Disease Research Laboratory slide test, the rapid plasma reagin card test, the unheated serum regain test, and the toluidine red unheated serum test.

- Treponemal tests are more sensitive than nontreponemal tests and are used to confirm the diagnosis (i.e., the fluorescent treponemal antibody absorption).

## TREATMENT

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- Treatment recommendations from the CDC for syphilis are presented in Table 46-6. Parenteral **penicillin G** is the treatment of choice for all stages of syphilis. Benzathine penicillin G is the only penicillin effective for single-dose therapy.
- Patients with abnormal cerebrospinal fluid findings should be treated as having neurosyphilis.
- For pregnant patients, penicillin is the treatment of choice at the dosage recommended for that particular stage of syphilis. To ensure treatment success and prevent transmission to the fetus, some experts advocate an additional intramuscular dose of benzathine penicillin G, 2.4 million units, 1 week after completion of the recommended regimen.
- The majority of patients treated for primary and secondary syphilis experience the Jarisch-Herxheimer reaction after treatment, characterized by flu-like symptoms such as transient headache, fever, chills, malaise, arthralgia, myalgia, tachypnea, peripheral vasodilation, and aggravation of syphilitic lesions.
- The Jarisch-Herxheimer reaction should not be confused with penicillin allergy. Most reactions can be managed symptomatically with analgesics, antipyretics, and rest.
- CDC recommendations for serologic follow-up of patients treated for syphilis are given in Table 46-6. Quantitative nontreponemal tests should be performed at 6 and 12 months in all patients treated for primary and secondary syphilis and at 6, 12, and 24 months for early and late latent disease.
- For women treated during pregnancy, monthly, quantitative, nontreponemal tests are recommended in those at high risk of reinfection.

## CHLAMYDIA

- Infections caused by *C. trachomatis* are believed to be the most common STD in the United States that has more than doubled in the past 10 years. *C. trachomatis* is an obligate intracellular parasite that has some similarities to viruses and bacteria.

## CLINICAL PRESENTATION

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- In comparison with gonorrhea, chlamydial genital infections are more frequently asymptomatic, and when present, symptoms tend to be less noticeable. Table 46-7 summarizes the usual clinical presentation of chlamydial infections.
- Similar to gonorrhea, chlamydia may be transmitted to an infant during contact with infected cervicovaginal secretions. Nearly two-thirds of infants acquire chlamydial infection after endocervical exposure, with the primary morbidity associated with seeding of the infant's eyes, nasopharynx, rectum, or vagina.

**TABLE 46-6** Drug Therapy and Follow-Up of Syphilis

Stage/Type of Syphilis	Recommended Regimens <sup>a,b</sup>	Follow-Up Serology
Primary, secondary, or latent syphilis of less than 1-year's duration (early latent syphilis)	Benzathine penicillin G 2.4 million units IM in a single dose <sup>c</sup>	Quantitative nontreponemal tests at 6 and 12 months for primary and secondary syphilis; at 6, 12, and 24 months for early latent syphilis <sup>d</sup>
Latent syphilis of more than 1-year's duration (late latent syphilis) or syphilis of unknown duration	Benzathine penicillin G 2.4 million units IM once a week for 3 successive weeks (7.2 million units total)	Quantitative nontreponemal tests at 6, 12, and 24 months <sup>e</sup>
Neurosyphilis	Aqueous crystalline penicillin G 18–24 million units IV (3–4 million units every 4 hours or by continuous infusion) for 10–14 days <sup>f</sup> <i>or</i> Aqueous procaine penicillin G 2.4 million units IM daily plus probenecid 500 mg orally four times daily, both for 10–14 days <sup>e</sup>	Cerebrospinal fluid <sup>g</sup> examination every 6 months until the cell count is normal; if it has not decreased at 6 months or is not normal by 2 years, retreatment should be considered
Congenital syphilis	Aqueous crystalline penicillin G 50,000 units/kg IV every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days <i>or</i> Procaine penicillin G 50,000 units/kg IM daily for 10 days	Serologic follow-up only recommended if antimicrobials other than penicillin are used
Penicillin-allergic patients, <sup>g</sup> primary, secondary, or early latent syphilis	Doxycycline 100 mg orally two times daily for 2 weeks <sup>g,h</sup> <i>or</i> Tetracycline 500 mg orally four times daily for 2 weeks <sup>h</sup> <i>or</i> Ceftriaxone 1 g IM or IV daily for 8–10 days	Same as for non-penicillin-allergic patients
Latent syphilis of more than 1 year's duration (late latent syphilis) or syphilis of unknown duration	Doxycycline 100 mg orally two times a day for 28 days <sup>h,i</sup> <i>or</i> Tetracycline 500 mg orally four times daily for 28 days <sup>h,i</sup>	Same as for non-penicillin-allergic patients

<sup>a</sup>Recommendations are those of the Centers for Disease Control and Prevention.

<sup>b</sup>The Centers for Disease Control and Prevention recommends that all patients diagnosed with syphilis be tested for human immunodeficiency virus (HIV) infection.

<sup>c</sup>Some experts recommend multiple doses of benzathine penicillin G or other supplemental antibiotics in addition to benzathine penicillin G in HIV-infected patients with primary or secondary syphilis; HIV-infected patients with early latent syphilis should be treated with the recommended regimen for latent syphilis of more than 1-year's duration.

<sup>d</sup>More frequent follow-up (i.e., 3, 6, 9, 12, and 24 months) recommended for HIV-infected patients.

<sup>e</sup>More frequent follow-up (i.e., 6, 12, 18, and 24 months) recommended for HIV-infected patients.

<sup>f</sup>Some experts administer benzathine penicillin G 2.4 million units IM once per week for up to 3 weeks after completion of the neurosyphilis regimens to provide a total duration of therapy comparable to that used for late syphilis in the absence of neurosyphilis.

<sup>g</sup>For nonpregnant patients; pregnant patients should be treated with penicillin after desensitization.

<sup>h</sup>Pregnant patients allergic to penicillin should be desensitized and treated with penicillin.

<sup>i</sup>Limited data suggest that ceftriaxone may be effective, although the optimal dosage and treatment duration are unclear.

**TABLE 46-7** Presentation of *Chlamydia* Infections

	Males	Females
<b>General</b>	Incubation period—35 days Symptom onset—7–21 days	Incubation period—7–35 days Usual symptom onset—7–21 days
<b>Site of infection</b>	Most common—urethra Others—rectum (receptive anal intercourse), oropharynx, eye	Most common—endocervical canal Others—urethra, rectum (usually due to perineal contamination), oropharynx, eye
<b>Symptoms</b>	More than 50% of urethral and rectal infections are asymptomatic Urethral infection—mild dysuria, discharge Pharyngeal infection—asymptomatic to mild pharyngitis	More than 66% of cervical infections are asymptomatic Urethral infection—usually subclinical; dysuria and frequency uncommon Rectal and pharyngeal infection—symptoms same as for men
<b>Signs</b>	Scant to profuse, mucoid to purulent urethral or rectal discharge Rectal infection—pain, discharge, bleeding	Abnormal vaginal discharge or uterine bleeding, purulent urethral, or rectal discharge can be scant to profuse
<b>Complications</b>	Epididymitis, Reiter's syndrome (rare)	Pelvic inflammatory disease and associated complications (i.e., ectopic pregnancy, infertility) Reiter's syndrome (rare)

## DIAGNOSIS

- Culture of endocervical or urethral epithelial cell scrapings is the most specific method (close to 100%) for detection of chlamydia, but sensitivity is as low as 70%. Between 3 and 7 days are required for results.
- Tests that allow rapid identification of chlamydial antigens in genital secretions are the direct fluorescent antibody test, the enzyme immunoassay (requires just 30 minutes for results), the DNA hybridization probe and nucleic acid amplification tests.

## TREATMENT

- Recommended regimens for treatment of chlamydial infections are given in Table 46-8. Single-dose **azithromycin** and 7-day **doxycycline** are the agents of choice.
- For prophylaxis of ophthalmia neonatorum, various groups have proposed the use of **erythromycin** (0.5%) or **tetracycline** (1%) ophthalmic ointment in lieu of silver nitrate. Although silver nitrate and antibiotic ointments are effective against gonococcal ophthalmia neonatorum, silver nitrate is not effective for chlamydial disease and may cause a chemical conjunctivitis.
- Treatment of chlamydial infections with the recommended regimens is highly effective; therefore, posttreatment cultures are not routinely recommended.
- Infants with pneumonitis should receive follow-up testing, because erythromycin is only 80% effective.

## GENITAL HERPES

- The term *herpes* is used to describe two distinct but antigenically related serotypes of herpes simplex virus (HSV). HSV type 1 (HSV-1) is most

**TABLE 46-8** Treatment of Chlamydial Infections

Infection	Recommended Regimens <sup>a</sup>	Alternative Regimen
Uncomplicated urethral, endocervical, or rectal infection in adults	Azithromycin 1 g orally once, or doxycycline 100 mg orally twice daily for 7 days	Ofloxacin 300 mg orally twice daily for 7 days, or levofloxacin 500 mg orally once daily for 7 days, or erythromycin base 500 mg orally four times daily for 7 days, or erythromycin ethyl succinate 800 mg orally four times daily for 7 days
Urogenital infections during pregnancy	Azithromycin 1 g orally as a single dose or amoxicillin 500 mg orally three times daily for 7 days	Erythromycin base 250 mg orally four times daily for 14 days, or erythromycin ethyl succinate 800 mg orally four times daily for 7 days (or 400 mg orally four times daily for 14 days)
Conjunctivitis of the newborn or pneumonia in infants	Erythromycin base 50 mg/kg/day orally in four divided doses for 14 days <sup>b</sup>	—

<sup>a</sup>Recommendations are those of the Centers for Disease Control and Prevention.

<sup>b</sup>Topical therapy alone is inadequate and is unnecessary when systemic therapy is administered.

commonly associated with oropharyngeal disease; type 2 (HSV-2) is most closely associated with genital disease.

## CLINICAL PRESENTATION

- A summary of the clinical presentation of genital herpes is provided in Table 46-9.
- A presumptive diagnosis of genital herpes commonly is made on the basis of the presence of dark-field-negative, vesicular, or ulcerative genital lesions. A history of similar lesions or recent sexual contact with an individual with similar lesions also is useful in making the diagnosis.
- Tissue culture is the most specific (100%) and sensitive method (80% to 90%) of confirming the diagnosis of first-episode genital herpes.

## TREATMENT

- The goals of therapy in genital herpes infection are to shorten the clinical course, prevent complications, prevent the development of latency and/or subsequent recurrences, decrease disease transmission, and eliminate established latency.
- Palliative and supportive measures are the cornerstone of therapy for patients with genital herpes. Pain and discomfort usually respond to warm saline baths or the use of analgesics, antipyretics, or antipruritics.
- Specific treatment recommendations are given in Table 46-10.
- Oral acyclovir, valacyclovir, and famciclovir are the treatments of choice for outpatients with first-episode genital herpes. Treatment does not prevent latency or alter the subsequent frequency and severity of recurrences.
- Continuous oral antiviral therapy reduces the frequency and the severity of recurrences in 70% to 90% of patients experiencing frequent recurrences.
- Acyclovir, valacyclovir, and famciclovir have been used to prevent reactivation of infection in patients seropositive for HSV who undergo transplantation procedures or induction chemotherapy for acute leukemia.

**TABLE 46-9** Presentation of Genital Herpes Infections

<b>General</b>	Incubation period 2–14 days (mean, 4 days) Can be caused by either HSV-1 or HSV-2
<b>Classification of infection</b>	
First-episode primary	Initial genital infection in individuals lacking antibody to either HSV-1 or HSV-2
First-episode nonprimary	Initial genital infection in individuals with clinical or serologic evidence of prior HSV (usually HSV-1) infection
Recurrent	Appearance of genital lesions at some time following healing of first-episode infection
<b>Signs and symptoms</b>	
First-episode infections	Most primary infections are asymptomatic or minimally symptomatic Multiple painful pustular or ulcerative lesions on external genitalia developing over a period of 7–10 days; lesions heal in 2–4 weeks (mean, 21 days) Flu-like symptoms (e.g., fever, headache, malaise) during first few days after appearance of lesions Others—local itching, pain or discomfort; vaginal or urethral discharge, tender inguinal adenopathy, paresthesias, urinary retention Severity of symptoms greater in females than in males Symptoms are less severe (e.g., fewer lesions, more rapid lesion healing, fewer or milder systemic symptoms) with nonprimary infections Symptoms more severe and prolonged in the immunocompromised On average viral shedding lasts approximately 11–12 days for primary infections and 7 days for nonprimary infections
Recurrent	Prodrome seen in approximately 50% of patients prior to appearance of recurrent lesions; mild burning, itching, or tingling are typical prodromal symptoms Compared to primary infections, recurrent infections associated with (1) fewer lesions that are more localized, (2) shorter duration of active infection (lesions heal within 7 days), and (3) milder symptoms Severity of symptoms greater in females than in males Symptoms more severe and prolonged in the immunocompromised On average, viral shedding lasts approximately 4 days
<b>Therapeutic implications of HSV-1 versus HSV-2 genital infection</b>	Primary infections due to HSV-1 and HSV-2 virtually indistinguishable Recurrence rate is greater after primary infection with HSV-1 Recurrent infections with HSV-2 tend to be more severe
<b>Complications</b>	Secondary infection of lesions; extragenital infection due to autoinoculation; disseminated infection (primarily in immunocompromised patients); meningitis or encephalitis; neonatal transmission

HSV, herpes simplex virus.

- The safety of acyclovir therapy during pregnancy is not established, although there is no evidence of teratogenic effects in humans.

## TRICHOMONIASIS

- Trichomoniasis is caused by *Trichomonas vaginalis*, a flagellated, motile protozoan that is responsible for 3 million to 5 million cases per year in the United States.
- Coinfection with other STDs (such as gonorrhea) is common in patients diagnosed with trichomoniasis.

**TABLE 46-10** Treatment of Genital Herpes

Type of Infection	Recommended Regimens <sup>a,b</sup>	Alternative Regimen
First clinical episode of genital herpes <sup>c</sup>	Acyclovir 400 mg po three times daily for 7–10 days, <sup>d</sup> or Acyclovir 200 mg po five times daily for 7–10 days, <sup>d</sup> or Famciclovir 250 mg po three times daily for 7–10 days, <sup>d</sup> or Valacyclovir 1 g po twice daily for 7–10 days <sup>d</sup>	Acyclovir 5–10 mg/kg IV every 8 hours for 2–7 days or until clinical improvement occurs, followed by oral therapy to complete at least 10 days of total therapy <sup>e</sup>
Recurrent infection		
Episodic therapy	Acyclovir 400 mg po three times daily for 5 days, <sup>f</sup> or Acyclovir 800 mg po twice daily for 5 days, <sup>f</sup> or Acyclovir 800 mg po three times daily for 2 days, <sup>f</sup> or Famciclovir 125 mg po twice daily for 5 days, <sup>f</sup> or Valacyclovir 500 mg po twice daily for 3–5 days, <sup>f</sup> or Valacyclovir 1 g po once daily for 5 days <sup>f</sup>	
Suppressive therapy	Acyclovir 400 mg po twice daily, or Famciclovir 250 mg po twice daily, or Valacyclovir 500 mg or 1,000 mg po once daily <sup>g</sup>	

CDC, Centers for Disease Control and Prevention; HIV, human immunodeficiency virus.

<sup>a</sup>Recommendations are those of the CDC.

<sup>b</sup>HIV-infected patients can require more aggressive therapy.

<sup>c</sup>Primary or nonprimary first episode.

<sup>d</sup>Treatment duration can be extended if healing is incomplete after 10 days.

<sup>e</sup>Only for patients with severe symptoms or complications that necessitate hospitalization.

<sup>f</sup>Requires initiation of therapy within 24 hours of lesion onset or during the prodrome that precedes some outbreaks.

<sup>g</sup>Valacyclovir 500 mg appears less effective than valacyclovir 1,000 mg in patients with approximately 10 recurrences per year.

## CLINICAL PRESENTATION

- The typical presentation of trichomoniasis in males and females is presented in Table 46-11.
- *T. vaginalis* produces nonspecific symptoms also consistent with bacterial vaginosis, and thus laboratory diagnosis is required.
- The simplest and most reliable means of diagnosis is a wet-mount examination of the vaginal discharge. Trichomoniasis is confirmed if characteristic pear-shaped, flagellating organisms are observed. Newer diagnostic tests such as monoclonal antibody or DNA probe techniques, as well as polymerase chain reaction tests are highly sensitive and specific.

## TREATMENT

- **Metronidazole** and **tindazole** are the only antimicrobial agents available in the United States that are consistently effective in *T. vaginalis* infections.
- Treatment recommendations for *Trichomonas* infections are given in Table 46-12.
- GI complaints (e.g., anorexia, nausea, vomiting, diarrhea) are the most common adverse effects, with the single 2-g dose of metronidazole or

**TABLE 46-11** Presentation of *Trichomonas* Infections

	<b>Males</b>	<b>Females</b>
<b>General</b>	Incubation period 3–28 days Organism may be detectable within 48 hours after exposure to infected partner	Incubation period 3–28 days
<b>Site of infection</b>	Most common—urethra Others—rectum (usually due to rectal intercourse in men who have sex with men), oropharynx, eye	Most common—endocervical canal Others—urethra, rectum (usually due to perineal contamination), oropharynx, eye
<b>Symptoms</b>	May be asymptomatic (more common in males than females) or minimally symptomatic Urethral discharge (clear to mucopurulent) Dysuria, pruritus	May be asymptomatic or minimally symptomatic Scant to copious, typically malodorous vaginal discharge (50–75%) and pruritus (worsen during menses) Dysuria, dyspareunia
<b>Signs</b>	Urethral discharge	Vaginal discharge Vaginal pH 4.5–6 Inflammation/erythema of vulva, vagina, and/or cervix Urethritis
<b>Complications</b>	Epididymitis and chronic prostatitis (uncommon) Male infertility (decreased sperm motility and viability)	Pelvic inflammatory disease and associated complications (i.e., ectopic pregnancy, infertility) Premature labor, premature rupture of membranes, and low-birth-weight infants (risk of neonatal infections is low) Cervical neoplasia

tinidazole, occurring in 5% to 10% of treated patients. Some patients complain of a bitter metallic taste in the mouth.

- Patients intolerant of the single 2-g dose because of GI adverse effects usually tolerate the multidose regimen.

**TABLE 46-12** Treatment of Trichomoniasis

<b>Type</b>	<b>Recommended Regimen<sup>a</sup></b>	<b>Alternative Regimen</b>
Symptomatic and asymptomatic infections	Metronidazole 2 g po in a single dose <sup>b</sup> or Tinidazole 2 g po in a single dose	Metronidazole 500 mg po 2 times daily for 7 days <sup>c</sup> or Tinidazole 2 g po in a single dose <sup>d</sup>
Treatment in pregnancy	Metronidazole 2 g po in a single dose <sup>e</sup>	

CDC, Centers for Disease Control and Prevention.

<sup>a</sup>Recommendations are those of the CDC.

<sup>b</sup>Treatment failures should be treated with metronidazole 500 mg po twice daily for 7 days. Persistent failures should be managed in consultation with an expert. Metronidazole or tinidazole 2 g po daily for 5 days has been effective in patients infected with *Trichomonas vaginalis* strains mildly resistant to metronidazole, but experience is limited; higher doses also have been used.

<sup>c</sup>Metronidazole labeling approved by the FDA does not include this regimen. Dosage regimens for treatment of trichomoniasis included in the product labeling are the single 2-g dose; 250 mg three times daily for 7 days; and 375 mg twice daily for 7 days. The 250 mg and 375 mg dosage regimens are currently not included in the CDC recommendations.

<sup>d</sup>For treatment failures with metronidazole 2 g as a single dose.

<sup>e</sup>Metronidazole is pregnancy category B and tinidazole is pregnancy category C; both drugs are contraindicated in the first trimester of pregnancy. Some clinicians recommend deferring metronidazole treatment in asymptomatic pregnant women until after 37 weeks' gestation.

**TABLE 46-13** Treatment Regimens for Miscellaneous Sexually Transmitted Diseases

Infection	Recommended Regimen <sup>a</sup>	Alternative Regimen
Chancroid ( <i>Haemophilus ducreyi</i> )	Azithromycin 1 g orally in a single dose <i>or</i> Ceftriaxone 250 mg intramuscularly in a single dose <i>or</i> Ciprofloxacin 500 mg orally twice daily for 3 days <sup>b</sup> <i>or</i> Erythromycin base 500 mg orally four times daily for 7 days	—
Lymphogranuloma venereum	Doxycycline 100 mg orally twice daily for 21 days <sup>c</sup>	Erythromycin base 500 mg orally four times daily for 7 days
Human papillomavirus infection External genital warts	<i>Provider-administered therapies:</i> Cryotherapy (e.g., liquid nitrogen or cryoprobe) <i>or</i> Podophyllin 10–25% in compound tincture of benzoin applied to lesions; repeat weekly if necessary, <sup>d,e</sup> <i>or</i> Trichloroacetic acid 80–90% or bichloroacetic acid 80–90% applied to warts; repeat weekly if necessary <i>or</i> Surgical removal (tangential scissor excision, tangential shave excision, curettage, or electrosurgery) <i>Patient-applied therapies:</i> Podofilox 0.5% solution or gel applied twice daily for 3 days, followed by 4 days of no therapy; cycle is repeated as necessary for a total of four cycles <sup>e</sup> <i>or</i> Imiquimod 5% cream applied at bedtime three times weekly for up to 16 weeks <sup>e</sup>	Intralesional interferon or laser surgery
Vaginal, urethral meatus, and anal warts	Cryotherapy with liquid nitrogen, or trichloroacetic acid or bichloroacetic acid 80–90% as for external human papillomavirus warts; repeat weekly as necessary <sup>f</sup> Surgical removal (not for vaginal or urethral meatus warts)	—
Urethral meatus warts	Cryotherapy with liquid nitrogen, or podophyllin resin 10–25% in compound tincture of benzoin applied at weekly intervals <sup>e,g</sup>	—

<sup>a</sup>Recommendations are those of the Centers for Disease Control and Prevention.

<sup>b</sup>Ciprofloxacin is contraindicated for pregnant and lactating women and for persons aged <18 years.

<sup>c</sup>Azithromycin 1 g orally once weekly for 3 weeks can be effective.

<sup>d</sup>Some experts recommended washing podophyllin off after 1–4 hours to minimize local irritation.

<sup>e</sup>Safety during pregnancy is not established.

<sup>f</sup>Surgical removal of anal warts is also a recommended treatment.

<sup>g</sup>Some specialists recommend the use of podofilox and imiquimod for treating distal meatal warts.

- To achieve maximal cure rates and prevent relapse with the single 2-g dose of metronidazole, simultaneous treatment of infected sexual partners is necessary.
- Patients who fail to respond to an initial course usually respond to a second course of metronidazole or tinidazole therapy.
- Patients taking metronidazole should be instructed to avoid alcohol ingestion during therapy and for 1 to 2 days after completion of therapy because of a possible disulfiram-like effect.
- At present, no satisfactory treatment is available for pregnant women with *Trichomonas* infections. Metronidazole and tinidazole are contraindicated during the first trimester of pregnancy.
- Follow-up is considered unnecessary in patients who become asymptomatic after treatment with metronidazole.
- When patients remain symptomatic, it is important to determine if reinfection has occurred. In these cases, a repeat course of therapy, as well as identification and treatment or retreatment of infected sexual partners, is recommended.

## OTHER SEXUALLY TRANSMITTED DISEASES

- Several STDs other than those previously discussed occur with varying frequency in the United States and throughout the world. While an in-depth discussion of these diseases is beyond the scope of this chapter, recommended treatment regimens are given in Table 46-13.

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See Chap. 121, *Sexually Transmitted Diseases*, authored by Leroy C. Knodel, for a more detailed discussion of this topic.

## DEFINITION

- Bacterial infections of the skin can be classified as primary or secondary (Table 47-1). Primary bacterial infections are usually caused by a single bacterial species and involve areas of generally healthy skin (e.g., impetigo, erysipelas). Secondary infections, however, develop in areas of previously damaged skin and are frequently polymicrobial.
- The conditions that may predispose a patient to the development of skin and soft-tissue infections (SSTIs) include (1) a high concentration of bacteria, (2) excessive moisture of the skin, (3) inadequate blood supply, (4) availability of bacterial nutrients, and (5) damage to the corneal layer allowing for bacterial penetration.
- The majority of SSTIs are caused by gram-positive organisms and, less commonly, gram-negative bacteria present on the skin surface. *Staphylococcus aureus* and *Streptococcus pyogenes* account for the majority of SSTIs. Community-associated methicillin-resistant *S. aureus* (CA-MRSA) has recently emerged and it is often isolated in otherwise healthy patients.

## ERYSIPELAS

- Erysipelas (Saint Anthony's fire) is an infection of the superficial layers of the skin and cutaneous lymphatics. The infection is almost always caused by  $\beta$ -hemolytic streptococci, with *S. pyogenes* (Group A streptococci) responsible for most infections.
- The lower extremities are the most common sites for erysipelas. Patients often experience flu-like symptoms (fever and malaise) prior to the appearance of the lesions. The infected area is painful, often a burning pain. Erysipelas lesions are bright red and edematous with lymphatic streaking and clearly demarcated raised margins. Leukocytosis is common, and C-reactive protein is generally elevated.
- Mild to moderate cases of erysipelas in adults are treated with intramuscular **procaine penicillin G** or **penicillin VK**. For more serious infections, aqueous penicillin G, 2 million to 8 million units daily, should be administered IV. Penicillin-allergic patients can be treated with clindamycin or erythromycin.
- Evidence-based recommendations for treatment of SSTIs are found in Table 47-2, and recommended drugs and dosing regimens for outpatient treatment of mild to moderate SSTIs are found in Table 47-3.

## IMPETIGO

- Impetigo is a superficial skin infection that is seen most commonly in children. It is highly communicable and spreads through close contact. Most cases are caused by *S. pyogenes*, but *S. aureus* either alone or in combination with *S. pyogenes* has emerged as a principal cause of impetigo.

**TABLE 47-1** Bacterial Classification of Important Skin and Soft-Tissue Infections**Primary infections**

Erysipelas	Group A streptococci
Impetigo	<i>Staphylococcus aureus</i> , Group A streptococci
Lymphangitis	Group A streptococci; occasionally <i>S. aureus</i>
Cellulitis	Group A streptococci, <i>S. aureus</i> ; occasionally other gram-positive cocci, gram-negative bacilli, and/or anaerobes
Necrotizing fasciitis	
Type I	Anaerobes ( <i>Bacteroides</i> spp., <i>Peptostreptococcus</i> spp.) and facultative bacteria (streptococci, Enterobacteriaceae)
Type II	Group A streptococci

**Secondary infections**

Diabetic foot infections	<i>S. aureus</i> , streptococci, Enterobacteriaceae, <i>Bacteroides</i> spp., <i>Peptostreptococcus</i> spp., <i>Pseudomonas aeruginosa</i>
Pressure sores	<i>S. aureus</i> , streptococci, Enterobacteriaceae, <i>Bacteroides</i> spp., <i>Peptostreptococcus</i> spp., <i>P. aeruginosa</i>
Bite wounds	
Animal	<i>Pasteurella multocida</i> , <i>S. aureus</i> , streptococci, <i>Bacteroides</i> spp.
Human	<i>Eikenella corrodens</i> , <i>S. aureus</i> , streptococci, <i>Corynebacterium</i> spp., <i>Bacteroides</i> spp., <i>Peptostreptococcus</i> spp.
Burn wounds	<i>P. aeruginosa</i> , Enterobacteriaceae, <i>S. aureus</i> , streptococci

**CLINICAL PRESENTATION**

- Exposed skin, especially the face, is the most common site for impetigo.
- Pruritus is common, and scratching of the lesions may further spread infection through excoriation of the skin. Other systemic signs of infection are minimal.
- Weakness, fever, and diarrhea are sometimes seen with bullous impetigo.
- Nonbullous impetigo manifests initially as small, fluid-filled vesicles. These lesions rapidly develop into pus-filled blisters that readily rupture. Purulent discharge from the lesions dries to form golden yellow crusts that are characteristic of impetigo.
- In the bullous form of impetigo, the lesions begin as vesicles and turn into bullae containing clear yellow fluid. Bullae soon rupture, forming thin, light brown crusts.
- Regional lymph nodes may be enlarged.

**TREATMENT**

- Penicillinase-resistant penicillins (such as **dicloxacillin**) are the agents of first choice because of the increased isolation of *S. aureus*. First-generation cephalosporins (such as cephalexin) are also effective (see Table 47-3). **Penicillin** may be used for impetigo caused by *S. pyogenes*. It may be administered as either a single intramuscular dose of benzathine penicillin G (300,000 to 600,000 units in children, 1.2 million units in adults) or as oral penicillin VK given for 7 to 10 days. Penicillin-allergic patients can be treated with oral **clindamycin**.
- The duration of therapy is 7 to 10 days.
- **Mupirocin ointment** is also effective.

**TABLE 47-2** Evidence-Based Recommendations for Treatment of Skin and Soft-Tissue Infections

Recommendations	Recommendation Grade
<b>Folliculitis, furuncles, carbuncles</b>	
Folliculitis and small furuncles can be treated with moist heat; large furuncles and carbuncles require incision and drainage. Antimicrobial therapy is unnecessary unless extensive lesions or fever are present.	E-III
<b>Erysipelas</b>	
Most infections are caused by <i>Streptococcus pyogenes</i> . Penicillin (oral or intravenous depending on clinical severity) is the drug of choice.	A-I
If <i>Staphylococcus aureus</i> is suspected, a penicillinase-resistant penicillin or first-generation cephalosporin should be used.	A-I
<b>Impetigo</b>	
<i>S. aureus</i> accounts for the majority of infections; consequently, a penicillin-resistant penicillin or first-generation cephalosporin is recommended.	A-I
Topical therapy with mupirocin is equivalent to oral therapy.	A-I
<b>Cellulitis</b>	
Mild-moderate infections can generally be treated with oral agents (dicloxacillin, cephalexin, clindamycin) unless resistance is high in the community.	A-I
Serious infections should be treated intravenously with a penicillinase-resistant penicillin (nafcillin) or first-generation cephalosporin (cefazolin). Patients with penicillin allergies should be treated with vancomycin or clindamycin.	A-I
Vancomycin, linezolid, and daptomycin should be used to treat serious infections caused by methicillin-resistant <i>S. aureus</i> .	A-I
<b>Necrotizing fasciitis</b>	
Early and aggressive surgical debridement of all necrotic tissue is essential.	A-III
Necrotizing fasciitis caused by <i>S. pyogenes</i> should be treated with the combination of clindamycin and penicillin.	A-II
Clostridial gas gangrene (myonecrosis) should be treated with clindamycin and penicillin.	B-III
<b>Diabetic foot infections</b>	
Many mild to moderate infections can be treated with oral agents that possess high bioavailability.	A-II
All severe infections should be treated with intravenous therapy. After initial response, step-down therapy to oral agents can be used.	C-III
Broad-spectrum antimicrobial therapy is not generally required, except for some severe cases.	B-III
Definitive therapy should be based on results of appropriately collected cultures and sensitivities, as well as clinical response to empiric antimicrobial agents.	C-III
Optimal wound care, in addition to appropriate antimicrobial therapy, is essential for wound healing.	A-I
<b>Animal bites</b>	
Many bite wounds can be treated on an outpatient basis with amoxicillin-clavulanic acid.	B-II
Serious infections requiring intravenous antimicrobial therapy can be treated with a $\beta$ -lactam/ $\beta$ -lactamase inhibitor combination or second-generation cephalosporin with activity against anaerobes (cefoxitin).	B-II
Penicillinase-resistant penicillins, first-generation cephalosporins, macrolides, and clindamycin should not be used for treatment because of their poor activity against <i>Pasteurella multocida</i> .	D-III
<b>Human bites</b>	
Antimicrobial therapy should provide coverage against <i>Eikenella corrodens</i> , <i>S. aureus</i> , and $\beta$ -lactamase producing anaerobes.	B-III

Strength of recommendation: A, good evidence for use; B, moderate evidence for use; C, poor evidence for use, optional; D, moderate evidence to support not using; E, good evidence to support not using.

Quality of evidence: I, evidence from  $\geq 1$  properly randomized, controlled trials; II, evidence from  $\geq 1$  well-designed clinical trials without randomization, case-controlled analytic studies, multiple time series, or dramatic results from uncontrolled experiments; III, evidence from expert opinion, clinical experience, descriptive studies, or reports of expert committees.

**TABLE 47-3** Recommended Drugs and Dosing Regimens for Outpatient Treatment of Mild–Moderate Skin and Soft-Tissue Infections

Infection	Oral Adult Dose	Oral Pediatric Dose
Folliculitis	None; warm saline compresses usually sufficient	
Furuncles and carbuncles	Dicloxacillin 250–500 mg every 6 hours Cephalexin 250–500 mg every 6 hours Clindamycin 300–600 mg every 6–8 hours <sup>a</sup>	Dicloxacillin 25–50 mg/kg in four divided doses Cephalexin 25–50 mg/kg in four divided doses Clindamycin 10–30 mg/kg/day in three to four divided doses <sup>a</sup>
Erysipelas	Procaine penicillin G 600,000 units intramuscularly every 12 hours Penicillin VK 250–500 mg every 6 hours Clindamycin 150–300 mg every 6–8 hours <sup>a</sup> Erythromycin 250–500 mg every 6 hours <sup>a</sup>	Penicillin VK 25,000–90,000 units/kg in four divided doses Clindamycin 10–30 mg/kg in three to four doses <sup>a</sup> Erythromycin 30–50 mg/kg in four divided doses <sup>a</sup>
Impetigo	Dicloxacillin 250–500 mg every 6 hours Cephalexin 250–500 mg every 6 hours Cefadroxil 500 mg every 12 hours Clindamycin 150–300 mg every 6–8 hours <sup>a</sup> Mupirocin ointment every 8 hours <sup>a</sup>	Dicloxacillin 25–50 mg/kg in four divided doses Cephalexin 25–50 mg/kg in two to four divided doses Cefadroxil 30 mg/kg in two divided doses Clindamycin 10–30 mg/kg/day in three to four divided doses <sup>a</sup> Mupirocin ointment every 8 hours <sup>a</sup>
Lymphangitis	Initial IV therapy, followed by penicillin VK 250–500 mg every 6 hours Clindamycin 150–300 mg every 6–8 hours <sup>a</sup>	Initial IV therapy, followed by penicillin VK 25,000–90,000 units/kg in four divided doses Clindamycin 10–30 mg/kg/day in three to four divided doses <sup>a</sup>
Diabetic foot infections	Amoxicillin-clavulanic acid 875 mg/125 mg every 12 hours Fluoroquinolone (levofloxacin 750 mg every 24 or moxifloxacin 400 mg every 24 hours) + metronidazole 250–500 mg every 8 hours or clindamycin 300–600 mg every 6–8 hours <sup>a</sup>	

Animal bite	<p>Amoxicillin-clavulanic acid 875 mg/125 mg every 12 hours            Doxycycline 100–200 mg every 12 hours<sup>a</sup>            Dicloxacillin 250–500 mg every 6 hours + penicillin VK 250–500 mg every 6 hours</p> <p>Cefuroxime axetil 500 mg every 12 hours + metronidazole 250–500 mg every 8 hours or clindamycin 300–600 mg every 6–8 hours            Fluoroquinolone (levofloxacin 500–750 mg every 24 hours or moxifloxacin 400 mg every 24 hours) or clindamycin 300–600 mg every 6–8 hours<sup>a</sup></p> <p>Erythromycin 500 mg every 6 hours + metronidazole 250–500 mg every 8 hours or clindamycin 300–600 mg every 6–8 hours<sup>a</sup></p>	<p>Amoxicillin-clavulanic acid 40 mg/kg (of the amoxicillin component) in two divided doses</p> <p>Dicloxacillin 25–50 mg/kg in four divided doses + penicillin VK 40,000–90,000 units/kg in four divided doses</p> <p>Cefuroxime axetil 20–30 mg/kg in two divided doses + metronidazole 30 mg/kg in three to four divided doses or clindamycin 10–30 mg/kg/day in three to four divided doses            Trimethoprim–sulfamethoxazole 4–6 mg/kg (of the trimethoprim component) every 12 hours + metronidazole 30 mg/kg in three to four divided doses or clindamycin 10–30 mg/kg/day in three to four divided doses<sup>a</sup></p> <p>Erythromycin 30–50 mg/kg in four divided doses + every 12 hours + metronidazole 30 mg/kg in three to four divided doses or clindamycin 10–30 mg/kg/day in three to four divided doses<sup>a</sup></p>
Human bite	<p>Amoxicillin-clavulanic acid 875 mg/125 mg every 12 hours            Doxycycline 100–200 mg every 12 hours<sup>a</sup>            Dicloxacillin 250–500 mg every 6 hours + penicillin VK 250–500 mg every 6 hours</p> <p>Cefuroxime axetil 500 mg every 12 hours metronidazole 250–500 mg every 8 hours or clindamycin 300–600 mg every 6–8 hours            Fluoroquinolone (levofloxacin 500–750 mg every 24 hours or moxifloxacin 400 mg every 24 hours) + metronidazole 250–500 mg every 8 hours or clindamycin 300–600 mg every 6–8 hours<sup>a</sup></p>	<p>Amoxicillin-clavulanic acid 40 mg/kg (of the amoxicillin component) in two divided doses</p> <p>Dicloxacillin 25–50 mg/kg in four divided doses + penicillin VK 40,000–90,000 units/kg in four divided doses</p> <p>Cefuroxime axetil 20–30 mg/kg in two divided doses + metronidazole 30 mg/kg in three to four divided doses or clindamycin 10–30 mg/kg/day in three to four divided doses            Trimethoprim–sulfamethoxazole 4–6 mg/kg (of the trimethoprim component) every 12 hours + metronidazole 30 mg/kg in three to four divided doses or clindamycin 10–30 mg/kg/day in 3–4 divided doses<sup>a</sup></p>

<sup>a</sup>Recommended for patients with penicillin allergy.

## CELLULITIS

- Cellulitis is an acute, spreading infectious process that initially affects the epidermis and dermis and may subsequently spread within the superficial fascia. This process is characterized by inflammation but with little or no necrosis or suppuration of soft tissue.
- Cellulitis is most often caused by *S. pyogenes* or by *S. aureus* (see Table 47-1).
- Acute cellulitis with mixed aerobic-anaerobic flora generally occurs in diabetes, where the skin is near a traumatic site or surgical incision, at sites of surgical incisions to the abdomen or perineum, or when host defenses are compromised.

## CLINICAL PRESENTATION

- Cellulitis is characterized by erythema and edema of the skin. The lesion, which may be extensive, is painful and nonelevated and has poorly defined margins. Tender lymphadenopathy associated with lymphatic involvement is common. Malaise, fever, and chills are also commonly present. There is usually a history of an antecedent wound from minor trauma, an ulcer, or surgery.
- A Gram stain of a smear obtained by injection and aspiration of 0.5 mL of saline (using a small-gauge needle) into the advancing edge of the erythematous lesion may help in making the microbiologic diagnosis, but often yields negative results. Blood cultures are useful as bacteremia may be present in 30% of cases.

## TREATMENT

- The goal of therapy of acute bacterial cellulitis is rapid eradication of the infection and prevention of further complications.
- Antimicrobial therapy of bacterial cellulitis is directed toward the type of bacteria either documented to be present or suspected.
- Local care of cellulitis includes elevation and immobilization of the involved area to decrease local swelling.
- As streptococcal cellulitis is indistinguishable clinically from staphylococcal cellulitis, administration of a semisynthetic penicillin (**nafcillin** or **oxacillin**) or first-generation cephalosporin (**cefazolin**) is recommended until a definitive diagnosis, by skin or blood cultures, can be made (Table 47-4). If documented to be a mild cellulitis secondary to streptococci, oral **penicillin VK**, or intramuscular **procaine penicillin** may be administered. More severe streptococcal infections should be treated with IV antibiotics (such as **ceftriaxone** 50 to 100 mg/kg as a single dose).
- The usual duration of therapy for cellulitis is 5 to 10 days.
- In penicillin-allergic patients, oral or parenteral **clindamycin** may be used. Alternatively, a first-generation cephalosporin such as cefazolin (1 to 2 g IV every 6 to 8 hours) may be used cautiously for patients who have not experienced immediate or anaphylactic penicillin reactions and are penicillin skin test negative. In severe cases in which cephalosporins cannot be used because of documented methicillin resistance or severe allergic reactions to  $\beta$ -lactam antibiotics, IV **vancomycin** should be administered.

**TABLE 47-4** Initial Treatment Regimens for Cellulitis Caused by Various Pathogens

Antibiotic	Adult Dose and Route	Pediatric Dose and Route
<b>Staphylococcal or unknown gram-positive infection</b>		
Mild infection	Dicloxacillin 0.25–0.5 g orally every 6 hours <sup>a,b</sup>	Dicloxacillin 25–50 mg/kg/day orally in four divided doses <sup>a,b</sup>
Moderate–severe infection	Nafcillin or oxacillin 1–2 g IV every 4–6 hours <sup>a,b</sup>	Nafcillin or oxacillin 150–200 mg/kg/day (not to exceed 12 g/24 hours) IV in four to six equally divided doses <sup>a,b</sup>
<b>Streptococcal (documented)</b>		
Mild infection	Penicillin VK 0.5 g orally every 6 hours <sup>a</sup> or procaine penicillin G 600,000 units IM every 8–12 hours <sup>a</sup>	Penicillin VK 125–250 mg orally every 6–8 hours, or procaine penicillin G 25,000–50,000 units/kg (not to exceed 600,000 units) IM every 8–12 hours <sup>a</sup>
Moderate–severe infection	Aqueous penicillin G 1–2 million units IV every 4–6 hours <sup>a,c</sup>	Aqueous penicillin G 100,000–200,000 units/kg/day IV in four divided doses <sup>a</sup>
<b>Gram-negative bacilli</b>		
Mild infection	Cefaclor 0.5 g orally every 8 hours <sup>d</sup> or cefuroxime axetil 0.5 g orally every 12 hours <sup>d</sup>	Cefaclor 20–40 mg/kg/day (not to exceed 1 g) orally in three divided doses or cefuroxime axetil 0.125–0.25 g (tablets) orally every 12 hours
Moderate–severe infection	Aminoglycoside <sup>e</sup> or IV cephalosporin (first- or second-generation depending on severity of infection or susceptibility pattern) <sup>d</sup>	Aminoglycoside <sup>e</sup> or IV cephalosporin (first- or second-generation depending on severity of infection or susceptibility pattern)
<b>Polymicrobial infection without anaerobes</b>		
	Aminoglycoside <sup>e</sup> + penicillin G 1–2 million units every 4–6 hours or a semisynthetic penicillin (nafcillin 1–2 g every 4–6 hours) depending on isolation of staphylococci or streptococci <sup>b</sup>	Aminoglycoside <sup>e</sup> + penicillin G 100,000–200,000 units/kg/day IV in four divided doses or a semisynthetic penicillin (nafcillin 150–200 mg/kg/day [not to exceed 12 g/24 hours] IV in four to six equally divided doses) depending on isolation of staphylococci or streptococci <sup>b</sup>

*(continued)*

**TABLE 47-4** Initial Treatment Regimens for Cellulitis Caused by Various Pathogens (Continued)

Antibiotic	Adult Dose and Route	Pediatric Dose and Route
<b>Polymicrobial infection with anaerobes</b>		
Mild infection	Amoxicillin-clavulanate 0.875 g orally every 12 hours <i>or</i> A fluoroquinolone (ciprofloxacin 0.4 g orally every 12 hours or levofloxacin 0.5–0.75 g orally every 24 hours) plus clindamycin 0.3–0.6 g orally every 8 hours or metronidazole 0.5 g orally every 8 hours	Amoxicillin-clavulanic acid 20 mg/kg/day orally in three divided doses
Moderate–severe infection	Aminoglycoside <sup>e,f</sup> + clindamycin 0.6–0.9 g IV every 8 hours or metronidazole 0.5 g IV every 8 hours <i>or</i> Monotherapy with second- or third-generation cephalosporin (cefoxitin 1–2 g IV every 6 hours or ceftizoxime 1–2 g IV every 8 hours) <i>or</i> Monotherapy with imipenem 0.5 g IV every 6–8 hours, meropenem 1 g IV every 8 hours, ertapenem 1 g IV every 24 hours, extended-spectrum penicillins with a $\beta$ -lactamase inhibitor (piperacillin/tazobactam 4.5 g IV every 6 hours), or tigecycline 100 mg IV as loading dose, then 50 mg IV every 12 hours	Aminoglycoside <sup>e</sup> plus clindamycin 15 mg/kg/day IV in three divided doses or metronidazole 30–50 mg/kg/day IV in three divided doses

<sup>a</sup>For penicillin-allergic patients, use clindamycin 150–300 mg orally every 6–8 hours (pediatric dosing: 10–30 mg/kg/day in three to four divided doses).

<sup>b</sup>For methicillin-resistant staphylococci, use vancomycin 0.5–1 g every 6–12 hours (pediatric dosing 40 mg/kg/day in divided doses) with dosage adjustments made for renal dysfunction.

<sup>c</sup>For type II necrotizing fasciitis, use clindamycin 0.6–0.9 g IV every 8 hours (in children, clindamycin 15 mg/kg/day IV in 3 divided doses).

<sup>d</sup>For penicillin-allergic adults, use a fluoroquinolone (ciprofloxacin 0.5–0.75 g orally every 12 hours or 0.4 g IV every 12 hours; levofloxacin 0.5–0.75 g orally or IV every 24 hours; or moxifloxacin 0.4 g orally or IV every 24 hours).

<sup>e</sup>Gentamicin or tobramycin, 2 mg/kg loading dose, then maintenance dose as determined by serum concentrations.

<sup>f</sup>A fluoroquinolone or aztreonam 1 g IV every 6 hours may be used in place of the aminoglycoside in patients with severe renal dysfunction or other relative contraindications to aminoglycoside use.

- Initial therapy with trimethoprim–sulfamethoxazole appears to be effective for CA-MRSA and should be considered in geographic areas in which CA-MRSA are commonly encountered. Alternative agents for documented infections with resistant gram-positive bacteria such as methicillin-resistant staphylococci and vancomycin-resistant enterococci include linezolid, quinupristin/dalfopristin, daptomycin, and tigecycline.
- For cellulitis caused by gram-negative bacilli or a mixture of microorganisms, immediate antimicrobial chemotherapy as determined by Gram stain is essential, along with appropriate surgical excision of necrotic tissue and drainage. Gram-negative cellulitis may be treated appropriately with an aminoglycoside or first- or second-generation cephalosporin. If gram-positive aerobic bacteria are also present, penicillin G or a penicillinase-resistant penicillin should be added to the regimen. Therapy should be 10 to 14 days in duration.

## DIABETIC FOOT INFECTIONS

- Three key factors are involved in the causation of diabetic foot problems: neuropathy, ischemia, and immunologic defects. Any of these disorders can occur in isolation; however, they frequently occur together.
- There are three major types of diabetic foot infections: deep abscesses, cellulitis of the dorsum, and mal perforans ulcers of the sole of the foot. Osteomyelitis may occur in 30% to 40% of infections.
- Diabetic foot infections are typically polymicrobial (an average of 2.3 to 5.8 isolates per culture). Staphylococci (especially *S. aureus*) and streptococci are the most common pathogens, although gram-negative bacilli and anaerobes occur in 50% of cases. Common isolates include *Escherichia coli*, *Klebsiella* spp., *Proteus* spp., *P. aeruginosa*, *B. fragilis*, and *Peptostreptococcus* spp.
- Patients with peripheral neuropathy often do not experience pain but seek medical attention for swelling or erythema. Lesions vary in size and clinical features. A foul-smelling odor suggests anaerobic organisms. Temperature may be mildly elevated or normal.

## TREATMENT

- The goal of therapy is preservation of as much normal limb function as possible while preventing infectious complications. Most infections can be successfully treated on an outpatient basis with wound care and antibiotics.
- Necrotic tissue must be thoroughly debrided, with wound drainage and amputation as required.
- Diabetic glycemic control should be maximized to ensure optimal healing.
- The patient should initially be restricted to bed rest, leg elevation, and control of edema, if present.
- **Amoxicillin-clavulanate** is the agent of choice for oral outpatient treatment; however, this agent does not cover *P. aeruginosa*. Fluoroquinolones with metronidazole or clindamycin are reasonable alternatives.
- Serious polymicrobial infections may be treated with agents used for anaerobic cellulitis (see Table 47-3).

- Monotherapy with broad-spectrum parenteral antimicrobials, along with appropriate medical and/or surgical management, is often effective in treating moderate to severe infections (including those in which osteomyelitis is present).
- In penicillin-allergic patients, metronidazole or clindamycin plus either a fluoroquinolone, aztreonam, or, possibly, a third-generation cephalosporin is appropriate.
- Vancomycin is used frequently in severe infections with gram-positive pathogens. With increasing staphylococcal resistance, linezolid, quinupristin/dalfopristin, daptomycin, and tigecycline are alternatives.
- Treatment of soft-tissue infections in diabetic patients should generally be at least 7 to 14 days in duration, although some infections may require an additional 1 to 2 weeks of therapy. However, in cases of underlying osteomyelitis, treatment should continue for 6 to 12 weeks.

## INFECTED PRESSURE ULCERS

- A pressure sore is also called a “decubitus ulcer” and “bed sore.” A classification system for pressure sores is presented in Table 47-5. Many factors are thought to predispose patients to the formation of pressure ulcers: paralysis, paresis, immobilization, malnutrition, anemia, infection, and advanced age. Four factors thought to be most critical to their formation are pressure, shearing forces, friction, and moisture; however, there is still debate as to the exact pathophysiology of pressure sore formation. The areas of highest pressure are generated over the bony prominences.
- Most pressure sores are colonized by bacteria; however, bacteria frequently infect healthy tissue. A large variety of aerobic gram-positive and gram-negative bacteria, as well as anaerobes, are frequently isolated.

## CLINICAL PRESENTATION

- More than 95% of all pressure sores are located on the lower part of the body. The most common sites are the sacral and coccygeal areas, ischial tuberosities, and greater trochanter.
- Clinical infection is recognized by the presence of redness, heat, and pain. Purulent discharge, foul odor, and systemic signs (fever and leukocytosis) may be present.

**TABLE 47-5** Pressure Sore Classification

Stage 1	Pressure sore is generally reversible, is limited to the epidermis, and resembles an abrasion. It is best described as an irregularly shaped area of soft-tissue swelling with induration and heat.
Stage 2	A stage 2 sore may also be reversible; it extends through the dermis to the subcutaneous fat along with extensive undermining.
Stage 3	In this instance, the sore or ulcer extends further into subcutaneous fat along with extensive undermining.
Stage 4	The sore or ulcer is characterized by penetration into deep fascia involving both muscle and bone.

Note: Stage 3 and 4 lesions are unlikely to resolve on their own and often require surgical intervention.

- Pressure sores vary greatly in their severity, ranging from an abrasion to large lesions that can penetrate into the deep fascia involving both bone and muscle.
- Without treatment, an initial, small, localized area of ulceration can rapidly progress to 5 to 6 cm within days.

## PREVENTION AND TREATMENT

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- The goal of therapy is to clean and decontaminate the ulcer to promote wound healing by permitting the formation of healthy granulation tissue or to prepare the wound for an operative procedure. The main factors to be considered for successful wound care are (1) relief of pressure; (2) debridement of necrotic tissue; (3) wound cleansing; (4) dressing selection; and (5) prevention, diagnosis, and treatment of infection.
- Prevention is the single most important aspect in the management of pressure sores. Friction and shearing forces can be minimized by proper positioning. Skin care and prevention of soiling are important, with the intent being to keep the surface relatively free from moisture. Relief of pressure (even for 5 minutes once every 2 hours) is probably the single most important factor in preventing pressure sore formation.
- Medical management is generally indicated for lesions that are of moderate size and of relatively shallow depth (stage 1 or 2 lesions) and are not located over a bony prominence.
- Debridement can be accomplished by surgical or mechanical means (wet-to-dry dressing changes). Other effective therapies are hydrotherapy, wound irrigation, and dextrans. Pressure sores should be cleaned with normal saline.
- A number of agents have been used to disinfect pressure sores (e.g., povidone-iodine, iodophor, **sodium hypochlorite**, **hydrogen peroxide**, and **acetic acid**) as well as other types of open wounds; however, these agents should be avoided as they impair healing.
- See Table 47-4 for systemic treatment of an infected pressure sore. A short, 2-week trial of topical antibiotic (**silver sulfadiazine** or **triple antibiotic**) is recommended for a clean ulcer that is not healing or is producing a moderate amount of exudate despite appropriate care.

## INFECTED BITE WOUNDS

### DOG BITES

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- Patients at risk of acquiring an infection after a bite have had a puncture wound, have not sought medical attention within 12 hours of injury, and are older than 50 years of age.
- The infected dog bite is usually characterized by a localized cellulitis and pain at the site of injury. The cellulitis usually spreads proximally from the initial site of injury. If *Pasteurella multocida* is present, a rapidly progressing cellulitis with a gray malodorous discharge may be encountered.
- Most infections are polymicrobial, and the most frequently isolated organisms are *Pasteurella* spp., streptococci, staphylococci, *Moraxella*, and *Neisse-*

*ria*. The most common anaerobes are *Fusobacterium* spp., *Bacteroides* spp., *Porphyromonas*, and *Prevotella*.

- Wounds should be thoroughly irrigated with a sterile saline solution. Proper irrigation will reduce the bacterial count in the wound.
- The role of antimicrobials for noninfected dog bite wounds remains controversial because only 20% of wounds become infected. Antibiotic recommendations for empiric treatment include a 3- to 5-day course of therapy. Amoxicillin-clavulanic acid is commonly recommended for oral outpatient therapy. Alternative agents include doxycycline, or the combination of penicillin VK and dicloxacillin.
- **Tetracycline** or **trimethoprim-sulfamethoxazole** and **fluoroquinolones** are recommended as alternatives for infections caused by *P. multocida* or those allergic to penicillins (but not in children or pregnant women). **Erythromycin** may be considered an alternative in growing children or pregnant women.
- Treatment options for patients requiring intravenous therapy include  $\beta$ -lactam- $\beta$ -lactamase inhibitors (**ampicillin-sulbactam** or **piperacillin-tazobactam**), second-generation cephalosporins with antianaerobic activity (**cefotaxime**), and carbapenems.
- If the immunization history of a patient with anything other than a clean minor wound is not known, tetanus/diphtheria toxoids should be administered. Both tetanus/diphtheria toxoids and tetanus immune globulin should be administered to patients who have never been immunized.
- If a patient has been exposed to rabies, the treatment objectives consist of thorough irrigation of the wound, tetanus prophylaxis, antibiotic prophylaxis (if indicated), and immunization. Postexposure prophylaxis immunization consists of both passive antibody administration and vaccine administration.

## CAT BITES

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- Approximately 30% to 50% of cat bites become infected. These infections are frequently caused by *P. multocida*, which has been isolated in the oropharynx of 50% to 70% of healthy cats.
- The management of cat bites is similar to that discussed for dog bites. Antibiotic therapy with penicillin is the mainstay, and therapy is as described for dog bites.

## HUMAN BITES

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- Infections can occur in up to 10% to 50% of patients with human bites.
- Infections caused by these injuries are most often caused by the normal oral flora, which includes both aerobic and anaerobic microorganisms. The most frequent aerobic organisms are *Streptococcus* spp., *Staphylococcus* spp., and *Eikenella corrodens*. The most common anaerobic organisms are *Fusobacterium*, *Prevotella*, *Porphyromonas*, and *Peptostreptococcus* spp.
- Management of bite wounds consists of aggressive irrigation and topical wound dressing, surgical debridement, and immobilization of the affected area. Primary closure for human bites is not generally recommended. Tetanus toxoid and antitoxin may be indicated.

- If the biter is human immunodeficiency virus positive, the victim should have a baseline human immunodeficiency virus status determined and then repeated in 3 and 6 months. The bite should be thoroughly irrigated with a virucidal agent such as povidone-iodine. Victims may be offered antiretroviral chemoprophylaxis.
- Patients with noninfected bite injuries should be given prophylactic antibiotic therapy for 3 to 5 days. Amoxicillin-clavulanic acid (500 mg every 8 hours) is commonly recommended. Alternatives for penicillin-allergic patients include fluoroquinolones or trimethoprim-sulfamethoxazole in combination with clindamycin or metronidazole. First-generation cephalosporins, macrolides, clindamycin alone, or aminoglycosides are not recommended, as the sensitivity to *E. corrodens* is variable.
- Patients with serious injuries or clenched-fist injuries should be started on IV antibiotics (cefoxitin 1 g every 6 to 8 hours), ampicillin-sulbactam (1.5 to 3 g every 6 hours), or ertapenem (1 g every 24 hours).

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*See Chap. 114, Skin and Soft-Tissue Infections, authored by Douglas N. Fish, Susan L. Pendland, and Larry H. Danzinger, for a more detailed discussion of this topic.*

## DEFINITION

- Antibiotics administered before contamination of previously sterile tissues or fluids are considered prophylactic. The goal for prophylactic antibiotics is to prevent a surgical-site infection (SSI) from developing.
- Presumptive antibiotic therapy is administered when an infection is suspected but not yet proven. Therapeutic antibiotics are required for established infection.
- SSIs are classified as either incisional (such as cellulitis of the incision site) or involving an organ or space (such as with meningitis). Incisional SSIs may be superficial (skin or subcutaneous tissue) or deep (fascial and muscle layers). Both types, by definition, occur by postoperative day 30. This period extends to 1 year in the case of deep infection associated with prosthesis implantation.

## RISK FACTORS FOR SURGICAL WOUND INFECTION

- The traditional classification system developed by the National Research Council (NRC) stratifying surgical procedures by infection risk is reproduced in Table 48-1. The NRC wound classification for a specific procedure is determined intraoperatively and is the primary determinant of whether antibiotic prophylaxis is warranted.
- The Study on the Efficacy of Nosocomial Infection Control (SENIC) analyzed more than 100,000 surgery cases and identified abdominal operations, operations lasting more than 2 hours, contaminated or dirty procedures, and more than three underlying medical diagnoses as factors associated with an increased incidence of SSI. When the NRC classification described in Table 48-1 was stratified by the number of SENIC risk factors present, the infection rates varied by as much as a factor of 15 within the same operative category.
- The SENIC risk assessment technique has been modified to include the American Society of Anesthesiologists preoperative assessment score (Table 48-2). An American Society of Anesthesiologists score of 3 or above was associated with increased SSI risk.

## MICROBIOLOGY

- Bacteria involved in SSI are either acquired from the patient's normal flora (endogenous) or from contamination during the surgical procedure (exogenous).
- Loss of protective flora via antibiotics can upset the balance and allow pathogenic bacteria to proliferate and increase infectious risk.
- Normal flora can become pathogenic when translocated to a normally sterile tissue site or fluid during surgical procedures.

**TABLE 48-1** National Research Council Wound Classification, Risk of Surgical-Site Infection (SSI), and Indication for Antibiotics

Classification	SSI Rate (%)		Criteria	Antibiotics
	Preoperative Antibiotics	No Preoperative Antibiotics		
Clean	5.1	0.8	No acute inflammation or transection of GI, oropharyngeal, genitourinary, biliary, or respiratory tracts. Elective case, no technique break.	Not indicated unless high-risk procedure <sup>a</sup>
Clean-contaminated	10.1	1.3	Controlled opening of aforementioned tracts with minimal spillage/minor technique break. Clean procedures performed emergently or with major technique breaks.	Prophylactic antibiotics indicated
Contaminated	21.9	10.2	Acute, nonpurulent inflammation present. Major spillage/technique break during clean-contaminated procedure.	Prophylactic antibiotics indicated
Dirty	N/A	N/A	Obvious preexisting infection present (abscess, pus, or necrotic tissue present).	Therapeutic antibiotics required

N/A, not applicable.

<sup>a</sup>High-risk procedures include implantation of prosthetic materials and other procedures in which surgical-site infection is associated with high morbidity.

- According to the National Nosocomial Infections Surveillance System, the five most common pathogens encountered in surgical wounds are *Staphylococcus aureus*, coagulase-negative staphylococci, Enterococci, *Escherichia coli*, and *Pseudomonas aeruginosa*.
- Impaired host defenses, vascular occlusive states, traumatized tissues, or presence of a foreign body greatly decrease the number of bacteria required to cause an SSI.

**TABLE 48-2** American Society of Anesthesiologists Physical Status Classification

Class	Description
1	Normal healthy patient
2	Mild systemic disease
3	Severe systemic disease that is not incapacitating
4	Incapacitating systemic disease that is a constant threat to life
5	Not expected to survive 24 hours with or without operation

## ANTIBIOTIC ISSUES

## SCHEDULING ANTIBIOTIC ADMINISTRATION

- The following principles must be considered when providing antimicrobial surgical prophylaxis:
  - ✓ Antimicrobials should be delivered to the surgical site prior to the initial incision. They should be administered with anesthesia, just prior to initial incision. Antibiotics should not be prescribed to be given “on-call to the OR.”
  - ✓ Bactericidal antibiotic tissue concentrations should be maintained throughout the surgical procedure.
- Strategies to ensure appropriate antimicrobial prophylaxis use are described in Table 48-3.

## ANTIMICROBIAL SELECTION

- The choice of the prophylactic antimicrobial depends on the type of surgical procedure, most likely pathogenic organisms, safety and efficacy of the antimicrobial, current literature evidence supporting its use, and cost.
- Typically, gram-positive coverage is included in the choice of surgical prophylaxis, because organisms such as *S. aureus* and *S. epidermidis* are common skin flora.
- Parenteral antibiotic administration is favored because of its reliability in achieving suitable tissue concentrations.
- First-generation cephalosporins (particularly cefazolin) are the preferred choice, particularly for clean surgical procedures. Antianaerobic cephalosporins (such as cefoxitin or cefotetan) are appropriate choices when broad-spectrum anaerobic and gram-negative coverage is desired.
- Vancomycin may be considered for prophylactic therapy in surgical procedures involving implantation of a prosthetic device in which the rate

**TABLE 48-3** Strategies for Implementing an Institutional Program to Ensure the Appropriate Use of Antimicrobial Prophylaxis in Surgery

**1. Educate**

Develop an educational program that enforces the importance and rationale of timely antimicrobial prophylaxis.

Make this educational program available to all healthcare practitioners involved in the patient's care.

**2. Standardize the ordering process**

Establish a protocol (e.g., a preprinted order sheet) that standardizes antibiotic choice according to current published evidence, formulary availability, institutional resistance patterns, and cost.

**3. Standardize the delivery and administration process**

Use a system that ensures that antibiotics are prepared and delivered to the holding area in a timely fashion. Standardize the administration time to less than 1 hour preoperatively.

Designate responsibility and accountability for antibiotic administration.

Provide visible reminders to prescribe or administer prophylactic antibiotics (e.g., checklists).

Develop a system to remind surgeons or nurses to re-administer antibiotics intraoperatively during long procedures.

**4. Provide feedback**

Follow up with regular reports of compliance and infection rates.

of methicillin-resistant *S. aureus* (MRSA) is high. If the risk of MRSA is low and a  $\beta$ -lactam hypersensitivity exists, clindamycin can be used instead of cefazolin in order to limit vancomycin use.

## RECOMMENDATIONS FOR SPECIFIC TYPES OF SURGERIES

- Specific recommendations are summarized in Table 48-4.

### GASTRODUODENAL SURGERY

- The risk of infection rises with conditions that increase gastric pH and subsequent bacterial overgrowth, such as obstruction, hemorrhage, malignancy, or acid-suppression therapy (clean-contaminated).
- A single dose of IV **cefazolin** will provide adequate prophylaxis for most cases. Oral **ciprofloxacin** may be used for patients with  $\beta$ -lactam hypersensitivity.
- Postoperative therapeutic antibiotics may be indicated if perforation is detected during surgery, depending on whether an established infection is present.

### BILIARY TRACT SURGERY

- Antibiotic prophylaxis has been proven beneficial for surgery involving the biliary tract.
- Most frequently encountered organisms include *E. coli*, *Klebsiella*, and Enterococci. Single-dose prophylaxis with **cefazolin** is currently recommended. **Ciprofloxacin** and **levofloxacin** are alternatives for patients with  $\beta$ -lactam hypersensitivity.
- For low-risk patients undergoing elective laparoscopic cholecystectomy, antibiotic prophylaxis is of no benefit and is not recommended.
- Some surgeons use presumptive antibiotics for cases of acute cholecystitis or cholangitis and defer surgery until the patient is afebrile, in an attempt to decrease infection rates further, but this practice is controversial.
- Detection of an active infection during surgery (gangrenous gallbladder, suppurative cholangitis) is an indication for therapeutic postoperative antibiotics.

### COLORECTAL SURGERY

- Anaerobes and gram-negative aerobes predominate in SSIs (see Table 48-4), although gram-positive aerobes are also important. Therefore, the risk of an SSI in the absence of an adequate prophylactic regimen is substantial.
- Reducing bacteria load with a thorough bowel preparation regimen (4 L of polyethylene glycol solution administered orally the day before surgery) is controversial, even though it is used by most surgeons.
- The combination of 1 g of **neomycin** and 1 g of **erythromycin base** given orally 19, 18, and 9 hours preoperatively is the most commonly used oral regimen in the United States.
- Whether perioperative parenteral antibiotics, in addition to the standard preoperative oral antibiotic regimen, will lower SSI rates further is

**TABLE 48-4** Most Likely Pathogens and Specific Recommendations for Surgical Prophylaxis

Type of Operation	Likely Pathogens	Recommended Prophylaxis Regimen <sup>a</sup>	Comments	Grade of Recommendation <sup>b</sup>
<b>GI surgery</b>				
Gastroduodenal	Enteric gram-negative bacilli, gram-positive cocci, oral anaerobes	Cefazolin 1 g × 1	High-risk patients only (obstruction, hemorrhage, malignancy, acid suppression therapy, morbid obesity)	IA
Cholecystectomy	Enteric gram-negative bacilli, anaerobes	Cefazolin 1 g × 1 for high-risk patients Laparoscopic: None	High-risk patients only (acute cholecystitis, common duct stones, previous biliary surgery, jaundice, age >60 years, obesity, diabetes mellitus)	IA
Transjugular intrahepatic portosystemic shunt	Enteric gram-negative bacilli, anaerobes	Ceftriaxone 1 g × 1	Longer-acting cephalosporins preferred	IA
Appendectomy	Enteric gram-negative bacilli, anaerobes	Cefoxitin or cefotetan 1 g × 1	Second intraoperative dose of cefoxitin may be required if procedure lasts longer than 3 hours	IA
Colorectal	Enteric gram-negative bacilli, anaerobes	po: Neomycin 1 g + erythromycin base 1 g at 1 PM, 2 PM, and 11 PM 1 day preoperatively plus mechanical bowel preparation IV: Cefoxitin or cefotetan 1 g × 1	Benefits of oral plus IV is controversial except for colostomy reversal and rectal resection	IA
GI endoscopy	Variable depending on procedure but typically enteric gram-negative bacilli, gram-positive cocci, oral anaerobes	po: Amoxicillin 2 g × 1 IV: Ampicillin 2 g × 1 or cefazolin 1 g × 1	Only recommended for high-risk patients undergoing high-risk procedures	IA
<b>Urologic surgery</b>				
Prostate resection, bladder resection, cystoscopy	<i>Escherichia coli</i>	Cefazolin 1 g × 1	Generally not recommended for patients with sterile preoperative urine cultures	IB

<b>Gynecologic surgery</b>				
Cesarean section	Enteric gram-negative bacilli, anaerobes, group B streptococci, enterococci	Cefazolin 2 g × 1	Can be given before initial incision or after cord is clamped	IA
Hysterectomy	Enteric gram-negative bacilli, anaerobes, group B streptococci, enterococci	Vaginal: Cefazolin 1 g × 1 Abdominal: Cefotetan 1 g × 1 or cefazolin 1 g × 1	Metronidazole 1 g IV × 1 is recommended alternative for penicillin allergy	IA
<b>Head and neck surgery</b>				
Maxillofacial surgery	<i>Staphylococcus aureus</i> , streptococci oral anaerobes	Cefazolin 2 g or clindamycin 600 mg	Repeat intraoperative dose for operations longer than 4 hours	IA
Head and neck cancer resection	<i>S. aureus</i> , streptococci oral anaerobes	Clindamycin 600 mg at induction and every 8 hours × 2 more doses	Add gentamicin for clean-contaminated procedures	IA
<b>Cardiothoracic surgery</b>				
Cardiac surgery	<i>S. aureus</i> , <i>Staphylococcus epidermidis</i> , <i>Corynebacterium</i>	Cefazolin 1 g every 8 hours × 48 hours	Patients >80 kg should receive 2 g of cefazolin instead; in areas with high prevalence of <i>S. aureus</i> resistance, vancomycin should be considered	IA
Thoracic surgery	<i>S. aureus</i> , <i>S. epidermidis</i> , <i>Corynebacterium</i> , enteric gram-negative bacilli	Cefuroxime 750 mg IV every 8 hours × 48 hours	First-generation cephalosporins are deemed inadequate and shorter durations of prophylaxis have not been adequately studied	IA
<b>Vascular surgery</b>				
Abdominal aorta and lower extremity vascular surgery	<i>S. aureus</i> , <i>S. epidermidis</i> , enteric gram-negative bacilli	Cefazolin 1 g at induction and every 8 hours × 2 more doses	Although complications from infections may be infrequent, graft infections are associated with significant morbidity	IB

(continued)

**TABLE 48-4** Most Likely Pathogens and Specific Recommendations for Surgical Prophylaxis (Continued)

Type of Operation	Likely Pathogens	Recommended Prophylaxis Regimen <sup>a</sup>	Comments	Grade of Recommendation <sup>b</sup>
<b>Orthopedic surgery</b>				
Joint replacement	<i>S. aureus</i> , <i>S. epidermidis</i>	Cefazolin 1 g × 1 preoperatively, then every 8 hours × 2 more doses	Vancomycin reserved for penicillin-allergic patients or where institutional prevalence of methicillin-resistant <i>Staphylococcus aureus</i> warrants use	IA
Hip fracture repair	<i>S. aureus</i> , <i>S. epidermidis</i>	Cefazolin 1 g × 1 preoperatively, then every 8 hours for 48 hours	Compound fractures are treated as if infection is presumed	IA
Open/compound fractures	<i>S. aureus</i> , <i>S. epidermidis</i> , gram-negative bacilli, polymicrobial	Cefazolin 1 g × 1 preoperatively, then every 8 hours for a course of presumed infection	Gram-negative coverage (i.e., gentamicin) often indicated for severe open fractures	IA
<b>Neurosurgery</b>				
Cerebrospinal fluid shunt procedures	<i>S. aureus</i> , <i>S. epidermidis</i>	Cefazolin 1 g every 8 hours × 3 doses or ceftriaxone 2 g × 1	No agents have been shown to be better than cefazolin in randomized comparative trials.	IA
Craniotomy	<i>S. aureus</i> , <i>S. epidermidis</i>	Cefazolin 1 g × 1 or cefotaxime 1 g × 1	Trimethoprim–sulfamethoxazole (160/800 mg) IV × 1 can be substituted for patients with penicillin allergy	IA
Spinal surgery	<i>S. aureus</i> , <i>S. epidermidis</i>	Cefazolin 1 g × 1	Limited number of clinical trials comparing different treatment regimens	IB

<sup>a</sup>One-time doses are optimally infused at induction of anesthesia except as noted. Repeat doses may be required for long procedures.

<sup>b</sup>Strength of recommendations:

Category IA: Strongly recommended and supported by well-designed experimental, clinical, or epidemiologic studies.

Category IB: Strongly recommended and supported by some experimental, clinical, or epidemiologic studies and strong theoretical rationale.

Category II: Suggested and supported by suggestive clinical or epidemiologic studies or theoretical rationale.

controversial. Patients who cannot take oral medications should receive parenteral antibiotics.

- Postoperative antibiotics are unnecessary in the absence of any untoward events or findings during surgery.

## APPENDECTOMY

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- A cephalosporin with antianaerobic activity such as **cefoxitin** or **cefotetan** is currently recommended as a first-line agent. Cefotetan may be superior for longer operations because of its longer duration of action.
- Single-dose therapy with cefotetan is adequate. Intraoperative dosing of cefoxitin may be required if the procedure extends beyond 3 hours.
- Established intraabdominal infections require appropriate therapeutic postoperative antibiotics.

## UROLOGIC PROCEDURES

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- As long as the urine is sterile preoperatively, the risk of SSI after urologic procedures is low, and the benefit of prophylactic antibiotics in this setting is controversial. *E. coli* is the most frequently encountered organism.
- Antibiotic prophylaxis is warranted in high-risk patients (e.g., prolonged indwelling catheterization, positive urine cultures, and neutropenia) undergoing transurethral, perineal, or suprapubic resection of the prostate, resection of bladder tumors, or cystoscopy.
- Specific recommendations are listed in Table 48-4.
- Urologic procedures requiring an abdominal approach such as a nephrectomy or cystectomy require prophylaxis appropriate for a clean-contaminated abdominal procedure.

## CESAREAN SECTION

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- Antibiotics are efficacious to prevent SSIs for women undergoing cesarean section regardless of underlying risk factors.
- **Cefazolin**, 2 g IV, remains the drug of choice. Providing a broader spectrum by using cefoxitin against anaerobes or piperacillin for better coverage against *Pseudomonas* or enterococci, for example, does not lower postoperative infection rates any further in comparative studies.
- Antibiotics should be administered just after the umbilical cord is clamped, avoiding exposure of the infant to the drug.

## HYSTERECTOMY

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- Vaginal hysterectomies are associated with a high rate of postoperative infection when performed without the benefit of prophylactic antibiotics.
- A single preoperative dose of **cefazolin** or **cefoxitin** is recommended for vaginal hysterectomy. For patients with  $\beta$ -lactam hypersensitivity, a single preoperative dose of **metronidazole** or **doxycycline** is effective.
- Abdominal hysterectomy SSI rates are correspondingly lower than vaginal hysterectomy rates. However, prophylactic antibiotics are still recommended regardless of underlying risk factors.

- Both cefazolin and antianaerobic cephalosporins (e.g., **cefoxitin**, **cefotetan**) have been studied extensively for abdominal hysterectomy. Single-dose cefotetan is superior to single-dose cefazolin. The antibiotic course should not exceed 24 hours in duration.

## HEAD AND NECK SURGERY

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- Use of prophylactic antibiotics during head and neck surgery depends on the procedure type. Clean procedures, such as parotidectomy or a simple tooth extraction, are associated with low rates of SSI. Head and neck procedures involving an incision through a mucosal layer carry a high risk of SSI.
- Specific recommendations for prophylaxis are listed in Table 48-4.
- While typical doses of **cefazolin** are ineffective for anaerobic infections, the recommended 2-g dose produces concentrations high enough to be inhibitory to these organisms. A 24-hour duration has been used in most studies, but single-dose therapy may also be effective.
- For most head and neck cancer resections, 24 hours of clindamycin is appropriate.

## CARDIAC SURGERY

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- Although most cardiac surgeries are technically clean procedures, prophylactic antibiotics have been shown to lower rates of SSI.
- The usual pathogens are skin flora (see Table 48-4) and, rarely, gram-negative enteric organisms.
- Risk factors for developing an SSI after cardiac surgery include obesity, renal insufficiency, connective tissue disease, reexploration for bleeding, and poorly timed administration of antibiotics.
- **Cefazolin** has been extensively studied and is currently considered the drug of choice. Patients weighing 80 kg should receive 2 g cefazolin rather than 1 g. Doses should be administered no earlier than 60 minutes before the first incision and no later than the beginning of induction of anesthesia.
- Extending antibiotic administration beyond 48 hours does not lower SSI rates.
- **Vancomycin** use may be justified in hospitals with a high incidence of SSI with MRSA or when sternal wounds are to be explored for possible mediastinitis.

## NONCARDIAC VASCULAR SURGERY

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- Prophylactic antibiotics are beneficial, especially in procedures involving the abdominal aorta and the lower extremities.
- Twenty-four hours of prophylaxis with IV **cefazolin** is adequate. For patients with  $\beta$ -lactam allergy, 24 hours of oral **ciprofloxacin** is effective.

## ORTHOPEDIC SURGERY

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- Prophylactic antibiotics are beneficial in cases involving implantation of prosthetic material (pins, plates, artificial joints).
- The most likely pathogens mirror those of other clean procedures and include staphylococci and, infrequently, gram-negative aerobes.

- **Cefazolin** is the best-studied antibiotic and is thus the drug of choice. For hip fracture repairs and joint replacements, it should be administered for 24 hours. **Vancomycin** is not recommended unless a patient has a history of  $\beta$ -lactam hypersensitivity or the propensity for MRSA infection at the institution necessitates its use.

## NEUROSURGERY

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- The use of prophylactic antibiotics in neurosurgery is controversial.
- Single doses of **cefazolin** or, where required, **vancomycin** appear to lower SSI risk after craniotomy.

## MINIMALLY INVASIVE AND LAPAROSCOPIC SURGERY

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- The role of prophylactic antimicrobials depends on the type of procedure performed and preexisting risk factors for infection. There are insufficient clinical trials to provide general recommendations.

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*See Chap. 127, Antimicrobial Prophylaxis in Surgery, authored by Salmaan Kanji and John W. Devlin, for a more detailed discussion of this topic.*

## DEFINITION

- Tuberculosis (TB) is a communicable infectious disease caused by *Mycobacterium tuberculosis*. It can produce silent, latent infection as well as progressive, active disease.
- Globally, 2 billion people are infected and 2 million to 3 million people die from TB each year.
- *M. tuberculosis* is transmitted from person to person by coughing or sneezing. Close contacts of TB patients are most likely to become infected.
- Fifty-four percent of TB patients in the United States are foreign born, most often from Mexico, the Philippines, Vietnam, India, and China. In the United States, TB disproportionately affects ethnic minorities (African Americans, Hispanics, and Asians).
- Human immunodeficiency virus (HIV) is the most important risk factor for active TB, especially among people 25 to 44 years of age. An HIV-infected individual with TB infection is over 100-fold more likely to develop active disease than an HIV-seronegative patient.

## PATHOPHYSIOLOGY

- Primary infection is initiated by the alveolar implantation of organisms in droplet nuclei that are small enough (1 to 5  $\mu$ m) to escape the ciliary epithelial cells of the upper respiratory tract and reach the alveolar surface. Once implanted, the organisms multiply and are ingested by pulmonary macrophages, where they are killed, or, they continue to multiply. With bacterial multiplication, the macrophages eventually rupture, releasing many bacilli.
- Large numbers of activated macrophages surround the solid caseous (cheese-like) TB foci (the necrotic area) as a part of cell-mediated immunity. Delayed-type hypersensitivity also develops through activation and multiplication of T lymphocytes. Macrophages form granulomas to contain the organisms.
- Successful containment of *M. tuberculosis* requires activation of a subset of CD4 lymphocytes, referred to as *Th-1 cells*, which activate macrophages through secretion of interferon  $\gamma$ .
- Approximately 90% of patients who experience primary disease have no further clinical manifestations other than a positive skin test either alone or in combination with radiographic evidence of stable granulomas. Tissue necrosis and calcification of the originally infected site and regional lymph nodes may occur, resulting in the formation of a radiodense area referred to as a *Ghon complex*.
- Approximately 5% of patients (usually children, the elderly, or the immunocompromised) experience progressive primary disease at the site of the primary infection (usually the lower lobes) and frequently by dissemina-

tion, leading to meningitis and often to involvement of the upper lobes of the lung as well.

- Approximately 10% of patients develop reactivation disease, which arises subsequent to the hematogenous spread of the organism. In the United States, most cases of TB are believed to result from reactivation.
- Occasionally, a massive inoculum of organisms may be introduced into the bloodstream, causing widely disseminated disease and granuloma formation known as *miliary TB*.

## CLINICAL PRESENTATION

- The classic presentation of pulmonary TB is nonspecific, indicative only of a slowly evolving infectious process (Table 49-1). The onset of TB may be gradual.
- Physical examination is nonspecific, but suggestive of progressive pulmonary disease.
- Clinical features associated with extrapulmonary TB vary depending on the organ system(s) involved but typically consist of slowly progressive decline of organ function with low-grade fever and other constitutional symptoms.
- Patients with HIV may have atypical presentation. HIV-positive patients are less likely to have positive skin tests, cavitory lesions, or fever. HIV-positive patients have a higher incidence of extrapulmonary TB and are more likely to present with progressive primary disease.
- TB in the elderly is easily confused with other respiratory diseases. TB in the elderly is far less likely to present with positive skin tests, fevers, night sweats, sputum production, or hemoptysis.

## DIAGNOSIS

- The most widely used screening method for tuberculous infection is the tuberculin skin test, which uses purified protein derivative (PPD). Populations most likely to benefit from skin testing are listed in Table 49-2.
- The Mantoux method of PPD administration, which is the most reliable technique, consists of the intracutaneous injection of PPD containing 5

**TABLE 49-1** Clinical Presentation of Tuberculosis

### Signs and symptoms

Patients typically present with weight loss, fatigue, a productive cough, fever, and night sweats. Frank hemoptysis.

### Physical examination

Dullness to chest percussion, rales, and increased vocal fremitus are observed frequently on auscultation.

### Laboratory tests

Moderate elevations in the white blood cell count with a lymphocyte predominance.

### Chest radiograph

Patchy or nodular infiltrates in the apical area of the upper lobes or the superior segment of the lower lobes. Cavitation that may show air-fluid levels as the infection progresses.

**TABLE 49-2** Criteria for Tuberculin Positivity, by Risk Group

Reaction $\geq 5$ mm of Induration	Reaction $\geq 10$ mm of Induration	Reaction $\geq 15$ mm of Induration
Human immunodeficiency virus-positive persons	Recent immigrants (i.e., within the last 5 years) from high-prevalence countries	Persons with no risk factors for TB
Recent contacts of TB case patients	Injection drug users	
Fibrotic changes on chest radiograph consistent with prior TB	Residents and employees <sup>a</sup> of the following high-risk congregate settings: prisons and jails, nursing homes and other long-term facilities for the elderly, hospitals and other healthcare facilities, residential facilities for patients with acquired immunodeficiency syndrome, and homeless shelters	
Patients with organ transplants and other immunosuppressed patients (receiving the equivalent of prednisone for 1 month or more) <sup>b</sup>	Mycobacteriology laboratory personnel Persons with the following clinical conditions that place them at high risk: silicosis, diabetes mellitus, chronic renal failure, some hematologic disorders (e.g., leukemias and lymphomas), other specific malignancies (e.g., carcinoma of the head or neck and lung), weight loss of $\geq 10\%$ of ideal body weight, gastrectomy, and jejunioileal bypass Children younger than 4 years of age or infants, children, and adolescents exposed to adults at high risk	

TB, tuberculosis.

<sup>a</sup>For persons who are otherwise at low risk and are tested at the start of employment, a reaction of  $\geq 15$  mm induration is considered positive.

<sup>b</sup>Risk of TB in patients treated with corticosteroids increases with higher dose and longer duration.

Adapted from Centers for Disease Control and Prevention. Screening for tuberculosis and tuberculosis infection in high-risk populations: recommendations of the Advisory Council for the Elimination of Tuberculosis. *MMWR* 1995;44(No. RR-11):19–34.

tuberculin units. The test is read 48 to 72 hours after injection by measuring the diameter of the zone of induration.

- Some patients may exhibit a positive test after an initial negative test, and this is referred to as a *booster effect*.
- Confirmatory diagnosis of a clinical suspicion of TB must be made via chest x-ray and microbiologic examination of sputum or other infected material to rule out active disease.
- When active TB is suspected, attempts should be made to isolate *M. tuberculosis* from the infected site. Daily sputum collection over 3 consecutive days is recommended.

## DESIRED OUTCOME

- Rapid identification of new cases of TB
- Isolation of the patient with active disease to prevent spread
- Collection of appropriate samples for smears and cultures
- Prompt resolution of signs and symptoms of disease after initiation of treatment
- Achievement of a noninfectious state, thus ending isolation
- Adherence to the treatment regimen
- Cure as quickly as possible (generally with at least 6 months of treatment)

## TREATMENT

### GENERAL PRINCIPLES

- Drug treatment is the cornerstone of TB management. A minimum of two drugs, and generally three or four drugs, must be used simultaneously.
- Drug treatment is continued for at least 6 months and up to 2 to 3 years for some cases of multidrug-resistant TB (MDR-TB).
- Measures to assure adherence, such as directly observed therapy, are important.
- Patients with active disease should be isolated to prevent spread of the disease.
- Public health departments are responsible for preventing the spread of TB, finding where TB has already spread using contact investigation.
- Debilitated patients may require therapy for other medical conditions, including substance abuse and HIV infection, and some may need nutritional support.
- Surgery may be needed to remove destroyed lung tissue, space-occupying lesions, and some extrapulmonary lesions.

### PHARMACOLOGIC TREATMENT

#### Latent Infection

- As described in Table 49-3, chemoprophylaxis should be initiated in patients to reduce the risk of progression to active disease.
- **Isoniazid (INH)** 300 mg daily in adults is the preferred treatment for latent TB in the United States, generally given for 9 months.
- Individuals likely to be noncompliant may be treated with a regimen of 15 mg/kg (to a maximum of 900 mg) twice weekly with observation.
- Rifampin (RIF) 600 mg daily for 4 months can be used when INH resistance is suspected or when the patient cannot tolerate INH. Rifabutin 300 mg daily may be substituted for RIF for patients at high risk of drug interactions.
- Pregnant women, alcoholics, and patients with poor diets who are treated with INH should receive pyridoxine, 10 to 50 mg daily, to reduce the incidence of CNS effects or peripheral neuropathies.

#### Treating Active Disease

- Table 49-4 lists options for treatment of culture-positive pulmonary TB caused by drug-susceptible organisms. Doses of antituberculosis drugs are given in Table 49-5. The standard TB treatment regimen INH, RIF, pyrazinamide, and ethambutol for 2 months followed by INH and RIF for 4 months.
- Appropriate samples should be sent for culture and susceptibility testing prior to initiating therapy for all patients with active TB. This data should guide the initial drug selection for the new patient. If susceptibility data are not available, the drug resistance pattern in the area where the patient likely acquired TB should be used.
- If the patient is being evaluated for the retreatment of TB, it is imperative to know what drugs were used previously and for how long.

**TABLE 49-3** Recommended Drug Regimens for Treatment of Latent Tuberculosis (TB) Infection in Adults

Drug	Interval and Duration	Comments	Rating <sup>a</sup> (Evidence) <sup>b</sup>	
			HIV-	HIV+
Isoniazid	Daily for 9 months <sup>c,d</sup>	In HIV-infected patients, isoniazid may be administered concurrently with nucleoside reverse transcriptase inhibitors, protease inhibitors, or nonnucleoside reverse transcriptase inhibitors	A (II)	A (II)
	Twice weekly for 9 months <sup>c,d</sup>	Directly observed therapy must be used with twice-weekly dosing	B (II)	B (II)
Isoniazid	Daily for 6 months <sup>d</sup>	Not indicated for HIV-infected persons, those with fibrotic lesions on chest radiographs, or children	B (I)	C (I)
	Twice weekly for 6 months <sup>d</sup>	Directly observed therapy must be used with twice-weekly dosing	B (II)	C (I)
Rifampin	Daily for 4 months	For persons who are contacts of patients with isoniazid-resistant, rifampin-susceptible tuberculosis who cannot tolerate pyrazinamide	B (II)	B (III)

HIV, human immunodeficiency virus; -, negative; +, positive.

<sup>a</sup>Strength of recommendation: A, preferred; B, acceptable alternative; C, offer when A and B cannot be given.

<sup>b</sup>Quality of evidence: I, randomized clinical trial data; II, data from clinical trials that are not randomized or were conducted in other populations; III, expert opinion.

<sup>c</sup>Recommended regimen for children younger than 18 years of age.

<sup>d</sup>Recommended regimens for pregnant women. Some experts would use rifampin and pyrazinamide for 2 months as an alternative regimen in HIV-infected pregnant women, although pyrazinamide should be avoided during the first trimester.

Adapted from Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000;49(RR-6):31.

- Patients must complete 6 months or more of treatment. HIV-positive patients should be treated for an additional 3 months and at least 6 months from the time that they convert to smear and culture negativity. When INH and RIF cannot be used, treatment duration becomes 2 years or more, regardless of immune status.
- Patients who are slow to respond, those who remain culture positive at 2 months of treatment, those with cavitory lesions on chest radiograph, and HIV-positive patients should be treated for 9 months and for at least 6 months from the time they convert to smear and culture negativity.

### Drug Resistance

- If the organism is drug resistant, the aim is to introduce two or more active agents that the patient has not received previously. With MDR-TB, no standard regimen can be proposed. It is critical to avoid monotherapy or adding only a single drug to a failing regimen.
- Drug resistance should be suspected in the following situations:
  - ✓ Patients who have received prior therapy for TB
  - ✓ Patients from geographic areas with a high prevalence of resistance (New York City, Mexico, Southeast Asia, the Baltic countries, and the former Soviet states)

**TABLE 49-4** Drug Regimens for Culture-Positive Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms

Regimen	Initial Phase		Continuation Phase			Range of Total Doses (Minimal Duration)	Rating <sup>a</sup> (Evidence) <sup>b</sup>	
	Drugs	Interval and Doses <sup>c</sup> (Minimal Duration)	Regimen	Drugs	Interval and Doses <sup>c,d</sup> (Minimal Duration)		HIV-	HIV+
1	Isoniazid, rifampin, pyrazinamide, ethambutol	Seven days per week for 56 doses (8 weeks) or 5 days/week for 40 doses (8 weeks) <sup>c</sup>	1a	Isoniazid/rifampin	Seven days per week for 126 doses (18 weeks) or 5 days/week for 90 doses (18 weeks) <sup>c</sup>	182–130 (26 weeks)	A (I)	A (II)
			1b	Isoniazid/rifampin	Twice weekly for 36 doses (18 weeks)	92–76 (26 weeks)	A (I)	A (II) <sup>f</sup>
			1c <sup>g</sup>	Isoniazid/rifapentine	Once weekly for 18 doses (18 weeks)	74–58 (26 weeks)	B (I)	E (I)
2	Isoniazid, rifampin, pyrazinamide, ethambutol	Seven days per week for 14 doses (2 weeks), then twice weekly for 12 doses (6 weeks) or 5 days/week for 10 doses (2 weeks) <sup>e</sup> then twice weekly for 12 doses (6 weeks)	2a	Isoniazid/rifampin	Twice weekly for 36 doses (18 weeks)	62–58 (26 weeks)	A (II)	B (II) <sup>f</sup>
			2b <sup>g</sup>	Isoniazid/rifapentine	Once weekly for 18 doses (18 weeks)	44–40 (26 weeks)	B (I)	E (I)
3	Isoniazid, rifampin, pyrazinamide, ethambutol	Three times weekly for 24 doses (8 weeks)	3a	Isoniazid/rifampin	Three times weekly for 54 doses (18 weeks)	78 (26 weeks)	B (I)	B (II)
4	Isoniazid, rifampin, ethambutol	Seven days per week for 56 doses (8 weeks) or 5 days/week for 40 doses (8 weeks) <sup>c</sup>	4a	Isoniazid/rifampin	Seven days per week for 217 doses (31 weeks) or 5 days/week for 155 doses (31 weeks) <sup>e</sup>	273–195 (39 weeks)	C (I)	C (II)
			4b	Isoniazid/rifampin	Twice weekly for 62 doses (31 weeks)	118–102 (39 weeks)	C (I)	C (II)

HIV, human immunodeficiency virus.

<sup>a</sup>Ratings: A, preferred; B, acceptable alternative; C, offer when A and B cannot be given; E, should never be given.

<sup>b</sup>Evidence ratings: I, randomized clinical trial; II, data from clinical trials that were not randomized or were conducted in other populations; III, expert opinion.

<sup>c</sup>When directly observed therapy is used, drugs may be given 5 days per week and the necessary number of doses adjusted accordingly. Although there are no studies that compare five with seven daily doses, extensive experience indicates this would be an effective practice.

<sup>d</sup>Patients with cavitation on initial chest radiograph and positive cultures at completion of 2 months of therapy should receive a 7-month (31-week; either 217 doses [daily] or 62 doses [twice weekly]) continuation phase.

<sup>e</sup>Five-day-a-week administration is always given by directly observed therapy. Rating for 5-day-per-week regimens is A (III).

<sup>f</sup>Not recommended for HIV-infected patients with CD4<sup>+</sup> cell counts <100 cells/ $\mu$ L.

<sup>g</sup>Options 1c and 2b should be used only in HIV-negative patients who have negative sputum smears at the time of completion of 2 months of therapy and who do not have cavitation on initial chest radiograph. For patients started on this regimen and found to have a positive culture from the 2-month specimen, treatment should be extended an extra 3 months.

From Centers for Disease Control and Prevention. *Treatment of tuberculosis*. MMWR 2003;52(RR-11).

**TABLE 49-5** Doses<sup>a</sup> of Antituberculosis Drugs for Adults and Children<sup>b</sup>

Drug	Preparation	Adults/Children	Doses			
			Daily	1×/wk	2×/wk	3×/wk
<b>First-line drugs</b>						
Isoniazid	Tablets (50 mg, 100 mg, 300 mg); elixir (50 mg/5 mL); aqueous solution (100 mg/mL) for IV or intramuscular injection	Adults (max) Children (max)	5 mg/kg (300 mg) 10–15 mg/kg (300 mg)	15 mg/kg (900 mg) —	15 mg/kg (900 mg) 20–30 mg/kg (900 mg)	15 mg/kg (900 mg) —
Rifampin	Capsule (150 mg, 300 mg); powder may be suspended for oral administration; aqueous solution for IV injection	Adults <sup>c</sup> (max) Children (max)	10 mg/kg (600 mg) 10–20 mg/kg (600 mg)	— —	10 mg/kg (600 mg) 10–20 mg/kg (600 mg)	10 mg/kg (600 mg) —
Rifabutin	Capsule (150 mg)	Adults <sup>c</sup> (max) Children	5 mg/kg (300 mg) Appropriate dosing for children is unknown	— Appropriate dosing for children is unknown	5 mg/kg (300 mg) Appropriate dosing for children is unknown	5 mg/kg (300 mg) Appropriate dosing for children is unknown
Rifapentine	Tablet (150 mg, film coated)	Adults  Children	—  The drug is not approved for use in children	10 mg/kg (continuation phase) (600 mg usual adult dose)  The drug is not approved for use in children	—  The drug is not approved for use in children	—  The drug is not approved for use in children
Pyrazinamide	Tablet (500 mg, scored)	Adults  Children (max)	1,000 mg (40–55 kg) 1,500 mg (56–75 kg) 2,000 mg (76–90 kg) <sup>k</sup>	— — —	2,000 mg (40–55 kg) 3,000 mg (56–75 kg) 4,000 mg (76–90 kg) <sup>k</sup>	1,500 mg (40–55 kg) 2,500 mg (56–75 kg) 3,000 mg (76–90 kg) <sup>k</sup>
Ethambutol	Tablet (100 mg, 400 mg)	Adults  Children <sup>d</sup> (max)	15–30 mg/kg (2 g) 800 mg (40–55 kg) 1,200 mg (56–75 kg) 1,600 mg (76–90 kg) <sup>k</sup>	— — — —	50 mg/kg (2 g) 2,000 mg (40–55 kg) 2,800 mg (56–75 kg) 4,000 mg (76–90 kg) <sup>k</sup>	— 1,200 mg (40–55 kg) 2,000 mg (56–75 kg) 2,400 mg (76–90 kg) <sup>k</sup>
			15–20 mg/kg daily (1 g)	—	50 mg/kg (2.5 g)	—

## Second-line drugs

Cycloserine	Capsule (250 mg)	Adults (max)	10–15 mg/kg/day (1 g in two doses), usually 500–750 mg/day in two doses <sup>e</sup>	–	There are no data to support intermittent administration	There are no data to support intermittent administration	There are no data to support intermittent administration
Ethionamide	Tablet (250 mg)	Children (max)	10–15 mg/kg/day (1 g/day)	–	–	–	–
		Adults <sup>f</sup> (max)	15–20 mg/kg/day (1 g/day), usually 500–750 mg/day in a single daily dose or two divided doses <sup>f</sup>	–	There are no data to support intermittent administration	There are no data to support intermittent administration	There are no data to support intermittent administration
		Children (max)	15–20 mg/kg/day (1 g/day)	–	There are no data to support intermittent administration	There are no data to support intermittent administration	There are no data to support intermittent administration
Streptomycin	Aqueous solution (1-g vials) for IV or intramuscular administration	Adults (max)	<i>g</i>	<i>g</i>	<i>g</i>	<i>g</i>	<i>g</i>
		Children (max)	20–40 mg/kg/day (1 g)	–	–	20 mg/kg	–
Amikacin-kanamycin	Aqueous solution (500-mg and 1-g vials) for IV or intramuscular administration	Adults (max)	<i>g</i>	<i>g</i>	<i>g</i>	<i>g</i>	<i>g</i>
		Children (max)	15–30 mg/kg/day (1 g) IV or intramuscular as a single daily dose	–	–	15–30 mg/kg	–
Capreomycin	Aqueous solution (1-g vials) for IV or intramuscular administration	Adults (max)	<i>g</i>	<i>g</i>	<i>g</i>	<i>g</i>	<i>g</i>
		Children (max)	15–30 mg/kg/day (1 g) as a single daily dose	–	–	15–30 mg/kg	–
<i>p</i> -Aminosalicylic acid (PAS)	Granules (4-g packets) can be mixed with food; tablets (500 mg) are still available in some countries, but not in the United States; a solution for IV administration is available in Europe	Adults	8–12 g/day in two or three doses	–	There are no data to support intermittent administration	There are no data to support intermittent administration	There are no data to support intermittent administration
		Children (max)	200–300 mg/kg/day in two to four divided doses (10 g)	–	There are no data to support intermittent administration	There are no data to support intermittent administration	There are no data to support intermittent administration

(continued)

**TABLE 49-5** Doses<sup>a</sup> of Antituberculosis Drugs for Adults and Children<sup>b</sup> (Continued)

Drug	Preparation	Adults/Children	Doses			
			Daily	1×/wk	2×/wk	3×/wk
Levofloxacin	Tablets (250 mg, 500 mg, 750 mg); aqueous solution (500-mg vials) for IV injection	Adults	500–1,000 mg daily	There are no data to support intermittent administration	There are no data to support intermittent administration	There are no data to support intermittent administration
		Children	<i>h</i>	<i>h</i>	<i>h</i>	<i>h</i>
Moxifloxacin	Tablets (400 mg); aqueous solution (400 mg/250 mL) for IV injection	Adults	400 mg daily	There are no data to support intermittent administration	There are no data to support intermittent administration	There are no data to support intermittent administration
		Children	<i>i</i>	<i>i</i>	<i>i</i>	<i>i</i>
Gatifloxacin	Tablets (400 mg); aqueous solution (200 mg/20 mL; 400 mg/40 mL) for IV injection	Adults	400 mg daily	There are no data to support intermittent administration	There are no data to support intermittent administration	There are no data to support intermittent administration
		Children	<i>j</i>	<i>j</i>	<i>j</i>	<i>j</i>

<sup>a</sup>Dose per weight is based on ideal body weight. Children weighing more than 40 kg should be dosed as adults.

<sup>b</sup>For purposes of this document adult dosing begins at age 15 years.

<sup>c</sup>Dose may need to be adjusted when there is concomitant use of protease inhibitors or nonnucleoside reverse transcriptase inhibitors.

<sup>d</sup>The drug can likely be used safely in older children but should be used with caution in children less than 5 years of age, in whom visual acuity cannot be monitored. In younger children, ethambutol at the dose of 15 mg/kg per day can be used if there is suspected or proven resistance to isoniazid or rifampin.

<sup>e</sup>It should be noted that, although this is the dose recommended generally, most clinicians with experience using cycloserine indicate that it is unusual for patients to be able to tolerate this amount. Serum concentration measurements are often useful in determining the optimal dose for a given patient.

<sup>f</sup>The single daily dose can be given at bedtime or with the main meal.

<sup>g</sup>Dose: 15 mg/kg per day (1 g), and 10 mg/kg in persons older than 59 years of age (750 mg). Usual dose: 750–1,000 mg administered intramuscularly or IV, given as a single dose 5 to 7 days/week and reduced to two or three times per week after the first 2 to 4 months or after culture conversion, depending on the efficacy of the other drugs in the regimen.

<sup>h</sup>The long-term (more than several weeks) use of levofloxacin in children and adolescents has not been approved because of concerns about effects on bone and cartilage growth. However, most experts agree that the drug should be considered for children with tuberculosis caused by organisms resistant to both isoniazid and rifampin. The optimal dose is not known.

<sup>i</sup>The long-term (more than several weeks) use of moxifloxacin in children and adolescents has not been approved because of concerns about effects on bone and cartilage growth. The optimal dose is not known.

<sup>j</sup>The long-term (more than several weeks) use of gatifloxacin in children and adolescents has not been approved because of concerns about effects on bone and cartilage growth. The optimal dose is not known.

<sup>k</sup>Maximum dose regardless of weight.

- ✓ Patients who are homeless, institutionalized, IV drug abusers, and/or infected with HIV
- ✓ Patients who still have acid-fast bacilli–positive sputum smears after 2 months of therapy
- ✓ Patients who still have positive cultures after 2 to 4 months of therapy
- ✓ Patients who fail therapy or relapse after retreatment
- ✓ Patients known to be exposed to MDR-TB cases

### Special Populations

#### *Tuberculous Meningitis and Extrapulmonary Disease*

- In general, **INH**, **pyrazinamide**, **ethionamide**, and **cycloserine** penetrate the cerebrospinal fluid readily. Patients with CNS TB are often treated for longer periods (9 to 12 months). Extrapulmonary TB of the soft tissues can be treated with conventional regimens. TB of the bone is typically treated for 9 months, occasionally with surgical debridement.

#### *Children*

- TB in children may be treated with regimens similar to those used in adults, although some physicians still prefer to extend treatment to 9 months. Pediatric doses of drugs should be used.

#### *Pregnant Women*

- The usual treatment of pregnant women is INH, RIF, and ethambutol for 9 months.
- Women with TB should be cautioned against becoming pregnant, as the disease poses a risk to the fetus as well as to the mother. INH or ethambutol are relatively safe when used during pregnancy. Supplementation with B vitamins is particularly important during pregnancy. **RIF** has been rarely associated with birth defects, but those seen are occasionally severe, including limb reduction and CNS lesions. **Pyrazinamide** has not been studied in a large number of pregnant women, but anecdotal information suggests that it may be safe. **Ethionamide** may be associated with premature delivery, congenital deformities, and Down's syndrome when used during pregnancy. **Streptomycin** has been associated with hearing impairment in the newborn, including complete deafness. **Cycloserine** is not recommended during pregnancy.

#### *Renal Failure*

- In nearly all patients, INH and RIF do not require dose modifications in renal failure. Pyrazinamide and ethambutol typically require a reduction in dosing frequency from daily to three times weekly (Table 49-6).

## EVALUATION OF THERAPEUTIC OUTCOMES AND PATIENT MONITORING

- The most serious problem with TB therapy is nonadherence to the prescribed regimen. The most effective way to ensure adherence is with directly observed therapy.
- Symptomatic patients should be isolated and have sputum samples sent for acid-fast bacilli stains every 1 to 2 weeks until two consecutive smears are

**TABLE 49-6** Dosing Recommendations for Adult Patients with Reduced Renal Function and for Adult Patients Receiving Hemodialysis

Drug	Change in Frequency?	Recommended Dose and Frequency for Patients with Creatinine Clearance <30 mL/min or for Patients Receiving Hemodialysis
Isoniazid	No change	300 mg once daily, or 900 mg three times per week
Rifampin	No change	600 mg once daily, or 600 mg three times per week
Pyrazinamide	Yes	25–35 mg/kg per dose three times per week (not daily)
Ethambutol	Yes	15–25 mg/kg per dose three times per week (not daily)
Levofloxacin	Yes	750–1,000 mg per dose three times per week (not daily)
Cycloserine	Yes	250 mg once daily, or 500 mg/dose three times per week <sup>d</sup>
Ethionamide	No change	250–500 mg per dose daily
<i>p</i> -Aminosalicylic acid	No change	4 g per dose, twice daily
Streptomycin	Yes	12–15 mg/kg per dose two to three times per week (not daily)
Capreomycin	Yes	12–15 mg/kg per dose two to three times per week (not daily)
Kanamycin	Yes	12–15 mg/kg per dose two to three times per week (not daily)
Amikacin	Yes	12–15 mg/kg per dose two to three times per week (not daily)

Note: Standard doses are given unless there is intolerance.

The medications should be given after hemodialysis on the day of hemodialysis. Monitoring of serum drug concentrations should be considered to ensure adequate drug absorption, without excessive accumulation, and to assist in avoiding toxicity. Data currently are not available for patients receiving peritoneal dialysis. Until data become available, begin with doses recommended for patients receiving hemodialysis and verify adequacy of dosing, using serum concentration monitoring.

<sup>d</sup>The appropriateness of 250-mg daily doses has not been established. There should be careful monitoring for evidence of neurotoxicity.

negative. Once on maintenance therapy, patients should have sputum cultures performed monthly until negative, which generally occurs over 2 to 3 months. If sputum cultures continue to be positive after 2 months, drug susceptibility testing should be repeated, and serum drug concentrations should be checked.

- Patients should have blood urea nitrogen, serum creatinine, aspartate transaminase or alanine transaminase, and a complete blood count determined at baseline and periodically, depending on the presence of other factors that may increase the likelihood of toxicity (advanced age, alcohol abuse, and possibly pregnancy). Hepatotoxicity should be suspected in patients whose transaminases exceed five times the upper limit of normal or whose total bilirubin exceeds 3 mg/dL. At this point, the offending agent(s) should be discontinued, and alternatives selected.
- Therapy with INH results in a transient elevation in serum transaminases in 12% to 15% of patients and usually occurs within the first 8 to 12 weeks of therapy. Risk factors for hepatotoxicity include patient age, preexisting liver disease, and pregnancy or postpartum state. INH also may result in neurotoxicity, most frequently presenting as peripheral neuropathy or, in overdose, seizures, and coma. Patients with pyridoxine deficiency, such as alcoholics, children, and the malnourished, are at increased risk, as are patients who are slow acetylators of INH and those predisposed to neuropathy, such as those with diabetes.
- Elevations in hepatic enzymes have been attributed to RIF in 10% to 15% of patients, with overt hepatotoxicity occurring in less than 1%. More frequent adverse effects of RIF include rash, fever, and GI distress.

- RIF's induction of hepatic enzymes may enhance the elimination of a number of drugs, most notably protease inhibitors. Women who use oral contraceptives should be advised to use another form of contraception during therapy.
- The red colorizing effects of RIF on urine, other secretions, and contact lenses should be discussed with the patient.
- Retrobulbar neuritis is the major adverse effect noted in patients treated with ethambutol. Patients usually complain of a change in visual acuity and/or inability to see the color green. Vision testing should be performed on all patients who must receive ethambutol for more than 2 months.
- Impairment of eighth cranial nerve function is the most important adverse effect of streptomycin. Vestibular function is most frequently affected, but hearing may also be impaired. Audiometric testing should be performed in patients who must receive streptomycin for more than 2 months. Streptomycin occasionally causes nephrotoxicity.

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*See Chap. 116, Tuberculosis, authored by Charles A. Peloquin, for a more detailed discussion of this topic.*

## DEFINITION

- Infections of the urinary tract represent a wide variety of clinical syndromes, including urethritis, cystitis, prostatitis, and pyelonephritis.
- A urinary tract infection (UTI) is defined as the presence of microorganisms in the urine that cannot be accounted for by contamination. The organisms have the potential to invade the tissues of the urinary tract and adjacent structures.
- Lower tract infections include cystitis (bladder), urethritis (urethra), prostatitis (prostate gland), and epididymitis. Upper tract infections (such as pyelonephritis) involve the kidney and are referred to as *pyelonephritis*.
- Uncomplicated UTIs are not associated with structural or neurologic abnormalities that may interfere with the normal flow of urine or the voiding mechanism. Complicated UTIs are the result of a predisposing lesion of the urinary tract such as a congenital abnormality or distortion of the urinary tract, a stone, indwelling catheter, prostatic hypertrophy, obstruction, or neurologic deficit that interferes with the normal flow of urine and urinary tract defenses.
- Recurrent UTIs are characterized by multiple symptomatic episodes with asymptomatic periods occurring between these episodes. These infections are either due to reinfection or to relapse.
- Reinfections are caused by a different organism and account for the majority of recurrent UTIs.
- Relapse represents the development of repeated infections caused by the same initial organism.

## PATHOPHYSIOLOGY

- The bacteria causing UTIs usually originate from bowel flora of the host.
- UTIs can be acquired via three possible routes: the ascending, hematogenous, or lymphatic pathways.
- In females, the short length of the urethra and proximity to the perirectal area make colonization of the urethra likely. Bacteria are then believed to enter the bladder from the urethra. Once in the bladder, the organisms multiply quickly and can ascend the ureters to the kidney.
- Three factors determine the development of UTI: the size of the inoculum, virulence of the microorganism, and competency of the natural host defense mechanisms.
- Patients who are unable to void urine completely are at greater risk of developing UTIs and frequently have recurrent infections.
- An important virulence factor of bacteria is their ability to adhere to urinary epithelial cells by fimbriae, resulting in colonization of the urinary tract, bladder infections, and pyelonephritis. Other virulence factors include hemolysin, a cytotoxic protein produced by bacteria that lyses a wide range of cells

including erythrocytes, polymorphonuclear leukocytes, and monocytes; and aerobactin, which facilitates the binding and uptake of iron by *Escherichia coli*.

## MICROBIOLOGY

- The most common cause of uncomplicated UTIs is *E. coli*, accounting for more than 85% of community-acquired infections, followed by *Staphylococcus saprophyticus* (coagulase-negative staphylococcus), accounting for 5% to 15%.
- The urinary pathogens in complicated or nosocomial infections may include *E. coli*, which accounts for less than 50% of these infections, *Proteus* spp., *Klebsiella pneumoniae*, *Enterobacter* spp., *Pseudomonas aeruginosa*, staphylococci, and enterococci. *Candida* spp. have become common causes of urinary infection in the critically ill and chronically catheterized patient.
- The majority of UTIs are caused by a single organism; however, in patients with stones, indwelling urinary catheters, or chronic renal abscesses, multiple organisms may be isolated.

## CLINICAL PRESENTATION

- The typical symptoms of lower and upper UTIs are presented in Table 50-1.
- Symptoms alone are unreliable for the diagnosis of bacterial UTIs. The key to the diagnosis of a UTI is the ability to demonstrate significant numbers of microorganisms present in an appropriate urine specimen to distinguish contamination from infection.
- Elderly patients frequently do not experience specific urinary symptoms, but they will present with altered mental status, change in eating habits, or GI symptoms.
- A standard urinalysis should be obtained in the initial assessment of a patient. Microscopic examination of the urine should be performed by preparation of a Gram stain of unspun or centrifuged urine. The presence of at least one organism per oil-immersion field in a properly collected uncentrifuged specimen correlates with more than 100,000 bacteria/mL of urine.
- Criteria for defining significant bacteriuria are listed in Table 50-2.

**TABLE 50-1** Clinical Presentation of Urinary Tract Infections (UTIs) in Adults

### Signs and symptoms

Lower UTI: Dysuria, urgency, frequency, nocturia, suprapubic heaviness

Gross hematuria

Upper UTI: Flank pain, fever, nausea, vomiting, malaise

### Physical examination

Upper UTI: Costovertebral tenderness

### Laboratory tests

Bacteriuria

Pyuria (white blood cell count  $>10/\text{mm}^3$ )

Nitrite-positive urine (with nitrite reducers)

Leukocyte esterase-positive urine

Antibody-coated bacteria (upper UTI)

**TABLE 50-2** Diagnostic Criteria for Significant Bacteriuria

<p>≥10<sup>2</sup> CFU coliforms/mL or ≥10<sup>5</sup> CFU noncoliforms/mL in a symptomatic female</p> <p>≥10<sup>3</sup> CFU bacteria/mL in a symptomatic male</p> <p>≥10<sup>5</sup> CFU bacteria/mL in asymptomatic individuals on two consecutive specimens</p> <p>Any growth of bacteria on suprapubic catheterization in a symptomatic patient</p> <p>≥10<sup>2</sup> CFU bacteria/mL in a catheterized patient</p>
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CFU, colony forming unit.

- The presence of pyuria (more than 10 white blood cells/mm<sup>3</sup>) in a symptomatic patient correlates with significant bacteriuria.
- The nitrite test can be used to detect the presence of nitrate-reducing bacteria in the urine (such as *E. coli*). The leukocyte esterase test is a rapid dipstick test to detect pyuria.
- The most reliable method of diagnosing UTIs is by quantitative urine culture. Patients with infection usually have more than 10<sup>5</sup> bacteria/mL of urine, although as many as one-third of women with symptomatic infection have less than 10<sup>5</sup> bacteria/mL.
- A method to detect upper UTI is the antibody-coated bacteria test, an immunofluorescent method that detects bacteria coated with immunoglobulin in freshly voided urine.

## TREATMENT

### DESIRED OUTCOME

- The goals of treatment for UTIs are to prevent or treat systemic consequences of infection, eradicate the invading organism, and prevent recurrence of infection.

### GENERAL PRINCIPLES

- The management of a patient with a UTI includes initial evaluation, selection of an antibacterial agent and duration of therapy, and follow-up evaluation.
- The initial selection of an antimicrobial agent for the treatment of UTI is primarily based on the severity of the presenting signs and symptoms, the site of infection, and whether the infection is determined to be complicated or uncomplicated.

### PHARMACOLOGIC TREATMENT

- The ability to eradicate bacteria from the urinary tract is directly related to the sensitivity of the organism and the achievable concentration of the antimicrobial agent in the urine.
- The therapeutic management of UTIs is best accomplished by first categorizing the type of infection: acute uncomplicated cystitis, symptomatic abacteriuria, asymptomatic bacteriuria, complicated UTIs, recurrent infections, or prostatitis.
- Table 50-3 lists the most common agents used in the treatment of UTIs, along with comments concerning their general use.

**TABLE 50-3** Commonly Used Antimicrobial Agents in the Treatment of Urinary Tract Infections (UTIs)

Agent	Comments
<b>Oral therapy</b>	
Sulfonamides	These agents generally have been replaced by more agents due to resistance.
Trimethoprim-sulfamethoxazole	This combination is highly effective against most aerobic enteric bacteria except <i>Pseudomonas aeruginosa</i> . High urinary tract tissue levels and urine levels are achieved, which may be important in complicated infection treatment. Also effective as prophylaxis for recurrent infections.
<i>Penicillins</i>	Ampicillin is the standard penicillin that has broad-spectrum activity. Increasing <i>Escherichia coli</i> resistance has limited amoxicillin use in acute cystitis.
Ampicillin	Drug of choice for enterococci sensitive to penicillin. Amoxicillin-clavulanate is preferred for resistance problems.
Amoxicillin-clavulanic acid	
<i>Cephalosporins</i>	There are no major advantages of these agents over other agents in the treatment of UTIs, and they are more expensive. They may be useful in cases of resistance to amoxicillin and trimethoprim-sulfamethoxazole.
Cephalexin	These agents are not active against enterococci.
Cefaclor	
Cefadroxil	
Cefuroxime	
Cefixime	
Cefzil	
Cefpodoxime	
<i>Tetracyclines</i>	These agents have been effective for initial episodes of UTIs; however, resistance develops rapidly, and their use is limited. These agents also lead to candidal overgrowth. They are useful primarily for chlamydial infections.
Tetracycline	
Doxycycline	
Minocycline	
<i>Fluoroquinolones</i>	The newer quinolones have a greater spectrum of activity, including <i>P. aeruginosa</i> . These agents are effective for pyelonephritis and prostatitis.
Ciprofloxacin	Avoid in pregnancy and children. Moxifloxacin should not be used owing to inadequate urinary concentrations.
Norfloxacin	
Levofloxacin	
Nitrofurantoin	This agent is effective as both a therapeutic and prophylactic agent in patients with recurrent UTIs. Main advantage is the lack of resistance even after long courses of therapy. Adverse effects may limit use (GI intolerance, neuropathies, pulmonary reactions).
Azithromycin	Single-dose therapy for chlamydial infections.
Fosfomycin	Single-dose therapy for uncomplicated infections.
<b>Parenteral therapy</b>	
<i>Aminoglycosides</i>	Gentamicin and tobramycin are equally effective; gentamicin is less expensive. Tobramycin has better pseudomonal activity, which may be important in serious systemic infections. Amikacin generally is reserved for multiresistant bacteria.
Gentamicin	
Tobramycin	
Amikacin	
<i>Penicillins</i>	These agents generally are equally effective for susceptible bacteria. The extended-spectrum penicillins are more active against <i>P. aeruginosa</i> and enterococci and often are preferred over cephalosporins. They are very useful in renally impaired patients or when an aminoglycoside is to be avoided.
Ampicillin	
Ampicillin-sulbactam	
Ticarcillin-clavulanate	
Piperacillin-tazobactam	
<i>Cephalosporins, first-, second-, and third-generation</i>	Second- and third-generation cephalosporins have a broad spectrum of activity against gram-negative bacteria but are not active against enterococci and have limited activity against <i>P. aeruginosa</i> . Cefazidime and cefepime are active against <i>P. aeruginosa</i> . They are useful for nosocomial infections and urosepsis due to susceptible pathogens.
<i>Carbapenems</i>	These agents have broad spectrum of activity, including gram-positive, gram-negative, and anaerobic bacteria. Imipenem and meropenem are active against <i>P. aeruginosa</i> and enterococci, but ertapenem is not. All may be associated with candidal superinfections.
Imipenem-cilastatin	
Meropenem	
Ertapenem	

(continued)

**TABLE 50-3** Commonly Used Antimicrobial Agents in the Treatment of Urinary Tract Infections (UTIs) (Continued)

Agent	Comments
Aztreonam	A monobactam that is only active against gram-negative bacteria, including some strains of <i>P. aeruginosa</i> . Generally useful for nosocomial infections when aminoglycosides are to be avoided and in penicillin-sensitive patients.
<i>Fluoroquinolones</i> Ciprofloxacin Levofloxacin	These agents have broad-spectrum activity against both gram-negative and gram-positive bacteria. They provide urine and high-tissue concentrations and are actively secreted in reduced renal function.

- Table 50-4 presents an overview of various therapeutic options for outpatient therapy for UTI.
- Table 50-5 describes empiric treatment regimens for selected clinical situations.

**TABLE 50-4** Overview of Outpatient Antimicrobial Therapy for Lower Tract Infections in Adults

Indications	Antibiotic	Dose <sup>a</sup>	Interval	Duration
Lower tract Infections Uncomplicated	TMP-SMX	2 DS tablets	Single dose	1 day
	TMP-SMX	1 DS tablet	Twice a day	3 days
	Ciprofloxacin	250 mg	Twice a day	3 days
	Norfloxacin	400 mg	Twice a day	3 days
	Levofloxacin	250 mg	Once a day	3 days
	Amoxicillin	6 × 500 mg	Single dose	1 day
	Amoxicillin	500 mg	Twice a day	3 days
	Amoxicillin-clavulanate	500 mg	Every 8 hours	3 days
	TMP	100 mg	Twice a day	3 days
	Nitrofurantoin	100 mg	Every 6 hours	3 days
Complicated	Fosfomycin	3 g	Single dose	1 day
	TMP-SMX	1 DS tablet	Twice a day	7–10 days
	TMP	100 mg	Twice a day	7–10 days
	Norfloxacin	400 mg	Twice a day	7–10 days
	Ciprofloxacin	250–500 mg	Twice a day	7–10 days
	Levofloxacin	250 mg	Once a day	7–10 days
	Amoxicillin-clavulanate	500 mg	Every 8 hours	7–10 days
Recurrent infections	Nitrofurantoin	50 mg	Once a day	6 months
	TMP	100 mg	Once a day	6 months
	TMP-SMX	1/2 SS tablet	Once a day	6 months
Acute urethral syndrome Failure of TMP-SMX	TMP-SMX	1 DS tablet	Twice a day	3 days
	Azithromycin	1 g	Single dose	1 day
Acute pyelonephritis	Doxycycline	100 mg	Twice a day	7 days
	TMP-SMX	1 DS tablet	Twice a day	14 days
	Ciprofloxacin	500 mg	Twice a day	14 days
	Levofloxacin	250 mg	Once a day	14 days
	Amoxicillin-clavulanate	500 mg	Every 8 hours	14 days

DS, double strength; SS, single strength; TMP, trimethoprim; TMP-SMX, trimethoprim-sulfamethoxazole.

<sup>a</sup>Dosing intervals for normal renal function.

**TABLE 50-5** Empirical Treatment of Urinary Tract Infections and Prostatitis

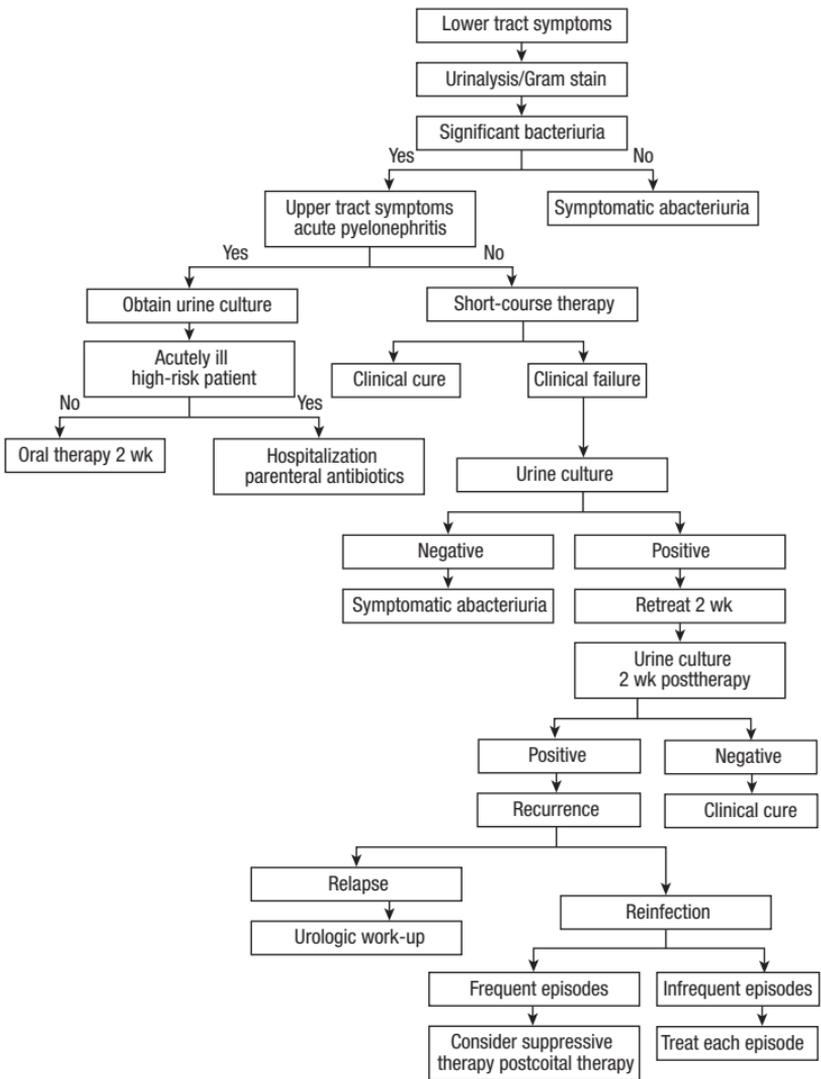
Diagnosis	Pathogens	Treatment Recommendation	Comments
Acute uncomplicated cystitis	<i>Escherichia coli</i> <i>Staphylococcus saprophyticus</i>	1. Trimethoprim-sulfamethoxazole × 3 days (A, I) <sup>a</sup> 2. Fluoroquinolone × 3 days (A, II) <sup>a</sup> 3. Nitrofurantoin × 7 days (B, I) <sup>a</sup> 4. $\beta$ -Lactams × 3 days (E, III) <sup>a</sup>	Short-course therapy more effective than single dose $\beta$ -Lactams as a group are not as effective in acute cystitis than trimethoprim-sulfamethoxazole or the fluoroquinolones <sup>a</sup>
Pregnancy	As above	1. Amoxicillin-clavulanate × 7 days 2. Cephalosporin × 7 days 3. Trimethoprim-sulfamethoxazole × 7 days	Avoid trimethoprim-sulfamethoxazole during third trimester
Acute pyelonephritis			
Uncomplicated	<i>E. coli</i>	1. Quinolone × 14 days (A, II) <sup>a</sup> 2. Trimethoprim-sulfamethoxazole (if susceptible) × 14 days (B, II) <sup>a</sup>	Can be managed as outpatient
Complicated	Gram-positive bacteria <i>E. coli</i> <i>Proteus mirabilis</i> <i>Klebsiella pneumoniae</i> <i>Pseudomonas aeruginosa</i> <i>Enterococcus faecalis</i>	1. Amoxicillin or amoxicillin-clavulanic acid × 14 days (B, III) <sup>a</sup> 1. Quinolone × 14 days (B, III) <sup>a</sup> 2. Extended-spectrum penicillin plus aminoglycoside (B, III) <sup>a</sup>	Severity of illness will determine duration of IV therapy; culture results should direct therapy Oral therapy may complete 14 days of therapy
Prostatitis	<i>E. coli</i> <i>K. pneumoniae</i> <i>Proteus</i> spp. <i>P. aeruginosa</i>	1. Trimethoprim-sulfamethoxazole × 4–6 weeks 2. Quinolone × 4–6 weeks	Acute prostatitis may require IV therapy initially Chronic prostatitis may require longer treatment periods or surgery

<sup>a</sup>Strength of recommendations: A, good evidence for; B, moderate evidence for; C, poor evidence for and against; D, moderate against; E, good evidence against. Quality of evidence: I, at least one proper randomized, controlled study; II, one well-designed clinical trial; III, evidence from opinions, clinical experience, and expert committees.

Data from Warren JW, Abrutyn E, Hebel JR, et al. Surviving sepsis campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med* 2004;32:858–873.

## Acute Uncomplicated Cystitis

- These infections are predominantly caused by *E. coli*, and antimicrobial therapy should be directed against this organism initially. Other causes include *S. saprophyticus* and occasionally *K. pneumoniae* and *Proteus mirabilis*.
- Because the causative organisms and their susceptibilities are generally known, a cost-effective approach to management is recommended that includes a urinalysis and initiation of empiric therapy without a urine culture (Fig. 50-1).
- Short-course therapy (3-day therapy) with **trimethoprim–sulfamethoxazole** or a **fluoroquinolone** (e.g., **ciprofloxacin**, **levofloxacin**, or **norfloxacin**) is superior to single-dose therapy for uncomplicated infection and



**FIGURE 50-1.** Management of urinary tract infections in females.

should be the treatment of choice. Amoxicillin or sulfonamides are not recommended because of the high incidence of resistant *E. coli*. Follow-up urine cultures are not necessary in patients who respond.

### Symptomatic Abacteriuria

- Single-dose or short-course therapy with **trimethoprim–sulfamethoxazole** has been used effectively, and prolonged courses of therapy are not necessary for the majority of patients.
- If single-dose or short-course therapy is ineffective, a culture should be obtained.
- If the patient reports recent sexual activity, therapy for *Chlamydia trachomatis* should be considered (azithromycin 1 g as a single dose or doxycycline 100 mg twice daily for 7 days).

### Asymptomatic Bacteriuria

- The management of asymptomatic bacteriuria depends on the age of the patient and, if female, whether she is pregnant. In children, treatment should consist of conventional courses of therapy, as described for symptomatic infections.
- In the nonpregnant female, therapy is controversial; however, it appears that treatment has little effect on the natural course of infections.
- Most clinicians feel that asymptomatic bacteriuria in the elderly is a benign disease and may not warrant treatment. The presence of bacteriuria can be confirmed by culture if treatment is considered.

## Complicated Urinary Tract Infections

### Acute Pyelonephritis

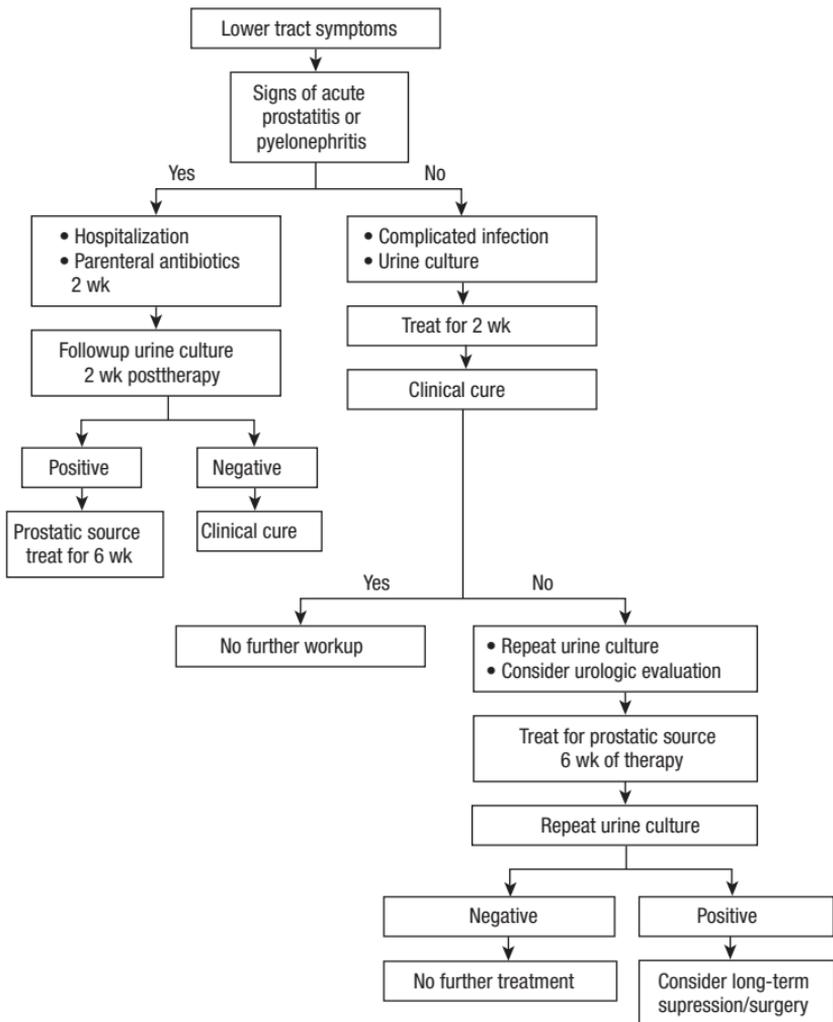
- The presentation of high-grade fever (greater than 38.3°C [100.9°F]) and severe flank pain should be treated as acute pyelonephritis, and aggressive management is warranted. Severely ill patients with pyelonephritis should be hospitalized and IV drugs administered initially. Milder cases may be managed with oral antibiotics in an outpatient setting.
- At the time of presentation, a Gram stain of the urine should be performed, along with urinalysis, culture, and sensitivities.
- In the mild to moderately symptomatic patient for whom oral therapy is considered, an effective agent should be administered for at least a 2-week period, although use of highly active agents for 7 to 10 days may be sufficient. Oral antibiotics that have shown efficacy in this setting include **trimethoprim–sulfamethoxazole** or **fluoroquinolones**. If a Gram stain reveals gram-positive cocci, *Streptococcus faecalis* should be considered and treatment directed against this pathogen (**ampicillin**).
- In the seriously ill patient, the traditional initial therapy has included an IV **fluoroquinolone**, an **aminoglycoside** with or without **ampicillin**, or an extended-spectrum **cephalosporin** with or without an aminoglycoside.
- If the patient has been hospitalized in the last 6 months, has a urinary catheter, or is in a nursing home, the possibility of *P. aeruginosa* and *enterococci* infection, as well as multiply-resistant organisms, should be considered. In this setting, **ceftazidime**, **ticarcillin-clavulanic acid**, **piperacillin**, **aztreonam**, **meropenem**, or **imipenem**, in combination with an

**aminoglycoside**, is recommended. If the patient responds to initial combination therapy, the aminoglycoside may be discontinued after 3 days.

- Follow-up urine cultures should be obtained 2 weeks after the completion of therapy to ensure a satisfactory response and to detect possible relapse.

### Urinary Tract Infections in Males

- The conventional view is that therapy in males requires prolonged treatment (Fig. 50-2).
- A urine culture should be obtained before treatment, because the cause of infection in men is not as predictable as in women.
- If gram-negative bacteria are presumed, **trimethoprim-sulfamethoxazole** or a **fluoroquinolone** is a preferred agent. Initial therapy is for 10 to 14



**FIGURE 50-2.** Management of urinary tract infections in males.

days. For recurrent infections in males, cure rates are much higher with a 6-week regimen of **trimethoprim–sulfamethoxazole**.

### Recurrent Infections

- Recurrent episodes of UTI (reinfections and relapses) account for a significant portion of all UTIs.
- These patients are most commonly women and can be divided into two groups: those with fewer than two or three episodes per year and those who develop more frequent infections.
- In patients with infrequent infections (i.e., fewer than three infections per year), each episode should be treated as a separately occurring infection. Short-course therapy should be used in symptomatic female patients with lower tract infection.
- In patients who have frequent symptomatic infections, long-term prophylactic antimicrobial therapy may be instituted (see Table 50-4). Therapy is generally given for 6 months, with urine cultures followed periodically.
- In women who experience symptomatic reinfections in association with sexual activity, voiding after intercourse may help prevent infection. Also, self-administered, single-dose prophylactic therapy with **trimethoprim–sulfamethoxazole** taken after intercourse has been found to significantly reduce the incidence of recurrent infection in these patients.
- Women who relapse after short-course therapy should receive a 2-week course of therapy. In patients who relapse after 2 weeks, therapy should be continued for another 2 to 4 weeks. If relapse occurs after 6 weeks of treatment, urologic examination should be performed, and therapy for 6 months or even longer may be considered.

## SPECIAL CONDITIONS

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### Urinary Tract Infection in Pregnancy

- In patients with significant bacteriuria, symptomatic or asymptomatic, treatment is recommended in order to avoid possible complications during the pregnancy. Therapy should consist of an agent with a relatively low adverse-effect potential (a **sulfonamide**, **cephalexin**, **amoxicillin**, **amoxicillin/clavulanate**, **nitrofurantoin**) administered for 7 days.
- Tetracyclines should be avoided because of teratogenic effects, and sulfonamides should not be administered during the third trimester because of the possible development of kernicterus and hyperbilirubinemia. Also, the fluoroquinolones should not be given because of their potential to inhibit cartilage and bone development in the newborn.

### Catheterized Patients

- When bacteriuria occurs in the asymptomatic, short-term catheterized patient (less than 30 days), the use of systemic antibiotic therapy should be withheld and the catheter removed as soon as possible. If the patient becomes symptomatic, the catheter should again be removed, and treatment as described for complicated infections should be started.
- The use of prophylactic systemic antibiotics in patients with short-term catheterization reduces the incidence of infection over the first 4 to 7 days.

In long-term catheterized patients, however, antibiotics only postpone the development of bacteriuria and lead to emergence of resistant organisms.

## PROSTATITIS

- Prostatitis is an inflammation of the prostate gland and surrounding tissue as a result of infection. It can be either acute or chronic. The acute form is characterized by a severe illness characterized by a sudden onset of fever and urinary and constitutional symptoms. Chronic bacterial prostatitis (CBP) represents a recurring infection with the same organism (relapse). Pathogenic bacteria and significant inflammatory cells must be present in prostatic secretions and urine to make the diagnosis of bacterial prostatitis.

## PATHOGENESIS AND ETIOLOGY

- The exact mechanism of bacterial infection of the prostate is not well understood. The possible routes of infection include ascending infection of the urethra, reflux of infected urine into prostatic ducts, invasion by rectal bacteria through direct extension or lymphatic spread, and by hematogenous spread.
- Gram-negative enteric organisms are the most frequent pathogens in acute bacterial prostatitis. *E. coli* is the predominant organism, occurring in 75% of cases.
- CBP is most commonly caused by *E. coli*, with other gram-negative organisms isolated much less often.

## CLINICAL PRESENTATION AND DIAGNOSIS

- The clinical presentation of bacterial prostatitis is presented in Table 50-6.
- Digital palpation of the prostate via the rectum may reveal a swollen, tender, warm, tense, or indurated prostate. Massage of the prostate will express a purulent discharge, which will readily grow the pathogenic organism. However, prostatic massage is contraindicated in acute bacterial prostatitis because of a risk of inducing bacteremia and associated pain.
- CBP is characterized by recurrent UTIs with the same pathogen.
- Urinary tract localization studies are critical to the diagnosis of CBP.

**TABLE 50-6** Clinical Presentation of Bacterial Prostatitis

### Signs and symptoms

Acute bacterial prostatitis: High fever, chills, malaise, myalgia, localized pain (perineal, rectal, sacrococcygeal), frequency, urgency, dysuria, nocturia, and retention

Chronic bacterial prostatitis: Voiding difficulties (frequency, urgency, dysuria), low back pain, and perineal and suprapubic discomfort

### Physical examination

Acute bacterial prostatitis: Swollen, tender, tense, or indurated gland

Chronic bacterial prostatitis: Boggy, indurated (enlarged) prostate in most patients

### Laboratory tests

Bacteriuria

Bacteria in expressed prostatic secretions

## TREATMENT

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- The majority of patients can be managed with oral antimicrobial agents, such as **trimethoprim–sulfamethoxazole** or the fluoroquinolones (**ciprofloxacin, levofloxacin**). When IV treatment is necessary, IV to oral sequential therapy with **trimethoprim–sulfamethoxazole** or a fluoroquinolone, such as ciprofloxacin or **ofloxacin**, would be appropriate.
- The total course of therapy should be 4 weeks, which may be prolonged to 6 to 12 weeks with chronic prostatitis.
- Parenteral therapy should be maintained until the patient is afebrile and less symptomatic. The conversion to an oral antibiotic can be considered if the patient has been afebrile for 48 hours or after 3 to 5 days of IV therapy.
- The choice of antibiotics in CBP should include those agents that are capable of crossing the prostatic epithelium into the prostatic fluid in therapeutic concentrations and that also possess the spectrum of activity to be effective.
- Currently, the fluoroquinolones (given for 4 to 6 weeks) appear to provide the best therapeutic option in the management of CBP.

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*See Chap. 120, Urinary Tract Infections and Prostatitis, authored by Elizabeth A. Coyle and Randall A. Prince, for a more detailed discussion of this topic.*

## DEFINITIONS

- Immunization is the process of introducing an antigen into the body to induce protection against an infectious agent without causing disease.
- Vaccines are substances administered to generate a protective immune response. Vaccines can be live attenuated or killed.
- Toxoids are inactivated bacterial toxins. They retain the ability to stimulate the formation of antitoxin, which are antibodies directed against the bacterial toxin.
- Adjuvants are inert substances, such as aluminum salts (i.e., alum), which enhance vaccine antigenicity by prolonging antigen absorption.
- Immune sera are sterile solutions containing antibody derived from human (immune globulin [IG]) or equine (antitoxin) sources.

## VACCINE AND TOXOID RECOMMENDATIONS

- The recommended schedules for routine immunization of children and adults are shown in Tables 51-1 and 51-2, respectively.
- In general, killed vaccines can be administered simultaneously at separate sites. Killed and live attenuated vaccines may be administered simultaneously at separate sites. If they cannot be administered simultaneously, they can be administered at any interval between doses with the exception of cholera (killed) and yellow fever (live) vaccines, which should be given at least 3 weeks apart. If live vaccines are not administered simultaneously, their administration should be separated by at least 4 weeks.
- Vaccination of pregnant women generally is deferred until after delivery because of concern over potential risk to the fetus. Administration of live attenuated vaccines should not be done during pregnancy, and inactivated vaccines may be administered to pregnant women when the benefits outweigh the risks. Hepatitis A, hepatitis B, meningococcal, inactivated polio, and pneumococcal polysaccharide vaccines should be administered to pregnant women who are at risk for contracting these infections.
- In general, severely immunocompromised individuals should not receive live vaccines.
- Patients with chronic conditions that cause limited immune deficiency (e.g., renal disease, diabetes, liver disease, and asplenia) and who are not receiving immunosuppressants may receive live attenuated and killed vaccines, and toxoids.
- Patients with active malignant disease may receive killed vaccines or toxoids but should not be given live vaccines. Live virus vaccines may be administered to persons with leukemia who have not received chemotherapy for at least 3 months.
- If a person has been receiving high-dose corticosteroids or have had a course lasting longer than 2 weeks, then at least 1 month should pass before immunization with live virus vaccines.

**TABLE 51-1** Childhood and Adolescent Immunization Schedule (2007)

**Recommended Immunization Schedule for Persons Aged 0–6 Years—UNITED STATES • 2007**

Vaccine ▼	Age ►	Birth	1 month	2 months	4 months	6 months	12 months	15 months	18 months	19–23 months	2–3 years	4–6 years
Hepatitis B <sup>1</sup>	HepB		HepB		see footnote 1	HepB			HepB Series			
Rotavirus <sup>2</sup>				Rota	Rota	Rota						
Diphtheria, Tetanus, Pertussis <sup>3</sup>				DTaP	DTaP	DTaP		DTaP				DTaP
<i>Haemophilus influenzae</i> type b <sup>4</sup>				Hib	Hib	Hib <sup>4</sup>	Hib		Hib			
Pneumococcal <sup>5</sup>				PCV	PCV	PCV	PCV				PCV PPV	
Inactivated Poliovirus				IPV	IPV	IPV						IPV
Influenza <sup>6</sup>						Influenza (Yearly)						
Measles, Mumps, Rubella <sup>7</sup>							MMR					MMR
Varicella <sup>8</sup>							Varicella					Varicella
Hepatitis A <sup>9</sup>							HepA (2 doses)				HepA Series	
Meningococcal <sup>10</sup>												MPSV4

 Range of recommended ages  
 Catch-up immunization  
 Certain high-risk groups

This schedule indicates the recommended ages for routine administration of currently licensed childhood vaccines, as of December 1, 2006, for children aged 0–6 years. Additional information is available at <http://www.cdc.gov/nip/recs/child-schedule.htm>. Any dose not administered at the recommended age should be administered at any subsequent visit, when indicated and feasible. Additional vaccines may be licensed and recommended during the year. Licensed combination vaccines may be used whenever any components of the combination are indicated and other components of the vaccine are

not contraindicated and if approved by the Food and Drug Administration for that dose of the series. Providers should consult the respective Advisory Committee on Immunization Practices statement for detailed recommendations. Clinically significant adverse events that follow immunization should be reported to the Vaccine Adverse Event Reporting System (VAERS). Guidance about how to obtain and complete a VAERS form is available at <http://www.vaers.hhs.gov> or by telephone, **800-822-7967**.

(continued)

**TABLE 51-1** Childhood and Adolescent Immunization Schedule (2007) (Continued)**1. Hepatitis B vaccine (HepB).** (Minimum age: birth)**At birth:**

- Administer monovalent HepB to all newborns before hospital discharge.
- If mother is hepatitis surface antigen (HBsAg)-positive, administer HepB and 0.5 mL of hepatitis B immune globulin (HBIG) within 12 hours of birth.
- If mother's HBsAg status is unknown, administer HepB within 12 hours of birth. Determine the HBsAg status as soon as possible and if HBsAg-positive, administer HBIG (no later than age 1 week).
- If mother is HBsAg-negative, the birth dose can only be delayed with physician's order and mother's negative HBsAg laboratory report documented in the infant's medical record.

**After the birth dose:**

- The HepB series should be completed with either monovalent HepB or a combination vaccine containing HepB. The second dose should be administered at age 1–2 months. The final dose should be administered at age  $\geq 24$  weeks. Infants born to HBsAg-positive mothers should be tested for HBsAg and antibody to HBsAg after completion of  $\geq 3$  doses of a licensed HepB series, at age 9–18 months (generally at the next well-child visit).

**4-month dose:**

- It is permissible to administer 4 doses of HepB when combination vaccines are administered after the birth dose. If monovalent HepB is used for doses after the birth dose, a dose at age 4 months is not needed.

**2. Rotavirus vaccine (Rota).** (Minimum age: 6 weeks)

- Administer the first dose at age 6–12 weeks. Do not start the series later than age 12 weeks.
- Administer the final dose in the series by age 32 weeks. Do not administer a dose later than age 32 weeks.
- Data on safety and efficacy outside of these age ranges are insufficient.

**3. Diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP).**

(Minimum age: 6 weeks)

- The fourth dose of DTaP may be administered as early as age 12 months, provided 6 months have elapsed since the third dose.
- Administer the final dose in the series at age 4–6 years.

**4. Haemophilus influenzae type b conjugate vaccine (Hib).**

(Minimum age: 6 weeks)

- If PRP-OMP (PedvaxHIB<sup>®</sup> or ComVax<sup>®</sup> [Merck]) is administered at ages 2 and 4 months, a dose at age 6 months is not required.
- TriHIBit<sup>®</sup> (DTaP/Hib) combination products should not be used for primary immunization but can be used as boosters following any Hib vaccine in children aged  $\geq 12$  months.

**5. Pneumococcal vaccine.** (Minimum age: 6 weeks for pneumococcal conjugate vaccine [PCV]; 2 years for pneumococcal polysaccharide vaccine [PPV])

- Administer PCV at ages 24–59 months in certain high-risk groups. Administer PPV to children aged  $\geq 2$  years in certain high-risk groups. See *MMWR* 2000;49(No. RR-9):1–35.

**6. Influenza vaccine.** (Minimum age: 6 months for trivalent inactivated influenza vaccine [TIV]; 5 years for live, attenuated influenza vaccine [LAIV])

- All children aged 6–59 months and close contacts of all children aged 0–59 months are recommended to receive influenza vaccine.
- Influenza vaccine is recommended annually for children aged  $\geq 59$  months with certain risk factors, health-care workers, and other persons (including household members) in close contact with persons in groups at high risk. See *MMWR* 2006;55(No. RR-10):1–41.
- For healthy persons aged 5–49 years, LAIV may be used as an alternative to TIV.
- Children receiving TIV should receive 0.25 mL if aged 6–35 months or 0.5 mL if aged  $\geq 3$  years.
- Children aged  $< 9$  years who are receiving influenza vaccine for the first time should receive 2 doses (separated by  $\geq 4$  weeks for TIV and  $\geq 6$  weeks for LAIV).

**7. Measles, mumps, and rubella vaccine (MMR).** (Minimum age: 12 months)

- Administer the second dose of MMR at age 4–6 years. MMR may be administered before age 4–6 years, provided  $\geq 4$  weeks have elapsed since the first dose and both doses are administered at age  $\geq 12$  months.

**8. Varicella vaccine.** (Minimum age: 12 months)

- Administer the second dose of varicella vaccine at age 4–6 years. Varicella vaccine may be administered before age 4–6 years, provided that  $\geq 3$  months have elapsed since the first dose and both doses are administered at age  $\geq 12$  months. If second dose was administered  $\geq 28$  days following the first dose, the second dose does not need to be repeated.

**9. Hepatitis A vaccine (HepA).** (Minimum age: 12 months)

- HepA is recommended for all children aged 1 year (i.e., aged 12–23 months). The 2 doses in the series should be administered at least 6 months apart.
- Children not fully vaccinated by age 2 years can be vaccinated at subsequent visits.
- HepA is recommended for certain other groups of children, including in areas where vaccination programs target older children. See *MMWR* 2006;55(No. RR-7):1–23.

**10. Meningococcal polysaccharide vaccine (MPSV4).** (Minimum age: 2 years)

- Administer MPSV4 to children aged 2–10 years with terminal complement deficiencies or anatomic or functional asplenia and certain other high risk groups. See *MMWR* 2005;54(No. RR-7):1–21.

Adapted from materials approved by the Advisory Committee on Immunization Practices (<http://www.cdc.gov/nip/acip>), the American Academy of Pediatrics (<http://www.aap.org>), and the American Academy of Family Physicians (<http://www.aafp.org>).

## Recommended Immunization Schedule for Persons Aged 7–18 Years—UNITED STATES • 2007

Vaccine ▼	Age ►	7–10 years	11–12 years	13–14 years	15 years	16–18 years
Tetanus, Diphtheria, Pertussis <sup>1</sup>	<i>see footnote 1</i>		Tdap		Tdap	
Human Papillomavirus <sup>2</sup>	<i>see footnote 2</i>		HPV (3 doses)		HPV Series	
Meningococcal <sup>3</sup>		MPSV4	MCV4		MCV4	MCV4
Pneumococcal <sup>4</sup>			PPV			
Influenza <sup>5</sup>			Influenza (Yearly)			
Hepatitis A <sup>6</sup>			HepA Series			
Hepatitis B <sup>7</sup>			HepB Series			
Inactivated Poliovirus <sup>8</sup>			IPV Series			
Measles, Mumps, Rubella <sup>9</sup>			MMR Series			
Varicella <sup>10</sup>			Varicella Series			



This schedule indicates the recommended ages for routine administration of currently licensed childhood vaccines, as of December 1, 2006, for children aged 7–18 years. Additional information is available at <http://www.cdc.gov/nip/recs/child-schedule.htm>. Any dose not administered at the recommended age should be administered at any subsequent visit, when indicated and feasible. Additional vaccines may be licensed and recommended during the year. Licensed combination vaccines may be used whenever any components of the combination are indicated and other components of the vaccine are not contraindicated and if approved by the Food

and Drug Administration for that dose of the series. Providers should consult the respective Advisory Committee on Immunization Practices statement for detailed recommendations. Clinically significant adverse events that follow immunization should be reported to the Vaccine Adverse Event Reporting System (VAERS). Guidance about how to obtain and complete a VAERS form is available at <http://www.vaers.hhs.gov> or by telephone, **800-822-7967**.

(continued)

**TABLE 51-1** Childhood and Adolescent Immunization Schedule (2007) (Continued)**1. Tetanus and diphtheria toxoids and acellular pertussis vaccine (Tdap).**

(Minimum age: 10 years for BOOSTRIX® and 11 years for ADACEL™)

- Administer at age 11–12 years for those who have completed the recommended childhood DTP/DTaP vaccination series and have not received a tetanus and diphtheria toxoids vaccine (Td) booster dose.
- Adolescents aged 13–18 years who missed the 11–12 year Td/DTaP booster dose should also receive a single dose of Tdap if they have completed the recommended childhood DTP/DTaP vaccination series.

**2. Human papillomavirus vaccine (HPV).** (Minimum age: 9 years)

- Administer the first dose of the HPV vaccine series to females at age 11–12 years.
- Administer the second dose 2 months after the first dose and the third dose 6 months after the first dose.
- Administer the HPV vaccine series to females at age 13–18 years if not previously vaccinated.

**3. Meningococcal vaccine.** (Minimum age: 11 years for meningococcal conjugate vaccine

[MCV4]; 2 years for meningococcal polysaccharide vaccine [MPSV4])

- Administer MCV4 at age 11–12 years and to previously unvaccinated adolescents at high school entry (at approximately age 15 years).
- Administer MCV4 to previously unvaccinated college freshmen living in dormitories; MPSV4 is an acceptable alternative.
- Vaccination against invasive meningococcal disease is recommended for children and adolescents aged ≥2 years with terminal complement deficiencies or anatomic or functional asplenia and certain other high-risk groups. See *MMWR* 2005;54(No. RR-7):1–21. Use MPSV4 for children aged 2–10 years and MCV4 or MPSV4 for older children.

**4. Pneumococcal polysaccharide vaccine (PPV).** (Minimum age: 2 years)

- Administer for certain high-risk groups. See *MMWR* 1997;46(No. RR-8):1–24, and *MMWR* 2000;49(No. RR-9):1–35.

**5. Influenza vaccine.** (Minimum age: 6 months for trivalent inactivated influenza vaccine [TIV]; 5 years for live, attenuated influenza vaccine [LAIV])

- Influenza vaccine is recommended annually for persons with certain risk factors, health-care workers, and other persons (including household members) in close contact with persons in groups at high risk. See *MMWR* 2006;55(No. RR-10):1–41.
- For healthy persons aged 5–49 years, LAIV may be used as an alternative to TIV.
- Children aged <9 years who are receiving influenza vaccine for the first time should receive 2 doses (separated by ≥4 weeks for TIV and ≥6 weeks for LAIV).

**6. Hepatitis A vaccine (HepA).** (Minimum age: 12 months)

- The 2 doses in the series should be administered at least 6 months apart.
- HepA is recommended for certain other groups of children, including in areas where vaccination programs target older children. See *MMWR* 2006;55 (No. RR-7):1–23.

**7. Hepatitis B vaccine (HepB).** (Minimum age: birth)

- Administer the 3-dose series to those who were not previously vaccinated.
- A 2-dose series of Recombivax HB® is licensed for children aged 11–15 years.

**8. Inactivated poliovirus vaccine (IPV).** (Minimum age: 6 weeks)

- For children who received an all-IPV or all-oral poliovirus (OPV) series, a fourth dose is not necessary if the third dose was administered at age ≥4 years.
- If both OPV and IPV were administered as part of a series, a total of 4 doses should be administered, regardless of the child's current age.

**9. Measles, mumps, and rubella vaccine (MMR).** (Minimum age: 12 months)

- If not previously vaccinated, administer 2 doses of MMR during any visit, with ≥4 weeks between the doses.

**10. Varicella vaccine.** (Minimum age: 12 months)

- Administer 2 doses of varicella vaccine to persons without evidence of immunity.
- Administer 2 doses of varicella vaccine to persons aged <13 years at least 3 months apart. Do not repeat the second dose, if administered ≥28 days after the first dose.
- Administer 2 doses of varicella vaccine to persons aged ≥13 years at least 4 weeks apart.

Adapted from materials approved by the Advisory Committee on Immunization Practices (<http://www.cdc.gov/nip/acip>), the American Academy of Pediatrics (<http://www.aap.org>), and the American Academy of Family Physicians (<http://www.aafp.org>).

## Catch-up Immunization Schedule for Persons Aged 4 Months–18 Years Who Start Late or Who Are More Than 1 Month Behind – UNITED STATES • 2007

The table below provides catch-up schedules and minimum intervals between doses for children whose vaccinations have been delayed. A vaccine series does not need to be restarted, regardless of the time that has elapsed between doses. Use the section appropriate for the child's age.

CATCH-UP SCHEDULE FOR PERSONS AGED 4 MONTHS–6 YEARS					
Vaccine	Minimum Age for Dose 1	Minimum Interval Between Doses			
		Dose 1 to Dose 2	Dose 2 to Dose 3	Dose 3 to Dose 4	Dose 4 to Dose 5
Hepatitis B <sup>1</sup>	Birth	4 weeks	8 weeks (and 16 weeks after first dose)		
Rotavirus <sup>2</sup>	6 wks	4 weeks	4 weeks		
Diphtheria, Tetanus, Pertussis <sup>3</sup>	6 wks	4 weeks	4 weeks	6 months	6 months <sup>3</sup>
<i>Haemophilus influenzae</i> type b <sup>4</sup>	6 wks	<p>4 weeks if first dose administered at age &lt;12 months</p> <p>8 weeks (as final dose) if first dose administered at age 12–14 months</p> <p>No further doses needed if first dose administered at age ≥15 months</p>	<p>4 weeks<sup>4</sup> if current age &lt;12 months</p> <p>8 weeks (as final dose)<sup>4</sup> if current age ≥12 months and second dose administered at age &lt;15 months</p> <p>No further doses needed if previous dose administered at age ≥15 months</p>	8 weeks (as final dose) This dose only necessary for children aged 12 months–5 years who received 3 doses before age 12 months	
Pneumococcal <sup>5</sup>	6 wks	<p>4 weeks if first dose administered at age &lt;12 months and current age &lt;24 months</p> <p>8 weeks (as final dose) if first dose administered at age ≥12 months or current age 24–59 months</p> <p>No further doses needed for healthy children if first dose administered at age ≥24 months</p>	<p>4 weeks if current age &lt;12 months</p> <p>8 weeks (as final dose) if current age ≥12 months</p> <p>No further doses needed for healthy children if previous dose administered at age ≥24 months</p>	8 weeks (as final dose) This dose only necessary for children aged 12 months–5 years who received 3 doses before age 12 months	
Inactivated Poliovirus <sup>6</sup>	6 wks	4 weeks	4 weeks	4 weeks <sup>6</sup>	
Measles, Mumps, Rubella <sup>7</sup>	12 mos	4 weeks			
Varicella <sup>8</sup>	12 mos	3 months			
Hepatitis A <sup>9</sup>	12 mos	6 months			

(continued)

**TABLE 51-1** Childhood and Adolescent Immunization Schedule (2007) (Continued)

CATCH-UP SCHEDULE FOR PERSONS AGED 7–18 YEARS					
Vaccine	Minimum Age for Dose 1	Minimum Interval Between Doses			
		Dose 1 to Dose 2	Dose 2 to Dose 3	Dose 3 to Dose 4	Dose 4 to Dose 5
Tetanus, Diphtheria/ Tetanus, Diphtheria, Pertussis <sup>10</sup>	7 yrs <sup>10</sup>	4 weeks	8 weeks if first dose administered at age <12 months 6 months if first dose administered at age ≥12 months	6 months if first dose administered at age <12 months	
Human Papillomavirus <sup>11</sup>	9 yrs	4 weeks	12 weeks		
Hepatitis A <sup>9</sup>	12 mos	6 months			
Hepatitis B <sup>1</sup>	Birth	4 weeks	8 weeks (and 16 weeks after first dose)		
Inactivated Poliovirus <sup>8</sup>	6 wks	4 weeks	4 weeks	4 weeks <sup>6</sup>	
Measles, Mumps, Rubella <sup>7</sup>	12 mos	4 weeks			
Varicella <sup>8</sup>	12 mos	4 weeks if first dose administered at age ≥13 years 3 months if first dose administered at age <13 years			

- 1. Hepatitis B vaccine (HepB).** *(Minimum age: birth)*
  - Administer the 3-dose series to those who were not previously vaccinated.
  - A 2-dose series of Recombivax HB<sup>®</sup> is licensed for children aged 11–15 years.
- 2. Rotavirus vaccine (Rota).** *(Minimum age: 6 weeks)*
  - Do not start the series later than age 12 weeks.
  - Administer the final dose in the series by age 32 weeks. Do not administer a dose later than age 32 weeks.
  - Data on safety and efficacy outside of these age ranges are insufficient.
- 3. Diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP).** *(Minimum age: 6 weeks)*
  - The fifth dose is not necessary if the fourth dose was administered at age ≥4 years.
  - DTaP is not indicated for persons aged ≥7 years.
- 4. Haemophilus influenzae type b conjugate vaccine (Hib).** *(Minimum age: 6 weeks)*
  - Vaccine is not generally recommended for children aged ≥5 years.
  - If current age <12 months and the first 2 doses were PRP-OMP (PedvaxHIB<sup>®</sup> or ComVax<sup>®</sup> [Merck]), the third (and final) dose should be administered at age 12–15 months and at least 8 weeks after the second dose.
  - If first dose was administered at age 7–11 months, administer 2 doses separated by 4 weeks plus a booster at age 12–15 months.
- 5. Pneumococcal conjugate vaccine (PCV).** *(Minimum age: 6 weeks)*
  - Vaccine is not generally recommended for children aged ≥5 years.
- 6. Inactivated poliovirus vaccine (IPV).** *(Minimum age: 6 weeks)*
  - For children who received an all-IPV or all-oral poliovirus (OPV) series, a fourth dose is not necessary if third dose was administered at age ≥4 years.
  - If both OPV and IPV were administered as part of a series, a total of 4 doses should be administered, regardless of the child's current age.
- 7. Measles, mumps, and rubella vaccine (MMR).** *(Minimum age: 12 months)*
  - The second dose of MMR is recommended routinely at age 4–6 years but may be administered earlier if desired.
  - If not previously vaccinated, administer 2 doses of MMR during any visit with ≥4 weeks between the doses.
- 8. Varicella vaccine.** *(Minimum age: 12 months)*
  - The second dose of varicella vaccine is recommended routinely at age 4–6 years but may be administered earlier if desired.
  - Do not repeat the second dose in persons aged <13 years if administered ≥28 days after the first dose.
- 9. Hepatitis A vaccine (HepA).** *(Minimum age: 12 months)*
  - HepA is recommended for certain groups of children, including in areas where vaccination programs target older children. See *MMWR* 2006;55(No. RR-7):1–23.
- 10. Tetanus and diphtheria toxoids vaccine (Td) and tetanus and diphtheria toxoids and acellular pertussis vaccine (Tdap).** *(Minimum ages: 7 years for Td, 10 years for BOOSTRIX<sup>®</sup>, and 11 years for ADACEL<sup>™</sup>)*
  - Tdap should be substituted for a single dose of Td in the primary catch-up series or as a booster if age appropriate; use Td for other doses.
  - A 5-year interval from the last Td dose is encouraged when Tdap is used as a booster dose. A booster (fourth) dose is needed if any of the previous doses were administered at age <12 months. Refer to ACIP recommendations for further information. See *MMWR* 2006;55(No. RR-3).
- 11. Human papillomavirus vaccine (HPV).** *(Minimum age: 9 years)*
  - Administer the HPV vaccine series to females at age 13–18 years if not previously vaccinated.

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**Information about reporting reactions after immunization is available online at <http://www.vaers.hhs.gov> or by telephone via the 24-hour national toll-free information line 800-822-7967. Suspected cases of vaccine-preventable disease should be reported to the state or local health department. Additional information, including precautions and contraindications for immunization, is available from the National Center for Immunization and Respiratory Diseases at <http://www.cdc.gov/nip/default.htm> or telephone, 800-CDC-INFO (800-232-4636).**

**TABLE 51-2 2007 Adult Immunization Schedule**
**Figure 1. Recommended adult immunization schedule, by vaccine and age group • United States, October 2007–September 2008**

Note: These recommendations must be read with the footnotes that follow.

Age group (yrs)▶ Vaccine ▼	19–49 years	50–64 years	≥65 years
Tetanus, diphtheria, pertussis (Td/Tdap) <sup>1*</sup>	1 dose Td booster every 10 yrs Substitute 1 dose of Tdap for Td		
Human papillomavirus (HPV) <sup>2*</sup>	3 doses females (0, 2, 6 months)		
Measles, mumps, rubella (MMR) <sup>3*</sup>	1 or 2 doses	1 dose	
Varicella <sup>4*</sup>	2 doses (0, 4–8 wks)		
Influenza <sup>5*</sup>	1 dose annually	1 dose annually	
Pneumococcal (polysaccharide) <sup>6,7</sup>	1–2 doses		1 dose
Hepatitis A <sup>8*</sup>	2 doses (0, 6–12 mos, or 0, 6–18 mos)		
Hepatitis B <sup>9*</sup>	3 doses (0, 1–2, 4–6 mos)		
Meningococcal <sup>10</sup>	1 or more doses		
Zoster <sup>11</sup>			1 dose

For all persons in this category who meet the age requirements and who lack evidence of immunity (e.g., lack documentation of vaccination or have as evidence of prior infection)

Recommended if some other risk factor is present (e.g., on the basis of medical, occupational, lifestyle, or other indications)

\*Covered by the Vaccine Injury Compensation Program.

 These schedules indicate the recommended age groups and medical indications for which administration of currently licensed vaccines is commonly indicated for adults ages 19 years and older, as of October 1, 2007. Licensed combination vaccines may be used whenever any components of the combination are indicated and when the vaccine's other components are not contraindicated. For detailed recommendations on all vaccines, including those used primarily for travelers or that are issued during the year, consult the manufacturers' package inserts and the complete statements from the Advisory Committee on Immunization Practices ([www.cdc.gov/vaccines/pubs/acip-list.htm](http://www.cdc.gov/vaccines/pubs/acip-list.htm)).

**Figure 2. Vaccines that might be indicated for adults based on medical and other indications • United States, October 2007–September 2008**

Indication ▶  Vaccine ▼	Pregnancy	Immuno-compromising conditions (excluding human immunodeficiency virus [HIV], medications, radiation) <sup>13</sup>	HIV infection <sup>1,12,13</sup>		Diabetes, heart disease, chronic pulmonary disease, chronic alcoholism	Asplenia <sup>12</sup> (Including elective splenectomy and terminal complement deficiencies)	Chronic liver disease	Kidney failure, end-stage renal disease, receipt of hemodialysis	Health-care personnel	
			CD4+ T lymphocyte count	<200 cells/μL						≥200 cells/μL
Tetanus, diphtheria, pertussis (Td/Tdap) <sup>1*</sup>			1-dose Td booster every 10 yrs Substitute 1 dose of Tdap for Td							
Human papillomavirus (HPV) <sup>2*</sup>			3 doses for females through age 26 years (0, 2, 6 mos)							
Measles, mumps, rubella (MMR) <sup>3*</sup>		Contraindicated	1 or 2 doses							
Varicella <sup>4*</sup>		Contraindicated	2 doses (0, 4–8 wks)							
Influenza <sup>5*</sup>			1 dose TIV annually							1 dose TIV or LAIV annually
Pneumococcal (polysaccharide) <sup>6,7</sup>		1–2 doses	1–2 doses						1–2 doses	
Hepatitis A <sup>8*</sup>			2 doses (0, 6–12 mos, or 0, 6–18 mos)							
Hepatitis B <sup>9*</sup>			3 doses (0, 1–2, 4–6 mos)							
Meningococcal <sup>10</sup>			1 or more doses							
Zoster <sup>11</sup>		Contraindicated	1 dose							



For all persons in this category who meet the age requirements and who lack evidence of immunity (e.g., lack documentation of vaccination or have as evidence of prior infection)



Recommended if some other risk factor is present (e.g., on the basis of medical, occupational, lifestyle, or other indications)

\*Covered by the Vaccine Injury Compensation Program.

These schedules indicate the recommended age groups and medical indications for which administration of currently licensed vaccines is commonly indicated for adults ages 19 years and older, as of October 1, 2007. Licensed combination vaccines may be used whenever any components of the combination are indicated and when the vaccine's other components are not contraindicated. For detailed recommendations on all vaccines, including those used primarily for travelers or that are issued during the year, consult the manufacturers' package inserts and the complete statements from the Advisory Committee on Immunization Practices ([www.cdc.gov/vaccines/pubs/acip-list.html](http://www.cdc.gov/vaccines/pubs/acip-list.html)).

(continued)

**TABLE 51-2 2007 Adult Immunization Schedule (Continued)****Footnotes****Recommended Adult Immunization Schedule • United States, October 2007 – September 2008**

For complete statements by the Advisory Committee on Immunization Practices (ACIP), visit [www.cdc.gov/vaccines/pubs/ACIP-list.htm](http://www.cdc.gov/vaccines/pubs/ACIP-list.htm).

**1. Tetanus, diphtheria, and acellular pertussis (Td/Tdap) vaccination.**

Tdap should replace a single dose of Td for adults aged <65 years who have not previously received a dose of Tdap. Only one of two Tdap products (Adacel<sup>®</sup>[sanofi pasteur]) is licensed for use in adults.

Adults with uncertain histories of a complete primary vaccination series with tetanus and diphtheria toxoid-containing vaccines should begin or complete a primary vaccination series. A primary series for adults is 3 doses of tetanus and diphtheria toxoid-containing vaccines; administer the first 2 doses at least 4 weeks apart and the third dose 6–12 months after the second. However, Tdap can substitute for any one of the doses of Td in the 3-dose primary series. The booster dose of tetanus and diphtheria toxoid-containing vaccine should be administered to adults who have completed a primary series and if the last vaccination was received ≥10 years previously. Tdap or Td vaccine may be used, as indicated.

If the person is pregnant and received the last Td vaccination ≥10 years previously, administer Td during the second or third trimester; if the person received the last Td vaccination in <10 years, administer Tdap during the immediate postpartum period. A one-time administration of 1 dose of Tdap with an interval as short as 2 years from a previous Td vaccination is recommended for postpartum women, close contacts of infants aged <12 months, and all health-care workers with direct patient contact. In certain situations, Td can be deferred during pregnancy and Tdap substituted in the immediate postpartum period, or Tdap can be administered instead of Td to a pregnant woman after an informed discussion with the woman.

Consult the ACIP statement for recommendations for administering Td as prophylaxis in wound management.

**2. Human papillomavirus (HPV) vaccination.**

HPV vaccination is recommended for all females aged ≤26 years who have not completed the vaccine series. History of genital warts, abnormal Papanicolaou test, or positive HPV DNA test is not evidence of prior infection with all vaccine HPV types; HPV vaccination is still recommended for these persons.

Ideally, vaccine should be administered before potential exposure to HPV through sexual activity; however, females who are sexually active should still be vaccinated. Sexually active females who have not been infected with any of the HPV vaccine types receive the full benefit of the vaccination. Vaccination is less beneficial for females who have already been infected with one or more of the HPV vaccine types.

A complete series consists of 3 doses. The second dose should be administered 2 months after the first dose; the third dose should be administered 6 months after the first dose.

Although HPV vaccination is not specifically recommended for females with the medical indications described in Figure 2, "Vaccines that might be indicated for adults based on medical and other indications," it is not a live-virus vaccine and can be administered. However, immune response and vaccine efficacy might be less than in persons who do not have the medical indications described or who are immunocompetent.

**3. Measles, mumps, rubella (MMR) vaccination.**

*Measles component:* Adults born before 1957 can be considered immune to measles. Adults born during or after 1957 should receive ≥1 dose of MMR unless they have a medical contraindication, documentation of ≥1 dose, history of measles based on health-care provider diagnosis, or laboratory evidence of immunity.

A second dose of MMR is recommended for adults who 1) have been recently exposed to measles or are in an outbreak setting; 2) have been previously vaccinated with killed measles vaccine; 3) have been vaccinated with an unknown type of measles vaccine during 1963–1967; 4) are students in postsecondary educational institutions; 5) work in a health-care facility; or 6) plan to travel internationally.

*Mumps component:* Adults born before 1957 can generally be considered immune to mumps. Adults born during or after 1957 should receive 1 dose of MMR unless they have a medical contraindication, history of mumps based on health-care provider diagnosis, or laboratory evidence of immunity.

A second dose of MMR is recommended for adults who 1) are in an age group that is affected during a mumps outbreak; 2) are students in postsecondary educational institutions; 3) work in a health-care facility; or 4) plan to travel internationally. For unvaccinated health-care workers born before 1957 who do not have other evidence of mumps immunity, consider administering 1 dose on a routine basis and strongly consider administering a second dose during an outbreak.

*Rubella component:* Administer 1 dose of MMR vaccine to women whose rubella vaccination history is unreliable or who lack laboratory evidence of immunity. For women of childbearing age, regardless of birth year, routinely determine rubella immunity and counsel women regarding congenital rubella syndrome. Women who do not have evidence of immunity should receive MMR vaccine upon completion or termination of pregnancy and before discharge from the health-care facility.

#### 4. Varicella vaccination.

All adults without evidence of immunity to varicella should receive 2 doses of single-antigen varicella vaccine unless they have a medical contraindication. Special consideration should be given to those who 1) have close contact with persons at high risk for severe disease (e.g., health-care personnel and family contacts of immunocompromised persons) or 2) are at high risk for exposure or transmission (e.g., teachers; child care employees; residents and staff members of institutional settings, including correctional institutions; college students; military personnel; adolescents and adults living in households with children; nonpregnant women of childbearing age; and international travelers).

Evidence of immunity to varicella in adults includes any of the following: 1) documentation of 2 doses of varicella vaccine at least 4 weeks apart; 2) U.S.-born before 1980 (although for health-care personnel and pregnant women birth before 1980 should not be considered evidence of immunity); 3) history of varicella based on diagnosis or verification of varicella by a health-care provider (for a patient reporting a history of or presenting with an atypical case, a mild case, or both, health-care providers should seek either an epidemiologic link with a typical varicella case or to a laboratory-confirmed case or evidence of laboratory confirmation, if it was performed at the time of acute disease); 4) history of herpes zoster based on health-care provider diagnosis; or 5) laboratory evidence of immunity or laboratory confirmation of disease.

Assess pregnant women for evidence of varicella immunity. Women who do not have evidence of immunity should receive the first dose of varicella vaccine upon completion or termination of pregnancy and before discharge from the health-care facility. The second dose should be administered 4–8 weeks after the first dose.

#### 5. Influenza vaccination.

*Medical indications:* Chronic disorders of the cardiovascular or pulmonary systems, including asthma; chronic metabolic diseases, including diabetes mellitus, renal or hepatic dysfunction, hemoglobinopathies, or immunosuppression (including immunosuppression caused by medications or human immunodeficiency virus [HIV]); any condition that compromises respiratory function or the handling of respiratory secretions or that can increase the risk of aspiration (e.g., cognitive dysfunction, spinal cord injury, or seizure disorder or other neuromuscular disorder); and pregnancy during the influenza season. No data exist on the risk for severe or complicated influenza disease among persons with asplenia; however, influenza is a risk factor for secondary bacterial infections that can cause severe disease among persons with asplenia.

*Occupational indications:* Health-care personnel and employees of long-term care and assisted-living facilities.

*Other indications:* Residents of nursing homes and other long-term care and assisted-living facilities; persons likely to transmit influenza to persons at high risk (e.g., in-home household contacts and caregivers of children aged 0–59 months, or persons of all ages with high-risk conditions); and anyone who would like to be vaccinated. Healthy, nonpregnant adults aged ≤49 years without high-risk medical conditions who are not contacts of severely immunocompromised persons in special care units can receive either intranasally administered live, attenuated influenza vaccine (FluMist<sup>®</sup>) or inactivated vaccine. Other persons should receive the inactivated vaccine.

#### 6. Pneumococcal polysaccharide vaccination.

*Medical indications:* Chronic pulmonary disease (excluding asthma); chronic cardiovascular diseases; diabetes mellitus; chronic liver diseases, including liver disease as a result of alcohol abuse (e.g., cirrhosis); chronic alcoholism, chronic renal failure or nephrotic syndrome; functional or anatomic asplenia (e.g., sickle cell disease or splenectomy [if elective splenectomy is planned, vaccinate at least 2 weeks before surgery]); immunosuppressive conditions; and cochlear implants and cerebrospinal fluid leaks. Vaccinate as close to HIV diagnosis as possible.

*Other indications:* Alaska Natives and certain American Indian populations and residents of nursing homes or other long-term care facilities.

#### 7. Revaccination with pneumococcal polysaccharide vaccine.

One-time revaccination after 5 years for persons with chronic renal failure or nephrotic syndrome; functional or anatomic asplenia (e.g., sickle cell disease or splenectomy); or immunosuppressive conditions. For persons aged ≥65 years, one-time revaccination if they were vaccinated ≥5 years previously and were aged <65 years at the time of primary vaccination.

#### 8. Hepatitis A vaccination.

*Medical indications:* Persons with chronic liver disease and persons who receive clotting factor concentrates.

*Behavioral indications:* Men who have sex with men and persons who use illegal drugs.

*Occupational indications:* Persons working with hepatitis A virus (HAV)-infected primates or with HAV in a research laboratory setting.

*Other indications:* Persons traveling to or working in countries that have high or intermediate endemicity of hepatitis A (a list of countries is available at [www.cdc.gov/travel/content/diseases.aspx](http://www.cdc.gov/travel/content/diseases.aspx)) and any person seeking protection from HAV infection.

Single-antigen vaccine formulations should be administered in a 2-dose schedule at either 0 and 6–12 months (Havrix<sup>®</sup>), or 0 and 6–18 months (Vaqta<sup>®</sup>). If the combined hepatitis A and hepatitis B vaccine (Twinrix<sup>®</sup>) is used, administer 3 doses at 0, 1, and 6 months.

#### 9. Hepatitis B vaccination.

*Medical indications:* Persons with end-stage renal disease, including patients receiving hemodialysis; persons seeking evaluation or treatment for a sexually transmitted disease (STD); persons with HIV infection; and persons with chronic liver disease.

*Occupational indications:* Health-care personnel and public-safety workers who are exposed to blood or other potentially infectious body fluids.

*Behavioral indications:* Sexually active persons who are not in a long-term, mutually monogamous relationship (e.g., persons with more than 1 sex partner during the previous 6 months); current or recent injection-drug users; and men who have sex with men.

(continued)

**TABLE 51-2 2007 Adult Immunization Schedule (Continued)**

*Other indications:* Household contacts and sex partners of persons with chronic hepatitis B virus (HBV) infection; clients and staff members of institutions for persons with developmental disabilities; international travelers to countries with high or intermediate prevalence of chronic HBV infection (a list of countries is available at [www.cdc.gov/travel/content/diseases.aspx](http://www.cdc.gov/travel/content/diseases.aspx)); and any adult seeking protection from HBV infection.

Settings where hepatitis B vaccination is recommended for all adults: STD treatment facilities; HIV testing and treatment facilities; facilities providing drug-abuse treatment and prevention services; health-care settings targeting services to injection-drug users or men who have sex with men; correctional facilities; end-stage renal disease programs and facilities for chronic hemodialysis patients; and institutions and nonresidential daycare facilities for persons with developmental disabilities.

*Special formulation indications:* For adult patients receiving hemodialysis and other immunocompromised adults, 1 dose of 40 µg/mL (Recombivax HB<sup>®</sup>), or 2 doses of 20 µg/mL (Engerix-B<sup>®</sup>) administered simultaneously.

#### 10. Meningococcal vaccination.

*Medical indications:* Adults with anatomic or functional asplenia, or terminal complement component deficiencies.

*Other indications:* First-year college students living in dormitories; microbiologists who are routinely exposed to isolates of *Neisseria meningitidis*; military recruits; and persons who travel to or live in countries in which meningococcal disease is hyperendemic or epidemic (e.g., the “meningitis belt” of sub-Saharan Africa during the dry season [December–June]), particularly if their contact with local populations will be prolonged. Vaccination is required by the government of Saudi Arabia for all travelers to Mecca during the annual Hajj.

Meningococcal conjugate vaccine is preferred for adults with any of the preceding indications who are aged ≤55 years, although meningococcal polysaccharide vaccine (MPSV4) is an acceptable alternative. Revaccination after 3–5 years might be indicated for adults previously vaccinated with MPSV4 who remain at increased risk for infection (e.g., persons residing in areas in which disease is epidemic).

#### 11. Herpes zoster vaccination.

A single dose of zoster vaccine is recommended for adults aged ≥60 years regardless of whether they report a prior episode of herpes zoster. Persons with chronic medical conditions may be vaccinated unless a contraindication or precaution exists for their condition.

#### 12. Selected conditions for which *Haemophilus influenzae* type b (Hib) vaccine may be used.

Hib conjugate vaccines are licensed for children aged 6 weeks–71 months. No efficacy data are available on which to base a recommendation concerning use of Hib vaccine for older children and adults with the chronic conditions associated with an increased risk for Hib disease. However, studies suggest good immunogenicity in patients who have sickle cell disease, leukemia, or HIV infection or who have had splenectomies; administering vaccine to these patients is not contraindicated.

#### 13. Immunocompromising conditions.

Inactivated vaccines are generally acceptable (e.g., pneumococcal, meningococcal, and influenza [trivalent inactivated influenza vaccine]), and live vaccines generally are avoided in persons with immune deficiencies or immune suppressive conditions. Information on specific conditions is available at [www.cdc.gov/vaccines/pubs/acip-list.htm](http://www.cdc.gov/vaccines/pubs/acip-list.htm).

- Responses to live and killed vaccines generally are suboptimal for human immunodeficiency virus (HIV)-infected patients and decrease as the disease progresses.
- General contraindications to vaccine administration include a history of anaphylactic reaction to a previous dose or an unexplained encephalopathy occurring within 7 days of a dose of pertussis vaccine. Immunosuppression and pregnancy are temporary contraindications to live vaccines.
- Whenever possible, transplant patients should be immunized before transplantation. Live vaccines generally are not given after transplantation.

### DIPHTHERIA TOXOID ADSORBED AND DIPHTHERIA ANTITOXIN

- Two strengths of diphtheria toxoid are available (pediatric [D] and adult, which contains less antigen). Primary immunization with D is indicated for children younger than 6 weeks of age. Generally, D is given along with acellular pertussis and tetanus vaccines (DTaP) at 2, 4, and 6 months of age, and then at 15 to 18 months and 4 to 6 years of age.
- For nonimmunized adults, a complete three-dose series of diphtheria toxoid should be administered, with the first two doses given at least 4 weeks apart and the third dose given 6 to 12 months after the second. The combined preparation, tetanus-diphtheria, is recommended in adults because it contains less diphtheria toxoid than DTaP, with fewer reactions seen from the diphtheria preparation. Booster doses are given every 10 years.
- Adverse effects to diphtheria toxoid include mild to moderate tenderness, erythema, and induration at the injection site.

### TETANUS TOXOID, TETANUS TOXOID ADSORBED, AND TETANUS IMMUNE GLOBULIN

- In children, primary immunization against tetanus is usually done in conjunction with diphtheria and pertussis vaccination using DTaP or a combination vaccine that includes hepatitis B and polio vaccines. A 0.5-mL dose is recommended at 2, 4, 6, and 15 to 18 months of age.
- In children 7 years and older and in adults who have not been previously immunized, a series of three 0.5 mL doses of tetanus-diphtheria are administered intramuscularly (IM) initially. The first two doses are given 1 to 2 months apart and the third dose 6 to 12 months later. Boosters are recommended every 10 years.
- Additional doses of tetanus toxoid are recommended as part of traumatic wound management if a patient has not received a dose of tetanus toxoid within the preceding 5 years (Table 51-3).
- Tetanus toxoid may be given to immunosuppressed patients if indicated.
- Tetanus IG is used to provide passive tetanus immunization after the occurrence of traumatic wounds in nonimmunized or suboptimally immunized persons (see Table 51-3). A dose of 250 to 500 units is administered IM. When administered with tetanus toxoid, separate sites for administration should be used.

**TABLE 51-3** Tetanus Prophylaxis

	Clean, Minor		All Other	
	Td	TIG	Td <sup>a</sup>	TIG
Vaccination history				
Unknown or less than three doses	Yes	No	Yes	Yes
Greater than or equal to three doses	No <sup>a,b</sup>	No	No <sup>a,c</sup>	No

Td, tetanus-diphtheria; TIG, tetanus immune globulin.

<sup>a</sup>A single dose of diphtheria, tetanus toxoids, and acellular pertussis should be used for the next dose of Td toxoid.

<sup>b</sup>Yes if >10 years since last dose.

<sup>c</sup>Yes if >5 years since last dose.

- Tetanus IG is also used for the treatment of tetanus. In this setting, a single dose of 3,000 to 6,000 units is administered IM.

### HAEMOPHILUS INFLUENZAE TYPE B VACCINES

- *Haemophilus influenzae* type b (Hib) vaccines currently in use are conjugate products, consisting of either a polysaccharide or oligosaccharide of polyribosylribitol phosphate (PRP) covalently linked to a protein carrier.
- Hib conjugate vaccines are indicated for routine use in all infants and children less than 5 years of age.
- The primary series of Hib vaccination consists of 0.5-mL IM doses at 2, 4, and 6 months of age (for HibTITER [HbOC] and ActHIB [PRP-T]) or doses at 2 and 4 months if PRP-OMP is used (Table 51-4). A booster dose is recommended at age 12 to 15 months.
- For infants aged 7 to 11 months who have not been vaccinated, three doses of HbOC, PRP-OMP, and PRP-T should be given: two doses, spaced 4 weeks apart, and then a booster dose at age 12 to 15 months (but at least 8 weeks since dose 2). For unvaccinated children aged 12 to 14 months, two doses should be given, with an interval of 2 months between them. In a child older than 15 months, a single dose of any of the four conjugate vaccines is indicated.

### HEPATITIS VACCINES

- Information on hepatitis vaccines can be found in Chap. 25.

### HUMAN PAPILLOMAVIRUS VACCINE

- The quadrivalent human papillomavirus vaccine is recommended as a three-dose series (0, 2, and 6 months) for all females 11 to 12 years old. The vaccine is licensed for females 9 to 26 years of age.

**TABLE 51-4** *Haemophilus influenzae* Type B Conjugate Vaccine Products

Vaccine	Trade Name	Protein Carrier
HbOC	HibTITER (Wyeth Vaccines)	Mutant diphtheria toxin protein
PRP-T	ActHIB (Aventis Pasteur)	Tetanus toxoid
PRP-OMP	PedvaxHIB (Merck)	<i>Neisseria meningitidis</i> serogroup B outer membrane protein

Note: The polysaccharide is polyribosylribitol phosphate (PRP).

- The vaccine is well tolerated with injection site reactions and headache and fatigue occurring as commonly as in placebo groups.

## INFLUENZA VIRUS VACCINE

- Annual influenza vaccination (optimally in October or November) is strongly recommended for individuals over the age of 6 months with chronic medical conditions that make them at increased risk for the complications of influenza. Indications for annual influenza vaccination are as follows:
  - ✓ All individuals 50 years of age and older
  - ✓ Residents of nursing homes
  - ✓ Adults and children with chronic cardiovascular or pulmonary diseases including asthma
  - ✓ Adults and children with chronic metabolic disease, renal dysfunction, hemoglobinopathies, or immunosuppression (including immunosuppression from drugs or HIV)
  - ✓ Children and teenagers receiving chronic aspirin therapy
  - ✓ Pregnant women
  - ✓ Healthcare workers in inpatient and outpatient settings
  - ✓ Employees of residential care facilities for high-risk patients
  - ✓ Household members of persons in high-risk groups
- Immunization of children aged 6 to 59 months is recommended. Influenza vaccine should be offered to anyone wishing to avoid influenza infection.
- Individuals who should not be vaccinated are those with anaphylactic hypersensitivity to eggs or other components of the vaccine or adults with febrile illness (until the fever abates).

## MEASLES VACCINE

- Measles vaccine is a live attenuated vaccine that is administered for primary immunization to persons 12 to 15 months of age or older, usually as a combination of measles, mumps, and rubella (MMR). A second dose is recommended at 4 to 6 years of age.
- The vaccine should not be given to immunosuppressed patients (except those infected with HIV) or pregnant women. HIV-infected persons who have never had measles or have never been vaccinated should be given measles-containing vaccine unless there is evidence of severe immunosuppression.
- The vaccine should not be given within 1 month of any other live vaccine unless the vaccine is given on the same day (as with the MMR vaccine).
- Measles vaccine is indicated in all persons born after 1956 or in those who lack documentation of wild virus infection either by history or antibody titers.

## MENINGOCOCCAL POLYSACCHARIDE VACCINE

- The meningococcal conjugate vaccine is recommended for all children 11 to 12 years old and others at high risk for invasive meningococcal infection, including high school students and college freshmen who live in dormitories. The polysaccharide vaccine is indicated in high-risk populations such as

those exposed to the disease, those in the midst of uncontrolled outbreaks, travelers to an area with epidemic hyperendemic meningococcal disease, or individuals who have terminal complement deficiencies or asplenia.

- The vaccine should be made available to students starting college who wish to decrease their risk for meningococcal disease.
- The vaccine is administered subcutaneously as a single 0.5-mL dose.

## MUMPS VACCINE

- The vaccine (usually given in conjunction with measles and rubella, MMR) is given beginning at age 12 to 15 months, with a second dose prior to entry into elementary school.
- Two doses of mumps vaccine are recommended for school age children, international travelers, college students, and healthcare workers born after 1956.
- Postexposure vaccination is of no benefit.
- Mumps vaccine should not be given to pregnant women or immunosuppressed patients. The vaccine should not be given within 6 weeks (preferably 3 months) of administration of IG.

## PERTUSSIS VACCINE

- Acellular pertussis vaccine is usually administered in combination with diphtheria and tetanus toxoids (as DTaP).
- The primary immunization series for pertussis vaccine consists of four doses given at ages 2, 4, 6, and 15 to 18 months. A booster dose is recommended at age 4 to 6 years. Adults up to age 64 should receive a pertussis-containing vaccine with their next tetanus vaccine.
- Systemic reactions, such as moderate fever, occur in 3% to 5% of those receiving vaccines. Very rarely, high fever, febrile seizures, persistent crying spells, and hypotonic hyporesponsive episodes occur after vaccination.
- There are only two absolute contraindications to pertussis administration: an immediate anaphylactic reaction to a previous dose or encephalopathy within 7 days of a previous dose, with no evidence of other cause.

## PNEUMOCOCCAL VACCINE

- Pneumococcal vaccine is a mixture of capsular polysaccharides from 23 of the 83 most prevalent types of *Streptococcus pneumoniae* seen in the United States.
- Pneumococcal vaccine is recommended for the following immunocompetent persons:
  - ✓ Persons 65 or more years of age. If an individual received vaccine more than 5 years earlier and was under age 65 at the time of administration, revaccination should be given.
  - ✓ Persons aged 2 to 64 years with chronic illness.
  - ✓ Persons aged 2 to 64 years with functional or anatomic asplenia. When splenectomy is planned, pneumococcal vaccine should be given at least 2 weeks before surgery.

- ✓ Persons aged 2 to 64 years living in environments where the risk of invasive pneumococcal disease or its complications is increased. This does not include daycare center employees and children.
- Pneumococcal vaccination is recommended for immunocompromised persons 2 years of age or older with:
  - ✓ HIV infection
  - ✓ Leukemia, lymphoma, Hodgkin's disease, or multiple myeloma
  - ✓ Generalized malignancy
  - ✓ Chronic renal failure of nephritic syndrome
  - ✓ Patients receiving immunosuppressive therapy
  - ✓ Organ or bone marrow transplant recipients
- A single revaccination should be given if 5 or more years have passed since the first dose in persons older than 10 years. In those who are 10 years or younger, revaccination should be given 3 years after the previous dose.
- Because children younger than 2 years of age do not respond adequately to the pneumococcal polysaccharide vaccine, a heptavalent pneumococcal conjugate vaccine was created that can be administered at 2, 4, and 6 months of age and between 12 and 15 months of age.

## POLIOVIRUS VACCINES

- Two types of trivalent poliovirus vaccines are currently licensed for distribution in the United States: an enhanced inactivated vaccine (IPV) and a live attenuated, oral vaccine (OPV). IPV is the recommended vaccine for the primary series and booster dose for children in the United States, whereas OPV is recommended in areas of the world that have circulating poliovirus.
- IPV is given to children aged 2, 4, and 6 to 18 months and 4 to 6 years. Primary poliomyelitis immunization is recommended for all children and young adults up to age 18 years. Allergies to any component of IPV, including streptomycin, polymyxin B, and neomycin, are contraindications to vaccine use.
- OPV is not recommended for persons who are immunodeficient or for normal individuals who reside in a household where another person is immunodeficient. OPV should not be given during pregnancy because of the small but theoretical risk to the fetus.

## RUBELLA VACCINE

- The vaccine is given with measles and mumps vaccines (MMR) at 12 to 15 months of age, then at 4 to 6 years.
- The vaccine should not be given to immunosuppressed individuals, although MMR vaccine should be administered to young children with HIV without severe immunosuppression as soon as possible after their first birthday. The vaccine should not be given to individuals with anaphylactic reaction to neomycin.
- Although the vaccine has not been associated with congenital rubella syndrome, its use in pregnancy is contraindicated. Women should be counseled not to become pregnant for 4 weeks after vaccination.

**TABLE 51-5** Indications and Dosage of Intramuscular Immune Globulin in Infectious Diseases

Primary immunodeficiency states	1.2 mL/kg IM, then 0.6 mL/kg every 2–4 weeks
Hepatitis A exposure	0.02 mL/kg IM within 2 weeks
Hepatitis A prophylaxis	0.02 mL/kg IM for exposure <3 months' duration 0.06 mL/kg IM for exposure up to 5 months' duration
Hepatitis B exposure	0.06 mL/kg (hepatitis B immunoglobulin preferred in known exposures)
Measles exposure	0.25 mL/kg (maximum dose 15 mL) as soon as possible 0.5 mL/kg (maximum dose 15 mL) as soon as possible for immunocompromised individuals
Varicella exposure	0.6–1.2 mL/kg as soon as possible when varicella-zoster immune globulin not available

## VARICELLA VACCINE

- Varicella virus vaccine is recommended for all children 12 to 18 months of age with a second dose prior to entering school between 4 and 6 years of age. It is also recommended for persons above this age if they have not had chickenpox. Persons aged 13 years and older should receive two doses separated by 4 to 8 weeks.
- The vaccine is contraindicated in immunosuppressed or pregnant patients.
- Children with asymptomatic or mildly symptomatic HIV should receive two doses of varicella vaccine 3 months apart.

## VARICELLA-ZOSTER VACCINE

- The zoster vaccine is recommended for immunocompetent individuals older than 60 years. It should not be used in immunocompromised individuals, including those with HIV or malignancies or in pregnant women.
- Administration of varicella-zoster IG is by the IM route (never IV).

## IMMUNE GLOBULIN

- IG is available as both IM (IGIM) and IV (IGIV) preparations.
- Table 51-5 lists the suggested dosages for IGIM in various disease states.
- The uses for IGIV are as follows:
  - ✓ Primary immunodeficiency states, including both antibody deficiencies and combined deficiencies
  - ✓ Idiopathic thrombocytopenic purpura
  - ✓ Chronic lymphocytic leukemia in patients who have had a serious bacterial infection
  - ✓ Kawasaki's disease (mucocutaneous lymph node syndrome)
  - ✓ Bone marrow transplant
  - ✓ Varicella-zoster

## RHO(D) IMMUNE GLOBULIN

- Rho(D) IG (RDIg) suppresses the antibody response and formation of anti-Rho(D) in Rho(D)-negative, D<sup>u</sup>-negative women exposed to Rho(D)-

positive blood and prevents the future chance of erythroblastosis fetalis in subsequent pregnancies with a Rho(D)-positive fetus.

- RDIg, when administered within 72 hours of delivery of a full-term infant, reduces active antibody formation from 12% to between 1% and 2%.
- RDIg is also used in the case of a premenopausal woman who is Rho(D) negative and has inadvertently received Rho(D)-positive blood or blood products.
- RDIg may be used after abortion, miscarriage, amniocentesis, or abdominal trauma.
- RDIg is administered IM only.

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*See Chap. 128, Vaccines, Toxoids, and Other Immunobiologics, authored by Mary S. Hayney, for a more detailed discussion of this topic.*

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## DEFINITIONS

- Epilepsy implies a periodic recurrence of seizures with or without convulsions. A seizure results from an excessive discharge of cortical neurons and is characterized by changes in electrical activity as measured by the electroencephalogram (EEG). A convulsion implies violent, involuntary contraction(s) of the voluntary muscles.

## PATHOPHYSIOLOGY

- Seizures result from excessive excitation, or from disordered inhibition of a population of neurons. Initially, a small number of neurons fire abnormally. Then normal membrane conductances and inhibitory synaptic currents break down, excitability spreads locally (focal seizure) or more widely (generalized seizure).
- Mechanisms that may contribute to synchronous hyperexcitability include:
  - ✓ Alterations of ion channels in neuronal membranes
  - ✓ Biochemical modifications of receptors
  - ✓ Modulation of second messaging systems and gene expression
  - ✓ Changes in extracellular ion concentrations
  - ✓ Alterations in neurotransmitter uptake and metabolism in glial cells
  - ✓ Modification in the ratio and function of inhibitory circuits
  - ✓ Local neurotransmitter imbalances (e.g., glutamate,  $\gamma$ -aminobutyric acid [GABA]), acetylcholine, norepinephrine, and serotonin)
- Large numbers of generalized tonic-clonic (GTC) seizures (more than 100) and multiple episodes of status epilepticus may be associated with neuronal damage. In particular, continued exposure to glutamate may contribute to neuronal damage.

## CLINICAL PRESENTATION

### GENERAL

- In most cases, the healthcare provider will not be in a position to witness a seizure. Many patients (particularly those with complex partial [CP] or GTC seizures) are amnesic to the actual seizure event. Obtaining an accurate history and description of the ictal event (including time course) from a third party is important.

## SYMPTOMS

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- Symptoms of a specific seizure depend on seizure type. Although seizures can vary between patients, they tend to be stereotyped within an individual.
- CP seizures may include somatosensory or focal motor features. They are associated with altered consciousness.
- Absence seizures have only very brief (seconds) periods of altered consciousness.
- GTC seizures are major convulsive episodes and are always associated with a loss of consciousness.

## SIGNS

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- Interictally (between seizure episodes), there are typically no objective, pathognomonic signs of epilepsy.

## LABORATORY TESTS

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- There are currently no diagnostic laboratory tests for epilepsy. In some cases, particularly following GTC (or perhaps CP) seizures, serum prolactin levels may be transiently elevated. Laboratory tests may be done to rule out treatable causes of seizures (e.g., hypoglycemia, altered serum electrolyte concentrations, infections, etc.) that do not represent epilepsy.

## OTHER DIAGNOSTIC TESTS

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- EEG is very useful in the diagnosis of various seizure disorders, but the EEG may be normal in some patients who still have the clinical diagnosis of epilepsy.
- A serum prolactin level obtained within 10 to 20 minutes of a tonic-clonic seizure can help differentiate seizure activity from pseudoseizure activity, but not from syncope.
- Although magnetic resonance imaging is very useful (especially imaging of the temporal lobes), computed tomography typically is not helpful except in the initial evaluation for a brain tumor or cerebral bleeding.
- The International Classification of Epileptic Seizures (Table 52-1) classifies epilepsy on the basis of clinical description and electrophysiologic findings.
- Partial (focal) seizures begin in one hemisphere of the brain and, unless they become secondarily generalized, result in an asymmetric seizure. Partial seizures manifest as alterations in motor functions, sensory or somatosensory symptoms, or automatisms. If there is no loss of consciousness, the seizures are called *simple partial*. If there is loss of consciousness, they are termed *complex partial*, and the patients may have automatisms, memory loss, or aberrations of behavior.
- Absence seizures generally occur in young children or adolescents and exhibit a sudden onset, interruption of ongoing activities, a blank stare, and possibly a brief upward rotation of the eyes. Absence seizures have a characteristic two to four cycle/second spike and slow-wave EEG pattern.
- In generalized seizures, motor symptoms are bilateral, and there is altered consciousness.

**TABLE 52-1** International Classification of Epileptic Seizures

- I. Partial seizures (seizures begin locally)
  - A. Simple (without impairment of consciousness)
    - 1. With motor symptoms
    - 2. With special sensory or somatosensory symptoms
    - 3. With psychic symptoms
  - B. Complex (with impairment of consciousness)
    - 1. Simple partial onset followed by impairment of consciousness—with or without automatisms
    - 2. Impaired consciousness at onset—with or without automatisms
  - C. Secondarily generalized (partial onset evolving to generalized tonic-clonic seizures)
- II. Generalized seizures (bilaterally symmetrical and without local onset)
  - A. Absence
  - B. Myoclonic
  - C. Clonic
  - D. Tonic
  - E. Tonic-clonic
  - F. Atonic
  - G. Infantile spasms
- III. Unclassified seizures
- IV. Status epilepticus

*Data from Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. Epilepsia 1981;22:489-501; and Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia 1989;30:389-399.*

- GTC seizures may be preceded by premonitory symptoms (i.e., an aura). A tonic-clonic seizure that is preceded by an aura is likely a partial seizure that is secondarily generalized. Tonic-clonic seizures begin with a short tonic contraction of muscles followed by a period of rigidity. The patient may lose sphincter control, bite the tongue, or become cyanotic. The episode may be followed by unconsciousness, and frequently the patient goes into a deep sleep.
- Myoclonic jerks are brief shock-like muscular contractions of the face, trunk, and extremities. They may be isolated events or rapidly repetitive.
- In atonic seizures, there is a sudden loss of muscle tone that may be described as a head drop, dropping of a limb, or slumping to the ground.

## DIAGNOSIS

- The patient and family should be asked to characterize the seizure for frequency, duration, precipitating factors, time of occurrence, presence of an aura, ictal activity, and postictal state.
- Physical, neurologic, and laboratory examination (SMA-20, complete blood cell count, urinalysis, and special blood chemistries) may identify an etiology. A lumbar puncture may be indicated if there is fever.

## DESIRED OUTCOME

- The goal of treatment is to control or reduce the frequency of seizures, minimize side effects, and ensure compliance, allowing the patient to live

as normal a life as possible. Complete suppression of seizures must be balanced against tolerability of side effects, and the patient should be involved in defining the balance.

## TREATMENT

### GENERAL APPROACH

- The treatment of choice depends on the type of epilepsy (Table 52-2) and on drug-specific adverse effects and patient preferences. Fig. 52-1 is a suggested algorithm for treatment of epilepsy.
- Begin with monotherapy; about 50% to 70% of patients can be maintained on one antiepileptic drug (AED), but all are not seizure free.
- Up to 60% of patients with epilepsy are noncompliant, and this is the most common reason for treatment failure.
- Drug therapy may not be indicated in patients who have had only one seizure or those whose seizures have minimal impact on their lives. Patients who have had two or more seizures should generally be started on AEDs.
- Factors favoring successful withdrawal of AEDs include a seizure-free period of 2 to 4 years, complete seizure control within 1 year of onset, an onset of seizures after age 2 years and before age 35 years, and a normal EEG. Poor prognostic factors include a history of a high frequency of seizures, repeated episodes of status epilepticus, a combination of seizure types, and development of abnormal mental functioning. A 2-year, seizure-free period is suggested for absence and rolandic epilepsy, while a 4-year, seizure-free period is suggested for simple partial, CP, and absence associated with tonic-clonic seizures. According to the American Academy of Neurology guidelines, discontinuation of AEDs may be considered if the patient is seizure free for 2 to 5 years, if there is a single type of partial seizure or primary GTC seizures, if the neurologic examination and IQ are normal, and if the EEG normalized with treatment. AED withdrawal should always be done gradually.

### MECHANISM OF ACTION

- The mechanism of action of most AEDs includes effects on ion channels (sodium and Ca), inhibitory neurotransmission (increasing CNS GABA), or excitatory neurotransmission (decreasing or antagonizing glutamate and aspartate). AEDs that are effective against GTC and partial seizures probably work by delaying recovery of sodium channels from activation. Drugs that reduce corticothalamic T-type Ca currents are effective against generalized absence seizures.

### SPECIAL CONSIDERATIONS IN THE FEMALE PATIENT

- Estrogen has a seizure-activating effect, whereas progesterone has a seizure-protective effect. Enzyme-inducing AEDs, including topiramate and oxcarbazepine, may cause treatment failures in females taking **oral contraceptives**; a supplemental form of birth control is advised if breakthrough bleeding occurs.

**TABLE 52-2** Drugs of Choice for Specific Seizure Disorders

Seizure Type	First-Line Drugs	Alternative Drugs <sup>a</sup>	Comments
<b>Partial seizures (newly diagnosed)</b>			
U.S. guidelines	Adults & adolescents: Carbamazepine Gabapentin Lamotrigine Oxcarbazepine Phenobarbital Phenytoin Topiramate Valproic acid		<i>FDA approved:</i> Carbamazepine Oxcarbazepine Phenobarbital Phenytoin Topiramate Valproic acid
U.K. guidelines	Carbamazepine Lamotrigine Oxcarbazepine Topiramate Valproic acid		
ILAE guidelines	Adults: Carbamazepine Phenytoin Valproic acid  Children: Oxcarbazepine  Elderly: Gabapentin Lamotrigine Carbamazepine Lamotrigine Oxcarbazepine	Adults: Gabapentin Lamotrigine Oxcarbazepine Phenobarbital Topiramate  Children: Carbamazepine Phenobarbital Phenytoin Topiramate Valproic acid  Elderly: Carbamazepine	
U.S. Expert Panel 2005	Carbamazepine Lamotrigine Oxcarbazepine	Levetiracetam	
<b>Partial seizures (refractory monotherapy)</b>			
U.S. guidelines	Lamotrigine Oxcarbazepine Topiramate		<i>FDA approved:</i> Carbamazepine Lamotrigine Oxcarbazepine Phenobarbital Phenytoin Valproic acid
U.K. guidelines	Lamotrigine Oxcarbazepine Topiramate		
<b>Partial seizures (refractory adjunct)</b>			
U.S. guidelines	Adults: Gabapentin Lamotrigine Levetiracetam Oxcarbazepine		<i>FDA approved:</i> Carbamazepine Gabapentin Lamotrigine Levetiracetam  <i>(continued)</i>

**TABLE 52-2** Drugs of Choice for Specific Seizure Disorders (Continued)

Seizure Type	First-Line Drugs	Alternative Drugs <sup>a</sup>	Comments
	Tiagabine Topiramate Zonisamide <i>Children:</i> Gabapentin Lamotrigine Oxcarbazepine		Oxcarbazepine Phenobarbital Phenytoin Pregabalin Tiagabine Valproic acid Zonisamide
U.K. guidelines	Topiramate Gabapentin Lamotrigine Levetiracetam Oxcarbazepine Tiagabine Topiramate		
<b>Generalized seizures absence (newly diagnosed)</b>			
U.S. guidelines	Lamotrigine		<i>FDA approved:</i> Ethosuximide Valproic acid
U.K. guidelines	Lamotrigine		
ILAE guidelines	None	Ethosuximide Lamotrigine Valproic acid	
U.S. Expert Panel 2005	Ethosuximide Valproic acid	Lamotrigine	
<b>Primary generalized (tonic-clonic)</b>			
U.S. guidelines	Topiramate		<i>FDA approved:</i> Lamotrigine Topiramate
U.K. guidelines	Lamotrigine Topiramate		
ILAE guidelines	None	<i>Adults:</i> Carbamazepine Lamotrigine Oxcarbazepine Phenobarbital Phenytoin Topiramate Valproic acid <i>Children:</i> Carbamazepine Phenobarbital Phenytoin Topiramate Valproic acid	
U.S. Expert Panel 2005	Valproic acid	Lamotrigine Topiramate	
<b>Juvenile myoclonic epilepsy</b>			
			<i>FDA approved:</i> Levetiracetam (myoclonic seizures) <i>(continued)</i>

**TABLE 52-2** Drugs of Choice for Specific Seizure Disorders (Continued)

Seizure Type	First-Line Drugs	Alternative Drugs <sup>a</sup>	Comments
ILAE	None	Clonazepam Lamotrigine Levetiracetam Topiramate Valproic acid Zonisamide	
U.S. Expert Panel 2005	Valproic acid	Levetiracetam Topiramate Zonisamide	

ILAE, International League Against Epilepsy.

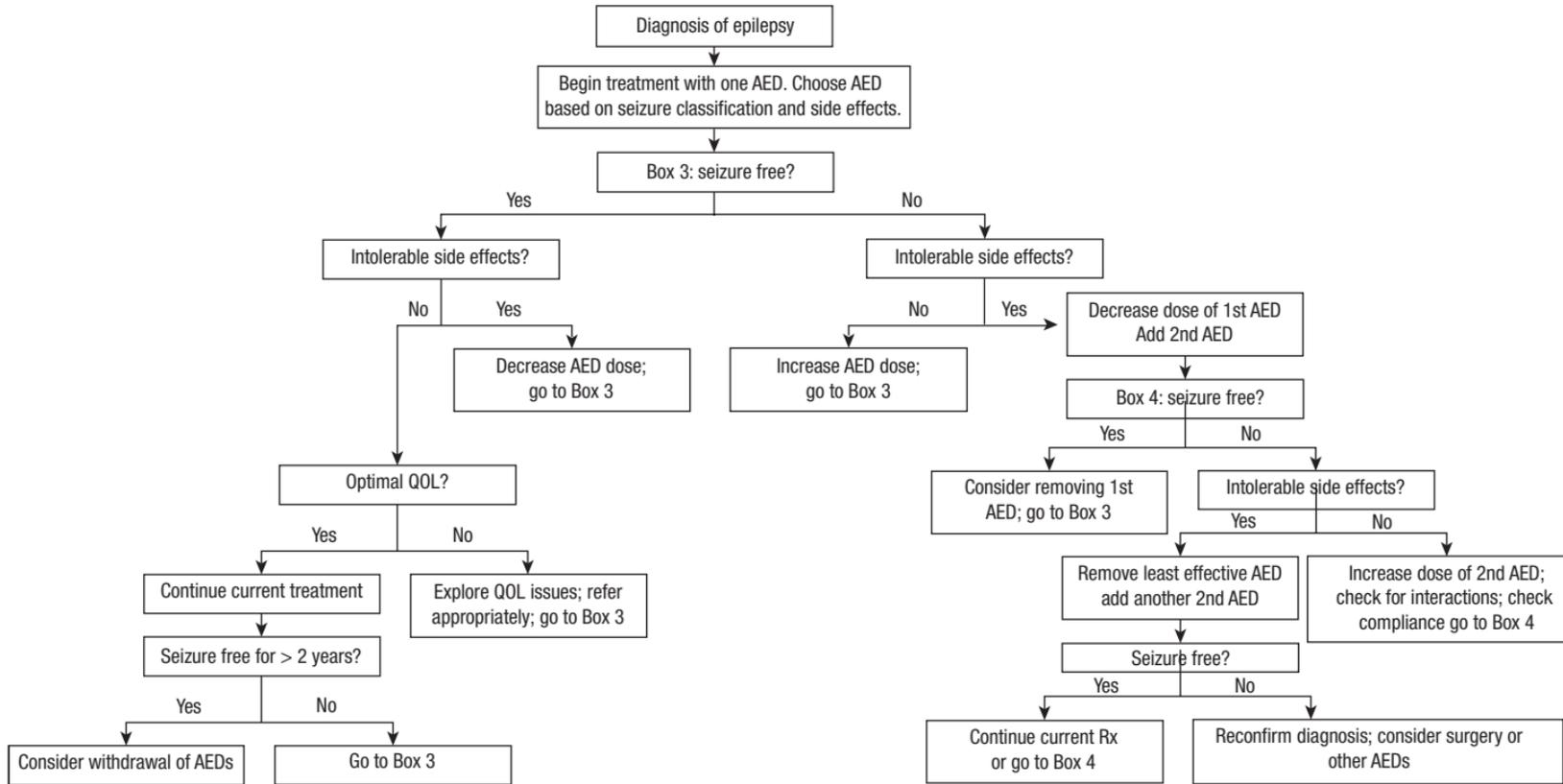
<sup>a</sup>Includes possibly effective drugs.

Data from French JA, Kanner AM, Bautista J, et al. *Neurology* 2004;62:1252–1260; French JA, Kanner AM, Bautista J, et al. *Neurology* 2004;62:1261–1273; National Institute for Clinical Excellence. 2006, <http://www.nice.org.uk>; National Institute for Clinical Excellence. 2006, <http://www.nice.org.uk>; Glauser T, Ben-Menachem E, Bourgeois B, et al. *Epilepsia* 2006;47:1094–1120; and Karceski S, Morrell MJ, Carpenter D. *Expert opinion. Epilepsy Behav* 2005;7:51–564.

- For catamenial epilepsy (seizures just before or during menses) or seizures that occur at the time of ovulation, conventional AEDs should be tried first, but hormonal therapy (**progestational agents**) may also be effective. Intermittent **acetazolamide** has also been used.
- About 25% to 30% of women have increased seizure frequency during pregnancy, and a similar percentage have decreased frequency.
- AED monotherapy is preferred in pregnancy. Clearance of **phenytoin**, **carbamazepine**, **phenobarbital**, **ethosuximide**, **lamotrigine**, and **clorazepate** increases during pregnancy, and protein binding may be altered. There is a higher incidence of adverse pregnancy outcomes in women with epilepsy, and the risk of congenital malformations is 4% to 6% (twice as high as in nonepileptic women). **Barbiturates** and **phenytoin** are associated with congenital heart malformations and facial clefts. **Valproic acid** and **carbamazepine** are associated with spina bifida (0.5% to 1%) and hypospadias. Other adverse outcomes are growth, psychomotor, and mental retardation. Some of these events can be prevented by adequate **folate** intake; **prenatal vitamins with folic acid** (approximately 0.4 to 5 mg/day) should be given to women of child-bearing potential who are taking AEDs. Higher folate doses should be used in women with a history of a previous pregnancy with a neural tube defect. **Vitamin K**, 10 mg/day orally, given to the mother during the last month before delivery can prevent neonatal hemorrhagic disorder.

## PHARMACOKINETICS

- AED pharmacokinetic data are summarized in Table 52-3. For populations known to have altered plasma protein binding, free rather than total serum concentrations should be measured if the AED is highly protein bound. Conditions altering AED protein binding include chronic renal failure, liver disease, hypoalbuminemia, burns, pregnancy, malnutrition, displac-



**FIGURE 52-1.** Algorithm for treatment of epilepsy. (AED, antiepileptic drug; QOL, quality of life.)

**TABLE 52-3** Antiepileptic Drug Pharmacokinetic Data

AED	t <sub>1/2</sub> (h)	Time to Steady State (days)	Unchanged (%)	V <sub>D</sub> (L/kg)	Clinically Important Metabolite	Protein Binding (%)
Carbamazepine	12 M; 5–14 Co	21–28 for completion of auto-induction	<1	1–2	10,11-epoxide	40–90
Ethosuximide	A 60; C 30	6–12	10–20	0.67	No	0
Felbamate	16–22	5–7	50	0.73–0.82	No	~25
Gabapentin <sup>a</sup>	5–40 <sup>b</sup>	1–2	100	0.65–1.04	No	0
Lamotrigine	25.4 M	3–15	0	1.28	No	40–50
Levetiracetam	7–10	2		0.7	No	<10
Oxcarbazepine	3–13	2		0.7	10-hydroxy-carbamazepine	40
Phenobarbital	A 46–136; C 37–73	14–21	20–40	0.6	No	50
Phenytoin	A 10–34; C 5–14	7–28	<5	0.6–8.0	No	90
Pregabalin	A 6–7 <sup>b</sup>	1–2	90	0.5	No	0
Primidone	A 3.3–19; C 4.5–11	1–4	40	0.43–1.1	PB	80
Tiagabine	5–13		Negligible		No	95
Topiramate	18–21	4–5	50–70	0.55–0.8 (male); 0.23–0.4 (female)	No	15
Valproic acid	A 8–20; C 7–14	1–3	<5	0.1–0.5	May contribute to toxicity	90–95 binding saturates
Zonisamide	24–60	5–15		0.8–1.6	No	40–60

A, adult; AED, antiepileptic drug; C, child; Co, combination therapy; M, monotherapy; PB, phenobarbital; V<sub>D</sub>, volume of distribution.

<sup>a</sup>The bioavailability of gabapentin is dose dependent.

<sup>b</sup>Half-life depends on renal function.

Data from Fought E. Pharmacokinetic considerations in prescribing antiepileptic drugs. *Epilepsia* 2001;42(Suppl 4):19–23; Leppik IE. Contemporary Diagnosis and Management of the Patient with Epilepsy, 6th ed. Newton, PA: Handbooks in Health Care, 2006:92–149; and Bourgeois BFD. Pharmacokinetics and pharmacodynamics of antiepileptic drugs. In: Wyllie E. ed. *The Treatment of Epilepsy*, 4th ed. Philadelphia: Lippincott Williams & Wilkins, 2006:656–669.

ing drugs, and age (neonates and the elderly). Unbound concentration monitoring is especially useful for **phenytoin**.

- Neonates and infants may metabolize drugs more slowly, and children may metabolize drugs more rapidly than adults. Lower doses of AEDs are often required in the elderly. Some elderly patients have increased receptor sensitivity to CNS drugs, making the accepted therapeutic range invalid.

## THE ROLE OF SERUM CONCENTRATION MONITORING

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- Seizure control may occur before the “minimum” of the accepted therapeutic serum range is reached, and some patients may need serum concentrations beyond the “maximum.” The therapeutic range for AEDs may be different for different seizure types (e.g., higher for CP seizures than for GTC seizures). Clinicians should determine the optimal serum concentration for each patient. Serum concentrations can be useful to document lack of or loss of efficacy, to establish noncompliance, and to guide therapy in patients with renal and/or hepatic disease and patients taking multiple drugs, as well as in women who are pregnant or taking **oral contraceptives**.

## EFFICACY

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- The traditional treatment of tonic-clonic seizures is **phenytoin** or **phenobarbital**, but the use of **carbamazepine** and **valproic acid** is increasing, as efficacy is equal and side effects are more favorable.
- **Carbamazepine** and **valproic acid** had equal retention rates for tonic-clonic seizures, but **carbamazepine** was superior for partial seizures, and **valproic acid** caused more adverse effects.
- Studies suggest that as monotherapy for partial seizures, **lamotrigine** is as effective as **carbamazepine** and **phenytoin**; lamotrigine may be better tolerated. Clinical data suggest that **oxcarbazepine** is as effective as **phenytoin**, **valproic acid**, and **immediate-release carbamazepine**, with perhaps fewer side effects.
- Absence seizures are best treated with **ethosuximide**, **valproic acid**, and perhaps **lamotrigine**. For a combination of absence and other generalized or partial seizures, **valproic acid** is preferred. If valproic acid is ineffective in treating a mixed seizure disorder that includes absence, **ethosuximide** should be used in combination with another AED.
- The newer AEDs were first approved as adjunctive therapy for patients with refractory partial seizures. To date, **lamotrigine**, **topiramate**, and **oxcarbazepine** have received FDA approval for use in monotherapy in patients with partial seizures. **Felbamate** has monotherapy approval but causes significant side effects.

## ADVERSE EFFECTS

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- Chronic and acute adverse effects of AEDs are listed in Table 52-4. Concentration-dependent side effects can often be alleviated by decreasing the dose or avoided by increasing the dose very slowly.

**TABLE 52-4** Antiepileptic Drug Side Effects

AED	Acute Side Effects		
	<i>Concentration Dependent</i>	<i>Idiosyncratic</i>	Chronic Side Effects
Carbamazepine	Diplopia Dizziness Drowsiness Nausea Unsteadiness Lethargy	Blood dyscrasias Rash	Hyponatremia
Ethosuximide	Ataxia Drowsiness GI distress Unsteadiness Hiccups	Blood dyscrasias Rash	Behavior changes Headache
Felbamate	Anorexia Nausea Vomiting Insomnia Headache	Aplastic anemia Acute hepatic failure	Not established
Gabapentin	Dizziness Fatigue Somnolence Ataxia	Pedal edema	Weight gain
Lamotrigine	Diplopia Dizziness Unsteadiness Headache	Rash	Not established
Levetiracetam	Sedation Behavioral disturbance	Not established	Not established
Oxcarbazepine	Sedation Dizziness Ataxia Nausea	Rash	Hyponatremia
Phenobarbital	Ataxia Hyperactivity Headache Unsteadiness Sedation Nausea	Blood dyscrasias Rash	Behavior changes Connective tissue disorders Intellectual blunting Metabolic bone disease Mood change Sedation
Phenytoin	Ataxia Nystagmus Behavior changes Dizziness Headache Incoordination Sedation Lethargy Cognitive impairment Fatigue Visual blurring	Blood dyscrasias Rash Immunologic reaction	Behavior changes Cerebellar syndrome Connective tissue changes Skin thickening Folate deficiency Gingival hyperplasia Hirsutism Coarsening of facial features Acne Cognitive impairment Metabolic bone disease Sedation

*(continued)*

**TABLE 52-4** Antiepileptic Drug Side Effects (Continued)

AED	Acute Side Effects		
	<i>Concentration Dependent</i>	<i>Idiosyncratic</i>	Chronic Side Effects
Pregabalin	Dizziness Somnolence Blurred vision	Pedal edema Creatine kinase elevation Decrease platelets	Weight gain
Primidone	Behavior changes Headache Nausea Sedation Unsteadiness	Blood dyscrasias Rash	Behavior change Connective tissue disorders Cognitive impairment Sedation
Tiagabine	Dizziness Fatigue Difficulties concentrating Nervousness Tremor Blurred vision Depression Weakness	Spike-wave stupor	Not established
Topiramate	Difficulties concentrating Psychomotor slowing Speech or language problems Somnolence, fatigue Dizziness Headache	Metabolic acidosis Acute angle glaucoma Oligohidrosis	Kidney stones Weight loss
Valproic acid	GI upset Sedation Unsteadiness Tremor Thrombocytopenia	Acute hepatic failure Acute pancreatitis Alopecia	Polycystic ovary–like syndrome Weight gain Hyperammonemia Menstrual cycle irregularities
Zonisamide	Sedation Dizziness Cognitive impairment Nausea	Rash Oligohidrosis	Kidney stones Weight loss

AED, antiepileptic drug.

Data from French JA, Kanner AM, Bautista J, et al. Efficacy and tolerability of the new antiepileptic drugs: I. Treatment of new onset epilepsy. *Neurology* 2004;62:1252–1260; French JA, Kanner AM, Bautista J, et al. Efficacy and tolerability of the new antiepileptic drugs: II. Treatment of refractory epilepsy. *Neurology* 2004;62:1261–1273; and Leppik IE. *Contemporary Diagnosis and Management of the Patient with Epilepsy*, 6th ed. Newton, PA: Handbooks in Health Care, 2006:92–149.

- When acute organ failure occurs, it usually happens within the first 6 months of AED therapy.
- **Valproic acid** may cause less cognitive impairment than **phenytoin** and **phenobarbital**. Some of the newer agents (e.g., **gabapentin** and **lamotrigine**) have been shown to cause fewer cognitive impairments than the older agents (e.g., **carbamazepine**). **Topiramate** may cause substantial cognitive impairment.
- **Phenytoin**, **carbamazepine**, **phenobarbital**, **oxcarbazepine**, and **valproic acid** may interfere with vitamin D metabolism, causing asymptomatic high-turnover bone disease with normal bone density or decreased bone mineral

density and osteoporosis. Laboratory tests may reveal elevated bone-specific alkaline phosphatase and decreased serum Ca and 25-OH vitamin D.

## DRUG–DRUG INTERACTIONS

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- Drug interactions involving AEDs are shown in Table 52-5.
- **Phenobarbital, phenytoin, primidone, and carbamazepine** are potent inducers of cytochrome P450 (CYP450), epoxide hydrolase, and uridine diphosphate glucuronosyltransferase enzyme systems. **Valproic acid** inhibits many hepatic enzyme systems and displaces some drugs from plasma albumin.
- **Felbamate** and **topiramate** can act as inducers with some isoforms and inhibitors with others.
- Except for **levetiracetam** and **gabapentin**, which are eliminated mostly unchanged by the renal route, AEDs are metabolized wholly or in part by hepatic enzymes.

## DOSAGE AND ADMINISTRATION

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- Initial and maximal daily doses and target serum concentration ranges are shown in Table 52-6. Usually therapy is initiated at one-fourth to one-third of the anticipated maintenance dose, and gradually increased over 3 or 4 weeks to an effective dose. Serum concentrations may be useful, but the therapeutic range must be correlated with clinical outcome.

## SPECIFIC ANTIPILEPTIC DRUGS

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### Carbamazepine

- **Carbamazepine** may act primarily by inhibition of voltage-gated sodium channels.
- Food may enhance bioavailability.
- Controlled- and sustained-release preparations dosed every 12 hours are bioequivalent to immediate-release preparations dosed every 6 hours. These dosage forms, compared with immediate-release preparations, have lower peaks and higher troughs.
- The liver metabolizes 98% to 99% of a dose of carbamazepine (mostly by CYP3A4), and the major metabolite is carbamazepine-10,11-epoxide, which is active.
- Carbamazepine can induce its own metabolism (autoinduction); this effect begins within 3 to 5 days of dosing initiation and takes 21 to 28 days to become complete.
- Carbamazepine is considered an AED of first choice for newly diagnosed partial seizures and for primary GTC seizures that are not considered an emergency.
- Neurosensory side effects (e.g., diplopia, blurred vision, nystagmus, ataxia, dizziness, and headache) are the most common, occurring in 35% to 50% of patients initially. It may induce hyponatremia, and the incidence may increase with age. Hyponatremia occurs less frequently than with oxcarbazepine.
- Leukopenia is the most common hematologic side effect (up to 10%) but is usually transient. It may be persistent in 2% of patients. Carbamazepine may

**TABLE 52-5** Interactions between Antiepileptic Drugs

<b>AED</b>	<b>Added Drug</b>	<b>Effect</b>
Carbamazepine (CBZ)	Felbamate	Incr. 10,11 epoxide Decr. CBZ
	Phenobarbital	Decr. CBZ
	Phenytoin	Decr. CBZ
	Valproic acid	Incr. 10,11 epoxide
Ethosuximide	Carbamazepine	Decr. ethosuximide
	Phenobarbital	Decr. ethosuximide
	Phenytoin	Decr. ethosuximide
Felbamate (FBM)	Carbamazepine	Decr. FBM
	Phenytoin	Decr. FBM
	Valproic acid	Incr. FBM
Gabapentin	No known interactions	
Lamotrigine (LTG)	Carbamazepine	Decr. LTG
	Phenobarbital	Decr. LTG
	Phenytoin	Decr. LTG
	Primidone	Decr. LTG
	Valproic acid	Incr. LTG
Levetiracetam	No known interactions	
Oxcarbazepine	Carbamazepine	Decr. MHD
	Phenobarbital	Decr. MHD
	Phenytoin	Decr. MHD
Phenobarbital (PB)	Felbamate	Incr. PB
	Phenytoin	Incr. or decr. PB
	Valproic acid	Incr. PB
Phenytoin (PHT)	Carbamazepine	Decr. PHT
	Felbamate	Incr. PHT
	Methsuximide	Incr. PHT
	Phenobarbital	Incr. or decr. PHT
	Valproic acid	Decr. Total PHT
	Vigabatrin	Decr. PHT
Pregabalin	No known interactions	
Primidone (PRM)	Carbamazepine	Decr. PRM Incr. PB
	Phenytoin	Decr. PRM Incr. PB
	Valproic acid	Incr. PRM Incr. PB
Tiagabine (TGB)	Carbamazepine	Decr. TGB
	Phenytoin	Decr. TGB
Topiramate (TPM)	Carbamazepine	Decr. TPM
	Phenytoin	Decr. TPM
	Valproic acid	Decr. TPM
Valproic acid (VPA)	Carbamazepine	Decr. VPA
	Felbamate	Incr. VPA
	Lamotrigine	Decr. VPA (slight)
	Phenobarbital	Decr. VPA
	Phenytoin	Decr. VPA
	Primidone	Decr. VPA
	Topiramate	Decr. VPA

*(continued)*

**TABLE 52-5** Interactions between Antiepileptic Drugs (Continued)

AED	Added Drug	Effect
Zonisamide	Carbamazepine	Decr. zonisamide
	Phenobarbital	Decr. zonisamide
	Phenytoin	Decr. zonisamide

AED, antiepileptic drug; Decr., decreased; Incr., increased; MHD, 10-monohydroxymetabolite.

Data from Faught E. Pharmacokinetic considerations in prescribing antiepileptic drugs. *Epilepsia* 2001;42(Suppl 4):19–23; Leppik IE. *Contemporary Diagnosis and Management of the Patient with Epilepsy*, 6th ed. Newton, PA: Handbooks in Health Care, 2006:92–149; and Bourgeois BFD. Pharmacokinetics and pharmacodynamics of antiepileptic drugs. In: Wyllie E. ed. *The Treatment of Epilepsy*, 4th ed. Philadelphia: Lippincott Williams & Wilkins, 2006:656–669.

be continued unless the white blood cell count drops to less than 2,500/mm<sup>3</sup> and the absolute neutrophil count drops to less than 1,000/mm<sup>3</sup>.

- Rashs may occur in 10% of patients. Other side effects include hepatitis, osteomalacia, cardiac conduction defects, and lupus-like reactions.
- Carbamazepine may interact with other drugs by inducing their metabolism. **Valproic acid** increases concentrations of the 10,11-epoxide metabolite without affecting the concentration of carbamazepine. The interaction of **erythromycin** and **clarithromycin** (CYP3A4 inhibition) with carbamazepine is particularly significant.
- Loading doses are used only in critically ill patients.
- Although some patients, especially those on monotherapy, can be maintained on twice-a-day dosing, others may require more frequent administration, especially children. Larger doses can be given at bedtime. Dose increases can be made every 2 to 3 weeks.
- The sustained- and controlled-release dosage forms allow for twice-a-day dosing. The sustained-release capsule can be opened and sprinkled on food.

### Ethosuximide

- **Ethosuximide** is believed to act primarily by inhibition of T-type calcium (Ca) channel.
- It is a first-line treatment for absence seizures.
- There is some evidence for nonlinear metabolism at higher doses. Metabolites are believed to be inactive.
- A loading dose is not required. Titration over 1 to 2 weeks to maintenance doses of 20 mg/kg/day (divided into two doses) usually results in serum concentrations of 50 mcg/mL.

### Felbamate

- **Felbamate** appears to act by blocking N-methyl-D-aspartate responses and by modulating GABA<sub>A</sub> receptors.
- It is approved for treating atonic seizures in patients with Lennox-Gastaut syndrome and is effective for partial seizures as well.
- Because of the reports of aplastic anemia (1 in 3,000 patients) and hepatitis (1 in 10,000 patients), it is now recommended only for patients refractory to other AEDs. Risk factors for aplastic anemia may be a history of cytopenia, AED allergy or toxicity, viral infection, and/or immunologic problems.

**TABLE 52-6** Antiepileptic Drug Dosing and Target Serum Concentration Ranges

	Trade Name	Usual Initial Dose	Usual Maximum Daily Dose	Target Serum Concentration Range
<b>Barbiturates</b>				
Mephobarbital	Mebaral	50–100 mg/day	400–600 mg	Not defined
Phenobarbital	Various	1–3 mg/kg/day (10–20 mg/kg LD)	180–300 mg	10–40 mcg/mL
Primidone	Mysoline	100–125 mg/day	750–2,000 mg	5–10 mcg/mL
<b>Benzodiazepines</b>				
Clonazepam	Klonopin	1.5 mg/day	20 mg	20–80 ng/mL
Clorazepate	Tranxene	7.5–22.5 mg/day	90 mg	Not defined
Diazepam	Valium	po: 4–40 mg IV: 5–10 mg	po: 4–40 mg IV: 5–30 mg	100–1,000 ng/mL
Lorazepam	Ativan	po: 2–6 mg IV: 0.05 mg/kg IM: 0.05 mg/kg	po: 10 mg IV: 0.044 mg/kg	10–30 ng/mL
<b>Hydantoins</b>				
Ethotoin	Peganone	<1,000 mg/day	2,000–4,000 mg with food	15–50 mcg/mL
Mephenytoin	Mesantoin	50–100 mg/day	200–800 mg	25–40 mcg/mL
Phenytoin	Dilantin	po: 3–5 mg/kg (200–400 mg) (15–20 mg/kg LD)	po: 500–600 mg	Total: 10–20 mcg/mL Unbound: 0.5–3 mcg/mL
<b>Succinimides</b>				
Ethosuximide	Zarontin	500 mg/day	500–2,000 mg	40–80 mcg/mL
Methsuximide	Celontin	300 mg/day	300–1,200 mg	<i>N</i> -desmethyl metabolite 10–40 mcg/mL

<b>Other</b>				
Carbamazepine	Tegretol	400 mg/day	400–2,400 mg	4–14 mcg/mL
Felbamate	Felbatol	1,200 mg/day	3,600 mg	40–100 mcg/mL <sup>a</sup>
Gabapentin	Neurontin	900 mg/day	4,800 mg	4–16 mcg/mL <sup>a</sup>
Lamotrigine	Lamictal	25 mg every other day if on VPA; 25–50 mg/day if not on VPA	100–150 mg if on VPA; 300–500 mg if not on VPA	4–20 mcg/mL <sup>a</sup>
Levetiracetam	Keppra	500–1,000 mg/day	3,000–4,000 mg	5–40 mcg/mL <sup>a</sup>
Oxcarbazepine	Trileptal	300–600 mg/day	2,400–3,000 mg	12–30 mcg/mL <sup>a</sup> (MHD)
Pregabalin	Lyrica	150 mg/day	600 mg	Not defined
Tiagabine	Gabitril	4–8 mg/day	80 mg	100–300 mcg/mL <sup>a</sup>
Topiramate	Topamax	25–50 mg/day	200–1,000 mg	2–25 mcg/mL
Valproic acid	Depakene	15 mg/kg (500–1,000 mg)	60 mg/kg (3,000–5,000 mg)	50–150 mcg/mL <sup>a</sup>
	Depakote			
	Depacon			
Zonisamide	Zonegran	100–200 mg/day	600 mg	10–40 mcg/mL <sup>a</sup>

LD, loading dose; MHD, 10-monohydrate derivative; VPA, valproic acid.

<sup>a</sup>Based on data from clinical trials—no established therapeutic ranges.

Data from Leppik IE. *Contemporary Diagnosis and Management of the Patient with Epilepsy*, 6th ed. Newton, PA: Handbooks in Health Care, 2006:92–149; and Bourgeois BFD. *Pharmacokinetics and pharmacodynamics of antiepileptic drugs*. In: Wyllie E. ed. *The Treatment of Epilepsy*, 4th ed. Philadelphia: Lippincott Williams & Wilkins, 2006:656–669.

### Gabapentin

- **Gabapentin** inhibits high-voltage activated Ca channels and elevates human brain GABA levels. It is a second-line agent for patients with partial seizures who have failed initial treatment. It may also have a role in patients with less severe seizure disorders, such as new-onset partial epilepsy, especially in elderly patients.
- Bioavailability decreases with increasing doses. It is eliminated exclusively renally, and dosage adjustment is necessary in patients with impaired renal function.
- Dosing is initiated at 300 mg at bedtime and increased to 300 mg twice daily on the second day and 300 mg three times daily on the third day. Further titrations are then made. The manufacturer recommends maintenance doses up to 1,800 to 2,400 mg/day, but higher doses (5,000 to 10,000 mg/day) have been used safely. Most clinicians use doses of 2,400 to 4,800 mg/day.

### Lamotrigine

- **Lamotrigine** blocks voltage-dependent sodium channels and inhibits high-voltage activated Ca channels.
- It is useful as both adjunctive therapy for partial seizures and as monotherapy. It may also be a useful alternative for primary generalized seizures, such as absence and as adjunctive therapy for primary GTC seizures.
- The most frequent side effects are diplopia, drowsiness, ataxia, and headache. Rashes are usually mild to moderate, but Stevens-Johnson reaction has also occurred. The incidence of the more serious rashes appears to be increased in patients who are also receiving **valproic acid** and who have rapid dosage titration. Valproic acid substantially inhibits the metabolism of lamotrigine.

### Levetiracetam

- Levetiracetam's activity may be related to its binding to the synaptic vesicle protein SV2A.
- Renal elimination of unchanged drug accounts for 66% of drug clearance, and the dose should be adjusted for impaired renal function. The role of therapeutic drug monitoring is unknown. It has linear pharmacokinetics and is metabolized in blood by nonhepatic enzymatic hydrolysis.
- It is effective in the adjunctive treatment of partial seizures in adults who have failed initial therapy.
- Adverse effects include sedation, fatigue, coordination difficulties, agitation, irritability, and lethargy. A slight decline in red and white blood cells was noted in clinical trials.
- It is believed to have a low potential for pharmacokinetic drug interactions.
- The recommended initial dose is 500 mg orally twice daily. In some intractable seizure patients, the oral dose has been titrated rapidly over 3 days up to 3,000 mg/day (1,500 mg twice daily).

### Oxcarbazepine

- **Oxcarbazepine** (a prodrug) is structurally related to **carbamazepine**, but it is converted to a monohydrate derivative, which is the active component.
- It blocks voltage-sensitive sodium channels, modulates the voltage-activated Ca currents, and increases potassium conductance.

- It undergoes glucuronide conjugation and is eliminated by the kidneys. Patients with significant renal impairment may require a dose adjustment. The half-life ( $9.3 \pm 1.8$  hours) is shorter in patients taking enzyme-inducing drugs. The relationship between dose and serum concentration is linear. It does not autoinduce its own metabolism.
- It is indicated for use as monotherapy or adjunctive therapy for partial seizures in adults and as monotherapy and adjunctive therapy for partial seizures in patients as young as 4 years of age. It is also a potential first-line drug for patients with primary, generalized convulsive seizures.
- The most frequently reported side effects are dizziness, nausea, headache, diarrhea, vomiting, upper respiratory tract infections, constipation, dyspepsia, ataxia, and nervousness. It generally has fewer side effects than **phenytoin**, **valproic acid**, or **carbamazepine**. Hyponatremia has been reported in up to 25% of patients and is more likely in the elderly. About 25% to 30% of patients who have had a rash with **carbamazepine** will have a cross-reaction with oxcarbazepine.
- Concurrent use of oxcarbazepine with **ethinyl estradiol** and **levonorgestrel**-containing contraceptives may render these agents less effective. Oxcarbazepine may increase serum concentrations of **phenytoin** and decrease serum concentrations of **lamotrigine** (induction of uridine diphosphate glucuronosyltransferase).
- In adults, the starting dose of oxcarbazepine as monotherapy is 300 mg once or twice daily. This can be increased by 600 mg/day each week to a maximum dose of 2,400 mg/day. This is titrated to the target dose over 2 weeks. See manufacturer's recommendations for dosing by weight.
- In patients converted from **carbamazepine**, the typical maintenance doses of oxcarbazepine are 1.5 times the carbamazepine dose.

### Phenobarbital

- **Phenobarbital** may act by interacting with GABA receptors, blocking high voltage-activated Ca channels, and blocking  $\alpha$ -amino-3-hydroxy-5-methylisoxazole-4-propionic acid and kainate receptors.
- Phenobarbital is the drug of choice for neonatal seizures, but in other situations it is reserved for patients who have failed other AEDs.
- Phenobarbital is a potent enzyme inducer and interacts with many drugs. The amount of phenobarbital excreted renally can be increased by giving diuretics and urinary alkalinizers.
- The most common side effects are fatigue, drowsiness, and depression. Phenobarbital impairs cognitive performance. In children, hyperactivity can occur.
- **Ethanol** increases phenobarbital metabolism, but **valproic acid**, **cimetidine**, and **chloramphenicol** inhibit its metabolism.
- Phenobarbital can usually be dosed once daily, and bedtime dosing may minimize daytime sedation.

### Phenytoin

- **Phenytoin** inhibits voltage-dependent sodium channels.
- Phenytoin is a first-line AED for primary generalized convulsive seizures and for partial seizures. Its place in therapy will be reevaluated as more experience is gained with the newer AEDs.

- Absorption may be saturable. Absorption is affected by particle size, and the brand should not be changed without careful monitoring. Food may slow absorption. The intramuscular route is best avoided, as absorption is erratic. Fosphenytoin can safely be administered IV and intramuscularly. Equations are available to normalize the phenytoin concentration in patients with hypoalbuminemia or renal failure.
- Phenytoin is metabolized in the liver mainly by CYP2C9, but CYP2C19 is also involved. Zero-order kinetics occurs within the usual therapeutic range, so any change in dose may produce disproportional changes in serum concentrations.
- In nonacute situations, phenytoin may be initiated in adults at oral doses of 5 mg/kg/day and titrated upward. Subsequent dosage adjustments should be done cautiously because of nonlinearity in elimination. Most adult patients can be maintained on a single daily dose, but children often require more frequent administration. Only extended-release preparations should be used for single daily dosing.
- One author suggested that if the phenytoin serum concentration is less than 7 mcg/mL, the daily dose should be increased by 100 mg; if the concentration is 7 to 12 mcg/mL, the daily dose can be increased by 50 mg; and if the concentration is greater than 12 mcg/mL, the daily dose can be increased by 30 mg or less.
- Common but usually transient side effects are lethargy, incoordination, blurred vision, higher cortical dysfunction, and drowsiness. At concentrations greater than 50 mcg/mL, phenytoin can exacerbate seizures. Chronic side effects include gingival hyperplasia, impaired cognition, hirsutism, vitamin D deficiency, osteomalacia, folic acid deficiency, carbohydrate intolerance, hypothyroidism, and peripheral neuropathy.
- Phenytoin is prone to many drug interactions (see Table 52-5). If protein-binding interactions are suspected, free rather than total phenytoin concentrations are a better therapeutic guide.
- Phenytoin decreases **folic acid** absorption, but folic acid replacement enhances phenytoin clearance and can result in loss of efficacy. Phenytoin tablets and suspension contain phenytoin acid, while the capsules and parenteral solution are phenytoin sodium, which is 92% phenytoin. Clinicians should remember that there are two different strengths of phenytoin suspension and capsules.

### **Pregabalin**

- **Pregabalin** binds to the subunit of the voltage-gated Ca channel, resulting in a decrease in the release of several excitatory neurotransmitters.
- It is a second-line agent for partial seizures that have failed initial treatment.
- It is eliminated primarily by renal excretion as unchanged drug; dosage adjustment is required in patients with renal dysfunction.
- The most frequent side effects include dizziness, somnolence, ataxia, blurred vision, and weight gain.
- Drug interactions are unlikely to occur. It is a controlled substance.

### **Tiagabine**

- **Tiagabine** is a specific inhibitor of GABA reuptake into glial cells and other neurons.

- It is considered second-line therapy for patients with partial seizures who have failed initial therapy.
- The most frequently reported side effects are dizziness, asthenia, nervousness, tremor, diarrhea, and depression. These side effects are usually transient and can be diminished by taking it with food.
- It is oxidized by CYP3A4 enzymes, and other drugs may alter its clearance.
- Tiagabine is displaced from protein by **naproxen, salicylates, and valproate**.
- The minimal effective adult dose level is considered to be 30 mg/day.

### Topiramate

- **Topiramate** affects voltage-dependent sodium channels, GABA receptors, high voltage Ca channels, and kainate  $\alpha$ -amino-3-hydroxy-5-methylisoxazole-4-propionic acid subunits.
- It is a first-line AED for patients with partial seizures. It is also approved for tonic-clonic seizures in primary generalized epilepsy.
- Approximately 50% of the dose is excreted renally, and tubular reabsorption may be prominently involved.
- The most common side effects are ataxia, impaired concentration, confusion, memory difficulties, dizziness, fatigue, paresthesias, and somnolence. Nephrolithiasis occurs in 1.5% of patients. It has also been associated with acute narrow-angle glaucoma, oligohidrosis, and metabolic acidosis.
- Enzyme inducers may decrease topiramate serum levels.
- Dose increments may occur every 1 or 2 weeks. For patients on other AEDs, doses greater than 600 mg/day do not appear to lead to improved efficacy and may increase side effects.

### Valproic Acid and Divalproex Sodium

- **Valproic acid** may potentiate postsynaptic GABA responses, may have a direct membrane-stabilizing effect, and may affect potassium channels.
- The free fraction may increase as the total concentration increases, and free concentrations may be more useful than total concentrations, especially at higher concentrations or in patients with hypoalbuminemia. Protein binding is decreased in patients with head trauma.
- At least 10 metabolites have been identified, and some may be active. One may account for hepatotoxicity (4-ene-valproic acid), and it is increased by concurrent dosing with enzyme-inducing drugs. At least 67 cases of hepatotoxicity have been reported, and most deaths were in mentally retarded children less than 2 years old who were receiving multiple drug therapy.
- The extended-release formulation (Depakote ER) is 15% less bioavailable than the enteric-coated preparation (Depakote).
- It is first-line therapy for primary generalized seizures, such as absence, myoclonic, and atonic seizures, and is approved for adjunctive and monotherapy treatment of partial seizures. It can also be useful in mixed seizure disorders.
- Side effects are usually mild and include GI complaints, weight gain, drowsiness, ataxia, and tremor. GI complaints may be minimized with the enteric-coated formulation or by giving with food. Thrombocytopenia is common but is responsive to a decrease in dose.

- Although **carnitine** administration may partially ameliorate hyperammonemia, it is expensive, and there are only limited data to support routine supplemental use in patients taking valproic acid.
- Valproic acid is an enzyme inhibitor that increases serum concentrations of concurrently administered **phenobarbital** and may increase concentrations of **carbamazepine 10,11-epoxide** without affecting concentrations of the parent drug. It also inhibits the metabolism of **lamotrigine**.
- Twice-daily dosing is reasonable, but children and patients taking enzyme inducers may require three-or-four-times-daily dosing.
- The enteric-coated tablet **divalproex sodium** causes fewer GI side effects. It is metabolized in the gut to valproic acid. When switching from Depakote to Depakote-ER, the dose should be increased by 14% to 20%. Depakote ER may be given once daily.

### Zonisamide

- **Zonisamide** is a broad-spectrum **sulfonamide** AED that blocks voltage-sensitive sodium channels by reducing voltage-dependent T-type Ca channels; it also weakly inhibits carbonic anhydrase, and inhibits glutamate release.
- It is approved as adjunctive therapy for partial seizures, but it is potentially effective in a variety of partial and primary generalized seizure types.
- Zonisamide is metabolized primarily by CYP3A4, and about 30% is excreted unchanged.
- The most common side effects include somnolence, dizziness, anorexia, headache, nausea, word-finding difficulties, oligohidrosis, modest weight loss, and irritability. Symptomatic kidney stones may occur in 2.6% of patients. Hypersensitivity reactions may occur in 0.02% of patients, and it should be used with caution if at all in patients with a history of allergy to sulfonamides. Monitoring of renal function may be advisable in some patients.
- The initial dose in adults is 100 mg/day, and daily doses are increased by 100 mg every 2 weeks until a response is seen. The dosage range in adults is 100 to 600 mg/day. It is suitable for once-or-twice-daily dosing.

## EVALUATION OF THERAPEUTIC OUTCOMES

- Patients should be chronically monitored for seizure control, side effects, social adjustment, drug interactions, compliance, quality of life, and toxicity.
- Screening for neuropsychiatric disorders is also important. Clinical response is more important than serum drug concentrations.
- Patients should be asked to record severity and frequency of seizures in a seizure diary.

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*See Chap. 58, Epilepsy, authored by Susan J. Rogers and Jose E. Cavazos, for a more detailed discussion of this topic.*

## MIGRAINE HEADACHE

## DEFINITION

- Migraine is a common, recurrent, primary headache of moderate to severe intensity that interferes with normal functioning and is associated with GI, neurologic, and autonomic symptoms. In migraine with aura, a complex of focal neurologic symptoms precedes or accompanies the attack.

## PATHOPHYSIOLOGY

- Replacing previous neuronal and vascular theories of migraine pathophysiology, a combined theory has emerged. Activity in the trigeminovascular system may be regulated partly by serotonergic neurons within the brainstem. Pathogenesis may be related to a defect in the activity of neuronal calcium channels mediating neurotransmitter release in brainstem areas that modulate cerebral vascular tone and nociception. The result may be vasodilation of intracranial extracerebral blood vessels with activation of the trigeminovascular system.
- Twin studies suggest 50% heritability of migraine, with a multifactorial polygenic basis. Migraine triggers may be modulators of the genetic set point that predisposes to migraine headache.
- Specific populations of serotonin (5-hydroxytryptamine [5-HT]) receptors may be involved in the pathophysiology and treatment of migraine headache. Acute antimigraine drugs such as ergot alkaloids and triptan derivatives are agonists of vascular and neuronal 5HT<sub>1</sub> receptor subtypes, resulting in vasoconstriction and inhibition of vasoactive neuropeptide release and pain signal transmission.

## CLINICAL PRESENTATION

## Symptoms

- Migraine headache is characterized by recurring episodes of throbbing head pain, frequently unilateral. Migraine headaches can be severe and associated with nausea, vomiting, and sensitivity to light, sound, and/or movement.
- Approximately 20% to 60% of migraineurs experience premonitory symptoms (not to be confused with aura) in the hours or days before the onset of headache. Neurologic symptoms (phonophobia, photophobia, hyperosmia, difficulty concentrating) are most common, but psychological (anxiety, depression, euphoria, irritability, drowsiness, hyperactivity, restlessness), autonomic (e.g., polyuria, diarrhea, constipation), and constitutional (e.g., stiff neck, yawning, thirst, food cravings, anorexia) symptoms may also occur.
- A migraine aura is experienced by approximately 31% of migraineurs. The aura typically evolves over 5 to 20 minutes and lasts less than 60 minutes. Headache usually occurs within 60 minutes of the end of the aura. Visual auras can include both positive features (e.g., scintillations, photopsia,

teichopsia, fortification spectrum) and negative features (e.g., scotoma, hemianopsia). Sensory and motor symptoms such as paresthesias or numbness of the arms and face, dysphasia or aphasia, weakness, and hemiparesis may also occur.

- The migraine headache may occur at any time of day or night but usually occurs in the early morning hours on awakening. Pain is usually gradual in onset, peaking in intensity over minutes to hours, and lasting between 4 and 72 hours untreated. Pain is typically reported as moderate to severe and most often involves the frontotemporal region. The headache is usually unilateral and throbbing in nature. GI symptoms (e.g., nausea, vomiting) almost invariably accompany the headache. Other systemic symptoms include anorexia, constipation, diarrhea, abdominal cramps, nasal stuffiness, blurred vision, diaphoresis, facial pallor, and localized facial or periorbital edema. Sensory hyperacuity (photophobia, phonophobia, osmophobia) is frequently reported. Many patients seek a dark, quiet place for rest and relief.
- Once the headache pain wanes, a resolution phase characterized by exhaustion, malaise, and irritability ensues.

## DIAGNOSIS

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- A comprehensive headache history is the most important element in establishing the diagnosis of migraine.
- In the headache evaluation, diagnostic alarms should be identified. These include acute onset of the “first” or “worst” headache ever, accelerating pattern of headache following subacute onset, onset of headache after age 50 years, headache associated with systemic illness (e.g., fever, nausea, vomiting, stiff neck, and rash), headache with focal neurologic symptoms or papilledema, and new-onset headache in a patient with cancer or human immunodeficiency virus infection.
- A stable pattern of headaches, absence of daily headache, positive family history for migraine, normal neurologic examination, presence of food triggers, menstrual association, long-standing history, improvement with sleep, and subacute evolution are signs suggestive of migraine headache. Aura may signal the migraine headache but is not required for diagnosis.
- Perform a general medical and neurologic physical examination. Check for abnormalities: vital signs (fever, hypertension), funduscopy (papilledema, hemorrhage, and exudates), palpation and auscultation of the head and neck (sinus tenderness, hardened or tender temporal arteries, trigger points, temporomandibular joint tenderness, bruits, nuchal rigidity, and cervical spine tenderness), and neurologic examination (identify abnormalities or deficits in mental status, cranial nerves, deep tendon reflexes, motor strength, coordination, gait, and cerebellar function).
- Diagnostic and laboratory testing may be warranted if there are suspicious headache features or abnormal examination findings. Neuroimaging (computed tomography or magnetic resonance imaging) should be considered in patients with unexplained findings on the neurologic exam, those with additional risk factors, or those with an atypical headache history.

## LABORATORY TESTS

- In selected circumstances and secondary headache presentation, serum chemistries, urine toxicology profiles, thyroid function tests, Lyme studies, and other blood tests, such as a complete blood count, antinuclear antibody titer, erythrocyte sedimentation rate, and antiphospholipid antibody titer may be considered.

## DESIRED OUTCOME

- Acute therapy should provide consistent, rapid headache relief with minimal adverse effects and symptom recurrence, minimal disability and emotional distress, thereby enabling the patient to resume normal daily activities. Ideally, patients should be able to manage their headaches effectively without emergency department or physician office visits.

## TREATMENT

### Nonpharmacologic Treatment

- Application of ice to the head and periods of rest or sleep, usually in a dark, quiet environment, may be beneficial.
- Preventive management should begin with identification and avoidance of factors that provoke migraine attacks (Table 53-1).

**TABLE 53-1** Commonly Reported Triggers of Migraine

#### Food triggers

- Alcohol
- Caffeine/caffeine withdrawal
- Chocolate
- Fermented and pickled foods
- Monosodium glutamate (e.g., in Chinese food, seasoned salt, and instant foods)
- Nitrate-containing foods (e.g., processed meats)
- Saccharin/aspartame (e.g., diet foods or diet sodas)
- Tyramine-containing foods

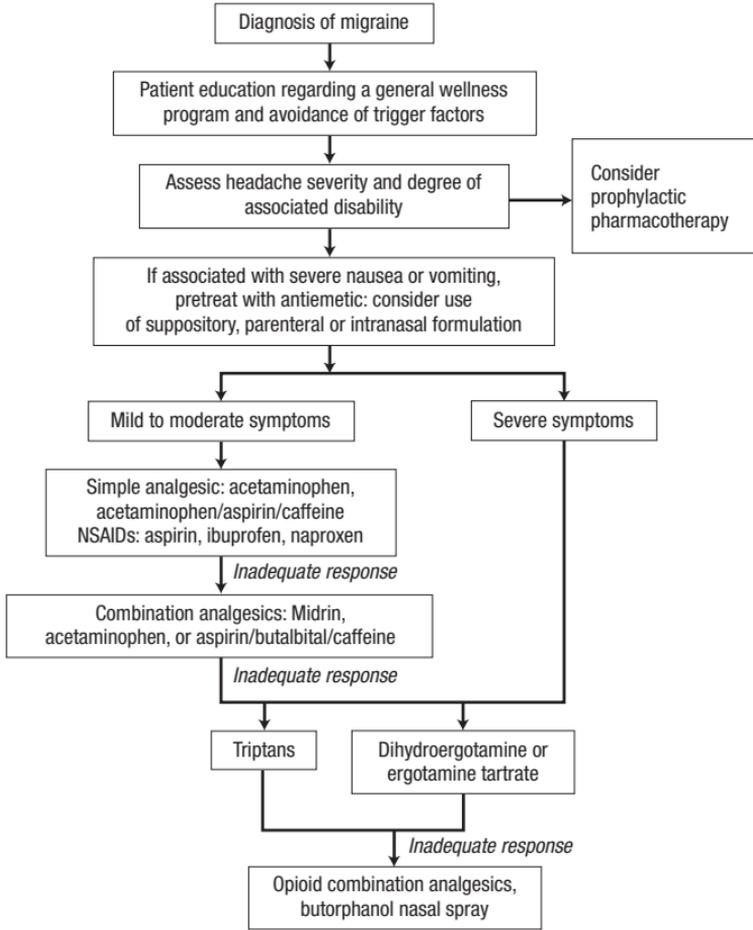
#### Environmental triggers

- Glare or flickering lights
- High altitude
- Loud noises
- Strong smells and fumes
- Tobacco smoke
- Weather changes

#### Behavioral–physiologic triggers

- Excess or insufficient sleep
- Fatigue
- Menstruation, menopause
- Skipped meals
- Strenuous physical activity (e.g., prolonged overexertion)
- Stress or post-stress

Data from Snow V, Weiss K, Wall EM, Mottur-Pilson C. Pharmacologic management of acute attacks of migraine and prevention of migraine headache. *Ann Intern Med* 2002;137:840–849; and Diamond M, Cady R. Initiating and optimizing acute therapy for migraine: The role of patient-centered stratified care. *Am J Med* 2005;118(Suppl 1):S18–27.



**FIGURE 53-1.** Treatment algorithm for migraine headaches. (NSAIDs, nonsteroidal antiinflammatory drugs.)

- Behavioral interventions (relaxation therapy, biofeedback, cognitive therapy) are preventive options for patients who prefer nondrug therapy or when drug therapy is ineffective or not tolerated.

### Pharmacologic Treatment of Acute Migraine

- A treatment algorithm for migraine headache is shown in Fig. 53-1. Acute migraine therapies (Table 53-2) are most effective when administered at the onset of migraine.
- Pretreatment with antiemetics (e.g., **prochlorperazine**, **metoclopramide**) 15 to 30 minutes prior to administering oral acute migraine therapy or use of nonoral treatments (rectal suppositories, nasal spray, injections) may be advisable when nausea and vomiting are severe. In addition to its antiemetic effects, the prokinetic agent metoclopramide helps reverse gastroparesis and enhances absorption of oral medications.
- The frequent or excessive use of acute migraine medications can result in a pattern of increasing headache frequency and drug consumption known

**TABLE 53-2** Acute Migraine Therapies<sup>a</sup>

Medication	Dosage	Comments
<b>Analgesics</b>		
Acetaminophen	1,000 mg at onset; repeat every 4–6 hours as needed	Maximum daily dose is 4 g
Acetaminophen 250 mg/aspirin 250 mg/caffeine 65 mg	2 tablets at onset and every 6 hours	Available over-the-counter as Excedrin Migraine
Aspirin or acetaminophen with butalbital, caffeine	1–2 tablets every 4–6 hours	Limit dose to 4 tablets/day and usage to 2 days/week
Isometheptene 65 mg/dichloralphenazone 100 mg/acetaminophen 325 mg (Midrin)	2 capsules at onset; repeat 1 capsule every hour as needed	Maximum of 6 capsules/day and 20 capsules/month
<b>Nonsteroidal antiinflammatory drugs</b>		
Aspirin	500–1,000 mg every 4–6 hours	Maximum daily dose is 4 g
Ibuprofen	200–800 mg every 6 hours	Avoid doses >2.4 g/day
Naproxen sodium	550–825 mg at onset; can repeat 220 mg in 3–4 hours	Avoid doses >1.375 g/day
Diclofenac potassium	50–100 mg at onset; can repeat 50 mg in 8 hours	Avoid doses >150 mg/day
<b>Ergotamine tartrate</b>		
Oral tablet (1 mg) with caffeine 100 mg	2 mg at onset; then 1–2 mg every 30 minutes as needed	Maximum dose is 6 mg/day or 10 mg/week; consider pretreatment with an antiemetic
Sublingual tablet (2 mg)	—	—
Rectal suppository (2 mg) with caffeine 100 mg	Insert 1/2 to 1 suppository at onset; repeat after 1 hour as needed	Maximum dose is 4 mg/day or 10 mg/week; consider pretreatment with an antiemetic
<b>Dihydroergotamine</b>		
Injection 1 mg/mL	0.25–1 mg at onset IM or subcutaneous; repeat every hour as needed	Maximum dose is 3 mg/day or 6 mg/week
Nasal spray	One spray (0.5 mg) in each nostril at onset; repeat sequence 15 minutes later (total dose is 2 mg or 4 sprays)	Maximum dose is 3 mg/day; prime sprayer four times before using; do not tilt head back or inhale through nose while spraying; discard open ampules after 8 hours
<b>Serotonin agonists (triptans)</b>		
Sumatriptan Injection	6 mg subcutaneous at onset; can repeat after 1 hour if needed	Maximum daily dose is 12 mg

*(continued)*

**TABLE 53-2 Acute Migraine Therapies<sup>a</sup> (Continued)**

Medication	Dosage	Comments
Oral tablets	25, 50, or 100 mg at onset; can repeat after 2 hours if needed	Optimal dose is 50–100 mg; maximum daily dose is 200 mg
Nasal spray	5, 10, or 20 mg at onset; can repeat after 2 hours if needed	Optimal dose is 20 mg; maximum daily dose is 40 mg; single-dose device delivering 5 or 20 mg; administer one spray in one nostril
Zolmitriptan		
Oral tablets	2.5 or 5 mg at onset as regular or orally disintegrating tablet; can repeat after 2 hours if needed	Optimal dose is 2.5 mg; maximum dose is 10 mg/day Do not divide ODT dosage form
Nasal spray	5 mg (one spray) at onset; can repeat after 2 hours if needed	Maximum daily dose is 10 mg/day
Naratriptan	1 or 2.5 mg at onset; can repeat after 4 hours if needed	Optimal dose is 2.5 mg; maximum daily dose is 5 mg
Rizatriptan	5 or 10 mg at onset as regular or orally disintegrating tablet; can repeat after 2 hours if needed	Optimal dose is 10 mg; maximum daily dose is 30 mg; onset of effect is similar with standard and orally disintegrating tablets; use 5-mg dose (15 mg/day max) in patients receiving propranolol
Almotriptan	6.25 or 12.5 mg at onset; can repeat after 2 hours if needed	Optimal dose is 12.5 mg; maximum daily dose is 25 mg
Frovatriptan	2.5 or 5 mg at onset; can repeat in 2 hours if needed	Optimal dose 2.5–5 mg; maximum daily dose is 7.5 mg (3 tablets)
Eletriptan	20 or 40 mg at onset; can repeat after 2 hours if needed	Maximum single dose is 40 mg; maximum daily dose is 80 mg
<b>Miscellaneous</b>		
Butorphanol nasal spray	1 spray in 1 nostril (1 mg) at onset; repeat in 1 hour if needed	Limit to 4 sprays/day; consider use only when nonopioid therapies are ineffective or not tolerated
Metoclopramide	10 mg IV at onset	Useful for acute relief in the office or emergency department setting
Prochlorperazine	10 mg IV or IM at onset	Useful for acute relief in the office or emergency department setting

ODT, orally disintegrating tablet.

<sup>a</sup>Limit use of symptomatic medications to 2 or 3 days/week when possible to avoid medication-misuse headache.

Data from Ferrari MD. Migraine. *Lancet* 1998;351:1043–1051; Silberstein SD, Goadsby PJ, Lipton RB. *Neurology* 2000;55(Suppl 2):S46–52; Matchar DB, Young WB, Rosenberg JA, et al. 2000. [www.aan.com/professionals/practice/guidelines](http://www.aan.com/professionals/practice/guidelines); Aukerman G, Knutson D, Miser WF. *Am Fam Physician* 2002;66:2123–2130, 2140–2141; and Eadie MJ. *CNS Drugs* 2001;15(2):105–118.

as medication-overuse headache. This occurs commonly with overuse of simple or combination analgesics, opiates, ergotamine tartrate, and triptans. This may be avoided by limiting use of acute migraine therapies to 2 or 3 days per week.

### *Analgesics and Nonsteroidal Antiinflammatory Drugs*

- **Simple analgesics** and **nonsteroidal antiinflammatory drugs (NSAIDs)** are effective as first-line treatment for mild to moderate migraine attacks. **Aspirin, ibuprofen, naproxen sodium, tolfenamic acid,** and the combination of **acetaminophen** plus **aspirin** and **caffeine** are effective.
- NSAIDs appear to prevent neurogenically mediated inflammation in the trigeminovascular system by inhibiting prostaglandin synthesis.
- In general, NSAIDs with a long half-life are preferred as less frequent dosing is needed. Rectal suppositories and intramuscular (IM) **ketorolac** are options for patients with severe nausea and vomiting.
- The combination of **acetaminophen, aspirin,** and **caffeine** is approved in the United States for relieving migraine pain and associated symptoms.
- Aspirin and acetaminophen are also available by prescription in combination with a short-acting barbiturate (**butalbital**). No randomized, placebo-controlled studies support the efficacy of butalbital-containing formulations for migraine.
- **Midrin** is a **proprietary** combination of **acetaminophen, isometheptene mucate** (a sympathomimetic amine), and **dichloralphenazone** (a chloral hydrate derivative) that has shown modest benefits in placebo-controlled trials. It may be an alternative for patients with mild to moderate migraine attacks.

### *Ergot Alkaloids and Derivatives*

- **Ergot alkaloids** are useful for moderate to severe migraine attacks. They are nonselective 5HT<sub>1</sub> receptor agonists that constrict intracranial blood vessels and inhibit the development of neurogenic inflammation in the trigeminovascular system. Venous and arterial constriction occurs. They also have activity at  $\alpha$ -adrenergic,  $\beta$ -adrenergic, and dopaminergic receptors.
- **Ergotamine tartrate** is available for oral, sublingual, and rectal administration. Oral and rectal preparations contain caffeine to enhance absorption and potentiate analgesia. Because oral ergotamine undergoes extensive first-pass hepatic metabolism, rectal administration is preferred. Dosage should be titrated to produce an effective but sub-nauseating dose.
- **Dihydroergotamine (DHE)** is available for intranasal and parenteral (IM, IV, subcutaneous [SC]) administration. Patients can be trained to self-administer DHE by the IM or SC routes.
- Nausea and vomiting are common adverse effects of ergotamine derivatives. Pretreatment with an antiemetic should be considered with ergotamine and IV DHE therapy. Other side effects include abdominal pain, weakness, fatigue, paresthesias, muscle pain, diarrhea, and chest tightness. Symptoms of severe peripheral ischemia (ergotism) include cold, numb, painful extremities; continuous paresthesias; diminished peripheral pulses; and claudication. Gangrenous extremities, myocardial infarction, hepatic

necrosis, and bowel and brain ischemia have been reported rarely with ergotamine. Ergotamine derivatives and triptans should not be used within 24 hours of each other.

- Contraindications include renal and hepatic failure; coronary, cerebral, or peripheral vascular disease; uncontrolled hypertension; sepsis; and women who are pregnant or nursing.
- DHE does not appear to cause rebound headache, but dosage restrictions for ergotamine tartrate should be strictly observed to prevent this complication.

### *Serotonin Receptor Agonists (Triptans)*

- **Sumatriptan, zolmitriptan, naratriptan, rizatriptan, almotriptan, frovatriptan, and eletriptan** are appropriate first-line therapies for patients with moderate to severe migraine or as rescue therapy when nonspecific medications are ineffective.
- These drugs are selective agonists of the 5HT<sub>1B</sub> and 5HT<sub>1D</sub> receptors. Relief of migraine headache results from (1) normalization of dilated intracranial arteries; (2) peripheral neuronal inhibition; and (3) inhibition of transmission through second-order neurons of the trigeminocervical complex. They also display varying affinity for 5HT<sub>1A</sub>, 5HT<sub>1E</sub>, and 5HT<sub>1F</sub> receptors.
- **Sumatriptan** is available for oral, intranasal, and SC administration. The SC injection is packaged as an autoinjector device for self-administration by patients. When compared with the oral formulation, SC administration offers enhanced efficacy and a more rapid onset of action (10 vs. 30 minutes). Intranasal sumatriptan also has a faster onset of effect (15 minutes) than the oral formulation and produces similar rates of response. Approximately 30% to 40% of patients who respond to sumatriptan experience headache recurrence within 24 hours; a second dose given at the time of recurrence is usually effective. However, routine administration of a second oral or SC dose does not improve initial efficacy rates or prevent subsequent recurrence.
- Second-generation triptans (all except sumatriptan) have higher oral bioavailability and longer half-lives than oral sumatriptan, which could theoretically improve within-patient treatment consistency and reduce headache recurrence. However, comparative clinical trials are necessary to determine their relative efficacy.
- Pharmacokinetic characteristics of the triptans are shown in Table 53-3.
- Clinical response to triptans varies among individual patients, and lack of response to one agent does not preclude effective therapy with another member of the class.
- Side effects of triptans include paresthesias, fatigue, dizziness, flushing, warm sensations, and somnolence. Minor injection site reactions are reported with SC use, and taste perversion and nasal discomfort may occur with intranasal administration. Up to 15% of patients report chest tightness, pressure, heaviness, or pain in the chest, neck, or throat. Although the mechanism of these symptoms is unknown, a cardiac source is unlikely in most patients. Isolated cases of myocardial infarction and coronary vasospasm with ischemia have been reported.
- Contraindications include ischemic heart disease, uncontrolled hypertension, cerebrovascular disease, and hemiplegic and basilar migraine. Trip-

**TABLE 53-3** Pharmacokinetic Characteristics of Triptans

Drug	Half-Life (hours)	Time to Maximal Concentration ( $t_{\max}$ )	Bioavailability (%)	Elimination
Almotriptan	3–4	1.4–3.8 hours	70	MAO-A, CYP3A4, CYP2D6
Eletriptan	5	1.4–2.8 hours	50	CYP3A4
Frovatriptan	25	2–4 hours	24–30	CYP1A2
Naratriptan	5–6	2–3 hours	63–74	CYP450 (various isoenzymes)
Rizatriptan	2–3		40–45	MAO-A
Oral tablets		1–1.5 hours		
Disintegrating		1.6–2.5 hours		
Sumatriptan	2			MAO-A
SC injection		12–15 minutes	97	
Oral tablets		2.5 hours	14	
Nasal spray		1–2.5 hours	17	
Zolmitriptan	3		40	CYP1A2, MAO-A
Oral		1.5 hours		
Disintegrating		3 hours		
Nasal		4 hours		

CYP, cytochrome P450; MAO-A, monoamine oxidase type A.

Data from Goadsby PJ, Lipton RB, Ferrari MD. *N Engl J Med* 2002;346:257–270; del Rio MS, Silberstein SD. *Curr Pain Headache Rep* 2001;5:170–178; Matthew NT, Loder EW. *Am J Med* 2005;118(Suppl 1):S28–35; Tfelt-Hansen P, DeVries P, Saxena PR. *Drugs* 2000;60:1259–1287; Deleu D, Hanssens Y. *J Clin Pharmacol* 2000;40:687–700; and Pringsheim T, Gawel M. *Curr Pain Headache Rep* 2002;6:140–146.

tans should not be given within 24 hours of ergotamine derivative administration. Administration within 2 weeks of therapy with monoamine oxidase inhibitors is not recommended. Concomitant use of the triptans with selective serotonin reuptake inhibitors or the serotonin-norepinephrine reuptake inhibitors can cause serotonin syndrome, a potentially life-threatening condition.

### Opioids

- Opioids and derivatives (e.g., **meperidine**, **butorphanol**, **oxycodone**, **hydromorphone**) provide effective relief of intractable migraine but should be reserved for patients with moderate to severe infrequent headaches in whom conventional therapies are contraindicated or as rescue medication after failure to respond to conventional therapies. Opioid therapy should be closely supervised.
- **Intranasal butorphanol** may provide an alternative to frequent office or emergency department visits for injectable migraine therapies. Onset of analgesia occurs within 15 minutes of administration. Adverse effects include dizziness, nausea, vomiting, drowsiness, and taste perversion. It also has the potential for dependence and addiction.

### Glucocorticoids

- Corticosteroids may be an effective rescue therapy for status migrainosus, which is a severe migraine that may last up to 1 week.

**TABLE 53-4** Prophylactic Migraine Therapies

Medication	Dose
<b><math>\beta</math>-Adrenergic antagonists</b>	
Atenolol	25–100 mg/day
Metoprolol <sup>a</sup>	50–300 mg/day in divided doses
Nadolol	80–240 mg/day
Propranolol <sup>a,b</sup>	80–240 mg/day in divided doses
Timolol <sup>b</sup>	20–60 mg/day in divided doses
<b>Antidepressants</b>	
Amitriptyline	25–150 mg at bedtime
Doxepin	10–200 mg at bedtime
Imipramine	10–200 mg at bedtime
Nortriptyline	10–150 mg at bedtime
Protriptyline	5–30 mg at bedtime
Fluoxetine	10–80 mg/day
Phenelzine <sup>c</sup>	15–60 mg/day in divided doses
Gabapentin	900–2,400 mg/day in divided doses
Topiramate <sup>b</sup>	100 mg/day in divided doses
Valproic acid/divalproex sodium <sup>b</sup>	500–1,500 mg/day in divided doses
Verapamil <sup>a</sup>	240–360 mg/day in divided doses
Methysergide <sup>b,c</sup>	2–8 mg/day in divided doses with food
<b>Nonsteroidal antiinflammatory drugs<sup>c</sup></b>	
Aspirin	1,300 mg/day in divided doses
Ketoprofen <sup>a</sup>	150 mg/day in divided doses
Naproxen sodium <sup>a</sup>	550–1,100 mg/day in divided doses
Vitamin B <sub>2</sub>	400 mg/day

<sup>a</sup>Sustained-release formulation available.

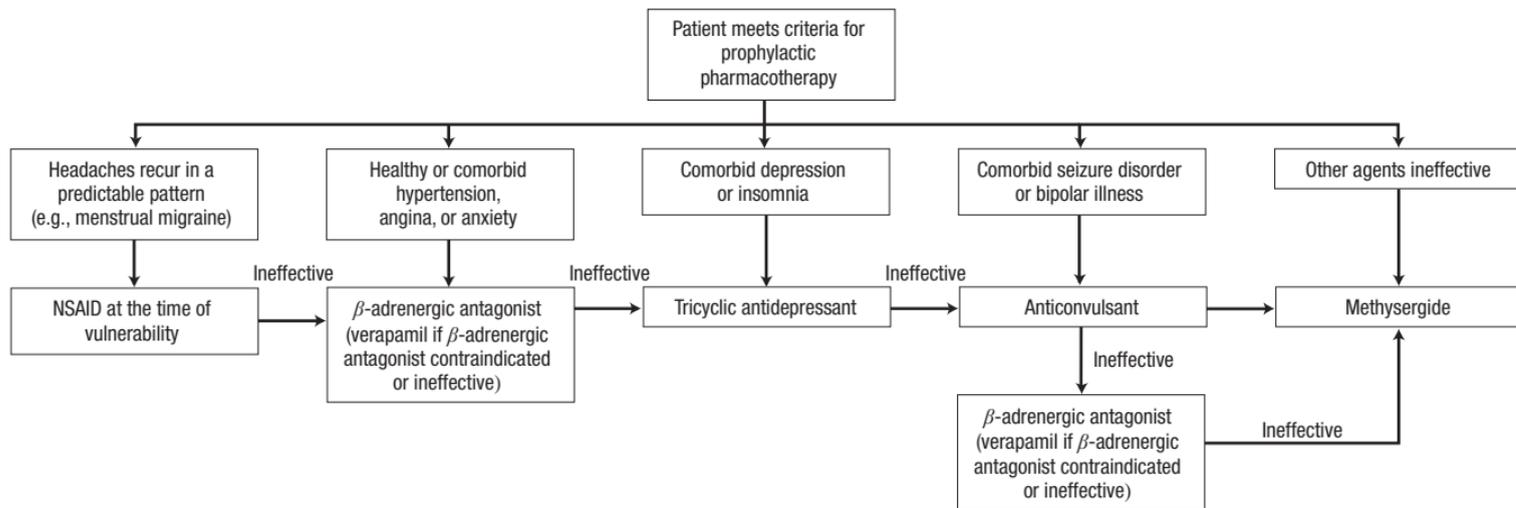
<sup>b</sup>FDA approved for prevention of migraine.

<sup>c</sup>Daily or prolonged use limited by potential toxicity.

Data from Silberstein SD. *Migraine. Lancet* 2004;363:381–391; Silberstein SD. *Neurology* 2000;55:754–763; Silberstein SD, Goadsby PJ, Lipton RB. *Neurology* 2000;55(Suppl 2):S46–52; and Rapoport AM, Bigal ME. *Neural Sci* 2004;25(Suppl 1):S177–185.

## Pharmacologic Prophylaxis of Migraine

- Prophylactic therapies (Table 53-4) are administered on a daily basis to reduce the frequency, severity, and duration of attacks, as well as to increase responsiveness to acute symptomatic therapies. A treatment algorithm for prophylactic management of migraine headache is shown in Fig. 53-2.
- Prophylaxis should be considered in the setting of recurring migraines that produce significant disability; frequent attacks requiring symptomatic medication more than twice per week; symptomatic therapies that are ineffective, contraindicated, or produce serious side effects; uncommon migraine variants that cause profound disruption and/or risk of neurologic injury; and patient preference to limit the number of attacks.
- Preventive therapy may also be administered intermittently when headaches recur in a predictable pattern (e.g., exercise-induced or menstrual migraine).
- Because efficacy of various prophylactic agents appears to be similar, drug selection is based on side-effect profiles and comorbid conditions of the patient. Individual response to a particular agent is unpredictable, and a



**FIGURE 53-2.** Treatment algorithm for prophylactic management of migraine headaches. (NSAID, nonsteroidal antiinflammatory drug.)

trial of 2 to 3 months duration is necessary to judge the efficacy of each medication.

- Only propranolol, timolol, valproic acid, and topiramate are approved by the FDA for migraine prevention.
- Prophylaxis should be initiated with low doses and advanced slowly until a therapeutic effect is achieved or side effects become intolerable.
- Prophylaxis is usually continued for at least 3 to 6 months after headache frequency and severity have diminished, and then gradually tapered and discontinued, if possible.

### ***$\beta$ -Adrenergic Antagonists***

- **$\beta$ -Blockers (propranolol, nadolol, timolol, atenolol, and metoprolol)** are the most widely used treatment for prevention of migraine.  **$\beta$ -Blockers** with intrinsic sympathomimetic activity are ineffective. They are reported to reduce the frequency of attacks by 50% in 60% to 80% of patients.
- Bronchoconstrictive and hyperglycemic effects can be minimized with  **$\beta_1$ -selective  $\beta$ -blockers**.
- Side effects include drowsiness, fatigue, sleep disturbances, vivid dreams, memory disturbance, depression, GI intolerance, sexual dysfunction, bradycardia, and hypotension.
- **$\beta$ -Blockers** should be used with caution in patients with heart failure, peripheral vascular disease, atrioventricular conduction disturbances, asthma, depression, and diabetes.

### ***Antidepressants***

- **Amitriptyline** appears to be the tricyclic antidepressant (TCA) of choice, but **imipramine, doxepin, nortriptyline, and protriptyline** have also been used.
- Their beneficial effects in migraine prophylaxis are independent of antidepressant activity and may be related to downregulation of central 5HT<sub>2</sub> and adrenergic receptors.
- TCAs are usually well tolerated at the lower doses used for migraine prophylaxis, but anticholinergic effects may limit use, especially in elderly patients or those with benign prostatic hyperplasia or glaucoma. Evening doses are preferred because of sedation.
- Data for **fluoxetine** are inconsistent, and prospective data evaluating **sertraline, paroxetine, fluvoxamine, and citalopram** are lacking.
- Selective serotonin reuptake inhibitors are considered to be less effective than TCAs for migraine prophylaxis and should not be considered first- or second-line therapy. However, they may be beneficial when depression is a significant contributor to headache. Preliminary data suggest a possible benefit with venlafaxine.

### ***Anticonvulsants***

- **Valproic acid** and **divalproex sodium** (a 1:1 molar combination of valproate sodium and valproic acid) can reduce the frequency, severity, and duration of headaches by at least 50% in up to 65% of migraineurs.
- Side effects of valproic acid and divalproex sodium include nausea (less common with divalproex sodium and gradual dosing titration), tremor,

somnolence, weight gain, hair loss, and hepatotoxicity (rare). The extended-release formulation of divalproex sodium is administered once daily and is better tolerated than the enteric-coated formulation.

- Serum levels less than 50 mcg/mL may be equal in efficacy to higher serum concentrations.
- **Topiramate** is recently approved by the FDA for migraine prophylaxis. Dose is initiated at 25 mg/day and increased slowly to minimize side effects, which may include paresthesias, fatigue, anorexia, diarrhea, weight loss, difficulty with memory, and nausea. Kidney stones, acute myopia, acute angle-closure glaucoma, and oligohidrosis have been infrequently reported.

### *Methysergide*

- **Methysergide** is a semisynthetic ergot alkaloid that is a potent 5HT<sub>2</sub> receptor antagonist. It appears to stabilize serotonergic neurotransmission in the trigeminovascular system to block the development of neurogenic inflammation.
- Its use is limited by the occurrence of potentially serious retroperitoneal, endocardial, and pulmonary fibrotic complications that have occurred during long-term uninterrupted use. It is reserved for patients with refractory headaches that do not respond to other preventive therapies.
- Consequently, a 4-week, medication-free period is recommended after each 6-month treatment period. Dosage should be tapered over 1 week to prevent rebound headaches.
- Monitoring for fibrotic complications should include periodic cardiac auscultation, chest x-ray, echocardiography, and abdominal magnetic resonance imaging. Patients should report symptoms of flank pain, dysuria, chest pain, and shortness of breath.
- Methysergide is best tolerated when taken with meals. Side effects other than GI intolerance are many and include insomnia, vivid dreams, hallucinations, claudication, and muscle cramps. The labeling should be consulted for additional side effects and contraindications.

### *Calcium Channel Blockers*

- **Verapamil** provided only modest benefit in decreasing the frequency of attacks in two placebo-controlled studies. It has little effect on the severity of migraine attacks. It is generally considered a second- or third-line prophylactic agent.

### *Nonsteroidal Antiinflammatory Drugs*

- NSAIDs are modestly effective for reducing the frequency, severity, and duration of migraine attacks, but potential GI and renal toxicity limit daily or prolonged use.
- They may be used intermittently to prevent headaches that recur in a predictable pattern (e.g., menstrual migraine). Treatment should be initiated 1 to 2 days before the time of headache vulnerability and continued until vulnerability is passed.

## TENSION-TYPE HEADACHE

### DEFINITION

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- Tension-type headache is the most common type of primary headache and is more common in women than men. Pain is usually mild to moderate and nonpulsatile. Episodic headaches may become chronic.

### PATHOPHYSIOLOGY

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- Pain is thought to originate from myofascial factors and peripheral sensitization of nociceptors. Central mechanisms are also involved. Mental stress, nonphysiologic motor stress, a local myofascial release of irritants, or a combination of these may be the initiating stimulus. In predisposed individuals, chronic, tension-type headache can evolve.
- After activation of supraspinal pain perception structures, a headache occurs because of central modulation of incoming peripheral stimuli.

### CLINICAL PRESENTATION

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- Premonitory symptoms and aura are absent, and pain is usually mild to moderate, bilateral, nonpulsatile, and in the frontal and temporal areas, but occipital and parietal areas can also be affected.
- Mild photophobia or phonophobia may occur. Pericranial or cervical muscles may have tender spots or localized nodules in some patients.

### TREATMENT

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- **Simple analgesics** (alone or in combination with caffeine) and **NSAIDs** are the mainstay of acute therapy.
- Nonpharmacologic therapies include reassurance and counseling, stress management, relaxation training, and biofeedback. Physical therapeutic options (e.g., heat or cold packs, ultrasound, electrical nerve stimulation, massage, acupuncture, trigger point injections, occipital nerve blocks) have performed inconsistently.
- **Acetaminophen, aspirin, ibuprofen, naproxen, ketoprofen, indomethacin, and ketorolac** are effective.
- High-dose NSAIDs and the combination of aspirin or acetaminophen with butalbital or, rarely, codeine, are effective options. The use of butalbital and codeine combinations should be avoided when possible.
- Acute medication for episodic headache should be taken no more often than 2 days/wk to prevent development of chronic tension-type headache.
- There is no evidence to support the efficacy of muscle relaxants for tension-type headache.
- Preventive treatment should be considered if headache frequency is more than two per week, duration is greater than 3 to 4 hours, or severity results in medication overuse or substantial disability.
- The TCAs are used most often for prophylaxis of tension headache. Injection of botulinum toxin into pericranial muscles has demonstrated efficacy in prophylaxis of chronic tension-type headache in two studies.

**EVALUATION OF THERAPEUTIC OUTCOMES**

- Patients should be monitored for frequency, intensity, and duration of headaches and for any change in the headache pattern.
- Patients taking abortive therapy should be monitored for frequency of use of prescription and nonprescription medications and for side effects of medications.
- Patterns of abortive medication use can be documented to establish the need for prophylactic therapy. Prophylactic therapies should also be monitored closely for adverse reactions, abortive therapy needs, adequate dosing, and compliance.

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*See Chap. 63, Headache Disorders, authored by Deborah S. Minor and Marion R. Wofford, for a more detailed discussion of this topic.*

## DEFINITION

- Pain is an unpleasant, subjective, sensory, and emotional experience associated with actual or potential tissue damage or described in terms of such damage.

## PATHOPHYSIOLOGY

## NOCICEPTIVE PAIN

- Nociceptive (acute) pain is either somatic (arising from skin, bone, joint, muscle, or connective tissue) or visceral (arising from internal organs such as the large intestine or pancreas).
- Stimulation of free nerve endings known as *nociceptors* is the first step leading to the sensation of pain. These receptors are found in both somatic and visceral structures and are activated by mechanical, thermal, and chemical factors. Release of bradykinins,  $K^+$ , prostaglandins, histamine, leukotrienes, serotonin, and substance P may sensitize and/or activate nociceptors. Receptor activation leads to action potentials that are transmitted along afferent nerve fibers to the spinal cord.
- Action potentials continue from the site of noxious stimuli to the dorsal horn of the spinal cord and then ascend to higher centers. The thalamus acts as a relay station and passes the impulses to central structures where pain is processed further.
- The body modulates pain through several processes. The endogenous opiate system consists of neurotransmitters (e.g., enkephalins, dynorphins, and  $\beta$ -endorphins) and receptors (e.g.,  $\mu$ ,  $\delta$ ,  $\kappa$ ) that are found throughout the CNS. Endogenous opioids bind to opioid receptors and modulate the transmission of pain impulses.
- The CNS also contains a descending system for control of pain transmission. This system originates in the brain and can inhibit synaptic pain transmission at the dorsal horn. Important neurotransmitters here include endogenous opioids, serotonin, norepinephrine,  $\gamma$ -aminobutyric acid, and neurotensin.

## NEUROPATHIC PAIN/FUNCTIONAL PAIN

- Neuropathic and functional pain is often described in terms of chronic pain. Neuropathic pain (e.g., postherpetic neuralgia, diabetic neuropathy) is a result of nerve damage, but functional pain (e.g., fibromyalgia, irritable bowel syndrome, tension-type headache) refers to abnormal operation of the nervous system. Pain circuits may rewire themselves and produce spontaneous nerve stimulation.
- Acute pain (e.g., surgery, trauma, labor, medical procedures) usually is nociceptive, but it can be neuropathic.

- Chronic pain can be nociceptive, neuropathic/functional, or both (e.g., pain that persists after the healing of the acute injury, pain related to a chronic disease, pain without an identifiable cause, and pain associated with cancer).

## CLINICAL PRESENTATION

### GENERAL

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- Patients may be in obvious acute distress (trauma pain) or appear to have no noticeable suffering.

### SYMPTOMS

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- Acute pain can be described as sharp or dull, burning, shock-like, tingling, shooting, radiating, fluctuating in intensity, varying in location, and occurring in a timely relationship with an obvious noxious stimulus. Chronic pain can present similarly, and often occurs without a timely relationship with a noxious stimulus.
- Over time, the chronic pain presentation may change (e.g., sharp to dull, obvious to vague).

### SIGNS

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- Acute pain can cause hypertension, tachycardia, diaphoresis, mydriasis, and pallor, but these signs are not diagnostic. These signs are seldom present in chronic pain.
- In acute pain, comorbid conditions are usually not present, and outcomes of treatment are generally predictable. In chronic pain, comorbid conditions are often present, and outcomes of treatment are often unpredictable.
- Pain is always subjective; thus pain is best diagnosed based on patient description, history, and physical exam. A baseline description of pain can be obtained by assessing PQRST characteristics (palliative and provocative factors, quality, radiation, severity, and temporal factors). Attention should be given to mental factors that may lower the pain threshold (anxiety, depression, fatigue, anger, fear). Behavioral, cognitive, social, and cultural factors may also affect the pain experience.
- Neuropathic pain is often chronic, not well described, and not easily treated with conventional analgesics. There may be exaggerated painful responses to normally noxious stimuli (hyperalgesia); or painful responses to normally nonnoxious stimuli (allodynia).

## DESIRED OUTCOMES

- The goals of therapy are to minimize pain and provide reasonable comfort at the lowest effective analgesic dose. With chronic pain, goals may include rehabilitation and resolution of psychosocial issues.

## TREATMENT

- The elderly and the young are at a higher risk for undertreatment of pain because of misunderstanding about the pathophysiology of their pain. Figs. 54-1 and 54-2 are algorithms for management of acute pain and pain in oncology patients.

## NONOPIOID AGENTS

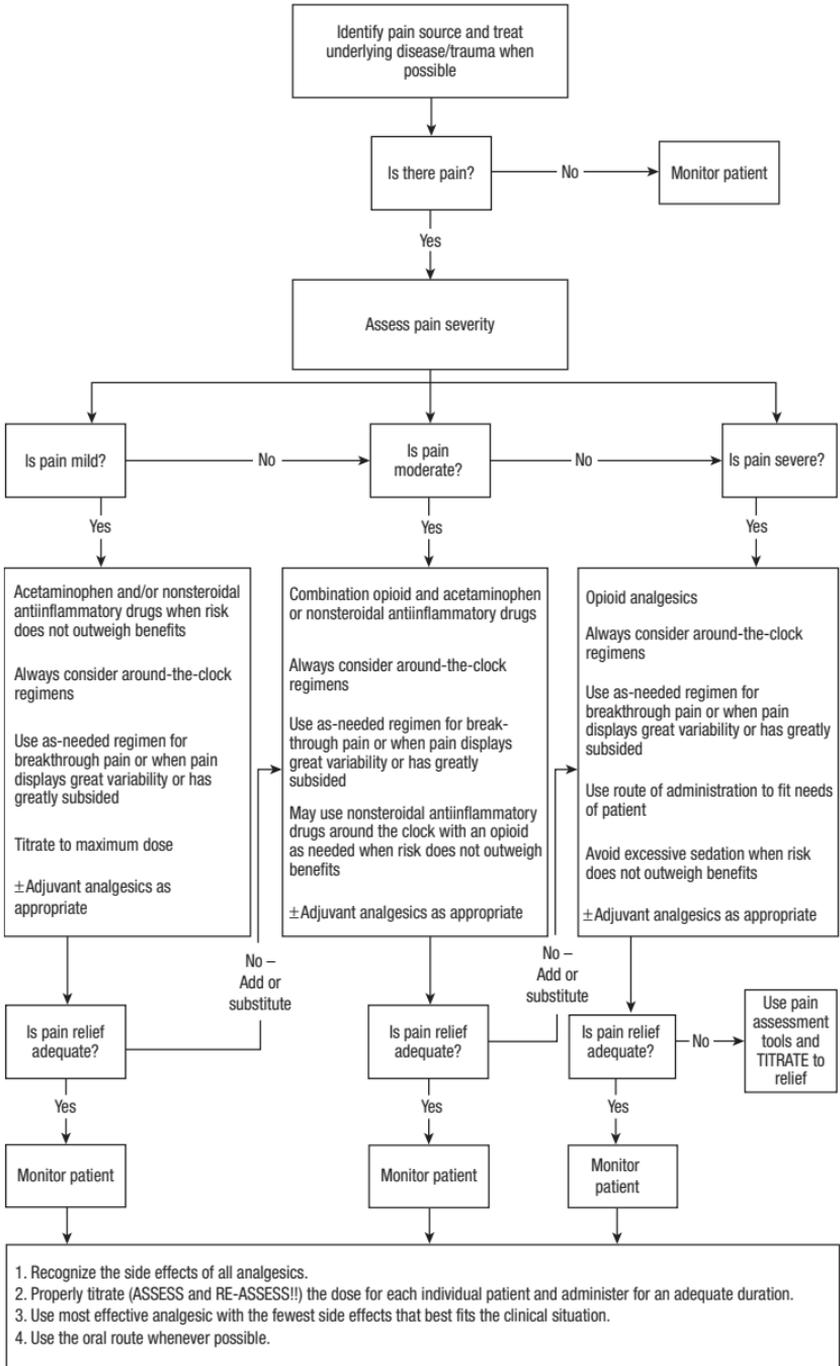
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- Analgesia should be initiated with the most effective analgesic with the fewest side effects. Adult dosage, half-life, and selected pharmacodynamics of FDA-approved nonopioid analgesics are shown in Tables 54-1 and 54-2.
- The nonopioids are preferred over the opioids for mild to moderate pain (see Table 54-1). The salicylates and nonsteroidal antiinflammatory drugs (NSAIDs) reduce prostaglandins produced by the arachidonic acid cascade, thereby decreasing the number of pain impulses received by the CNS.
- NSAIDs may be particularly useful for management of cancer-related bone pain.
- NSAIDs are more likely to cause GI side effects. The salicylate salts cause fewer GI side effects than aspirin and do not inhibit platelet aggregation.
- Aspirin-like compounds should not be given to children or teenagers with influenza or chickenpox, as Reye's syndrome may result.
- Acetaminophen has analgesic and antipyretic activity but little antiinflammatory action. It is highly hepatotoxic on overdose.

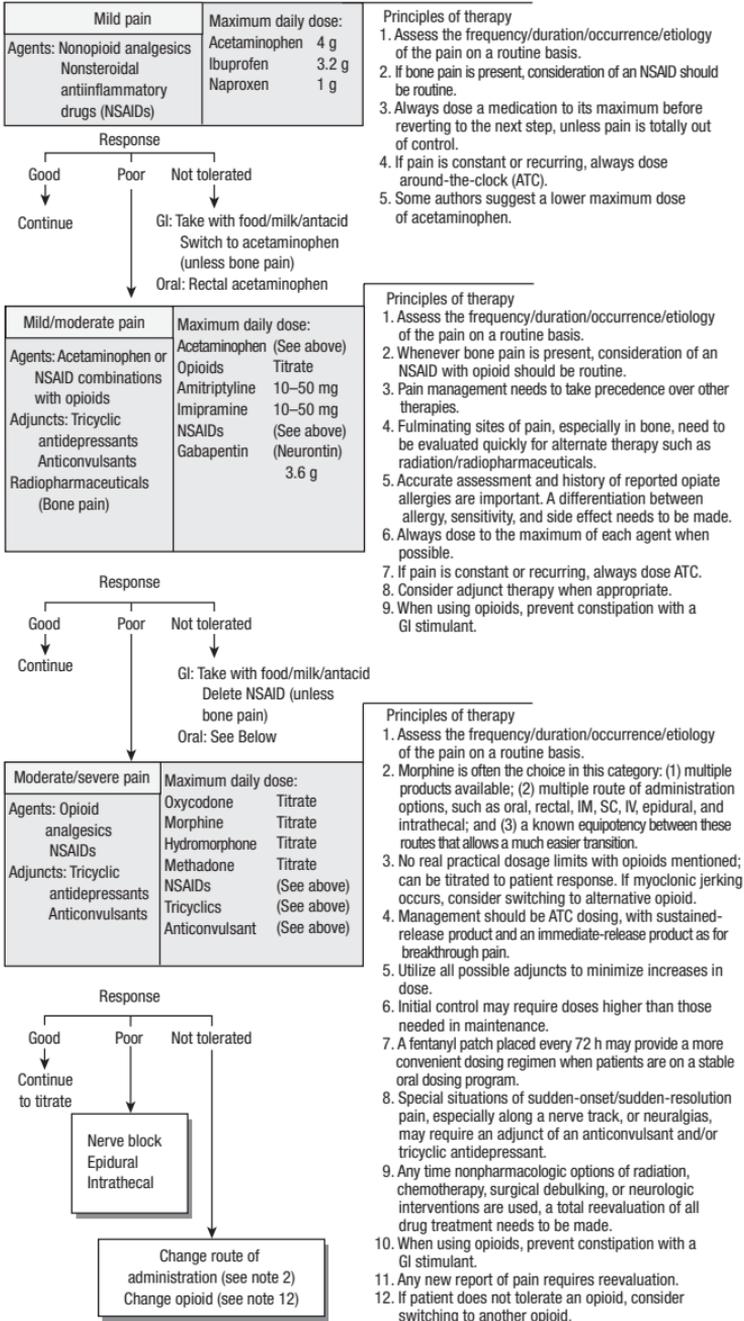
## OPIOID AGENTS

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- With oral opioids, the onset of action usually takes about 45 minutes, and peak effect usually is seen in about 1 to 2 hours.
- Equianalgesic doses, dosing guidelines, histamine-releasing characteristics, major adverse effects, and pharmacokinetics of opioids are shown in Tables 54-2, 54-3, and 54-4. The equianalgesic doses are only a guide, and doses must be individualized.
- Partial agonists and antagonists compete with agonists for opioid receptor sites and exhibit mixed agonist-antagonist activity. They may have selectivity for analgesic receptor sites and cause fewer side effects.
- In the initial stages of acute pain treatment, analgesics should be given around the clock. As the painful state subsides, as-needed schedules can be used. Around-the-clock administration is also useful for management of chronic pain.
- Patients with severe pain may receive very high doses of opioids with no unwanted side effects, but as pain subsides, patients may not tolerate even low doses.
- Most of the itching or rash reported with the opioids is due to histamine release and mast cell degranulation, not to a true allergic response.
- When allergies occur with one opioid, a drug from a different structural class of opioids may be tried with caution. For these purposes, the mixed agonist/antagonist class behaves most like the morphine-like agonists.



**FIGURE 54-1.** Algorithm for management of acute pain. (Data modified from Omnicare, Inc., Acute Pain Pathway.)



**FIGURE 54-2.** Algorithm for pain management in oncology patients. (Data modified from the Kaiser Permanente Algorithm for Pain Management in Patients with Advanced Malignant Disease and Clinical Practice Guideline No. 9. Management of Cancer Pain. Publication No. 94–0592, Rockville, MD: Department of Health, Public Health Service, Agency for Health Care Policy and Research [now called Agency for Healthcare Research and Quality], 1994.)

**TABLE 54-1** FDA-Approved Nonopioid Analgesics for Pain in Adults

<b>Class and Generic Name (Brand Name)</b>	<b>Half-Life (hour)</b>	<b>Usual Dosage Range (mg)</b>	<b>Maximal Dose (mg/day)</b>
<b>Salicylates</b>			
Acetylsalicylic acid <sup>d</sup> —aspirin (various)	0.25	325–1,000 q 4–6 h	4,000
Magnesium—anhydrous <sup>d</sup> (Doan's, various, various combina- tions of choline and magnesium are available)	Nd/Nd	304–607 q 4 h 607–934 q 6 h	3,738
Diflunisal (Dolobid, various)	8–12	500–1,000 initial 250–500 q 8–12 h	1,500
<b>para-Aminophenol</b>			
Acetaminophen <sup>d</sup> (Tylenol, various)	2–3	325–1,000 q 4–6 h	4,000 <sup>b</sup>
<b>Fenamates</b>			
Meclofenamate (various)	0.8–2.1	50–100 q 4–6 h	400
Mefenamic acid (Ponstel)	2	Initial 500 250 q 6 h (maximum 7 days)	1,000 <sup>c</sup>
<b>Pyranocarboxylic acid</b>			
Etodolac (various) (immediate release)	7.3	200–400 q 6–8 h	1,000
<b>Acetic acid</b>			
Diclofenac potassium (Cataflam, various)	1.9	In some patients, initial 100, 50 three times per day	150 <sup>d</sup>
<b>Propionic acids</b>			
Ibuprofen <sup>d</sup> (Motrin, various)	2–2.5	200–400 q 4–6 h	3,200 <sup>e</sup> 2,400 <sup>e</sup> 1,200 <sup>f</sup>
Fenoprofen (Nalfon, various)	3	200 q 4–6 h	3,200
Ketoprofen (various)	2	25–50 q 6–8 h	300
Naproxen (Naprosyn, Anaprox, various)	12–17	500 initial 500 q 12 h or 250 q 6–8 h	1,000 <sup>c</sup>
Naproxen sodium <sup>d</sup> (Aleve, various)	12–13	In some patients, 440 initial <sup>f</sup> 220 q 8–12 h <sup>f</sup>	660 <sup>f</sup>
<b>Pyrrolizine carboxylic acid</b>			
Ketorolac—parenteral (various)	5–6	30–60 (single IM dose only) 15–30 (single IV dose only) 15–30 every 6 h (maximum of 5 days)	30–60 15–30 60–120
Ketorolac—oral, indicated for continuation with parenteral only (various)	5–6	10 q 4–6 h (maximum of 5 days, which includes parenteral doses) In some patients, initial oral dose of 20	40
<b>Cyclooxygenase-2 inhibitors</b>			
Celecoxib (Celebrex)	11	Initial 400 followed by another 200 on first day, then 200 twice daily	400

*(continued)*

**TABLE 54-1** FDA-Approved Nonopioid Analgesics for Pain in Adults (Continued)

Nd, no data.

<sup>a</sup>Available both as a nonprescription over-the-counter preparation and as a prescription drug.

<sup>b</sup>Some experts believe 4,000 mg may be too high.

<sup>c</sup>Up to 1,250 mg on the first day.

<sup>d</sup>Up to 200 mg on the first day.

<sup>e</sup>Some individuals may respond better to 3,200 mg as opposed to 2,400 mg, although well-controlled trials show no better response; consider risk versus benefits when using 3,200 mg/day.

<sup>f</sup>Nonprescription dose.

Data from American Pain Society. *Principles of Analgesic Use in the Treatment of Acute Pain and Chronic Cancer Pain*, 5th ed. Glenview, IL: American Pain Society, 2003; Anonymous. *American Hospital Formulary Service*. In: McVoy GK, ed. *Drug Information*. Bethesda, MD: American Society of Hospital Pharmacists, 1987, 1991, 1994, 1997, 1999, 2001, 2003, 2004, 2005, 2006, 2007; Anonymous. *Facts and Comparisons*. Philadelphia: Lippincott, 1986, 1991, 1994, 1997, 2000, 2003, 2004, 2006, 2007; and Watkins PB, Kaplowitz N, Slattery TJ, et al. *Aminotransferase elevations in healthy adults receiving 4 grams of acetaminophen daily: A randomized controlled trial*. *JAMA* 2006;296:87-93.

**TABLE 54-2** Adult Dosing Guidelines for Opioids and Nonopioids

Agent(s)	Doses (titrate up or down based on patient response)	Notes
NSAIDs/acetaminophen/ aspirin	Dose to maximum before switching to another agent (see Table 54-1)	Used in mild-to-moderate pain May use in conjunction with opioid agents to decrease doses of each Regular alcohol use and high doses of acetaminophen may result in liver toxicity Care must be exercised to avoid overdose when combination products containing these agents are used
Morphine	po 5-30 mg q 3-4 h <sup>a</sup> IM 5-10 mg q 3-4 h <sup>a</sup> IV 1-2.5 mg q 5 minute prn <sup>a</sup> SR 15-30 mg q 12 h (may need to be q 8 h in some patients) Rectal 10-20 mg q 4 h <sup>a</sup>	Drug of choice in severe pain Use immediate-release product with SR product to control "breakthrough" pain in cancer patients Every-24-hour product available
Hydromorphone	po 2-4 mg q 3-6 h <sup>a</sup> IM 1-4 mg q 3-6 h <sup>a</sup> IV 0.1-0.5 mg q 5 minute prn <sup>a</sup> Rectal 3 mg q 6-8 h <sup>a</sup>	Use in severe pain More potent than morphine; otherwise, no advantages
Oxymorphone	IM 1-1.5 mg q 4-6 h <sup>a</sup> IV 0.5 mg initially po immediate release 5-10 mg q 4-6 h <sup>a</sup> po extended release 10-20 mg q 12 h <sup>a</sup> Rectal 5 mg q 4-6 h <sup>a</sup>	Use in severe pain No advantages over morphine Use immediate-release product with controlled-release product to control "breakthrough" pain in cancer or chronic pain patients
Levorphanol	po 2-3 mg q 6-8 h <sup>a</sup> (Levo-Dromoran) po 2-3 mg q 3-6 h <sup>a</sup> (Levorphanol Tartrate) IM 1-2 mg q 6-8 h <sup>a</sup>  IV 1 mg q 3-6 h <sup>a</sup>	Use in severe pain Extended half-life useful in cancer patients  In chronic pain, wait 3 days between dosage adjustments
Codeine	po 15-60 mg q 4-6 h <sup>a</sup> IM 15-60 mg q 4-6 h <sup>a</sup>	Use in moderate pain Weak analgesic; use with NSAIDs, aspirin, or acetaminophen

(continued)

**TABLE 54-2** Adult Dosing Guidelines for Opioids and Nonopioids (Continued)

Agent(s)	Doses (titrate up or down based on patient response)	Notes
Hydrocodone	po 5–10 mg q 4–6 h <sup>a</sup>	Use in moderate/severe pain Most effective when used with NSAIDs, aspirin, or acetaminophen Only available as combination product with other ingredients for pain and/or cough
Oxycodone	po 5–10 mg q 4–6 h <sup>a</sup> Controlled release 10–20 mg q 12 h	Use in moderate/severe pain Most effective when used with NSAIDs, aspirin, or acetaminophen Use immediate-release product with controlled-release product to control “breakthrough” pain in cancer or chronic pain patients
Meperidine	IM 50–150 mg q 3–4 h <sup>a</sup> IV 5–10 mg q 5 minutes prn <sup>a</sup>	Use in severe pain Oral not recommended Do not use in renal failure May precipitate tremors, myoclonus, and seizures Monoamine oxidase inhibitors can induce hyperpyrexia and/or seizures or opioid overdose symptoms
Fentanyl	IV 25–50 mcg/hour IM 50–100 mcg q 1–2 h <sup>a</sup> Transdermal 25 mcg/hour q 72 h Transmucosal (Actiq Lozenge) 200 mcg may repeat × 1, 30 minutes after first dose is started, then titrate Transmucosal (Fentora Buccal Tablet) 100 mcg, may repeat × 1, 30 minutes after first dose is started, then titrate Iontophoretic transdermal system 40 mcg per activation	Used in severe pain Do not use transdermal in acute pain  Transmucosal for “breakthrough” cancer pain in patients already receiving or tolerant to opioids  Iontophoretic transdermal system used for acute pain and can be reactivated every 10 minutes
Methadone	po 2.5–10 mg q 3–4 h (acute) <sup>a</sup> IM 2.5–10 mg q 8–12 h (acute) <sup>a</sup> (more frequent dosing may be needed during initial titration) po 5–20 mg q 6–8 h (chronic) <sup>a</sup>	Effective in severe chronic pain Sedation can be major problem Some chronic pain patients can be dosed every 12 hours Equianalgesic dose of methadone when compared with other opioids will decrease progressively the higher the previous opioid dose
Propoxyphene	po 100 mg q 4 h <sup>a</sup> (napsylate) po 65 mg q 4 h <sup>a</sup> (HCl) (maximum 600 mg daily of napsylate, 390 mg HCl)	Use in moderate pain Weak analgesic; most effective when used with NSAIDs, aspirin, or acetaminophen This drug is not recommended in the elderly Will cause carbamazepine levels to increase 100 mg of napsylate salt = 65 mg of HCl salt
Pentazocine	po 50–100 mg q 3–4 h <sup>b</sup> (maximum 600 mg daily)	Third-line agent for moderate-to-severe pain May precipitate withdrawal in opiate-dependent patients Parenteral doses not recommended

(continued)

**TABLE 54-2** Adult Dosing Guidelines for Opioids and Nonopioids (Continued)

Agent(s)	Doses (titrate up or down based on patient response)	Notes
Butorphanol	IM 1–4 mg q 3–4 h <sup>b</sup> IV 0.5–2 mg q 3–4 h <sup>b</sup> Intranasal 1 mg (1 spray) q 3–4 h <sup>b</sup> If inadequate relief after initial spray, may repeat in other nostril × 1 in 60–90 minutes Max two sprays (one per nostril) q 3–4 h <sup>b</sup>	Third-line agent for moderate-to-severe pain May precipitate withdrawal in opiate-dependent patients
Nalbuphine	IM/IV 10 mg q 3–6 h <sup>b</sup> (maximum 20 mg dose, 160 mg daily)	Second-line agent for moderate-to-severe pain May precipitate withdrawal in opiate-dependent patients
Buprenorphine	IM 0.3 mg q 6 h <sup>b</sup> Slow IV 0.3 mg q 6 h <sup>b</sup> May repeat × 1, 30–60 minutes after initial dose	Second-line agent for moderate-to-severe pain May precipitate withdrawal in opiate-dependent patients
Naloxone	IV 0.4–2 mg	Naloxone may not be effective in reversing respiratory depression When reversing opiate side effects in patients needing analgesia, dilute and titrate (0.1–0.2 mg q 2–3 minutes) so as not to reverse analgesia
Tramadol	po 50–100 mg q 4–6 h <sup>a</sup> If rapid onset not required, start 25 mg/day and titrate over several days Extended release po 100 mg q 24 h	Maximum dose for nonextended-release, 400 mg/24 h; maximum for extended release, 300 mg/24 h Decrease dose in patient with renal impairment and in the elderly

HCl, hydrochloride; NSAID, nonsteroidal antiinflammatory drug; prn, as needed; SR, sustained release.

<sup>a</sup>May start with an around-the-clock regimen and switch to prn if/when the painful signal subsides or is episodic.

<sup>b</sup>May reach a ceiling analgesic effect.

Data from American Pain Society. *Principles of Analgesic Use in the Treatment of Acute Pain and Chronic Cancer Pain*, 5th ed. Glenview, IL: American Pain Society, 2003; Gutstein HB, Akil H. Opioid analgesics. In: Brunton LL, Lazo AS, Parker KL, eds. *The Pharmacological Basis of Therapeutics*, 11th ed. New York: McGraw-Hill, 2006:547–590; Anonymous. American Hospital Formulary Service. In: McVoy GK, ed. *Drug Information*. Bethesda, MD: American Society of Hospital Pharmacists, 1987, 1991, 1994, 1997, 1999, 2001, 2003, 2004, 2005, 2006, 2007; and Anonymous. *Facts and Comparisons*. Philadelphia: Lippincott, 1986, 1991, 1994, 1997, 2000, 2003, 2004, 2006, 2007.

- With patient-controlled analgesia, patients self-administer preset amounts of IV opioids via a syringe pump electronically interfaced with a timing device; thus, patients can balance pain control with sedation.
- Administration of opioids directly into the CNS (Table 54-5; epidural and subarachnoid routes) is becoming prominent for acute pain, chronic noncancer pain, and cancer pain. These methods require careful monitoring because of reports of marked sedation, respiratory depression, pruritus, nausea, vomiting, urinary retention, and hypotension. **Naloxone** is used to reverse respiratory depression, but continuous infusion may be required.
- Intrathecal and epidural opioids are often administered by continuous infusion or patient-controlled analgesia. They are safe and effective when given simultaneously with intrathecal or epidural local anesthetics such as

**TABLE 54-3** Opioid Analgesics

Class and Generic Name (Brand Name)	Chemical Source	Relative Histamine Release	Route	Equianalgesic Dose in Adults (mg)	Onset (minutes)/ Half-Life (hours)
<b>Phenanthrenes (morphine-like agonists)</b>					
Morphine (various)	Naturally occurring	+++	IM po	10 30	10–20/2
Hydromorphone (Dilaudid, various)	Semisynthetic	+	IM po	1.5 7.5	10–20/2–3
Oxymorphone (Numorphan, Opana)	Semisynthetic	+	IM R po	1 5 <sup>a</sup> 10	10–20/2–3
Levorphanol (various)	Semisynthetic	+	IM (acute) po IM po	2 (acute) 4 (acute) 1 (chronic) 1 (chronic)	10–20/12–16
Codeine (various)	Naturally occurring	+++	IM po	15–30 <sup>b</sup> 15–30 <sup>b</sup>	10–30/3
Hydrocodone (available as combination)	Semisynthetic	N/A	po	5–10 <sup>b</sup>	30–60/4
Oxycodone (various)	Semisynthetic	+	po	20–30 <sup>c</sup>	30–60/2–3
<b>Phenylpiperidines (meperidine-like agonists)</b>					
Meperidine (Demerol, various)	Synthetic	+++	IM po	75 50–150 <sup>b</sup> This drug is not recommended	10–20/3–4
Fentanyl (Sublimaze, Duragesic, various)	Synthetic	+	IM Transdermal Buccal, transmucosal	0.1 25 mcg/hour <sup>d</sup> Variable <sup>e</sup>	7–15/3–4
<b>Diphenylheptanes (methadone-like agonists)</b>					
Methadone	Synthetic	+	IM	Variable <sup>f</sup> (acute)	

*(continued)*

**TABLE 54-3 Opioid Analgesics (Continued)**

Class and Generic Name (Brand Name)	Chemical Source	Relative Histamine Release	Route	Equianalgesic Dose in Adults (mg)	Onset (minutes)/ Half-Life (hours)
(Dolophine, various)			po IM	Variable <sup>f</sup> (acute) Variable <sup>f</sup> (chronic)	30–60/12–190
Propoxyphene (Darvon, various)	Synthetic	N/A	po po	Variable <sup>f</sup> (chronic) 65 <sup>b</sup>	30–60/6–12
<b>Agonist–antagonist derivatives</b>					
Pentazocine (Talwin, various)	Synthetic	N/A	IM po	Not recommended 50 <sup>b</sup>	15–30/2–3
Butorphanol (Stadol, various)	Synthetic	+	IM Intranasal	2 1 <sup>b</sup> (one spray)	10–20/3–4
Nalbuphine (Nubain, various)	Semisynthetic	N/A	IM	10	<15/5
Buprenorphine (Buprenex, various)	Semisynthetic	N/A	IM	0.4	10–20/2–3
<b>Antagonists</b>					
Naloxone (Narcan, various)	Synthetic	N/A	IV	0.4–2 <sup>g</sup>	1–2 (IV), 2–5 (IM)/0.5–1.3
<b>Central analgesic</b>					
Tramadol (Ultram, various)	Synthetic	N/A	po	50–100 <sup>b</sup>	<60/5–7

<sup>a</sup>The American Pain Society considers 5 mg rectal morphine = 5 mg rectal oxymorphone.

<sup>b</sup>Starting dose only (equianalgesia not shown).

<sup>c</sup>Starting doses lower (oxycodone 5–10 mg, meperidine 50–150 mg).

<sup>d</sup>Equivalent po morphine dose = 45–134 mg/day.

<sup>e</sup>For breakthrough pain only.

<sup>f</sup>The equianalgesic dose of methadone when compared with other opioids will decrease progressively the higher the previous opioid dose has been.

<sup>g</sup>Starting doses to be used in cases of opioid overdose.

Data from American Pain Society. *Principles of Analgesic Use in the Treatment of Acute Pain and Chronic Cancer Pain*, 5th ed. Glenview, IL: American Pain Society, 2003; Landau R. *Anesthesiology* 2006;105:334–337; Gutstein HB, Akil H. *Opioid analgesics*. In: Brunton LL, Lazo AS, Parker KL, eds. *The Pharmacological Basis of Therapeutics*, 11th ed. New York: McGraw-Hill, 2006:547–590; Pasero C, Portenoy RK, McCaffery M. In: McCaffery M, Pasero C, eds. *Pain*. St. Louis: Mosby, 1999:161–299; Anonymous. *American Hospital Formulary Service*. In: McVoy GK, ed. *Drug Information*. Bethesda, MD: American Society of Hospital Pharmacists, 1987, 1991, 1994, 1997, 1999, 2001, 2003, 2004, 2005, 2006, 2007; Anonymous. *Facts and Comparisons*. Philadelphia: Lippincott, 1986, 1991, 1994, 1997, 2000, 2003, 2004, 2006, 2007; and Nasser SM, Ewan PW. *Clin Expert Allergy* 2001;31:1014–1020.

**TABLE 54-4** Major Adverse Effects of Opioid Analgesics

Effect	Manifestation
Mood changes	Dysphoria, euphoria
Somnolence	Lethargy, drowsiness, apathy, inability to concentrate
Stimulation of chemoreceptor trigger zone	Nausea, vomiting
Respiratory depression	Decreased respiratory rate
Decreased gastrointestinal motility	Constipation
Increase in sphincter tone	Biliary spasm, urinary retention (varies among agents)
Histamine release	Urticaria, pruritus, rarely exacerbation of asthma (varies among agents)
Tolerance	Larger doses for same effect
Dependence	Withdrawal symptoms upon abrupt discontinuation

Data from Stimmel B. *Pain, Analgesia and Addiction: The Pharmacology of Pain*. New York: Raven Press, 1983:1, 2, 63, 241–245, 259, 266; Miyoshi HR, Leckband SG. *Systemic opioids and analgesics*. In: Loeser JD, Butler SH, Chapman CR, et al, eds. *Bonica's Management of Pain*. Philadelphia: Lippincott Williams & Wilkins, 2000:1682–1709; and Reisine T, Pasternak G. *Opioid analgesics and antagonists*. In: Hardman JG, Limbird LE, Molinoff PB, et al, eds. *The Pharmacological Basis of Therapeutics*, 9th ed. New York: McGraw-Hill, 1995:521–555.

**bupivacaine.** All agents administered directly into the CNS should be preservative-free.

### Morphine and Congeners (Phenanthrenes)

- **Morphine** is considered by many clinicians to be the first-line agent for moderate to severe pain. Nausea and vomiting are more likely in ambulatory patients and with the initial dose.
- Respiratory depression increases progressively as doses are increased. It often manifests as a decrease in respiratory rate, and the cough reflex is also depressed. Patients with underlying pulmonary dysfunction are at risk for increased respiratory compromise. Respiratory depression can be reversed by **naloxone**.
- The combination of opioid analgesics with alcohol or other CNS depressants amplifies CNS depression and is potentially harmful and possibly lethal.

**TABLE 54-5** Intraspinal Opioids

Agent	Single Dose (mg)	Onset of Pain Relief (minutes)	Duration of Pain Relief (hours)	Continual Infusion Dose (mg/hours)
<b>Epidural route</b>				
Morphine	1–6	30	6–24	0.1–1
Hydromorphone	0.8–1.5	5–8	4–6	0.1–0.3
Fentanyl	0.025–0.1	5	1–8	0.025–0.1
Sufentanil	0.01–0.06	5	2–4	0.01–0.05
<b>Subarachnoid route</b>				
Morphine	0.1–0.3	15	8–34	–
Fentanyl	0.005–0.025	5	3–6	–

Data from American Pain Society. *Principles of Analgesic Use in the Treatment of Acute Pain and Chronic Cancer Pain*, 5th ed. Glenview, IL: American Pain Society, 2003 and Ready BL. *Regional analgesics with intraspinal opioids*. In: Loeser JD, Butler SH, Chapman CR, et al, eds. *Bonica's Management of Pain*. Philadelphia: Lippincott Williams & Wilkins, 2000:1953–1966.

- **Morphine** produces venous and arteriolar dilation, which may result in orthostatic hypotension. Hypovolemic patients are more susceptible to morphine-induced hypotension. Morphine is often considered the opioid of choice to treat pain associated with myocardial infarction, as it decreases myocardial oxygen demand.
- Morphine can cause constipation, spasms of the sphincter of Oddi, urinary retention, and pruritus (secondary to histamine release) (see Table 54-4). In head trauma patients who are not ventilated, morphine-induced respiratory depression can increase intracranial pressure and cloud the neurologic examination results.

### **Meperidine and Congeners (Phenylpiperidines)**

- **Meperidine** is less potent and has a shorter duration of action than morphine.
- With high doses or in patients with renal failure, the metabolite normeperidine accumulates, causing tremor, muscle twitching, and possibly seizures. In most settings, it offers no advantages over morphine, and it should not be used long term. It should be avoided in the elderly and those with renal dysfunction.
- Meperidine should not be combined with monoamine oxidase inhibitors because of the possibility of severe respiratory depression or excitation, delirium, hyperpyrexia, and convulsions.
- **Fentanyl** is a synthetic opioid structurally related to meperidine. It is often used in anesthesiology as an adjunct to general anesthesia. It is more potent and shorter acting than meperidine. Transdermal fentanyl can be used for treatment of chronic pain requiring opioid analgesics. After a patch is applied, it takes 12 to 24 hours to obtain optimal analgesic effect, and analgesia may last 72 hours. It may take 6 days after increasing a dose before new steady-state levels are achieved. Thus, the fentanyl patch should not be used for acute pain. A fentanyl lozenge and a buccal dosage form are available for treatment of breakthrough cancer pain.

### **Methadone and Congeners (Diphenylheptanes)**

- **Methadone** has oral efficacy, extended duration of action, and ability to suppress withdrawal symptoms in heroin addicts. With repeated doses, the analgesic duration of action of methadone is prolonged, but excessive sedation may also result. Although effective for acute pain, it is usually used for chronic cancer pain.

### **Opioid Agonist–Antagonist Derivatives**

- This class produces analgesia and has a ceiling effect on respiratory depression and lower abuse potential than morphine. However, psychotomimetic responses (e.g., hallucinations and dysphoria with **pentazocine**), a ceiling analgesic effect, and the propensity to initiate withdrawal in opioid-dependent patients have limited their widespread use.

### **Opioid Antagonists**

- **Naloxone** is a pure opioid antagonist that binds competitively to opioid receptors but does not produce an analgesic response. It is used to reverse the toxic effects of agonist and agonist-antagonist opioids.

## Central Analgesic

- **Tramadol**, a centrally acting analgesic for moderate to moderately severe pain, binds to  $\mu$  opiate receptors and weakly inhibits norepinephrine and serotonin reuptake.
- Tramadol has a side-effect profile similar to that of other opioid analgesics. It may also enhance the risk of seizures. It may be useful for treating chronic pain, especially neuropathic pain, but it has little advantage over other opioid analgesics for acute pain.

## Combination Therapy

- The combination of an opioid and nonopioid oral analgesic often results in analgesia superior to monotherapy and may allow for lower doses of each agent. An NSAID with a scheduled opioid dose is often effective for painful bone metastases.

## REGIONAL ANALGESIA

- Regional analgesia with local anesthetics (Table 54-6) can provide relief of both acute and chronic pain. Anesthetics can be positioned by injection (i.e., in joints, in the epidural or intrathecal space, along nerve roots) or applied topically.
- High plasma concentrations can cause CNS excitation and depression (dizziness, tinnitus, drowsiness, disorientation, muscle twitching, seizures, and respiratory arrest). Cardiovascular effects include myocardial depression and other effects. Skillful technical application, frequent administration, and specialized follow-up procedures are required.

**TABLE 54-6** Local Anesthetics for Regional Analgesia<sup>a</sup>

Agent (Brand Name)	Onset (minutes)	Duration (hours)
<b>Esters</b>		
Procaine (Novocain, various)	2–5	0.25–1
Chlorprocaine (Nesacaine)	6–12	0.5
Tetracaine (Pontocaine)	≤15	2–3
<b>Amides</b>		
Mepivacaine (Polocaine, various)	3–5	0.75–1.5
Bupivacaine (Marcaine, various)	5	2–4
Lidocaine (Xylocaine, various)	<2	0.5–1
Prilocaine (Citanest)	<2	≥1
Levobupivacaine <sup>b</sup> (Chirocaine)	≈10	≈8
Articaine with epinephrine <sup>c</sup> (Septodont)	1–6	1
Ropivacaine <sup>d</sup> (Naropin)	11–26	1.7–3.2

<sup>a</sup>Unless otherwise indicated, values are for infiltrative anesthesia.

<sup>b</sup>Epidural administration in cesarean section.

<sup>c</sup>Dental anesthesia.

<sup>d</sup>Epidural administration.

Data from Anonymous. *American Hospital Formulary Service*. In: McVoy GK, ed. *Drug Information*. Bethesda, MD: American Society of Hospital Pharmacists, 1987, 1991, 1994, 1997, 1999, 2001, 2003, 2004, 2005, 2006, 2007; and Anonymous. *Facts and Comparisons*. Philadelphia: Lippincott, 1986, 1991, 1994, 1997, 2000, 2003, 2004, 2006, 2007.

## SPECIAL CONSIDERATIONS IN CANCER PAIN

- An algorithm for pain management in oncology patients is shown in Fig. 54-2. Pharmacologic therapies should be coupled with psychological, surgical, and supportive therapies.
- Individualization of therapy is essential, and continuous assessment of pain response, side effects, and behavior is required.
- **NSAIDs** are especially effective for bone pain. **Strontium-89** and **samarium SM 153 leixidronam** are also effective.
- Around-the-clock schedules in conjunction with as-needed doses are employed when patients experience breakthrough pain.
- **Methadone** has regained prominence in treating cancer pain. It has a prolonged mechanism of action, *N*-methyl-D-aspartate receptor antagonist activity (d-isomer), and is inexpensive. However, it can be difficult to titrate.

## SPECIAL CONSIDERATIONS IN CHRONIC NONCANCER PAIN

- As pain becomes more chronic, hypertension, tachycardia, and diaphoresis become less evident, and depression, sleep disturbances, anxiety, irritability, work problems, and family instability tend to dominate.
- An integrated, systematic approach (e.g., pain clinic) is preferred. Placebos should not be used. Maximal benefit may take months to years.

## EVALUATION OF THERAPEUTIC OUTCOMES

- Pain intensity, pain relief, and medication side effects must be assessed on a regular basis. The timing and regularity of assessment depend on the type of pain and the medications administered. Postoperative pain and acute exacerbations of cancer pain may require hourly assessment, whereas chronic nonmalignant pain may need only daily (or less frequent) monitoring.
- With chronic pain, monitoring tools such as the Brief Pain Inventory, Initial Pain Assessment Inventory, or McGill Pain Questionnaire may be useful. Quality of life must also be assessed on a regular basis in all patients.
- The best management of opioid-induced constipation is prevention. Patients should be counseled on proper intake of fluids and fiber, and a laxative should be added with chronic opioid use.
- If acute pain does not subside within the anticipated time frame (usually 1 to 2 weeks), further investigation of the cause is warranted.

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*See Chap. 62, Pain Management, authored by Terry J. Baumann and Jennifer Strickland, for a more detailed discussion of this topic.*

## DEFINITION

- Parkinson's disease (PD) has highly characteristic neuropathologic findings and clinical presentation, including motor deficits and, in some cases, mental deterioration.

## PATHOPHYSIOLOGY

- The two hallmark features in the substantia nigra pars compacta are loss of neurons and the presence of Lewy bodies. There is a positive correlation between the degree of nigrostriatal dopamine loss and severity of motor symptoms. PD is relatively asymptomatic until profound depletion (70% to 80%) of substantia nigra pars compacta neurons has occurred.
- Reduced activation of dopamine-1 and dopamine-2 receptors results in greater inhibition of the thalamus. Clinical improvement may be more tied to restoring activity at the dopamine-2 receptor than at the dopamine-1 receptor. Loss of presynaptic nigrostriatal dopamine neurons results in inhibition of thalamic activity and activity in the motor cortex.
- Degeneration of nigrostriatal dopamine neurons results in a relative increase of striatal cholinergic activity, which contributes to the tremor of PD.

## CLINICAL PRESENTATION

- PD develops insidiously and progresses slowly. Clinical features are summarized in Table 55-1. Initial symptoms may be sensory, but as the disease progresses, one or more classic primary features presents (e.g., resting tremor, rigidity, bradykinesia, postural instability that may lead to falls).
- Resting tremor is often the sole presenting complaint. However, only two-thirds of PD patients have tremor on diagnosis, and some never develop this sign. Tremor is present most commonly in the hands, often begins unilaterally, and sometimes has a characteristic "pill-rolling" quality. Resting tremor is usually abolished by volitional movement and is absent during sleep.
- Muscular rigidity involves increased muscular resistance to passive range of motion and can be cogwheel in nature.
- Intellectual deterioration is not inevitable, but some patients deteriorate in a manner indistinguishable from Alzheimer's disease.

## DIAGNOSIS

- Clinically probably PD is diagnosed when at least two of the following are present: limb muscle rigidity, resting tremor (at 3 to 6 Hz and abolished by movement), or bradykinesia. Definite PD is diagnosed when there is at least two of the following: resting tremor, rigidity, bradykinesia, and a positive response to antiparkinson medication.

**TABLE 55-1** Presentation of Parkinson's Disease (PD)**General features**

For clinically probable PD, the patient exhibits at least two of the following: resting tremor, rigidity, or bradykinesia. Asymmetric onset (unilaterality) of these features is usual.

Postural instability (difficulty with maintaining balance) is more common in advanced PD.

**Motor symptoms**

The patient experiences decreased manual dexterity, difficulty arising from a seated position, diminished arm swing during ambulation, dysarthria (slurred speech), dysphagia (difficulty with swallowing), festinating gait (tendency to pass from a walking to a running pace), flexed posture (axial, upper/lower extremities), "freezing" at initiation of movement, hypomimia (reduced facial animation), hypophonia (reduced voice volume), and micrographia (diminution of handwritten letters/symbols).

**Autonomic and sensory symptoms**

The patient experiences bladder and anal sphincter disturbances, constipation, diaphoresis, fatigue, olfactory disturbance, orthostatic blood pressure changes, pain, paresthesia, paroxysmal vascular flushing, seborrhea, sexual dysfunction, and sialorrhea (drooling).

**Mental status changes**

The patient experiences anxiety, apathy, bradyphrenia (slowness of thought processes), confusional state, dementia, depression, hallucinosis/psychosis (typically drug-induced), and sleep disorders (excessive daytime sleepiness, insomnia, obstructive sleep apnea, and rapid eye movement sleep behavior disorder).

**Laboratory tests**

No laboratory tests are available to diagnose PD.

**Other diagnostic tests**

Genetic testing is not routinely helpful.

Neuroimaging may be useful for excluding other causes of PD.

Medication history should be obtained to rule out drug-induced parkinsonism

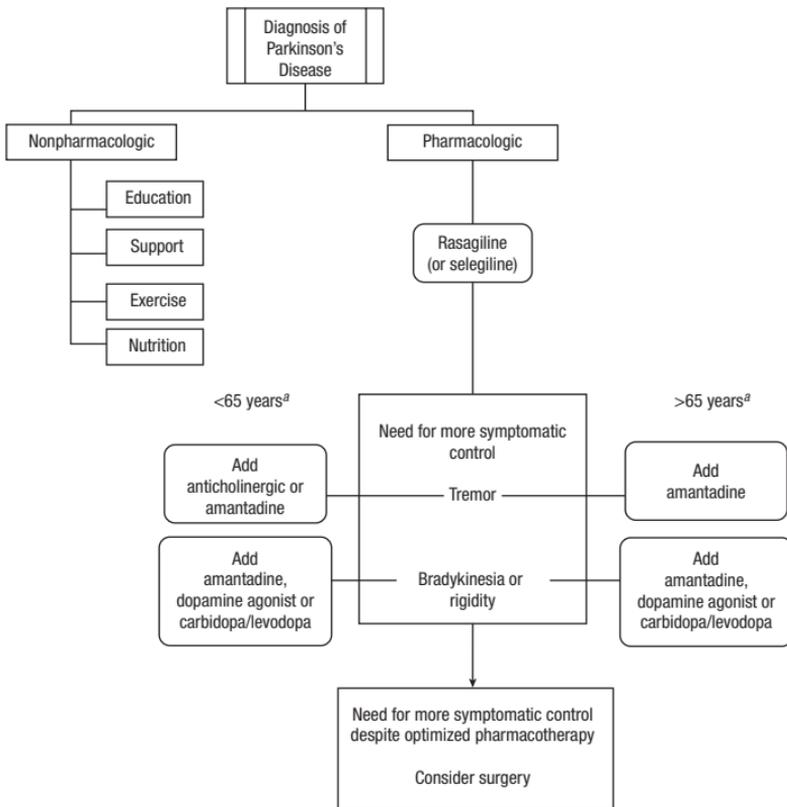
- A number of other conditions must also be excluded, such as medication-induced parkinsonism (e.g., induced by antipsychotics, phenothiazine antiemetics, or metoclopramide). Other diagnostic criteria include lack of other neurologic impairment.

**DESIRED OUTCOME**

- The goals of treatment are to minimize symptoms, disability, and side effects while maintaining quality of life. Education of patients and caregivers is critical, and exercise and proper nutrition are essential.

**TREATMENT****PHARMACOLOGIC THERAPY**

- An algorithm for management of early and late PD is shown in Fig. 55-1.
- A summary of available antiparkinsonian medications is listed in Table 55-2.
- Monotherapy usually begins with a monoamine oxidase-B (MAO-B) inhibitor, or if the patient is physiologically young, a dopamine agonist.
- When additional relief is needed, the addition of **levodopa (L-dopa)** should be considered. With the development of motor fluctuations, addition of a catechol-O-methyltransferase (COMT) inhibitor should be considered to extend L-dopa duration of activity.
- For management of L-dopa-induced dyskinesias, the addition of **amantadine** should be considered.



<sup>a</sup>Age is not the sole determinant for drug choice. Other factors such as cognitive function and overall safety and tolerability of drug (especially, in the elderly) should be considered.

**FIGURE 55-1.** General approach to the management of early to advanced Parkinson's disease.

## Anticholinergic Medications

- Anticholinergic drugs can be effective for tremor and dystonic features in some patients but rarely show substantial benefit for bradykinesia or other disabilities. They can be used as monotherapy or in conjunction with other antiparkinsonian drugs. They differ little from each other in therapeutic potential or adverse effects.
- Anticholinergic side effects include dry mouth, blurred vision, constipation, and urinary retention. More serious reactions include forgetfulness, sedation, depression, and anxiety. Patients with preexisting cognitive deficits and the elderly are at greater risk for central anticholinergic side effects.

## Amantadine

- Amantadine is often effective for mild symptoms, especially tremor. It may also decrease dyskinesia at relatively high doses (400 mg/day).

**TABLE 55-2** Drugs Used in Parkinson's Disease

Generic Name	Trade Name	Dosage Range <sup>a</sup> (mg/day)	Dosage Forms (mg)
Anticholinergic drugs			
Benzotropine	Cogentin	0.5–4	0.5, 1, 2
Trihexyphenidyl	Artane	1–6	2, 5
Carbidopa/levodopa products			
Carbidopa/L-dopa	Sinemet	300–1,000 <sup>b</sup>	10/100, 25/100, 25/250
Carbidopa/L-dopa ODT	Parcopa	300–1,000 <sup>b</sup>	10/100, 25/100, 25/250
Carbidopa/L-dopa CR	Sinemet CR	400–1,000 <sup>b</sup>	25/100, 50/200
Carbidopa/L-dopa/entacapone	Stalevo	600–1,600 <sup>c</sup>	12.5/50/200, 25/100/200, 37.5/150/200
Carbidopa	Lodosyn	25–75	25
Dopamine agonists			
Apomorphine	Apokyn	3–12	30 per 3 mL
Bromocriptine	Parlodel	15–40	2.5, 5
Pramipexole	Mirapex	1.5–4.5	0.125, 0.25, 0.5, 1, 1.5
Ropinirole	Requip	9–24	0.25, 0.5, 1, 2, 3, 4, 5
Rotigotine	Neupro	2–6	2, 4, 6
COMT inhibitors			
Entacapone	Comtan	200–1,600	200
Tolcapone	Tasmar	300–600	100, 200
MAO-B inhibitors			
Rasagiline	Azilect	0.5–1	0.5, 1
Selegiline	Eldepryl	5–10	5
Selegiline ODT	Zelapar	1.25–2.5	1.25, 2.5
Anticholinergic drugs			
Benzotropine	Cogentin	0.5–4	0.5, 1, 2
Trihexyphenidyl	Artane	1–6	2, 5, 2/5 mL
Miscellaneous			
Amantadine	Symmetrel	200–300	100

COMT, catechol-O-methyltransferase; CR, controlled release; MAO, monoamine oxidase; ODT, orally disintegrating tablet.

<sup>a</sup>Dosages may vary beyond stated range.

<sup>b</sup>Dosages expressed as L-dopa component.

<sup>c</sup>Dosages expressed as entacapone component.

- Adverse effects include sedation, vivid dreams, dry mouth, depression, hallucinations, anxiety, dizziness, psychosis, and confusion. Livedo reticularis (a diffuse mottling of the skin in upper or lower extremities) is a common but reversible side effect.
- Doses should be reduced in patients with renal dysfunction.

### Levodopa and Carbidopa/Levodopa

- **L-dopa**, the most effective drug available, is the immediate precursor of dopamine. It crosses the blood–brain barrier, whereas dopamine does not. Ultimately, all PD patients will require L-dopa.
- The decision whether to start L-dopa as soon as the diagnosis is made or only when symptoms compromise social, occupational, or psychological well-being has generated controversy.
- In the CNS and elsewhere, L-dopa is converted by L-amino acid decarboxylase (L-AAD) to dopamine. In the periphery, L-AAD can be blocked by administering **carbidopa** or **benserazide**, which does not cross the blood–

brain barrier. Carbidopa therefore increases the CNS penetration of exogenously administered L-dopa and decreases adverse effects (e.g., nausea, vomiting, cardiac arrhythmias, postural hypotension, vivid dreams) from peripheral L-dopa metabolism to dopamine.

- Starting L-dopa at 300 mg/day (in divided doses) in combination with carbidopa often achieves adequate relief of disability. The usual maximal dose of L-dopa is 800 to 1,000 mg/day.
- About 75 mg of carbidopa is required to effectively block L-AAD, but some patients may need more. Carbidopa/L-dopa is most widely used in a 25-mg/100-mg tablet, but 25-mg/250-mg and 10-mg/100-mg dosage forms are also available. Controlled-release preparations of carbidopa/L-dopa are available in 50-mg/200-mg and 25-mg/100-mg strengths. For patients with difficulty swallowing, an orally disintegrating tablet is available. If peripheral adverse effects are prominent, 25-mg carbidopa (Lodosyn) tablets are available.
- There is marked intra- and intersubject variability in time to peak plasma concentrations after oral L-dopa. Meals delay gastric emptying, but antacids promote gastric emptying. L-dopa is absorbed primarily in the proximal duodenum by a saturable large neutral amino acid transport system. Large neutral amino acids (including high protein meals) can interfere with bioavailability.
- L-dopa is not bound to plasma proteins, and the elimination half-life is about 1 hour. The addition of carbidopa can extend the half-life to 1.5 hours, and the addition of a COMT inhibitor (e.g., **entacapone**) can extend it to about 2 to 2.5 hours.
- Long-term L-dopa-associated motor complications can be disabling. The most common of these are end-of-dose “wearing off” and “peak-dose dyskinesias.” Ten percent of PD patients will develop involuntary movements. Table 55-3 shows the motor complications associated with long-term treatment with carbidopa/L-dopa and suggested management strategies.
- “End-of-dose wearing off” is common and related to the increasing loss of neuronal storage capability for dopamine and the short half-life of L-dopa. Bedtime administration of a dopamine agonist or a sustained release formulation product (e.g., carbidopa/L-dopa CR, ropinirole CR, Rotigotine transdermal patch) can help reduce nocturnal off episodes and improve functioning upon awakening.

**TABLE 55-3** Common Motor Complications and Possible Treatments

Effect	Possible Treatments
End-of-dose “wearing off” (motor fluctuation)	Increase frequency of carbidopa/L-dopa doses; add either COMT inhibitor or MAO-B inhibitor or dopamine agonist; consider surgery
“Delayed-on” or “no-on” response	Give carbidopa/L-dopa on empty stomach; use carbidopa/L-dopa ODT; avoid carbidopa/L-dopa CR; use apomorphine subcutaneous; consider surgery
Start hesitation (“freezing”)	Increase carbidopa/L-dopa dose; add a dopamine agonist or MAO-B inhibitor; utilize physiotherapy along with assistive walking devices or sensory cues (e.g., rhythmic commands, stepping over objects)
Peak-dose dyskinesia	Provide smaller doses of carbidopa/L-dopa; add amantadine; consider surgery

COMT, catechol-O-methyltransferase; CR, controlled release; MAO, monoamine oxidase; ODT, orally disintegrating tablet.

- “Delayed-on” or “no-on” can result from delayed gastric emptying or decreased absorption in the duodenum. Crushing the tablet of carbidopa/L-dopa and taking with a glass of water or using the orally disintegrating tablet formulation on an empty stomach can help. Subcutaneous apomorphine may also be used as rescue therapy.
- “Freezing,” a sudden, episodic inhibition of lower extremity motor function may be worsened by anxiety and may increase the risk of falls.
- Dyskinesias are involuntary choreiform movements, usually involving the neck, trunk, and extremities. They are usually associated with peak striatal dopamine levels. Less commonly, dyskinesias also can develop during the rise and fall of L-dopa effects (the dyskinesias-improvement-dyskinesias or diphasic pattern of response).
- “Off-period dystonia,” sustained muscle contractions that occur more commonly in distal lower extremity (e.g., foot), occur often in the early morning hours. They may be treated with bedtime administration of sustained-release products, use of baclofen, or selective denervation with botulinum toxin.

### Monoamine Oxidase B Inhibitors

- At therapeutic doses, **selegiline** and **rasagiline** are unlikely to induce a “cheese reaction” (hypertension, headache) unless excessive amounts of dietary tyramine (400 mg or greater) are ingested. However, concomitant MAO-B inhibitors with meperidine and other selected analgesics is contraindicated. Selegiline and rasagiline may be neuroprotective.
- Selegiline (deprenyl; Eldepryl) is an irreversible MAO-B inhibitor that blocks dopamine breakdown and can modestly extend the duration of action of L-dopa (up to 1 hour). It often permits reduction of L-dopa dose by as much as one-half.
- Selegiline also increases the peak effects of L-dopa and can worsen preexisting dyskinesias or psychiatric symptoms such as delusions and hallucinations. Other adverse effects include insomnia, jitteriness.
- Metabolites of selegiline are l-methamphetamine and l-amphetamine.
- Studies evaluating its neuroprotective properties suggest that selegiline can delay the need for L-dopa by about 9 months and has symptomatic effects, but there is no firm evidence that it can slow neurodegeneration.
- Rasagiline, another MAO-B inhibitor, has similar effects as selegiline in enhancing L-dopa effects and modest beneficial effect as monotherapy. Early initiation is associated with better long-term outcomes.
- When an adjunctive agent is required for managing motor fluctuations, rasagiline is considered a first-line agent (as is entacapone).

### Catechol-O-Methyltransferase Inhibitors

- **Tolcapone** (Tasmar) and **entacapone** (Comtan) are used only in conjunction with carbidopa/L-dopa to prevent the peripheral conversion of L-dopa to dopamine (increasing the area under the curve of L-dopa by approximately 35%). Thus, “on” time is increased by about 1 hour. These agents significantly decrease “off” time and decrease L-dopa requirements. Concomitant use of nonselective MAO inhibitors should be avoided to prevent inhibition of the pathways for normal catecholamine metabolism.

- COMT inhibition is more effective than controlled-release carbidopa/L-dopa in providing consistent extension of effect and avoids the delay in time to maximal effect seen with controlled-release L-dopa products.
- The starting and recommended dose of tolcapone is 100 mg three times daily as an adjunct to carbidopa/L-dopa. Its use is limited by the potential for fatal liver toxicity. Strict monitoring of liver function is required, and tolcapone should be discontinued if liver function tests are above the upper limit of normal or any signs or symptoms suggestive of hepatic failure exist. It should be reserved for patients with fluctuations that have not responded to other therapies.
- Because entacapone has a shorter half-life, 200 mg is given with each dose of carbidopa/L-dopa up to eight times a day. Dopaminergic adverse effects may occur and are managed easily by reducing the carbidopa/L-dopa dose. Brownish-orange urine discoloration may occur (as with tolcapone), but there is no evidence of hepatotoxicity from entacapone.

### Dopamine Agonists

- The ergot derivative **bromocriptine** (Parlodel) and the nonergots **pramipexole** (Mirapex), **rotigotine** (Neupro), and **ropinirole** (Requip) are beneficial adjuncts in patients with deteriorating response to L-dopa, those experiencing fluctuation in response to L-dopa, and those with limited clinical response to L-dopa due to inability to tolerate higher doses. They decrease the frequency of “off” periods and provide an L-dopa-sparing effect.
- The dose of dopamine agonists is best determined by slow titration to enhance tolerance and to find the least dose that provides optimal benefit.
- The nonergots are safer and are effective as monotherapy in mild-moderate PD as well as adjuncts to L-dopa.
- Bromocriptine is not commonly used because of an increased risk of pulmonary fibrosis and reduced efficacy compared to the other agonists.
- There is less risk of developing motor complications from monotherapy with dopamine agonists than from L-dopa. Because younger patients are more likely to develop motor fluctuations, dopamine agonists are preferred in this population. Older patients are more likely to experience psychosis from dopamine agonists; therefore, carbidopa/L-dopa may be the best initial medication in elderly patients, particularly if cognitive problems or dementia is present.
- Common side effects of dopamine agonists are nausea, confusion, hallucinations, lightheadedness, lower-extremity edema, postural hypotension, sedation, and vivid dreams. Less common are compulsive behaviors, psychosis, and sleep attacks. Hallucinations and delusions can be managed using a stepwise approach (Table 55-4). When added to L-dopa, dopamine agonists may worsen dyskinesias.
- **Pramipexole** is initiated at a dose of 0.125 mg three times daily and increased every 5 to 7 days as tolerated. It is primarily renally excreted, and the initial dose must be adjusted in renal insufficiency.
- **Rotigotine** is available as a transdermal patch for once-daily administration, initiated at 2 mg/day and increased by 2 mg/day on a weekly basis to a maximum of 6 mg for early PD.

**TABLE 55-4** Stepwise Approach to Management of Drug-Induced Hallucinations and Psychosis in Parkinson's Disease

1. General measures such as evaluating for electrolyte disturbance (especially hypercalcemia or hyponatremia), hypoxemia, or infection (especially encephalitis, sepsis, or urinary tract infection).
2. Simplify the antiparkinsonian regimen as much as possible by discontinuing or reducing the dosage of medications with the highest risk-to-benefit ratio first.<sup>d</sup>
  - a. Discontinue anticholinergics, including other nonparkinsonian medications with anticholinergic activity such as antihistamines or tricyclic antidepressants.
  - b. Taper and discontinue amantadine.
  - c. Discontinue monoamine oxidase-B inhibitor.
  - d. Taper and discontinue dopamine agonist.
  - e. Consider reduction of L-dopa (especially at the end of day) and discontinuation of catechol-O-methyltransferase inhibitors.
3. Consider atypical antipsychotic medication if disruptive hallucinations or psychosis persists.
  - a. Quetiapine 12.5–25 mg at bedtime; gradually increase by 25 mg each week if necessary, until hallucinations or psychosis improves *or*
  - b. Clozapine 12.5–50 mg at bedtime; gradually increase by 25 mg each week if necessary until hallucinations or psychosis improves (requires frequent monitoring for leukopenia).

<sup>d</sup>If dosage reduction or medication discontinuation is either infeasible or undesirable, go to step 3.

- **Ropinirole** is initiated at 0.25 mg three times daily and increased by 0.25 mg three times daily on a weekly basis to a maximum of 24 mg/day. It is metabolized by cytochrome P450 1A2; fluoroquinolones and smoking may alter ropinirole clearance.
- **Apomorphine** is a nonergot dopamine agonist given as a subcutaneous “rescue” injection. For patients with advanced PD with intermittent off episodes despite optimized therapy, subcutaneous apomorphine triggers an “on” response within 20 minutes, and duration of effect is up to 100 minutes. Most patients require 0.06 mg/kg. Prior to injection, patients should be premedicated with the antiemetic trimethobenzamide. It is contraindicated with the serotonin-3-receptor blockers (e.g., ondansetron).

## EVALUATION OF THERAPEUTIC OUTCOMES

- Patients and caregivers should be educated so that they can participate in treatment by recording medication administration times and duration of “on” and “off” periods.
- Symptoms, side effects, and activities of daily living must be scrupulously monitored and therapy individualized. Concomitant medications which may worsen motor symptoms, memory, falls, or behavioral symptoms should be discontinued if possible.

See Chap. 61, *Parkinson's Disease*, authored by Jack J. Chen, Merlin V. Nelson, and David M. Swope, for a more detailed discussion of this topic.

## DEFINITION

- Status epilepticus (SE) is any seizure lasting longer than 30 minutes whether or not consciousness is impaired, or recurrent seizures without an intervening period of consciousness between seizures. SE is a medical emergency with significant morbidity and mortality, and aggressive treatment of seizures which last 5 minutes or more is strongly recommended. Table 56-1 shows the classification of SE. This chapter focuses on generalized convulsive status epilepticus (GCSE), the most common and severe form of SE.

## PATHOPHYSIOLOGY

- Seizure initiation is likely caused by an imbalance between excitatory (e.g., glutamate, calcium, sodium, substance P, and neurokinin B) neurotransmission and inhibitory ( $\gamma$ -aminobutyric acid, adenosine, potassium, neuropeptide Y, opioid peptides, and galanin) neurotransmission.
- Seizure maintenance is largely caused by glutamate acting on postsynaptic *N*-methyl-D-aspartate and  $\alpha$ -amino-3-hydroxy-5-methyl-isoxazole-4-propionate/akinate receptors. Sustained depolarization can result in neuronal death.
- There is evidence that  $\gamma$ -aminobutyric acid A receptors may be modified during SE and become less responsive to endogenous agonists and antagonists.
- Two phases of GCSE have been identified. During phase I, each seizure produces marked increases in plasma epinephrine, norepinephrine, and steroid concentrations that may cause hypertension, tachycardia, and cardiac arrhythmias. Muscle contractions and hypoxia can cause acidosis, and hypotension, shock, rhabdomyolysis, secondary hyperkalemia, and acute tubular necrosis may ensue.
- Phase II begins 60 minutes into the seizure, and the patient begins to decompensate. The patient may become hypotensive, and cerebral blood flow may be compromised. Glucose may be normal or decreased, and hyperthermia, respiratory deterioration, hypoxia, and ventilatory failure may develop.
- In prolonged seizures, motor activity may cease, but electrical seizures may persist.

## MORBIDITY AND MORTALITY

- Younger children, the elderly, and those with preexisting epilepsy have a higher propensity for sequelae.
- Recent estimates suggest a mortality rate of up to 10% in children, 20% in adults, and 38% in the elderly.
- Variables affecting outcome are (1) the time between onset of GCSE and the initiation of treatment, and (2) the duration of the seizure. The

**TABLE 56-1** International Classification of Status Epilepticus (SE)

Convulsive		Nonconvulsive	
<i>International</i>	<i>Traditional Terminology</i>	<i>International</i>	<i>Traditional Terminology</i>
Primary generalized SE <ul style="list-style-type: none"> <li>• Tonic-clonic<sup>a,b</sup></li> <li>• Tonic<sup>c</sup></li> <li>• Clonic<sup>c</sup></li> <li>• Myoclonic<sup>b</sup></li> <li>• Erratic<sup>d</sup></li> </ul>	Grand mal, epilepticus convulsivus	Absence <sup>c</sup>	Petit mal, spike-and-wave stupor, spike-and-slow-wave or 3/s spike-and-wave, epileptic fugue, epilepsia minor continua, epileptic twilight, minor SE
Secondary generalized SE <sup>a,b</sup> <ul style="list-style-type: none"> <li>• Tonic</li> <li>• Partial seizures with secondary generalization</li> </ul>		Partial SE <sup>a,b</sup> <ul style="list-style-type: none"> <li>Simple partial               <ul style="list-style-type: none"> <li>Somatomotor</li> <li>Dysphasic</li> <li>Other types</li> </ul> </li> <li>Complex partial</li> </ul>	Focal motor, focal sensory, epilepsia partialis continua, adversive SE <ul style="list-style-type: none"> <li>Elementary</li> <li>Temporal lobe, psychomotor, epileptic fugue state, prolonged epileptic stupor, prolonged epileptic confusional state, continuous epileptic twilight state</li> </ul>

<sup>a</sup>Most common in older children.<sup>b</sup>Most common in adolescents and adults.<sup>c</sup>Most common in infants and young children.<sup>d</sup>Most common in neonates.

mortality rate is 2.6% for those with seizures lasting 10 to 29 minutes and 19% for those with seizures lasting longer than 30 minutes. Another report showed that those with seizures lasting longer than 60 minutes had a mortality rate of 32%.

## CLINICAL PRESENTATION AND DIAGNOSIS

### SYMPTOMS

- Impaired consciousness (e.g., ranging from obtunded to markedly lethargic and somnolent)
- Disorientation (once GCSE is controlled)
- Pain associated with injuries (e.g., tongue lacerations, shoulder dislocations, head and facial trauma)

### SIGNS

#### Early

- Generalized convulsions
- Acute injuries or CNS insults that cause extensor or flexor posturing
- Hypothermia or fever suggestive of intercurrent illnesses (e.g., sepsis or meningitis)
- Incontinence

- Normal blood pressure or hypotension
- Respiratory compromise

### Late Signs

- Clinical seizures may or may not be apparent
- Pulmonary edema with respiratory failure
- Cardiac failure (dysrhythmias, arrest, cardiogenic shock)
- Hypotension/hypertension
- Disseminated intravascular coagulation, multiorgan failure
- Rhabdomyolysis
- Hyperpyremia

## DIAGNOSIS

### Initial Laboratory Tests

- Complete blood count (CBC) with differential
- Serum chemistry profile (e.g., electrolytes, calcium, magnesium, glucose, serum creatinine, alanine aminotransferase [ALT], aspartate aminotransferase [AST])
- Urine drug/alcohol screen
- Blood cultures
- Arterial blood gas (ABG) to assess for metabolic and respiratory acidosis
- Serum drug concentrations if previous anticonvulsant use is suspected or known

### Other Diagnostic Tests

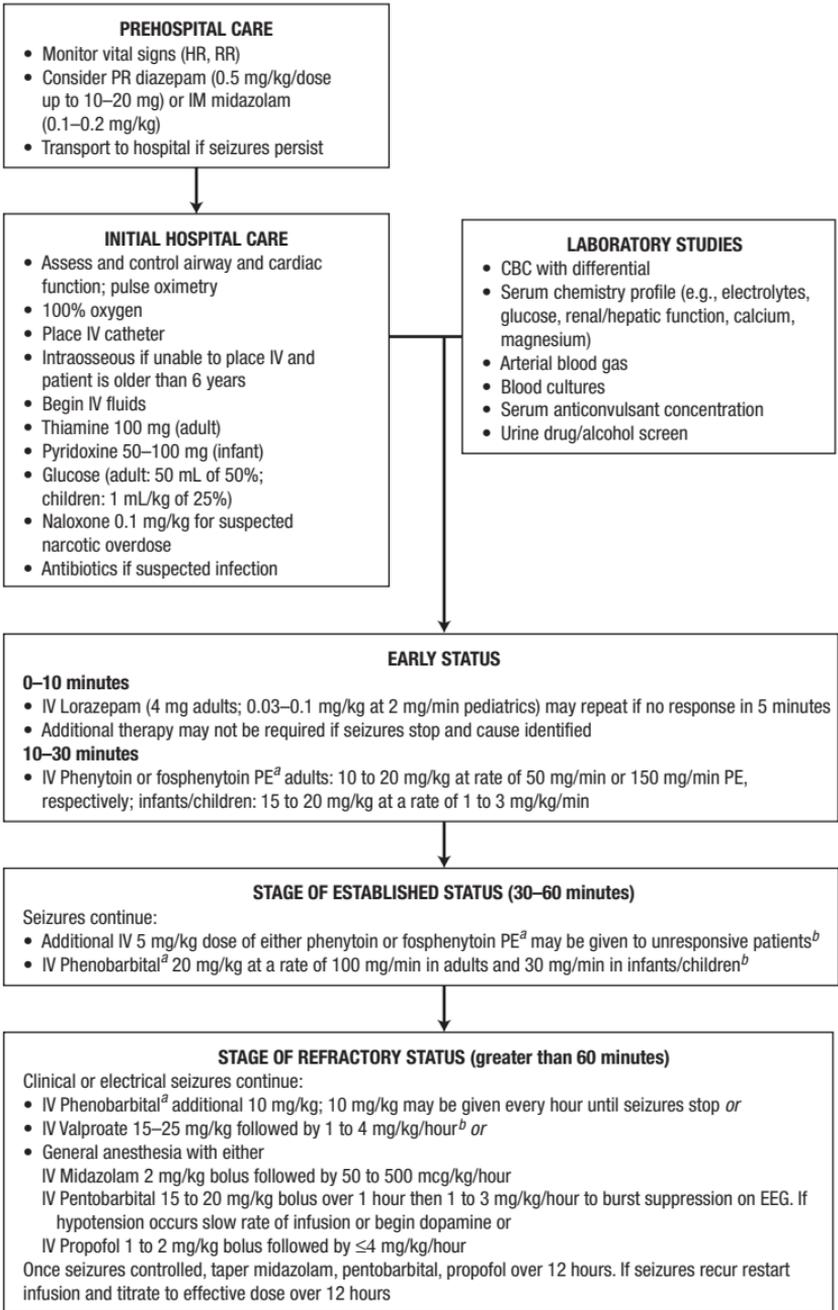
- Spinal tap if CNS infection suspected
- Electroencephalograph (EEG) should be obtained immediately and once clinical seizures are controlled
- Computed tomography (CT) with and without contrast
- Magnetic resonance imaging (MRI)
- Radiograph if indicated to diagnose fractures
- Electrocardiogram (ECG), especially if ingestion is confirmed

## DESIRED OUTCOME

- The goals of treatment are (1) terminate clinical and electrical seizure activity, (2) minimize side effects, (3) prevent recurrent seizures, and (4) avoid pharmacoresistent epilepsy and/or neurologic sequelae.

## TREATMENT

- For any tonic-clonic seizure that does not stop automatically or when doubt exists regarding the diagnosis, treatment should begin during the diagnostic workup. An algorithm for treatment of GCSE is shown in Fig. 56-1. Loading and maintenance doses used in the pharmacologic management of GCSE are shown in Table 56-2.
- Concurrent with initiation of anticonvulsants, vital signs should be assessed and an adequate airway should be established and ventilation maintained. Oxygen should be administered. If there is poor air exchange,



<sup>a</sup>Because variability exists in dosing, monitor serum concentration.

<sup>b</sup>If seizure is controlled, begin maintenance dose and optimize using serum concentration monitoring.

**FIGURE 56-1.** Algorithm for the management of generalized convulsive status epilepticus. (CBC, complete blood cell count; EEG, electroencephalogram; HR, heart rate; PE, phenytoin sodium equivalents; PR, per rectum; RR, respiratory rate.)

**TABLE 56-2** Medications Used in the Initial Treatment of Generalized Convulsive Status Epilepticus

Anticonvulsant (Route)	Loading Dose (Maximum Dose)		Rate of Infusion		Maintenance Dose	
	Adult	Pediatric	Adult	Pediatric	Adult	Pediatric
Diazepam (IV bolus)	0.25 mg/kg <sup>a,b,c</sup> (40 mg)	0.25–0.5 mg/kg <sup>a,c</sup> (0.75 mg/kg)	<5 mg/min	<5 mg/min	Not used	Not used
Fosphenytoin IV	15–20 mg PE/kg	15–20 mg PE/kg	150 mg PE/min	3 mg PE/kg/min	4–5 mg PE/kg/day	5–10 mg PE/kg/day
Lorazepam (IV bolus)	4 mg <sup>a,b,c</sup> (8 mg)	0.1 mg/kg <sup>a,c</sup> (4 mg)	2 mg/min	2 mg/min	Not used	Not used
Midazolam IV	200 mcg/kg <sup>a,d</sup>	150 mcg/kg <sup>a,d</sup>	0.5–1 mg/min	2–3 min	50–500 mcg/kg/h <sup>e</sup>	60–120 mcg/kg/h <sup>e</sup>
Phenobarbital IV	10–20 mg/kg <sup>e</sup>	15–20 mg/kg <sup>e</sup>	100 mg/min	30 mg/min	1–4 mg/kg/day <sup>e</sup>	3–5 mg/kg/day <sup>e</sup>
Phenytoin IV	10–20 mg/kg <sup>f</sup>	10–20 mg/kg <sup>f</sup>	50 mg/min <sup>g</sup>	1–3 mg/kg/min	4–5 mg/kg/day <sup>e</sup>	5–10 mg/kg/day <sup>e</sup>

PE, phenytoin sodium equivalents.

<sup>a</sup>Doses can be repeated every 10 to 15 minutes until the maximum dosage is given.

<sup>b</sup>Initial doses in the elderly are 2 to 5 mg.

<sup>c</sup>Larger doses can be required if patients chronically on a benzodiazepine (e.g., clonazepam).

<sup>d</sup>Can be given by the intramuscular, rectal, or buccal routes.

<sup>e</sup>Titrate dose as needed.

<sup>f</sup>Administer additional loading dose based on serum concentration.

<sup>g</sup>The rate should not exceed 25 mg/min in elderly patients and those with known atherosclerotic cardiovascular disease.

the patient should be intubated and ventilated mechanically. Temperature should be monitored frequently.

- Normal to high blood pressure should be maintained.
- All patients should receive IV glucose, and **thiamine** (100 mg IV) should be given prior to glucose in adults.
- Metabolic and/or respiratory acidosis should be assessed by ABG measurements to determine pH, PaO<sub>2</sub>, PaCO<sub>2</sub>, and HCO<sub>3</sub>. If pH is less than 7.2, secondary to metabolic acidosis, sodium bicarbonate should be given.

## BENZODIAZEPINES

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- A **benzodiazepine** (BZ) should be administered as soon as possible if the patient is actively seizing. Generally one or two IV doses will stop seizures within 2 to 3 minutes. Diazepam, lorazepam, and midazolam are equally effective. If seizures have stopped, a longer-acting anticonvulsant should be given.
- **Diazepam** is extremely lipophilic and quickly distributed into the brain, but redistributes rapidly into body fat, causing a very short duration of effect (0.25 to 0.5 hours). Therefore, a longer-acting anticonvulsant (e.g., **phenytoin**, **phenobarbital**) should be given immediately after the diazepam. The initial dose of diazepam can be repeated if the patient does not respond within 5 minutes.
- **Lorazepam** is currently considered the BZ of choice. It takes longer to reach peak brain levels than diazepam but has a longer duration of action (12 to 24 hours). Patients chronically on BZs may require larger doses. The administration rate of diazepam and lorazepam should not exceed 5 and 2 mg/min, respectively, because the propylene glycol in the vehicle can cause dysrhythmia and hypotension.
- **Midazolam** is water soluble and diffuses rapidly into the CNS but has a very short half-life (0.8 hours). It must be given by continuous infusion. There is increasing interest in using it buccally and intramuscularly when IV access cannot be obtained readily.
- With BZ administration, a brief period of cardiorespiratory depression (less than 1 minute) may occur and can necessitate assisted ventilation or require intubation, especially if BZs are used with a barbiturate. Hypotension may occur with high doses of BZs.

## PHENYTOIN

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- **Phenytoin** has a long half-life (20 to 36 hours), but it cannot be delivered fast enough to be considered a first-line agent. It takes longer to control seizures than do the BZs because it enters the brain more slowly. It causes less respiratory depression and sedation than the **BZs** or **phenobarbital**, but it is associated with administration-related cardiovascular toxicity (the vehicle is 40% propylene glycol). These administration-related problems are more likely to occur with large loading doses or in critically ill patients with marginal blood pressure.
- Phenytoin should be diluted to less than or equal to 5 mg/mL in normal saline. The maximum rate of infusion is 50 mg/min in adults (25 mg/min in

the elderly) and 3 mg/kg/min in children less than 50 kg. Vital signs and ECG should be obtained during administration. If arrhythmias or hypotension occurs or if the QT interval widens, the rate should be slowed. Maintenance doses should be started within 12 to 24 hours of the loading dose.

- If the patient has been on phenytoin prior to admission and the phenytoin concentration is known, this should be considered in determining a loading dose.
- A reduction in the loading dose is recommended for elderly patients, and a larger loading dose is required in obese patients.
- For seizures continuing after the initial loading dose, some practitioners have recommended an additional loading dose of 5 mg/kg (after waiting 60 minutes for response), but additional phenytoin may result in toxicity and exacerbation of seizures. There is no evidence that a total loading dose greater than 20 mg/kg will be of benefit in these patients.
- Phenytoin is associated with pain and burning during infusion. Phlebitis may occur with chronic infusion, and tissue necrosis is likely on infiltration. Intramuscular administration is not recommended.

## FOSPHENYTOIN

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- **Fosphenytoin**, the water-soluble phosphate ester of phenytoin, is a phenytoin prodrug.
- The dose of fosphenytoin sodium is expressed as phenytoin sodium equivalents (PE).
- Adverse reactions include nystagmus, dizziness, and ataxia. Paresthesias and pruritus typically disappear within 5 to 10 minutes after the infusion.
- In adults, the rate of administration should be 100 to 150 mg PE/min. Pediatric patients should receive fosphenytoin at a rate of 1 to 3 mg PE/kg/min.
- Continuous ECG, blood pressure, and respiratory status monitoring is recommended for all loading doses of fosphenytoin. Serum phenytoin concentrations should not be obtained for at least 2 hours after IV and 4 hours after intramuscular administration of fosphenytoin.

## PHENOBARBITAL

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- The Working Group on Status Epilepticus recommends that **phenobarbital** be given after a BZ plus phenytoin has failed. Most practitioners agree that phenobarbital is the long-acting anticonvulsant of choice in patients with hypersensitivity to the hydantoins or in those with cardiac conduction abnormalities.
- In order to avoid overdosing, estimated lean body mass should be used in obese patients.
- Peak brain concentrations occur 12 to 60 minutes after IV dosing. On average, seizures are controlled within minutes of the loading dose.
- If the initial loading dose does not stop the seizures within 20 to 30 minutes, an additional 10- to 20-mg/kg dose may be given. If seizures continue, a third 10-mg/kg load may be given. There is no maximum dose beyond which further doses are likely to be ineffective. Once seizures are controlled, the maintenance dose should be started within 12 to 24 hours.

- The risk of apnea and hypopnea can be more profound in patients already treated with BZs. If significant hypotension develops, the infusion should be slowed or stopped.

## REFRACTORY GENERALIZED CONVULSIVE STATUS EPILEPTICUS

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- When adequate doses of a BZ, phenytoin, and phenobarbital have failed, the condition is termed *refractory*. Failure to aggressively treat early increases the likelihood of nonresponse. Doses of agents used to treat refractory GCSE are given in Table 56-3.
- A metaanalysis showed that among patients refractory to GCSE, pentobarbital had a 92% response rate, compared to midazolam (80%) and propofol (73%). Breakthrough seizures were least common with pentobarbital (12%, compared with propofol [15%] and midazolam [51%]). Hypotension was more common with midazolam and propofol.

### Benzodiazepines

- **Midazolam** has been suggested by some practitioners as the first-line treatment for refractory GCSE. Most patients respond within 1 hour, but the infusion rate should be increased every 15 minutes in those who do not. Tachyphylaxis can develop, and dosing should be guided by EEG response.
- Once seizures are terminated, dosages can be decreased by 1 mcg/kg/min every 2 hours. Successful discontinuation is enhanced by maintaining serum **phenytoin** concentrations above 20 mg/L and **phenobarbital** concentrations above 40 mg/L.
- Hypotension, poikilothermia, and respiratory depression can occur and may require supportive therapies.
- Refractory GCSE has also been treated with large-dose continuous infusion **lorazepam** or **diazepam**. Lorazepam contains propylene glycol, which can accumulate and cause marked osmolar gap, metabolic acidosis, and renal toxicity.

### Medically Induced Coma

- If there is inadequate response to high doses of **midazolam**, anesthetizing is recommended. Intubation and respiratory support are mandatory during **barbiturate** coma, and continuous monitoring of vital signs is essential. A short-acting barbiturate (e.g., **pentobarbital** or **thiopental**) is generally preferred (see Fig. 56-1).
- **Pentobarbital** should be initiated with a loading dose in accordance with the guidelines given in Table 56-3. Serum concentrations of 30 to 40 mg/L are necessary to induce an isoelectric EEG. If hypotension occurs, the rate of administration should be slowed or dopamine should be administered. The loading dose should be followed immediately by an infusion according to Table 56-3, increasing gradually until there is burst suppression on the EEG or adverse effects occur. Twelve hours after a burst suppression pattern is obtained, the rate of pentobarbital infusion should be titrated downward every 2 to 4 hours to determine if GCSE is in remission.

**TABLE 56-3** Medications Used to Treat Refractory Generalized Convulsive Status Epilepticus

Anticonvulsant (Route)	Loading Dose		Infusion Duration		Maintenance Dose	
	Adult	Pediatric	Adult	Pediatric	Adult	Pediatric
Levetiracetam IV	500–1,000 mg	NA	33–66 mg/min	NA	750–9,000 mg/day	NA
Lidocaine IV	50–100 mg	1 mg/kg (maximum dose = 3–5 mg/kg in first hour)	≤2 minutes	≤2 minutes	1.5–3.5 mg/kg/hour	1.2–3 mg/kg/hour
Midazolam IV	200 mcg/kg <sup>a</sup>	150 mcg/kg <sup>a</sup>	0.5–1 mg/min	0.5–1 mg/min	50–500 mcg/kg/hour <sup>b</sup>	60–120 mcg/kg/hour <sup>b</sup>
Pentobarbital IV	10–20 mg/kg	15–20 mg/kg	Over 1–2 hours	Over 1–2 hours	1–5 mg/kg/hour <sup>b</sup>	1–5 mg/kg/hour <sup>b</sup>
Propofol IV	2 mg/kg	3 mg/kg	Over 10 seconds	Over 20–30 seconds	5–10 mg/kg/hour	2–18 mg/kg/hour <sup>c</sup>
Topiramate po	300–1,600 mg	5–10 mg/kg	NA	NA	400–1,600 mg/day	5–10 mg/kg/day
Valproate IV	15–45 mg/kg	20–25 mg/kg	3 mg/kg/min	3 mg/kg/min	1–4 mg/kg/hour <sup>b</sup>	1–4 mg/kg/hour <sup>b</sup>

NA, not available.

<sup>a</sup>Doses can be repeated twice every 10 to 15 minutes until the maximum dosage is given.

<sup>b</sup>Titrate dose as needed.

<sup>c</sup>Generally recommended not to exceed a dose of 4 mg/kg/hour and a duration of 48 hours.

**Valproate**

- Refer to Table 56-3 for dosing guidelines for adults and children. The manufacturer recommends that IV **valproate** be given no faster than 3 mg/kg/min.
- Some have suggested that the maintenance infusion rate should be adjusted as follows: (1) if no metabolic enzyme inducers are present, the continuous infusion rate is 1 mg/kg/hour; (2) if one or more inducers are present (e.g., phenobarbital, phenytoin), the rate is 2 mg/kg/hour; and (3) if inducers and pentobarbital coma are present, the rate is 4 mg/kg/hour.
- There are no reports of respiratory depression; hemodynamic instability is rare, but vital signs should be monitored closely during the loading dose.

**Propofol**

- **Propofol** is very lipid soluble, has a large volume of distribution, and has a rapid onset of action. It has comparable efficacy to **midazolam** for refractory GCSE. It has been associated with metabolic acidosis, hemodynamic instability, and bradyarrhythmias that are refractory to treatment.
- An adult dose can provide more than 1,000 cal/day as lipid and cost over \$1,000/day.

**Lidocaine**

- Lidocaine is not recommended unless other agents have failed. Table 56-3 shows the recommended dosing guidelines. It has a rapid onset of action. Fasciculations, visual disturbances, and tinnitus may occur at serum concentrations between 6 and 8 mg/L. Seizures and obtundation may develop when serum concentrations exceed 8 mg/L.
- Levetiracetam, topiramate, and the general anesthetics, halothane, isoflurane, and ketamine are being evaluated for refractory GCSE, but their efficacy, safety, or overall suitability have not been established to date.

**EVALUATION OF THERAPEUTIC OUTCOMES**

- An EEG is a key tool that allows practitioners to determine when abnormal electrical activity has been aborted and may assist in determining which anticonvulsant was effective. Vital signs must be monitored during the infusion. It may also be necessary to monitor the ECG in some patients. The infusion site must be assessed for any evidence of infiltration before and during administration of phenytoin.

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*See Chap. 59, Status Epilepticus, authored by Stephanie J. Phelps, Collin A. Hovinga, and James W. Wheless, for a more detailed discussion of this topic.*

## DEFINITION

- Nutrition assessment allows identification of individuals at risk for under- and overnutrition.
- Undernutrition is the result of inadequate nutrition intake, impaired absorption of nutrients, or inappropriate use of ingested nutrients. Changes in subcellular, cellular, and/or organ function can occur and increase the risk of morbidity and mortality.

## CLASSIFICATION OF NUTRITIONAL DISEASES

- Undernutrition can result from a deficiency in protein and calories or from a single nutrient (e.g., vitamins, trace elements).
- Types of protein-energy malnutrition are marasmus (deficiency in total intake or nutrient utilization), kwashiorkor (relative protein deficiency), and mixed marasmus-kwashiorkor.
- Single-nutrient deficiencies can occur, usually in combination with any protein-energy malnutrition.
- For information on overnutrition or obesity, see Chap. 59.

## NUTRITION SCREENING

- Nutrition screening provides a systematic way to identify individuals at risk for undernutrition.
- Risk factors for undernutrition include any disease state, complicating condition, treatment, or socioeconomic condition that results in decreased nutrient intake, altered metabolism, and/or malabsorption. The presence of three to four risk factors puts a person at risk for undernutrition.
- The Joint Commission on Accreditation of Healthcare Organizations standards require a nutrition screening typically within 24 to 72 hours of hospital admission. Patients determined not to be at risk for malnutrition should be reevaluated every 7 to 14 days. Patients determined to be at risk for malnutrition need a nutrition assessment and care plan.
- The goals of nutrition assessment are to identify the presence (or risk) of developing undernutrition and complications, estimate nutrition needs, and establish baseline parameters for assessing the outcome of therapy.

## NUTRITION ASSESSMENT

- Nutrition assessment is the first step in developing a nutrition care plan and includes a clinical evaluation, anthropometric measurements, and biochemical and immune function studies.

### CLINICAL EVALUATION

- Medical and dietary history should include weight changes within 6 months, dietary intake changes, GI symptoms, functional capacity, and disease states.
- Physical examination should focus on assessment of lean body mass (LBM) and physical findings of vitamin, trace element, and essential fatty acid deficiencies.

### ANTHROPOMETRIC MEASUREMENTS

- Anthropometric measurements are gross measurements of body cell mass used to evaluate LBM and fat stores. The most common measurements are weight, height, limb size (e.g., skinfold thickness and midarm muscle, wrist, and waist circumferences), and bioelectrical impedance analysis (BIA).
- Interpretation of actual body weight should consider ideal weight for height, usual body weight, fluid status, and age. Change over time can be calculated as percentage of usual body weight. Unintentional weight loss of more than 10% in less than 6 months correlates with poor clinical outcome in adults.
- Ideal body weight provides a population reference standard against which the actual body weight can be compared to detect both under- and overnutrition (Table 57-1). See Table 57-2 for body weight equations.
- The best indicator of adequate nutrition in children is appropriate growth. Weight and height should be plotted on the appropriate growth curve and compared with usual growth velocities (Table 57-3). Additionally, the average weight gain for infants is 24 to 35 g/day for term infants and 10 to 25 g/day for preterm infants.
- Body mass index (BMI) is another index of weight-for-height that is highly correlated with body fat. Interpretation of BMI should include consideration of gender, frame size, and age. BMI values greater than 25 kg/m<sup>2</sup> are indicative of overweight, and values less than 18.5 kg/m<sup>2</sup> are indicative of undernutrition. BMI is calculated as follows:

$$\text{Body weight (kg)} / [\text{height (m)}]^2$$

- Measurements of skinfold thickness estimate subcutaneous fat, midarm muscle circumference estimates skeletal muscle mass, and waist circumference estimates abdominal fat content.
- BIA is a simple, noninvasive, and relatively inexpensive way to measure LBM. It is based on differences between fat tissue and lean tissue's resistance to conductivity. Fluid status should be considered in interpretation of BIA results.

**TABLE 57-1** Evaluation of Body Weight

<b>Actual body weight (ABW) compared to ideal body weight (IBW)</b>	
ABW <69% IBW	Severe malnutrition
ABW 70–79% IBW	Moderate malnutrition
ABW 80–89% IBW	Mild malnutrition
ABW 90–120% IBW	Normal
ABW >120% IBW	Overweight
ABW ≥150% IBW	Obese
ABW ≥200% IBW	Morbidly obese
<b>Actual body weight (ABW) compared to usual body weight (UBW)</b>	
ABW 85–95% UBW	Mild malnutrition
ABW 75–84% UBW	Moderate malnutrition
ABW <75% UBW	Severe malnutrition
<b>Body mass index (BMI) (kg/m<sup>2</sup>) or (lb/in<sup>2</sup>)</b>	
<b>Adults</b>	
<16	Severe malnutrition
16–16.9	Moderate malnutrition
17–18.5	Mild malnutrition
19–25	Healthy (19–34 years of age)
21–27	Healthy (older than 35 years of age)
25–30	Overweight (19–34 years of age)
27.5–29.9	Overweight (older than 35 years of age)
30–40	Moderate obesity
>40	Severe or morbid obesity
<b>Children</b>	
BMI-for-age <5th percentile	Underweight
BMI-for-age 5th–85th percentile	Healthy
BMI-for-age >85th percentile	At risk for overweight
BMI-for-age ≥95th percentile	Overweight

## BIOCHEMICAL AND IMMUNE FUNCTION STUDIES

- LBM can be assessed by measuring serum visceral proteins (Table 57-4). They are best for assessing uncomplicated semistarvation and recovery, and poor for assessing status during acute stress. Visceral proteins must be interpreted relative to overall clinical status because they are affected by factors other than nutrition.
- Nutrition affects immune status both directly and indirectly. Total lymphocyte count and delayed cutaneous hypersensitivity reactions are immune function tests useful in nutrition assessment.

**TABLE 57-2** Body Weight Equations

<b>Ideal body weight (IBW)</b>	
Adult males:	IBW (kg) = 50 + (2.3 × height in inches >5 feet)
Adult females:	IBW (kg) = 45.5 + (2.3 × height in inches >5 feet)
Children (1–18 years):	IBW (kg) = ([height in cm] <sup>2</sup> × 1.65)/1,000
<b>Adjusted body weight for obesity</b>	
Adjusted IBW = {[Actual body weight (kg) – IBW (kg)] × 0.25} + IBW	

**TABLE 57-3** Expected Growth Velocities in Term Infants and Children

Age	Weight (g/day)	Height (cm/mo)
0–3 months	24–35	2.8–3.4
4–6 months	15–21	1.7–2.4
7–12 months	10–13	1.3–1.6
1–3 years	5–9	0.6–1
4–6 years	5–6	0.5–0.6
7–10 years	7–11	0.4–0.5

**Example of growth assessment:**

Age: 2 months; weight: 3.9 kg; weight at 1 month of age, 3.1 kg; days since last wt: 30

Growth velocity =  $[(3.9 \text{ kg} - 3.1 \text{ kg}) \times 1,000 \text{ g/kg}] / 30 \text{ days} = 26.7 \text{ g/day}$

Interpretation: normal growth

- Total lymphocyte count is obtained from a complete blood count with differential (% lymphocytes  $\times$  total number of white blood cells). Values less than 1,500 cells/mm<sup>3</sup> and 900 cells/mm<sup>3</sup> are associated with moderate and severe nutrition depletion, respectively.
- Delayed cutaneous hypersensitivity is commonly assessed using antigens to which the patient has been previously sensitized. The recall antigens used most frequently are mumps, *Candida albicans*, streptokinase-streptodornase, *Trichophyton*, coccidioidin, and purified protein derivative. Anergy is associated with malnutrition.

**SPECIFIC NUTRIENT DEFICIENCIES**

- Biochemical assessment of trace element, vitamin, and essential fatty acid deficiencies should be based on the nutrient's function, but few practical

**TABLE 57-4** Visceral Proteins Used for Assessment of Lean Body Mass

Serum Protein	Half-Life (days)	Function	Factors Resulting in Increased Values	Factors Resulting in Decreased Values
Albumin	18–20	Maintains plasma oncotic pressure; transports small molecules	Dehydration, anabolic steroids, insulin, infection	Overhydration, edema, kidney insufficiency, nephrotic syndrome, poor dietary intake, impaired digestion, burns, congestive heart failure, cirrhosis, thyroid/adrenal/pituitary hormones, trauma, sepsis
Transferrin	8–9	Binds iron in plasma and transports iron to bone	Iron deficiency, pregnancy, hypoxia, chronic blood loss, estrogens	Chronic infection, cirrhosis, burns, enteropathies, nephrotic syndrome, cortisone, testosterone
Prealbumin (trans-thyretin)	2–3	Binds triiodothyronine and to a lesser extent thyroxine; carrier for retinol-binding protein	Kidney dysfunction	Cirrhosis, hepatitis, stress, inflammation, surgery, hyperthyroidism, cystic fibrosis, kidney dysfunction, zinc deficiency

methods are available. Therefore, most assays measure serum concentrations of the individual nutrient.

- Clinical syndromes are associated with deficiencies of the following trace elements: zinc, copper, manganese, selenium, chromium, iodine, fluoride, molybdenum, and iron.
- Single vitamin deficiencies are uncommon; multiple vitamin deficiencies more commonly occur with undernutrition. For information on iron-deficiency and other anemias, see Chap. 33.
- Essential fatty acid deficiency is rare but can occur with prolonged lipid-free parenteral nutrition, very low fat enteral formulas, severe fat malabsorption, or severe malnutrition. The body can synthesize all fatty acids except for linoleic and linolenic acid, which should constitute approximately 2% to 4% of total calorie intake.
- Carnitine can be synthesized from lysine and methionine, but synthesis is decreased in premature infants. Low carnitine levels can occur in premature infants receiving parenteral nutrition or carnitine-free diets.

## ASSESSMENT OF NUTRIENT REQUIREMENTS

- Assessment of nutrient requirements must be made in the context of patient-specific factors (e.g., age, gender, size, disease state, clinical condition, nutrition status, physical activity).
- To replace recommended dietary allowances, the Food and Nutrition Board created the dietary reference intakes made up of seven nutrient groups.

## ENERGY REQUIREMENTS

- Adults should consume 45% to 65% of total calories from carbohydrates, 20% to 35% from fat, and 10% to 35% from protein. Recommendations are similar for children, except that infants and younger children should consume 40% to 50% of total calories from fat.
- Daily energy requirements are 20 to 25 kcal/kg for healthy adults, 25 to 30 kcal/kg for malnourished or metabolically stressed adults, and 30 to 40 kcal/kg for adults with major burns. Unfortunately, this simple approach fails to consider age- and gender-related differences in energy metabolism.
- Daily energy requirements for children are approximately 150% of basal metabolic rate with additional calories to support activity and growth (Table 57-5). Requirements increase with fever, sepsis, major surgery, trauma, burns, long-term growth failure, and chronic conditions (e.g., bronchopulmonary dysplasia, congenital heart disease, and cystic fibrosis).
- Equations are available to estimate resting energy expenditure (Table 57-6). The result should be multiplied by a factor to correct for stress or activity level based on clinical judgment.
- Each equation for estimating energy requirements has advantages and disadvantages, but none has been shown to be superior to another. The most popular is the Harris-Benedict equation.
- The most accurate clinical tool for estimating energy requirements is indirect calorimetry or metabolic gas monitoring. This noninvasive proce-

**TABLE 57-5** Dietary Reference Intakes for Energy and Protein in Healthy Children

Age (Reference age/weight)	Estimated Energy Requirement (kcal/day)		Protein RDA (g/kg/day) <sup>a</sup>
	Male	Female	
0–6 months (3 mo/6 kg)	570	520	1.52 <sup>a</sup>
7–12 months (9 mo/9 kg)	743	676	1.5
1–2 years (24 mo/12 kg)	1,046	992	
1–3 years (24 mo/12 kg)			1.1
3–8 years (6 yr/20 kg)	1,742	1,642	
4–8 years (6 yr/20 kg)			0.95
9–13 years (11 yr/M: 36 kg; F: 37 kg)	2,279	2,071	0.95
14–18 years (16 yr/M: 61 kg; F: 54 kg)	3,152	2,368	0.85

F, female; M, male; RDA, recommended dietary allowance.

<sup>a</sup>Adequate intake.

**TABLE 57-6** Equations to Estimate Energy Expenditure in Adults and Children<sup>a</sup>

#### Adults

##### Harris-Benedict (kcal/day)

Men:  $BEE = 66 + [13.7W(\text{kg})] + [5H(\text{cm})] - (6.8A)$

Women:  $BEE = 655 + [9.6W(\text{kg})] + [1.8H(\text{cm})] - (4.7A)$

##### DRI equations (kcal/day)

Men:  $EER = 662 - 9.53A + (PA \times 15.91W) + 539.6H(m)$

Women:  $EER = 354 - 6.91A + (PA \times 9.36W) + 726H(m)$

PA = 1 if sedentary; 1.12 if low active; 1.27 if active; and 1.45 if very active.

#### Children

##### FAO/WHO/UNU (kcal/day)

0–3 years of age

Boys:  $BMR = 60.9W - 54$

Girls:  $BMR = 61W - 51$

4–10 years of age

Boys:  $BMR = 22.7W + 495$

Girls:  $BMR = 22.5W + 499$

11–18 years of age

Boys:  $BMR = 17.5W + 651$

Girls:  $BMR = 12.2W + 746$

##### DRI equations (kcal/day)

Birth through 2 years of age

$EER = (89W - 100) + GF$

GF = 175 kcal if 0–3 months; 56 kcal if 4–6 months; 22 kcal if 7–12 months; 20 kcal if 13–35 months

3–18 years of age

Boys:  $EER = 88.5 - (61.9A) + PA [26.7W + 903H(m)] + GF$

Girls:  $EER = 135.3 - (30.8A) + PA [10W + 934H(m)] + GF$

GF = 20 kcal if 3–8 years; 25 kcal if 9–18 years.

PA = 1 if sedentary; 1.13–1.16 if low activity; 1.26–1.31 if normal activity; and 1.42–1.56 if very active

A, age in years; BEE, basal energy expenditure; BMR, basal metabolic rate; DRI, Dietary Reference Intakes; EER, estimated energy requirement; FAO/WHO/UNU, Food and Agriculture Organization/World Health Organization/United Nations University; GF, growth factor, H, height in centimeters (cm) or meters (m), as indicated; PA, physical activity factor; W, weight in kilograms.

<sup>a</sup>No real consensus exists as to which formula is best in all situations. Many clinicians use both to calculate a range of acceptable intakes.

ture determines oxygen consumption ( $\text{VO}_2$ , mL/min) and carbon dioxide production ( $\text{VCO}_2$ , mL/min). Measured resting energy expenditure (MREE, kcal/day) is then calculated using the abbreviated Weir equation:

$$\text{MREE} = (3.9 \text{ VO}_2 + 1.1 \text{ VCO}_2) \times 1.44$$

- Data from indirect calorimetry can also be used to determine a respiratory quotient. Values greater than 1 suggest overfeeding, whereas values less than 0.7 suggest a ketogenic diet, fat gluconeogenesis, or ethanol oxidation. Respiratory quotient (RQ) is calculated as follows:

$$\text{RQ} = \text{VCO}_2/\text{VO}_2$$

- Limitations of indirect calorimetry include limited availability, calibration errors, and other errors.

## PROTEIN, FLUID, AND MICRONUTRIENT REQUIREMENTS

### Protein

- Protein requirements are based on age, nutrition status, disease state, and clinical condition. The usual recommended daily protein allowances are 0.8 g/kg for adults, 1.5 to 2 g/kg for patients with metabolic stress (e.g., infection, trauma, and surgery), and 2.5 to 3 g/kg for patients with burns. See Table 57-5 for recommendations for children.
- Daily protein requirements can be individualized by measuring the nitrogen in a 24-hour urine collection (UUN), because nitrogen is found only in protein and at a relatively constant ratio of 1 g/6.25 g protein. Nitrogen output is then compared with nitrogen intake. Nitrogen output is approximated by the following:

$$\text{Nitrogen output (g/day)} = \text{UUN} + 4$$

### Fluid

- Daily adult fluid requirements are approximately 30 to 35 mL/kg, 1 mL/kcal, or 1,500 mL/m<sup>2</sup>.
- Daily fluid requirements for children and preterm infants who weigh less than 10 kg are at least 100 mL/kg. An additional 50 mL/kg should be provided for each kilogram of body weight between 11 and 20 kg, and 20 mL/kg for each kilogram above 20 kg.
- Fluid requirements increase with increased insensible or GI losses, fever, sweating, and increased metabolism. Fluid requirements decrease with kidney or cardiac failure and hypoalbuminemia with starvation.
- Fluid status is assessed by monitoring urine output and specific gravity, serum electrolytes, and weight changes. An hourly urine output of at least 1 mL/kg for children and 50 mL for adults is needed to ensure tissue perfusion.

### Micronutrients

- Requirements for micronutrients (i.e., electrolytes, trace elements, and vitamins) vary with age, gender, route of administration, and underlying clinical conditions.

**TABLE 57-7** Drug Effects on Vitamin Status

Drug	Possible Vitamin Effect
Antacids	Thiamine deficiency
Antibiotics	Vitamin K deficiency
Anticonvulsants	Vitamin D and folic acid impaired absorption
Antineoplastics	Folic acid antagonism and malabsorption
Antipsychotics	Decreased riboflavin
Cathartics	Increased requirements for vitamins D, C, and B <sub>6</sub>
Cholestyramine	Vitamins A, D, E, and K, $\beta$ -carotene malabsorption
Colestipol	Vitamins A, D, E, and K, $\beta$ -carotene malabsorption
Corticosteroids	Decreased vitamins A, D, and C
Diuretics (loop)	Thiamine deficiency
Histamine <sub>2</sub> -antagonists	Vitamin B <sub>12</sub> deficiency
Isoniazid	Vitamin B <sub>6</sub> deficiency
Mineral oil	Vitamins A, D, E, and K malabsorption
Orlistat	Vitamins A, D, E, and K malabsorption
Pentamidine	Folic acid deficiency
Proton pump inhibitors	Vitamin B <sub>12</sub> deficiency

- Sodium, potassium, magnesium, and phosphorus requirements are typically decreased in patients with kidney failure, whereas calcium requirements are increased (see Chaps. 76 and 78).

## DRUG–NUTRIENT INTERACTIONS

- Concomitant drug therapy can alter serum concentrations of vitamins (Table 57-7), minerals, and electrolytes.
- Some drug delivery systems contain nutrients. For example, the vehicle for propofol is 10% lipid emulsion and most IV therapies include dextrose or sodium.

## EVALUATION OF THERAPEUTIC OUTCOMES

- Most markers of nutrition status are not ideal. They were first used in epidemiologic studies of large populations and, when applied to individuals, lack specificity and sensitivity.
- Weight and serum albumin concentration have the best correlation with clinical outcome; the cost-effectiveness of other biochemical parameters is not known.
- Anthropometric measures are probably most useful with long-term nutrition support.
- Continuous reassessment is required because nutrition requirements are dynamic.

See Chap. 143, *Assessment of Nutrition Status and Nutrition Requirements*, authored by Katherine Hammond Chessman and Vanessa J. Kumpf, for a more detailed discussion of this topic.

## DEFINITION

- Enteral nutrition (EN) is the delivery of nutrients by tube or mouth into the GI tract. This chapter focuses on delivery through a feeding tube.

## PATHOPHYSIOLOGY

- Digestion and absorption are the GI processes that generate usable fuels for the body. Understanding the mechanisms of these processes can enhance rational use of EN support.
- Digestion is the stepwise conversion of complex chemical and physical nutrients via mechanical, enzymatic, and physicochemical processes into molecular forms that can be absorbed from the GI tract.
- Nutrients are absorbed across the intestinal cell membrane and reach the systemic circulation through the portal venous or splanchnic lymphatic systems, provided the GI or biliary tract does not excrete them.
- Many factors can alter these stepwise processes and interfere with digestion and absorption, such as functional immaturity of the neonatal gut.

## CLINICAL PRESENTATION AND INDICATIONS

- Clinical presentation of protein-energy malnutrition and nutrition assessment are discussed in Chap. 57.
- EN is indicated for the patient who cannot or will not eat enough to meet nutritional requirements and who has a functioning GI tract. Additionally, a method of enteral access must be possible. Potential indications include neoplastic disease, organ failure, hypermetabolic states, GI disease, and neurologic impairment.
- The only absolute contraindications are mechanical obstruction and necrotizing enterocolitis. Conditions that challenge the success of EN include severe diarrhea, protracted vomiting, enteric fistulae, severe GI hemorrhage, and intestinal dysmotility.
- EN has replaced parenteral nutrition (PN) (see Chap. 60) as the preferred method for the feeding of critically ill patients requiring specialized nutrition support. Advantages of EN over PN include maintaining GI tract structure and function; fewer metabolic, infectious, and technical complications; and lower costs.
- The optimal time to initiate EN is controversial. Early initiation within 24 to 48 hours of hospitalization is recommended for critically ill patients because this approach appears to decrease infectious complications and reduce mortality. If patients are only mildly to moderately stressed and well nourished, initiation can be delayed until oral intake is inadequate for 7 to 14 days.

## DESIRED OUTCOME

- The goal of EN is to provide calories, macronutrients, and micronutrients to patients who are unable to achieve these requirements from an oral diet.

## TREATMENT

### ENTERAL ACCESS

- EN can be administered through four routes, which have different indications, tube placement options, advantages, and disadvantages (Table 58-1). The choice depends on the anticipated duration of use and the feeding site (i.e., stomach versus small bowel).
- Short-term access is generally easier, less invasive, and less costly than long-term access. Feeding tubes used for short-term access are not suitable for long-term use owing to patient discomfort, long-term complications, and mechanical failure.
- The most frequently used short-term routes are accessed by inserting a tube through the nose and threading it into the stomach (nasogastric), duodenum (nasoduodenal), or jejunum (nasojejunal).
- The stomach is generally the least expensive and least labor-intensive access site; however, patients who have impaired gastric emptying are at risk for aspiration and pneumonia.
- Greater skill is required to place the feeding tube beyond the pylorus. Prokinetic agents, such as **metoclopramide** or **erythromycin**, facilitate passage of the tube into the small intestine.
- Long-term access should be considered when EN is anticipated for more than 4 to 6 weeks. The most popular option is gastrostomy followed by jejunostomy.
- The gastrostomy exit site requires general stoma care to prevent inflammation and infection. Jejunostomy may be appropriate in patients at high risk of gastroesophageal reflux disease and aspiration, and with impaired gastric motility or delayed gastric emptying.

### ADMINISTRATION METHODS

- EN can be administered by continuous, cyclic, bolus, and intermittent methods. The choice depends on the feeding tube location, patient's clinical condition, intestinal function, residence environment, and tolerance to tube feeding.
- Continuous EN is preferred for initiation, for critically ill patients, and for patients with limited absorption capacity because of rapid GI transit time or severely impaired digestion. Continuous EN has the advantage of being well tolerated. It has the disadvantages of cost and inconvenience owing to pump and administration sets.
- Cyclic EN has the advantage of allowing breaks from the infusion system, thereby increasing mobility, especially if EN is administered nocturnally.
- Bolus EN is most commonly used in long-term care residents who have a gastrostomy. This method has the advantage of requiring little administra-

**TABLE 58-1** Options and Considerations in the Selection of Enteral Access

<b>Access</b>	<b>Indications</b>	<b>Tube Placement Options</b>	<b>Advantages</b>	<b>Disadvantages</b>
Nasogastric or orogastric	Short-term Intact gag reflex Normal gastric emptying	Manually at bedside	Ease of placement Allows for all methods of administration Inexpensive Multiple commercially available tubes and sizes	Potential tube displacement Potential increased aspiration risk
Nasoduodenal or nasojejunal	Short-term Impaired gastric motility or emptying High risk of GER or aspiration	Manually at bedside Fluoroscopically Endoscopically	Potential reduced aspiration risk Allows for early postinjury or postoperative feeding Multiple commercially available tubes and sizes	Manual transpyloric passage requires greater skill Potential tube displacement or clogging Bolus or intermittent feeding not tolerated
Gastrostomy	Long-term Normal gastric emptying	Surgically Endoscopically Radiologically Laparoscopically	Allows for all methods of administration Large-bore tubes less likely to clog Multiple commercially available tubes and sizes Low-profile buttons available	Attendant risks associated with each type of procedure Potential increased aspiration risk
Jejunostomy	Long-term Impaired gastric motility or gastric emptying High risk of GER or aspiration	Surgically Endoscopically Radiologically Laparoscopically	Allows for early postinjury or postoperative feeding Potential reduced aspiration risk Multiple commercially available tubes and sizes	Requires stoma site care Attendant risks associated with each type of procedure Bolus or intermittent feeding not tolerated Requires stoma site care

GER, gastroesophageal reflux.

tion time (e.g., 5 to 10 minutes) and minimal equipment (e.g., a syringe). Bolus EN has the potential disadvantages of causing cramping, nausea, vomiting, aspiration, and diarrhea.

- Intermittent EN is similar to bolus EN except that the feeding is administered over 20 to 60 minutes, which improves tolerability but requires more equipment (e.g., reservoir bag and infusion pump). Like bolus EN, intermittent EN mimics normal eating patterns. As compared with continuous EN, bolus or intermittent EN minimizes the development of cholestatic liver disease.

## FORMULATIONS

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- Historically, EN formulations were created to provide essential nutrients including macronutrients (e.g., carbohydrates, fats, and proteins) and micronutrients (e.g., electrolytes, trace elements, vitamins, and water).
- Over time, formulations have been enhanced to improve tolerance and meet specific patient needs. For example, nutraceuticals or pharmaconutrients are added to modify the disease process or improve clinical outcome; however, these health claims are not regulated by the FDA.
- Fiber, in the form of soy polysaccharides, has been added to several EN formulations. In addition to providing an excellent energy source, potential benefits include trophic effects on colonic mucosa, promotion of sodium and water absorption, and regulation of bowel function.
- Osmolality is a function of the size and quantity of ionic and molecular particles primarily related to protein, carbohydrate, electrolyte, and mineral content. Osmolality is commonly thought to affect GI tolerability, but there is a lack of supporting evidence.
- EN formulations are classified by their composition and intended patient population (Table 58-2). Most formularies should contain no more than one product per category.
- Most EN products are ready-to-use prepackaged liquids, which have the advantages of convenience and lower susceptibility to microbiologic contamination. The major disadvantage is storage space. Closed-system containers provide a prefilled, sterile 1- to 1.5-L supply of EN formula that do not require refrigeration and have longer hang times than ready-to-use products.
- Polymeric formulations contain a well-proportioned mix of macronutrients, with or without fiber, and are best suited for tube feeding due to lack of sweetening to maintain isotonicity. Standard formulations have a nonprotein calorie–nitrogen ratio of 125:1 to 150:1.
- High-protein formulations have a nonprotein calorie–nitrogen ratio of less than 125:1. Candidates for these formulations require more than 1.5 g of protein/kg/day and are generally critically ill because of trauma, burns, pressure sores, surgical wounds, or high fistula output.
- High caloric density formulations are indicated for patients requiring restriction of fluids, electrolytes, or both, such as patients with renal insufficiency or congestive heart failure.
- Elemental or peptide-based formulations have partially hydrolyzed protein or fat components. Peptide-based formulations replace some of the protein with dipeptides and tripeptides, thereby optimizing absorption in patients with impaired digestive or absorptive capacity.

**TABLE 58-2** Adult Enteral Feeding Formulation Classification System

Category	Features	Indications
Standard polymeric	Isotonic 1–1.2 kcal/mL NPC:N 125:1 to 150:1 May contain fiber	Designed to meet the needs of the majority of patients. Patients with functional GI tract. Not suitable for oral use.
High protein	NPC:N <125:1 May contain fiber	Patients with protein requirements >1.5 g/kg/day, such as trauma, burns, pressure sores, or wounds.
High caloric density	1.5–2 kcal/mL Lower electrolyte content per calorie	Patients receiving propofol. Patients requiring fluid and/or electrolyte restriction, such as renal insufficiency.
Elemental	Hypertonic High proportion of free amino acids Low in fat	Patients who require low fat. Use has generally been replaced by peptide-based formulations.
Peptide-based	Contains dipeptides and tripeptides Contains MCTs	Indications/benefits not clearly established. Trial may be warranted in patients who do not tolerate intact protein due to malabsorption.
Disease-specific		
Renal	Caloric dense Protein content varies Low electrolyte content	Alternative to high caloric density formulations, but generally more expensive.
Hepatic	Increased branched-chain and decreased aromatic amino acids	Patients with hepatic encephalopathy.
Pulmonary	High fat, low carbohydrate	Patients with compromised pulmonary function.
Diabetic	High fat, low carbohydrate	Alternative to standard, fiber-containing formulation in patients with uncontrolled hyperglycemia.
Immunomodulating	Supplemented with glutamine, arginine, nucleotides, and/or omega-3 fatty acids	Indications not clearly established. Select nutrients may be beneficial or harmful in subgroups of critically ill patients.
Oral supplement	Sweetened for taste Hypertonic	Patients who require supplementation to an oral diet.

MCT, medium-chain triglyceride; NPC:N, nonprotein calorie-to-nitrogen ratio.

- Disease state-specific formulations are designed to meet specific nutrient requirements and to manage metabolic abnormalities. Unfortunately, scientific and clinical research supporting their efficacy is minimal, except for low carbohydrate formulations supplemented with specific fatty acids and antioxidants for patients with acute respiratory distress syndrome.
- Oral supplements are not intended for tube feeding. They are sweetened to improve taste and are therefore hypertonic.
- A *module* is a powder or liquid that can be added to a commercially available product. Alternatively, a modular product can be mixed to concentrate nutrients in less volume.
- Hydration formulations are used to maintain hydration or treat dehydration. They can be administered by mouth or feeding tube. The glucose content of these formulations can decrease fecal water loss and generate a positive electrolyte balance.

## INITIATION AND ADVANCEMENT OF ENTERAL NUTRITION REGIMENS

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- Schedules for progression from initial to target rates should be individualized. The need to reach nutrient goal should be balanced with the need for tolerance.
- In adults, continuous EN feedings are typically started at 20 to 50 mL/hour and advanced by 10 to 25 mL/hour every 4 to 8 hours until the goal is achieved. Intermittent EN feedings are started at 120 mL every 4 hours and advanced by 30 to 60 mL every 8 to 12 hours.
- In children, EN feedings are typically started at 1 to 2 mL/kg/hour for continuous feeding or 20 to 25 mL/kg per bolus and advanced by 2 mL/kg/hour every 4 to 12 hours.
- In premature infants, feedings are started at lower rates or volumes, usually 10 to 20 mL/kg/day.
- The practice of diluting hyperosmolar EN formulations should be avoided unless necessary to increase fluid intake.

## COMPLICATIONS

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- Patients should be monitored for metabolic, GI, and mechanical complications (Table 58-3).
- Metabolic complications associated with EN are analogous to those of PN (see Chap. 60), but the occurrence is lower.
- GI complications include nausea, vomiting, abdominal distension, cramping, aspiration, diarrhea, and constipation. Gastric residual volume is thought to increase the risk of vomiting and aspiration. Residual volume is measured by aspirating the stomach contents into a syringe attached to the open end of the feeding tube. Although the definition is controversial, residual is probably excessive if it is greater than 200 to 500 mL in adults, or if it is twice the bolus volume or hourly infusion rate in children. The determination should be based on a trend rather than an isolated finding and should be made in conjunction with the presence of symptoms.
- The stepwise approach for managing excessive gastric residual volume with GI symptoms is slowing, not stopping, the tube feeding; initiating metoclopramide; considering a transpyloric feeding tube; trying a proton pump inhibitor or histamine<sub>2</sub>-receptor antagonist; and minimizing use of narcotics, sedatives, and other agents that delay gastric emptying.
- In addition to avoiding excessive gastric residuals, methods for preventing aspiration pneumonia include keeping the head of the bed at 30° to 45° during feeding and for 30 to 60 minutes after intermittent infusions and changing from bolus to intermittent or continuous administration.
- Management of diarrhea should be directed at identifying and correcting the cause. The most common causes are sorbitol contained in many liquid medications, drug therapy, infection, malabsorption, and factors related to tube feeding (e.g., rapid delivery or advancement, intolerance to composition, large volume administered into small bowel, and formula contamination). Switching to a fiber-containing, lower fat, peptide-based, or lactose-free formulation can be beneficial. After excluding infectious etiologies,

**TABLE 58-3** Suggested Monitoring for Patients on Enteral Nutrition

Parameter	During Initiation of EN Therapy	During Stable EN Therapy
Vital signs	Every 4–6 hours	As needed with suspected change (i.e., fever)
Clinical assessment		
Weight	Daily	Weekly
Length/height (children)	Weekly–monthly	Monthly
Head circumference (<3 years of age)	Weekly–monthly	Monthly
Total intake/output	Daily	As needed with suspected change in intake/output
Tube feeding intake	Daily	Daily
Enterostomy tube site assessment	Daily	Daily
GI tolerance		
Stool frequency/volume	Daily	Daily
Abdomen assessment	Daily	Daily
Nausea or vomiting	Daily	Daily
Gastric residual volumes	Every 4–8 hours (varies)	As needed when delayed gastric emptying suspected
Tube placement	Prior to starting, then ongoing	Ongoing
Laboratory		
Electrolytes, blood urea nitrogen/serum creatinine, glucose	Daily	Every 1–3 months
Calcium, magnesium, phosphorus	Three to seven times/week	Every 1–3 months
Liver function tests	Weekly	Every 1–3 months
Trace elements, vitamins	If deficiency/toxicity suspected	If deficiency/toxicity suspected

EN, enteral nutrition.

pharmacologic intervention (e.g., opiates, **diphenoxylate**, or **loperamide**) can be used to control severe diarrhea.

- Mechanical complications include tube occlusion or malposition and nasopulmonary intubation. Techniques for clearing occluded tubes include pancreatic enzymes in sodium bicarbonate and using a declogging device. Techniques for maintaining patency include flushing with at least 30 mL of water before and after medication administration and intermittent feedings and at least every 8 hours during continuous feeding.

## DRUG DELIVERY VIA FEEDING TUBE

- Administering drugs via tube feeding is a common practice, but drug dissolution or therapeutic effect can be altered if the tube tip is placed in the small bowel. If the drug is a solid that can be crushed (e.g., *not* a sublingual, sustained-release, or enteric-coated formulation) or is a capsule, the powder can be mixed with 15 to 30 mL of solvent and administered. Otherwise, a liquid dosage preparation should be used. Multiple medications should be administered separately, each followed by flushing the tube with 5 mL or more of water.
- Mixing of liquid medications with EN formulations can cause physical incompatibilities that inhibit drug absorption and clog small-bore feeding tubes. Incompatibility is more common with formulations containing intact (vs. hydrolyzed) protein and medications formulated as acidic

**TABLE 58-4** Medications with Special Considerations for Enteral Feeding Tube Administration

Drug	Interaction	Comments
Phenytoin	Reduced bioavailability in the presence of enteral nutrition Possible binding of phenytoin to calcium caseinates or protein hydrolysates in enteral feeding	A suggestion to minimize interaction is to hold tube feeding 1–2 hours before and after phenytoin, but this has no proven benefit Adjust tube feeding rate to account for time held for phenytoin administration Monitor phenytoin serum concentrations and clinical response closely Consider switching to IV phenytoin route if unable to reach therapeutic serum concentration
Fluoroquinolones Tetracycline	Potential for reduced bioavailability because of complexation of drug with divalent and trivalent cations found in enteral feeding	Consider holding tube feeding before and after administration Avoid jejunal administration of ciprofloxacin Monitor clinical response
Warfarin	Decreased absorption of warfarin because of enteral feeding; therapeutic effect antagonized by vitamin K in enteral formulations	Adjust warfarin dose based on international normalized ratio Anticipate need to increase warfarin dose when enteral feedings are started and decrease dose when enteral feedings are stopped
Omeprazole Lansoprazole	Administration via feeding tube complicated by acid-labile medication within delayed-release, base-labile granules	Granules become sticky when moistened with water and may occlude small-bore tubes Suggested that granules be mixed with acidic liquid when given via a gastric feeding tube An oral liquid suspension can be extemporaneously prepared for administration via a feeding tube <sup>a</sup>

<sup>a</sup>Quercia RA, Fan C, Liu X, et al. Stability of omeprazole in an extemporaneously prepared oral liquid. *Am J Health Syst Pharm* 1997;54:1833–1836; and Dunn A, White M, Reddy P, et al. Delivery of omeprazole and lansoprazole granules through a nasogastric tube in vitro. *Am J Health Syst Pharm* 1999;56:2327–2330.

syrops. Mixing of liquid medications and EN formulations should be avoided whenever possible.

- The most significant drug–nutrient interactions result in reduced bioavailability and suboptimal pharmacologic effect (Table 58-4). Continuous feeding requires interruption for drug administration and medications should be spaced between bolus feedings.

## EVALUATION OF THERAPEUTIC OUTCOMES

- Assessing the outcome of EN includes monitoring objective measures of body composition, protein and energy balance, and subjective outcome for physiologic muscle function and wound healing.
- Measures of disease-related morbidity include length of hospital stay, infectious complications, and patient’s sense of well-being. Ultimately, the successful use of EN avoids the need for PN.

See Chap. 146, *Enteral Nutrition*, authored by Vanessa J. Kumpf and Katherine Hammond Chessman, for a more detailed discussion of this topic.

## DEFINITION

- Obesity is the state of excess body fat stores, which should be distinguished from overweight (i.e., excess body weight relative to a person's height).

## PATHOPHYSIOLOGY

### ETIOLOGY

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- The etiology of obesity is usually unknown, but it is likely multifactorial and related to varying contributions from genetic, environmental, and physiologic factors.
- Genetic factors appear to be the primary determinants of obesity in some individuals, whereas environmental factors are more important in others. The specific gene that codes for obesity is unknown; there is probably more than one gene.
- Environmental factors include reduced physical activity or work; abundant and readily available food supply; increased fat intake; increased consumption of refined simple sugars; and decreased ingestion of vegetables and fruits.
- Excess caloric intake is a prerequisite to weight gain and obesity, but whether the primary consideration is total calorie intake or macronutrient composition is debatable.
- Many neurotransmitters and neuropeptides stimulate or depress the brain's appetite network, impacting total caloric intake.
- Activity is thought to play a role in obesity, but studies designed to test the benefit of increased physical activity yield inconsistent results.
- Weight gain can be caused by medical conditions (e.g., hypothyroidism, Cushing's syndrome, hypothalamic lesion) or genetic syndromes (e.g., Prader-Willi's syndrome), but these are unusual to rare causes of obesity.
- Medications associated with weight gain include insulin, sulfonylureas, and thiazolidinediones for diabetes, some antidepressants, antipsychotics, and several anticonvulsants.

### PHYSIOLOGY AND COMORBIDITIES

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- The degree of obesity is determined by the net balance of energy ingested relative to energy expended over time. The single largest determinant of energy expenditure is metabolic rate, which is expressed as *resting energy expenditure* or *basal metabolic rate*. The two terms are frequently used interchangeably because they differ by less than 10%.
- The major types of adipose tissue are (1) white adipose tissue, which manufactures, stores, and releases lipid; and (2) brown adipose tissue, which dissipates energy via uncoupled mitochondrial respiration. Obesity research includes evaluation of the activity of adrenergic receptors and their effect on adipose tissue with respect to energy storage and expenditure or thermogenesis.

- Obesity is associated with serious health risks and increased mortality. Central obesity reflects high levels of intraabdominal or visceral fat that is associated with the development of hypertension, dyslipidemia, type 2 diabetes, and cardiovascular disease.
- Obesity is associated with alterations in pulmonary function, osteoarthritis, and changes in the female reproductive system.

## CLINICAL PRESENTATION AND DIAGNOSIS

- Excess body fat can be determined by skinfold thickness, body density using underwater body weight, bioelectrical impedance and conductivity, dual-energy x-ray absorptiometry, computed axial tomography scan, and magnetic resonance imaging. Unfortunately, many of these methods are too expensive and time consuming for routine use.
- Body mass index (BMI) and waist circumference (WC) are recognized, acceptable markers of excess body fat, which independently predict disease risk (Table 59-1).
- BMI is calculated as weight (kg) divided by the square of the height (m<sup>2</sup>).
- WC, the most practical method of characterizing central adiposity, is the narrowest circumference between the last rib and top of the iliac crest.

## DESIRED OUTCOME

- The goal of therapy should be reasonable and should consider initial body weight, patient motivation and desire, comorbidities, and patient age. If, for example, the primary goal is improved blood glucose, blood cholesterol, or hypertension, then the endpoint should be target levels of glycosylated hemoglobin, low-density lipoprotein cholesterol, or blood pressure; weight loss goals may be as little as 5%. If the primary goal is relief of osteoarthritis or sleep apnea, then weight loss of 10% or 20% may be more appropriate.

**TABLE 59-1** Classification of Overweight and Obesity by BMI, Waist Circumference, and Associated Disease Risk

	BMI (kg/m <sup>2</sup> )	Obesity Class	Disease Risk <sup>a</sup> (Relative to Normal Weight and Waist Circumference)	
			Men ≤40 in. (≤102 cm) Women ≤35 in. (≤88 cm)	>40 inches (>102 cm) >35 inches (>88 cm)
Underweight	<18.5		—	—
Normal <sup>b</sup>	18.5–24.9		—	—
Overweight	25.0–29.9		Increased	High
Obesity	30.0–34.9	I	High	Very high
	35.0–39.9	II	Very high	Very high
Extreme obesity	≥40	III	Extremely high	Extremely high

<sup>a</sup>Disease risk for type 2 diabetes, hypertension, and cardiovascular disease.

<sup>b</sup>Increased waist circumference can also be a marker for increased risk even in persons of normal weight.

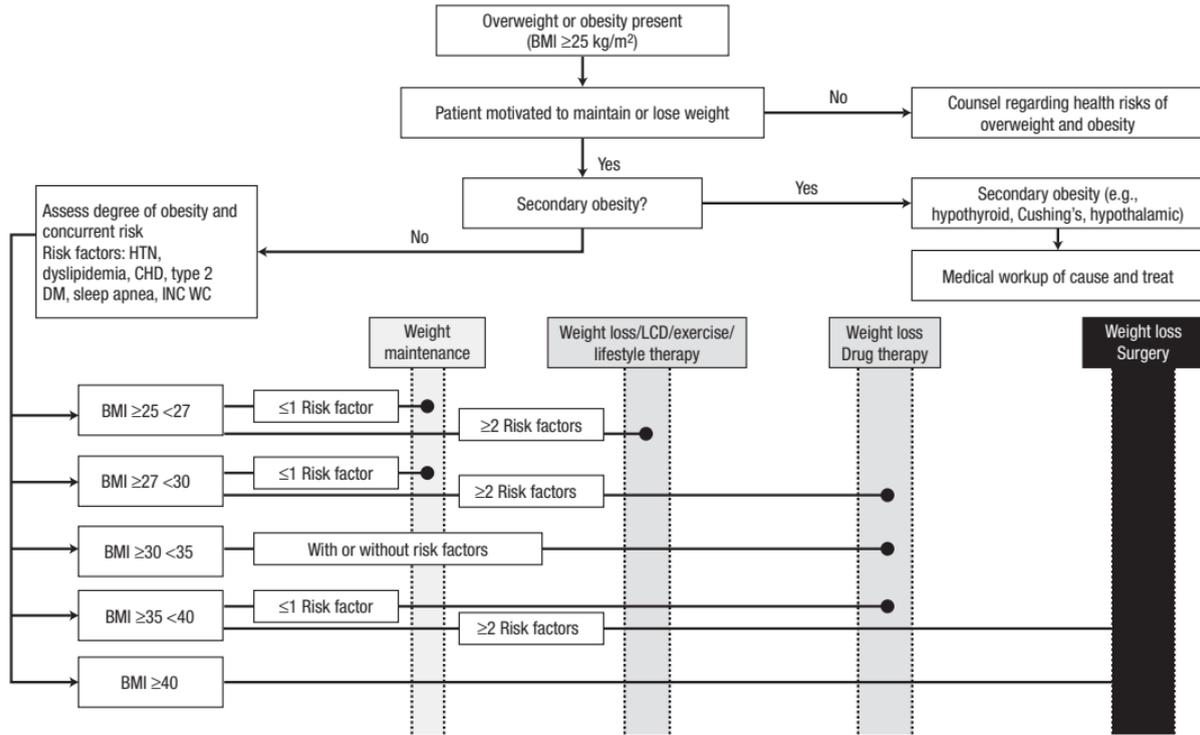
## TREATMENT

- Successful obesity treatment plans incorporate diet, exercise, behavior modification with or without pharmacologic therapy, and/or surgery (Fig. 59-1).
- The primary aim of behavior modification is to help patients choose lifestyles conducive to safe and sustained weight loss. Behavioral therapy is based on principles of human learning, which use stimulus control and reinforcement to substitute desirable for learned, undesirable behavior.
- Many diets exist to aid weight loss. Regardless of the program, energy consumption must be less than energy expenditure. A reasonable goal is loss of 0.5 to 1 kg per week with a diet balanced in fat, carbohydrate, and protein intake.
- Surgery, which reduces the stomach volume or absorptive surface of the alimentary tract, remains the most effective intervention for obesity. Although modern techniques are safer than older procedures and have an operative mortality of 1%, there are still many potential complications. Therefore, surgery should be reserved for those with BMI greater than 35 or 40 kg/m<sup>2</sup> and significant comorbidity.

## PHARMACOLOGIC THERAPY

(Table 59-2)

- The debate regarding the role of pharmacotherapy remains heated, fueled by the need to treat a growing epidemic and by the fallout from the removal of several agents from the market because of adverse reactions.
- The National Task Force on the Prevention and Treatment of Obesity concluded that short-term use of anorectic agents is difficult to justify because of the predictable weight regain that occurs upon discontinuation. Long-term use may have a role for patients who have no contraindications, but further study is needed before widespread, routine use is implemented.
- **Orlistat** induces weight loss by lowering dietary fat absorption, and it also improves lipid profiles, glucose control, and other metabolic markers. Soft stools, abdominal pain or colic, flatulence, fecal urgency, and/or incontinence occur in 80% of individuals, are mild to moderate in severity, and improve after 1 to 2 months of therapy. Orlistat interferes with the absorption of fat-soluble vitamins and **cyclosporine**.
- **Sibutramine** is more effective than placebo with the most significant weight loss during the first 6 months of use. Dry mouth, anorexia, insomnia, constipation, increased appetite, dizziness, and nausea occur two to three times more often than with placebo. Sibutramine should not be used in patients with coronary artery disease, stroke, congestive heart failure, arrhythmias, or monoamine oxidase inhibitor use.
- **Phentermine** (30 mg in the morning or 8 mg before meals) has less powerful stimulant activity and lower abuse potential than amphetamines and was an effective adjunct in placebo-controlled studies. Adverse effects (e.g., increased blood pressure, palpitations, arrhythmias, mydriasis, altered insulin or oral hypoglycemic requirements) and interactions with monoamine oxidase inhibitors have implications for patient selection.



**FIGURE 59-1.** Pharmacotherapy treatment algorithm. A select population of individuals, based on body mass index (BMI) and waist circumference (WC) together with concurrent risk factors, may benefit from medication therapy as an adjunct to a program of weight loss that includes diet, exercise, and behavioral modification. (CHD, coronary heart disease; DM, diabetes mellitus, HTN, hypertension; INC WC, >40 inches for males and >35 inches for females; LCD, low-calorie diet.)

**TABLE 59-2** Pharmacotherapeutic Agents for Weight Loss

Class	Status	Daily Dosage (mg)
<b>GI lipase inhibitor</b>		
Orlistat (Xenical)	Long-term use	360
<b>Noradrenergic/serotonergic agent</b>		
Sibutramine (Meridia)	Long-term use	5–15
<b>Noradrenergic agents</b>		
Phendimetrazine (Prelu-2, Bontril, Plegine)	Short-term use	70–105
Phentermine (Fastin, Oby-trim, Adipex-P, Ionamin)	Short-term use	15–37.5
Diethylpropion (Tenuate, Tenuate Dospan)	Short-term use	75

- **Diethylpropion** (25 mg before meals or 75 mg of extended-release formulation every morning) is more effective than placebo in achieving short-term weight loss. Diethylpropion is one of the safest noradrenergic appetite suppressants and can be used in patients with mild to moderate hypertension or angina, but it should not be used in patients with severe hypertension or significant cardiovascular disease.
- **Amphetamines** should generally be avoided because of their powerful stimulant and addictive potential.
- Herbal, natural, and food-supplement products are often used to promote weight loss (Table 59-3). The FDA does not strictly regulate these products, so the ingredients may be inactive and present in variable concentrations. After more than 800 reports of serious adverse events (e.g., seizures, stroke, and death) were attributed to ephedrine alkaloids, the FDA decided to exclude them from dietary supplements.

## EVALUATION OF THERAPEUTIC OUTCOMES

- Evaluation requires careful clinical, biochemical, and, if necessary, psychological evaluation. Progress should be assessed in a healthcare setting once or twice monthly for the first 1 to 2 months, then monthly. Each encounter

**TABLE 59-3** Herbal/Natural Products and Food Supplements Used for Weight Loss<sup>a</sup>

Herbal/Natural/Food, Supplements	Active Moiety	Proposed Mechanism
Chromium picolinate	Chromium	Unclear
St. John's wort	Hypericin	Serotonergic/monoamine oxidase inhibition
Hoodia	P57	Unclear
White willow bark	Salicylate	Inhibit norepinephrine breakdown
Calcium pyruvate	Pyruvate	Unclear
Guarana extract	Caffeine	Noradrenergic
Various tea extracts	Caffeine	Noradrenergic
Garcinia cambogia extract (citrin)	Hydroxycitric acid	Unclear
Chitosan	Cationic polysaccharide	Block fat absorption

<sup>a</sup>Safety and efficacy not documented.

should document weight, WC, BMI, blood pressure, medical history, and tolerability of drug therapy.

- Medication therapy should be discontinued after 3 to 4 months if the patient has failed to demonstrate weight loss or maintenance of prior weight.
- Diabetic patients require more intense medical monitoring and self-monitoring of blood glucose. Some anorectic agents have direct effects that improve glucose tolerance.
- Patients with hyperlipidemia or hypertension should be monitored to assess the effects of weight loss on appropriate end points.

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*See Chap. 148, Obesity, authored by John V. St. Peter and Charles J. Billington, for a more detailed discussion of this topic.*

**DEFINITION**

- Parenteral nutrition (PN) provides macro- and micronutrients by central or peripheral venous access to meet specific nutritional requirements of the patient, promote positive clinical outcomes, and improve quality of life. PN is also referred to as *total parenteral nutrition* or *hyperalimentation*.

**INDICATIONS**

- Identifying candidates and deciding when to initiate PN are difficult decisions because data are conflicting, and published guidelines are not consistent.
- In general, PN should be considered when a patient cannot meet nutritional requirements through use of the GI tract. Consensus guidelines are based on clinical experience and investigations in specific populations (Table 60-1).
- PN should be considered after suboptimal nutritional intake for 1 day in preterm infants, 2 to 3 days in term infants, 5 to 7 days in well-nourished children, and 7 to 14 days in older children and adults. The route and type of PN depend on the patient's clinical state and expected length of PN therapy (Fig. 60-1).

**DESIRED OUTCOME**

- Optimal nutrition therapy requires defining the patient's nutrition goals, determining the nutrient requirements to achieve those goals, delivering the required nutrients, and assessing the nutrition regimen.
- Goals of nutrition support include correcting caloric and nitrogen imbalances, fluid or electrolyte abnormalities, and vitamin or trace element abnormalities, without causing or worsening other metabolic complications.
- Specific caloric goals include adequate energy intake to promote growth and development in children, energy equilibrium and preservation of fat stores in well-nourished adults, and positive energy balance in malnourished patients with depleted fat stores.
- Specific nitrogen goals are positive nitrogen balance or nitrogen equilibrium and improvement in serum concentration of protein markers (e.g., transferrin or prealbumin).

**TREATMENT****PARENTERAL NUTRITION COMPONENTS**

- Both macronutrients (i.e., water, protein, dextrose, and IV fat emulsion [IVFE]) and micronutrients (i.e., vitamins, trace elements, and electrolytes) are necessary to maintain normal metabolism.

**TABLE 60-1** Indications for Adult Parenteral Nutrition

1. Inability to absorb nutrients via the GI tract because of one or more of the following:
  - a. Massive small bowel resection: usually patients with less than 100 cm of small bowel distal to the ligament of Treitz without a colon, or less than 50 cm of small bowel with an intact colon.
  - b. Intractable vomiting when adequate EN is not expected for 7–14 days.
  - c. Severe diarrhea.
  - d. Bowel obstruction.
  - e. GI fistulae: PN is indicated in patients with prolonged inadequate nutritional intake longer than 5–7 days who are not candidates for EN.
2. Cancer: antineoplastic therapy, radiation therapy, or HSCT
  - a. PN may be used in moderately to severely malnourished patients receiving active anticancer treatment who are not candidates for EN.
  - b. PN is not routinely indicated for well-nourished or mildly malnourished patients undergoing surgery, chemotherapy, or radiation therapy.
  - c. PN is unlikely to benefit patients with advanced cancer whose malignancy is unresponsive to treatment. However, use may be appropriate for carefully selected patients who have failed trials of less-invasive medical therapies and have good performance status, an estimated life expectancy of longer than 40–60 days, and strong social and financial support.
3. Pancreatitis: PN may be used in patients with severe pancreatitis with prolonged inadequate nutritional intake longer than 5–7 days who are not candidates for EN. PN should be used when EN exacerbates abdominal pain, ascites, or fistula output.
4. Critical care
  - a. PN should be used in those patients in whom EN is contraindicated or is unlikely to provide adequate nutritional requirements within 5–10 days.
  - b. Organ failure (liver, renal, or respiratory): PN should be used in patients with moderate to severe catabolism when EN is contraindicated.
  - c. Burns: PN should be used in those patients in whom EN is contraindicated or is unlikely to provide adequate nutritional requirements within 4–5 days.
5. Perioperative PN
  - a. Preoperative: for 7–14 days for patients with moderate to severe malnutrition who are undergoing major GI surgery, if the operation can be safely postponed.
  - b. Postoperative: PN should be used in patients in whom EN is contraindicated or is unlikely to provide adequate nutritional requirements within 7–10 days.
6. Hyperemesis gravidarum: when EN is not tolerated.
7. Eating disorders: PN should be considered for patients with anorexia nervosa and severe malnutrition who are unable or unwilling to ingest adequate nutrition.

EN, enteral nutrition; HSCT, hematopoietic stem cell transplantation; PN, parenteral nutrition.

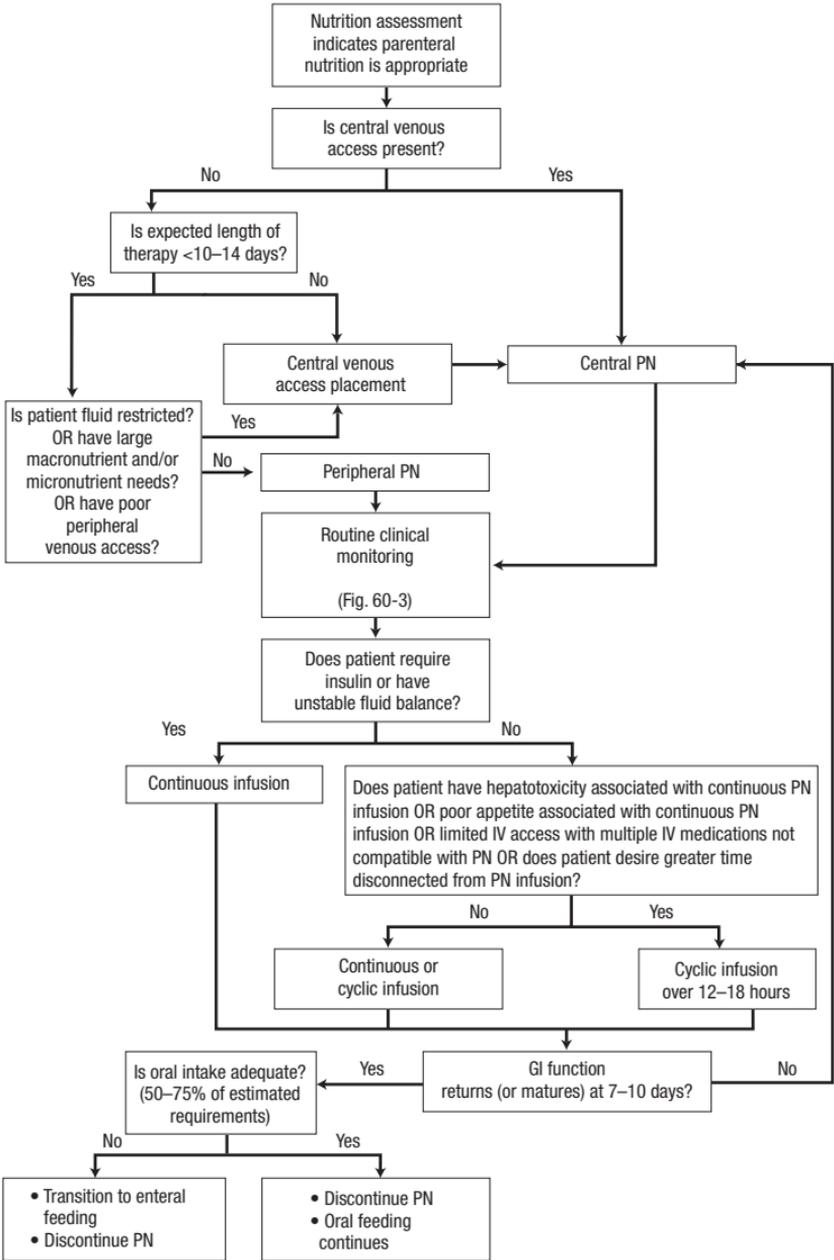
From ASPEN Board of Directors and the Clinical Guidelines Taskforce. Administration of specialized nutrition support. *JPEN J Parenter Enteral Nutr* 2002;26:185A–215A; and ASPEN Board of Directors and the Clinical Guidelines Taskforce. Specific guidelines for disease—Adults. *JPEN J Parenter Enteral Nutr* 2002;26:615A–965A.

## MACRONUTRIENTS

- Macronutrients are used for energy (dextrose, fat) and as structural substrates (protein, fats).

### Amino Acids

- Protein is provided as crystalline amino acids (CAAs).
- When oxidized, 1 g of protein yields four calories. Including the caloric contribution from protein in calorie calculations is controversial; therefore, PN calories can be calculated as either total or nonprotein calories.
- Standard CAA products contain a balanced profile of essential, semiessential, and nonessential L-amino acids and are designed for patients with “normal” organ function and nutritional requirements. Standard CAA



**FIGURE 60-1.** The route of parenteral nutrition (PN) and the infusion type depend on the patient’s clinical status and the expected length of therapy.

products differ in amino acid, total nitrogen, and electrolyte content but have similar effects on protein markers.

- Conditionally essential amino acids such as taurine, aspartic acid, and glutamic acid are available in some commercially available CAA solutions.

Other conditionally essential amino acids, such as cysteine, carnitine, and glutamine, are not included because they are unstable or insoluble. Cysteine and carnitine are commonly added to PN solutions compounded for newborns.

- More concentrated CAA solutions (i.e., 15% to 20%) are attractive for patients who have large protein needs, such as the critically ill, but are fluid restricted.
- Modified amino acid solutions are designed for patients with altered protein requirements associated with hepatic encephalopathy, renal failure, and metabolic stress or trauma. However, these solutions are expensive and their role in disease-specific PN regimens is controversial.

### Dextrose

- The primary energy source in PN solutions is carbohydrate, usually as dextrose monohydrate. Available concentrations range from 5% to 70%. When oxidized, 1 g of hydrated dextrose provides 3.4 kcal.
- Recommended doses for routine clinical care rarely exceed 5 mg/kg/min in older children and adults. Higher infusion rates contribute to the development of hyperglycemia, excess carbon dioxide production, and increased biochemical markers for liver function. Doses in infants and young children can exceed 5 mg/kg/min.
- Glycerol is a non-insulin-dependent source of carbohydrate that can be used to avoid stress-related hyperglycemia in critically ill patients. A major disadvantage of the available glycerol solution is the dilute concentration of carbohydrate and amino acids (3% of each). Most patients require 3 to 4 L/day of glycerol solution and supplemental IVFE to meet minimal energy requirements.

### Fat Emulsion

- Commercially available IVFEs provide calories and essential fatty acids. These products differ in triglyceride source, fatty acid content, and essential fatty acid concentration.
- When oxidized, 1 g of fat yields 9 kcal. Because of the caloric contribution from egg phospholipid and glycerol, caloric content of IVFE is 1.1 kcal/mL for the 10%, 2 kcal/mL for the 20%, and 3 kcal/mL for the 30% emulsions.
- Essential fatty acid deficiency can be prevented by giving IVFE, 0.5 to 1 g/kg/day for neonates and infants and 100 g/wk for adults.
- IVFE 10% and 20% products can be administered by a central or peripheral vein, added directly to PN solution as a total nutrient admixture (TNA) or three-in-one system (lipids, protein, glucose, and additives), or piggybacked with a CAA and dextrose solution. IVFE 30% is approved only for TNA preparation.
- IVFE is contraindicated in patients with an impaired ability to clear lipid emulsion and should be administered cautiously to patients with egg allergy.
- The caloric contribution from **propofol** infusions can require adjustment of a patient's nutrition regimen. The caloric contribution from **amphotericin** liposomal and lipid complex formulations is not clinically relevant.

## MICRONUTRIENTS: VITAMINS, TRACE ELEMENTS, AND ELECTROLYTES

- Micronutrients are required to support metabolic activities for cellular homeostasis such as enzyme reactions, fluid balance, and regulation of electrophysiologic processes.
- Multivitamin products have been formulated to comply with guidelines for adults, children, and infants. These products contain 13 essential vitamins including vitamin K.
- Requirements for trace elements depend on the patient's age and clinical condition (e.g., higher doses of zinc in patients with high-output ostomies or diarrhea).
- Zinc, copper, chromium, manganese, and possibly selenium and molybdenum are the only trace elements that require supplementation during PN.
- Requirements for trace elements during organ failure are not clearly defined. Manganese and copper should be restricted or withheld in patients with cholestatic liver disease. Chromium, molybdenum, and selenium should be restricted or withheld in patients with renal failure.
- Sodium, potassium, calcium, magnesium, phosphorus, chloride, and acetate are necessary components of PN for maintenance of numerous cellular functions.
- Patients with normal organ function and serum electrolyte concentrations should receive daily maintenance doses of electrolytes during PN.
- Electrolyte requirements depend on the patient's age, disease state, organ function, drug therapy, nutrition status, and extrarenal losses.

## ORDERING, COMPOUNDING, AND STORING SOLUTIONS

- The patient's clinical condition determines the appropriate route of administration (see Fig. 60-1).
- Peripheral PN (PPN) is a relatively safe and simple method of nutritional support. PPN candidates do not have large nutritional requirements, are not fluid restricted, and are expected to begin enteral intake within 10 to 14 days.
- Thrombophlebitis is a common complication; this risk is greater with solution osmolarities greater than 600 to 900 mOsm/L (Table 60-2).
- Solutions for PPN have lower final concentrations of amino acid (3% to 5%), dextrose (5% to 10%) and micronutrients as compared to central parenteral nutrition (CPN).

**TABLE 60-2** Osmolarities of Selected Parenteral Nutrients

Nutrient	Osmolarity
Amino acid	100 mOsm/%
Dextrose	50 mOsm/%
Lipid emulsion	1.7 mOsm/%
Sodium (acetate, chloride, phosphate)	2 mOsm/mEq
Potassium (acetate, chloride, phosphate)	2 mOsm/mEq
Magnesium sulfate	1 mOsm/mEq
Calcium gluconate	1.4 mOsm/mEq

- Primary advantages of PPN include lower risks of infectious, metabolic, and technical complications.
- CPN is useful in patients who require PN for more than 7 to 14 days and who have large nutrient requirements, poor peripheral venous access, or fluctuating fluid requirements.
- CPN solutions are highly concentrated hypertonic solutions that must be administered through a large central vein.
- Disadvantages include risks associated with catheter insertion, use, and care. Central venous access has a greater potential for infection.
- PN regimens for adults can be based on formulas (Fig. 60-2), computer programs, or standardized order forms. Order forms are popular because they help educate practitioners and foster cost-efficient nutrition support by minimizing errors in ordering, compounding, and administering.
- PN regimens for infants and children typically require an individualized approach, which is highly variable among institutions.
- The type of solution being prepared dictates the methods of compounding, storage, and infusion. The two most common types of PN solutions are 2-in-1 solutions with or without IVFE piggybacked into the PN line, and TNAs.
- Methods for compounding PN solutions vary among institutions and often involve automated compounders. Sterility should be assured during compounding, storage, and administration.
- CAA and dextrose solutions are generally stable for 1 to 2 months if refrigerated at 4°C and protected from light, but TNA formulations are inherently unstable.
- Appropriate resources should be consulted for compatibility and stability information before mixing components (e.g., manufacturer's information, *Trissel's Handbook on Injectable Drugs*, and *King Guide to Parenteral Admixtures*).
- Precipitation of calcium and phosphorus is a common interaction that is potentially life-threatening.
- Bicarbonate should not be added to acidic PN solutions; a bicarbonate precursor salt (e.g., acetate) is preferred.
- Vitamins can be adversely affected by changes in solution pH, other additives, storage time, solution temperature, and exposure to light. Vitamins should be added to the PN solution near the time of administration and should not be in the PN solution for more than 24 hours.
- Using the PN admixture as a drug vehicle consolidates dosage units and has other advantages; however, compatibility and stability data are not available for many PN solutions. Medications frequently added to PN solutions include regular insulin and histamine<sub>2</sub> antagonists.

## **ADMINISTERING PARENTERAL NUTRITION SOLUTIONS**

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- PN solutions should be administered with an infusion pump.
- A 0.22-micrometer filter is recommended for CAA and dextrose solutions to remove particulate matter, air, and microorganisms. Because IVFE particles measure approximately 0.5 micrometers, IVFE should be administered separately and piggybacked into the PN line beyond the in-line filter.

Calculation of an Adult Parenteral Nutrition Regimen

Patient case: A patient's daily nutritional requirements have been estimated to be 100 g protein and 2,000 total kcal. The patient has a central venous access and reports no history of hyperlipidemia or egg allergy. The patient is not fluid restricted. The PN solution will be compounded as an individualized regimen using a single-bag, 24-hour infusion of a 2-in-1 solution with intravenous fat emulsion (IVFE) piggybacked into the PN infusion line. Determine the total PN volume and administration rate by calculating the macronutrient stock solution volumes required to provide the desired daily nutrients. The stock solutions used to compound this regimen are 10% crystalline amino acids (CAA), 70% dextrose, and 20% IVFE.

- Determine the daily IVFE calories and volume
  - 2,000 kcal/day  $\times$  30–40% of total calories as fat = 600–800 kcal/day  
Choose IVFE 20% 250 mL/day  $\times$  2 kcal/mL = 500 kcal/day
- Determine the 70% dextrose stock solution volume
  - Determine dextrose calories  
Dextrose calories = TOTAL – IVFE – Protein  
2,000 kcal – 500 kcal IVFE – (4 kcal/g  $\times$  100 g CAA) = 1,100 kcal
  - Calculate required dextrose (grams)  
1,100 kcal  $\div$  3.4 kcal/g dextrose = 324 g dextrose
  - Determine 70% dextrose volume  
70 g/100 mL = 324 g/X mL 70% dextrose;      X = 463 mL 70% dextrose
- Calculate the 10% CAA stock solution volume
  - 10 g/100 mL = 100 g/X mL 10% CAA;      X = 1,000 mL 10% CAA
- Determine the 2-in-1 PN volume and administration rate
  - Calculate CAA/dextrose volume  
463 mL 70% dextrose + 1,000 mL 10% CAA = 1,463 mL CAA–dextrose
  - Add 100–200 mL for additives  
Total 2-in-1 volume = approximately 1,600–1,700 mL/day
  - Calculate the administration rate  
1,600–1,700 mL/day  $\div$  24 hours = 67–71 mL/hour; round to 65–70 mL/hour
- Choose final 2-in-1 PN regimen and determine provided nutrient amounts:
  - Final 2-in-1 regimen  
100 g CAA/324 gm dextrose in 1,680 mL/day to infuse at 70 mL/hour  
+ 20% IVFE 250 mL to infuse at 2 mL/hour
  - Calculate macronutrient calories

20% IVFE calories:	250 mL $\times$ 2 kcal/mL =	500 kcal
Dextrose calories:	324 g $\times$ 3.4 kcal/g =	1,102 kcal
Protein calories:	100 g $\times$ 4 kcal/g =	400 kcal
Total kcal:		<u>2,002 kcal</u>
Nonprotein kcal:		1,602 kcal

**FIGURE 60-2.** Calculation of an adult parenteral nutrition (PN) regimen. (CAA, crystalline amino acid.)

**TABLE 60-3** Metabolic Abnormalities Associated with Parenteral Nutrition Macronutrients

Abnormality	Possible Etiologies
Hyperglycemia	Metabolic stress, infection, corticosteroids, pancreatitis, diabetes mellitus, peritoneal dialysis, excessive dextrose administration
Hypoglycemia	Abrupt dextrose withdrawal, excessive insulin
Excess carbon dioxide production	Excess dextrose administration
Hypertriglyceridemia	Metabolic stress, familial hyperlipidemia, pancreatitis, excess IVFE dose; rapid IVFE infusion rate
Abnormal liver function tests (elevated ALT, AST, Alk Phos, Bili)	Metabolic stress, infection, excess carbohydrate intake, excess caloric intake, EFAD; long-term PN therapy

Alk Phos, alkaline phosphatase; ALT, alanine aminotransferase (SGPT); AST, aspartate aminotransferase (SGOT); Bili, bilirubin; EFAD, essential fatty acid deficiency; IVFE, intravenous fat emulsion; PN, parenteral nutrition.

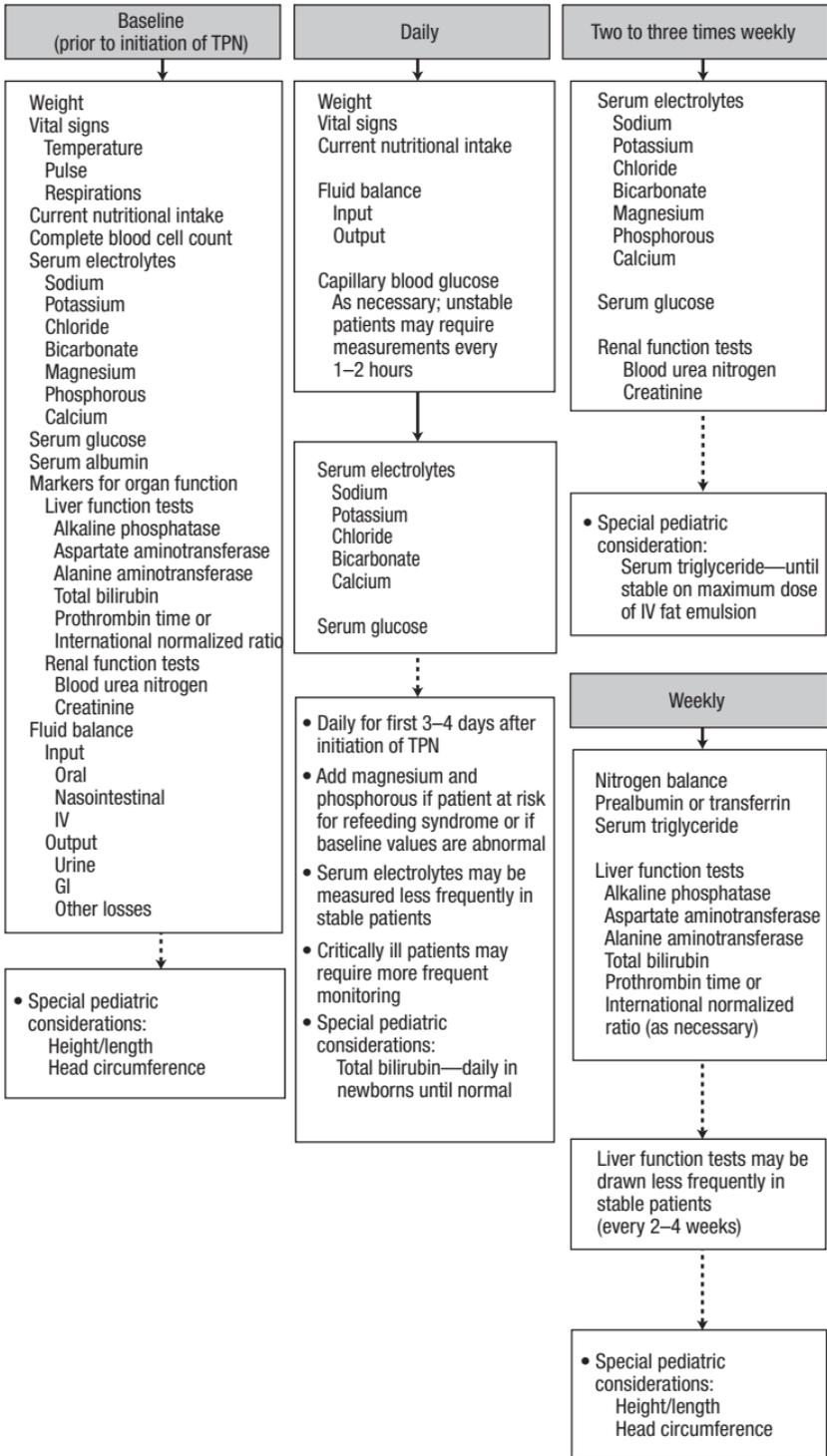
- Routine use of in-line filters with TNA solutions is controversial. A 1.2-micrometer filter can be used to prevent catheter occlusion caused by precipitates or lipid aggregates, and to remove *Candida albicans*.
- Although protocols for initiating PN differ, the rate is typically increased gradually over 12 to 24 hours to prevent hyperglycemia. When discontinuing PN, the infusion rate is gradually decreased to prevent hypoglycemia.
- The starting dose of IVFE is 0.5 g/kg/day in neonates and 0.5 to 1 g/kg/day in older children. This dose is increased by 0.5 to 1 g/kg/day to a maximum of 3 to 4 g/kg/day. The dose of IVFE in adults ranges from 1 to 2.5 g/kg/day, not to exceed 30% to 60% of total calories.
- Administering IVFE over 12 to 24 hours in adults and 20 to 24 hours (0.15 g/kg/hour) in neonates appears to be the best strategy for promoting IVFE clearance and minimizing negative immune function effects.
- Cyclic PN (e.g., 12 to 18 hours/day) is useful in hospitalized patients who have limited venous access and require other medications necessitating interruption of PN infusion, to prevent or treat hepatotoxicities associated with continuous PN therapy, and to allow home patients to resume normal lifestyles. Patients with severe glucose intolerance or unstable fluid balance may not tolerate cyclic PN.

## COMPLICATIONS

- PN can cause mechanical or technical (e.g., malfunctions in delivery system and catheter-related complications), infectious (e.g., colonization of the catheter or direct microbial invasion of the skin), metabolic (Table 60-3), and nutritional complications.

## EVALUATION OF THERAPEUTIC OUTCOMES

- Routine evaluation should include assessment of the clinical condition of the patient, with a focus on nutritional and metabolic effects of the PN regimen.



**FIGURE 60-3.** Monitoring strategy for parenteral nutrition. (TPN, total parenteral nutrition.)

- Biochemical and clinical parameters should be monitored routinely in patients receiving PN (Fig. 60-3).

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*See Chap. 145, Parenteral Nutrition, authored by Todd W. Mattox and Pamela D. Reiter, for a more detailed discussion of this topic.*

## DEFINITION

- Breast cancer is a malignancy originating from breast tissue. This chapter distinguishes between early stages, which are potentially curable, and metastatic breast cancer (MBC), which is usually incurable.

## EPIDEMIOLOGY

- The strongest risk factors for breast cancer are female gender and increasing age. Additional risk factors include endocrine factors (e.g., early menarche, nulliparity, late age at first birth, hormone replacement therapy), genetic factors (e.g., personal and family history, mutations of tumor suppresser genes [*BRCA1* and *BRCA2*]), and environmental and lifestyle factors (e.g., radiation exposure).
- Breast cancer cells often spread undetected by contiguity, lymph channels, and through the blood early in the course of the disease, resulting in metastatic disease after local therapy. The most common metastatic sites are lymph nodes, skin, bone, liver, lungs, and brain.

## CLINICAL PRESENTATION

- The initial sign in more than 90% of women with breast cancer is a painless lump that is typically solitary, unilateral, solid, hard, irregular, and non-mobile. Less common initial signs are pain and nipple changes. More advanced cases present with prominent skin edema, redness, warmth, and induration.
- Symptoms of MBC depend on the site of metastases, but may include bone pain, difficulty breathing, abdominal pain or enlargement, jaundice, and mental status changes.
- Many women first detect some breast abnormalities themselves, but it is increasingly common for breast cancer to be detected during routine screening mammography in asymptomatic women.

## DIAGNOSIS

- Initial workup for a woman presenting with a localized lesion or suggestive symptoms should include a careful history, physical examination of the breast, three-dimensional mammography, and, possibly, other breast imaging techniques such as ultrasound.

- Breast biopsy is indicated for a mammographic abnormality that suggests malignancy or a mass that is palpable on physical examination.

## STAGING

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- Stage is based on the size of the primary tumor ( $T_{1-4}$ ), presence and extent of lymph node involvement ( $N_{1-3}$ ), and presence or absence of distant metastases ( $M_{0-1}$ ). Simplistically stated, these stages may be represented as follows:
  - ✓ *Early Breast Cancer*
    - Stage 0: Carcinoma in situ or disease that has not invaded the basement membrane.
    - Stage I: Small primary tumor without lymph node involvement.
    - Stage II: Involvement of regional lymph nodes.
  - ✓ *Locally Advanced Breast Cancer*
    - Stage III: Usually a large tumor with extensive nodal involvement in which node or tumor is fixed to the chest wall; also includes inflammatory breast cancer, which is rapidly progressive.
  - ✓ *Advanced or Metastatic Breast Cancer*
    - Stage IV: Metastases in organs distant from the primary tumor.

## PATHOLOGIC EVALUATION

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- The development of malignancy is a multistep process with preinvasive (or noninvasive) and invasive phases. The goal of treatment for noninvasive carcinomas is to prevent the development of invasive disease.
- The pathologic evaluation of breast lesions establishes the histologic diagnosis and presence or absence of prognostic factors.
- Most breast carcinomas are adenocarcinomas and are classified as ductal or lobular.

## PROGNOSTIC FACTORS

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- The ability to predict prognosis is used to design treatment recommendations to maximize quantity and quality of life.
- Tumor size and the presence and number of involved axillary lymph nodes are primary factors in assessing the risk for breast cancer recurrence and subsequent metastatic disease. Other disease characteristics that provide prognostic information include histologic subtype, nuclear or histologic grade, lymphatic and vascular invasion, and proliferation indices.
- Hormone receptors are used as indicators of prognosis and to predict response to hormone therapy.
- HER2/*neu* (HER2) overexpression is associated with transmission of growth signals that control aspects of normal cell growth and division. Overexpression of HER2 may be associated with a poor prognosis. HER2 status should be obtained for all invasive breast cancers.
- Genetic profiling tools provide additional prognostic information to aid in treatment decisions for subgroups of patients with otherwise favorable prognostic features.

## DESIRED OUTCOME

- The goal of therapy with early and locally advanced breast cancer is cure. The goals of therapy with MBC are to improve symptoms, improve quality of life, and prolong survival.

## TREATMENT

- The treatment of breast cancer is rapidly evolving. Specific information regarding the most promising interventions can be found only in the primary literature.
- Treatment can cause substantial toxicity, which differs depending on the individual agent, administration method, and combination regimen. Because a comprehensive review of toxicities is beyond the scope of this chapter, appropriate references should be consulted.

## EARLY BREAST CANCER

### Local-Regional Therapy

- Surgery alone can cure most patients with in situ cancers and approximately one-half of those with stage II cancers.
- Breast-conserving therapy (BCT) is appropriate primary therapy for most women with stage I and II disease; it is preferable to modified radical mastectomy because it produces equivalent survival rates with cosmetically superior results. BCT consists of lumpectomy (i.e., excision of the primary tumor and adjacent breast tissue) followed by radiation therapy (RT) to prevent local recurrence.
- RT is administered to the entire breast over 4 to 6 weeks to eradicate residual disease after BCT. Reddening and erythema of the breast tissue with subsequent shrinkage of total breast mass are minor complications associated with RT.
- Simple or total mastectomy involves removal of the entire breast without dissection of underlying muscle or axillary nodes. This procedure is used for carcinoma in situ where the incidence of axillary node involvement is only 1% or with local recurrence following breast conservation therapy.
- Axillary lymph nodes should be sampled for staging and prognostic information. Lymphatic mapping with sentinel lymph node biopsy is a new, less invasive alternative to axillary dissection; however, the procedure is controversial because of the lack of long-term data.

### Systemic Adjuvant Therapy

- Systemic adjuvant therapy is the administration of systemic therapy following definitive local therapy (surgery, radiation, or both) when there is no evidence of metastatic disease but a high likelihood of disease recurrence. The goal of such therapy is cure.
- Chemotherapy, hormonal therapy, or both result in improved disease-free survival and/or overall survival (OS) for all treated patients.
- The National Comprehensive Cancer Network practice guidelines reflect the trend toward the use of chemotherapy in all women regardless of

menopausal status, and the addition of hormonal therapy in all women with receptor-positive disease regardless of age or menopausal status.

- Genetic tests are being prospectively validated as decision-support tools for adjuvant chemotherapy in node-negative patients to identify characteristics of the primary tumor that may predict for the likelihood of metastases and death.

### *Adjuvant Chemotherapy*

- Early administration of effective combination chemotherapy at a time of low tumor burden should increase the likelihood of cure and minimize emergence of drug-resistant tumor cell clones. Combination regimens have historically been more effective than single agent chemotherapy (Table 61-1).
- Anthracycline-containing regimens (e.g., **doxorubicin** and **epirubicin**) significantly reduce the rate of recurrence and improve OS 5 and 10 years after treatment as compared with regimens that contain **cyclophosphamide**, **methotrexate**, and **fluorouracil**. Both node-negative and node-positive patients benefit from anthracycline-containing regimens.
- The addition of taxanes, **docetaxel** and **paclitaxel**, a newer class of agents, to adjuvant regimens comprised of the drugs listed above resulted in consistently and significantly improved disease-free survival and OS in node-positive breast cancer patients.
- Chemotherapy should be initiated within 3 weeks of surgical removal of the primary tumor. The optimal duration of treatment is about 12 to 24 weeks.
- *Dose intensity* refers to the amount of drug administered per unit of time, which can be achieved by increasing dose, decreasing time, or both. *Dose density* is one way of achieving dose intensity by decreasing time between treatment cycles.
- Dose-dense regimens may be considered as options for adjuvant therapy for node-positive breast cancer.
- Increasing doses in standard regimens appears to not be beneficial and may be harmful.
- Decreasing doses in standard regimens should be avoided unless necessitated by severe toxicity.
- Short-term toxicities of adjuvant chemotherapy are generally well tolerated, especially with the availability of serotonin-antagonist and substance P/neurokinin 1-antagonist antiemetics and colony-stimulating factors.
- Survival benefit for adjuvant chemotherapy in stage I and II breast cancer is modest. The absolute reduction in mortality at 10 years is 5% in node-negative and 10% in node-positive disease.

### *Adjuvant Biologic Therapy*

- Trastuzumab in combination with adjuvant chemotherapy is indicated in patients with early stage, HER2-positive breast cancer. The risk of recurrence was reduced up to 50% in clinical trials.
- Unanswered questions with the use of adjuvant trastuzumab include optimal concurrent chemotherapy, optimal dose, schedule and duration of therapy, and use of other concurrent therapeutic modalities.

**TABLE 61-1** Common Chemotherapy Regimens for Breast Cancer

<b>Adjuvant Chemotherapy Regimens</b>	
<p><b>AC<sup>a</sup></b>            Doxorubicin 60 mg/m<sup>2</sup> IV, day 1            Cyclophosphamide 600 mg/m<sup>2</sup> IV, day 1            Repeat cycles every 21 days for four cycles</p> <p><b>FAC<sup>c</sup></b>            Fluorouracil 500 mg/m<sup>2</sup> IV, days 1 and 4            Doxorubicin 50 mg/m<sup>2</sup> IV continuous infusion over 72 hours<sup>v</sup>            Cyclophosphamide 500 mg/m<sup>2</sup> IV, day 1            Repeat cycles every 21–28 days for six cycles</p> <p><b>CAF<sup>e</sup></b>            Cyclophosphamide 600 mg/m<sup>2</sup> IV, day 1            Doxorubicin 60 mg/m<sup>2</sup> IV bolus, day 1            Fluorouracil 600 mg/m<sup>2</sup> IV, day 1            Repeat cycles every 21–28 days for six cycles</p> <p><b>FEC<sup>g</sup></b>            Fluorouracil 500 mg/m<sup>2</sup> IV, day 1            Epirubicin 100 mg/m<sup>2</sup> IV bolus, day 1            Cyclophosphamide 500 mg/m<sup>2</sup> IV, day 1            Repeat cycle every 21 days for six cycles</p> <p><b>CEF<sup>j</sup></b>            Cyclophosphamide 75 mg/m<sup>2</sup> per day orally on days 1–14            Epirubicin 60 mg/m<sup>2</sup> IV, days 1 and 8            Fluorouracil 600 mg/m<sup>2</sup> IV, days 1 and 8            Repeat cycles every 21 days for six cycles (requires prophylactic antibiotics or growth factor support)</p>	<p><b>AC → Paclitaxel<sup>b</sup></b>            Doxorubicin 60 mg/m<sup>2</sup> IV, day 1            Cyclophosphamide 600 mg/m<sup>2</sup> IV, day 1            Repeat cycles every 21 days for four cycles  <i>Followed by:</i>            Paclitaxel 175 mg/m<sup>2</sup> IV over 3 hours            Repeat cycles every 21 days for four cycles</p> <p><b>TAC<sup>d</sup></b>            Docetaxel 75 mg/m<sup>2</sup> IV, day 1            Doxorubicin 50 mg/m<sup>2</sup> IV bolus, day 1            Cyclophosphamide 500 mg/m<sup>2</sup> IV, day 1 (Doxorubicin should be given first)            Repeat cycles every 21 days for six cycles (must be given with growth factor support)</p> <p><b>Paclitaxel → FAC<sup>f</sup></b>            Paclitaxel 80 mg/m<sup>2</sup> per week IV over 1 hour every week for 12 weeks  <i>Followed by:</i>            Fluorouracil 500 mg/m<sup>2</sup> IV, days 1 and 4            Doxorubicin 50 mg/m<sup>2</sup> IV continuous infusion over 72 hours<sup>v</sup>            Cyclophosphamide 500 mg/m<sup>2</sup> IV, day 1            Repeat cycles every 21–28 days for four cycles<sup>f</sup></p> <p><b>CMF<sup>h,i</sup></b>            Cyclophosphamide 100 mg/m<sup>2</sup> per day orally, days 1–14            Methotrexate 40 mg/m<sup>2</sup> IV, days 1 and 8            Fluorouracil 600 mg/m<sup>2</sup> IV, days 1 and 8            Repeat cycles every 28 days for six cycles  <i>or</i>            Cyclophosphamide 600 mg/m<sup>2</sup> IV, day 1            Methotrexate 40 mg/m<sup>2</sup> IV, day 1            Fluorouracil 600 mg/m<sup>2</sup> IV, days 1 and 8            Repeat cycles every 21 days for six cycles</p> <p><b>Dose-Dense AC → Paclitaxel<sup>k</sup></b>            Doxorubicin 60 mg/m<sup>2</sup> IV bolus, day 1            Cyclophosphamide 600 mg/m<sup>2</sup> IV, day 1            Repeat cycles every 14 days for four cycles (must be given with growth factor support)  <i>Followed by:</i>            Paclitaxel 175 mg/m<sup>2</sup> IV over 3 hours            Repeat cycles every 14 days for four cycles (must be given with growth factor support)<sup>w</sup></p>
<b>Metastatic Single-Agent Chemotherapy</b>	
<p><b>Paclitaxel<sup>l,m</sup></b>            Paclitaxel 175 mg/m<sup>2</sup> IV over 3 hours            Repeat cycles every 21 days  <i>or</i>            Paclitaxel 80 mg/m<sup>2</sup> per week IV over 1 hour            Repeat dose every 7 days</p>	<p><b>Vinorelbine<sup>n</sup></b>            Vinorelbine 30 mg/m<sup>2</sup> IV, days 1 and 8            Repeat cycles every 21 days  <i>or</i>            Vinorelbine 25–30 mg/m<sup>2</sup> per week IV            Repeat cycles every 7 days (adjust dose based on absolute neutrophil count; see product information)</p>

(continued)

**TABLE 61-1** Common Chemotherapy Regimens for Breast Cancer (Continued)

<p><b>Docetaxel<sup>o,p</sup></b> Docetaxel 60–100 mg/m<sup>2</sup> IV over 1 hour Repeat cycles every 21 days <i>or</i> Docetaxel 30–35 mg/m<sup>2</sup> per week IV over 30 minutes Repeat dose every 7 days</p> <p><b>Capecitabine<sup>r</sup></b> Capecitabine 2,000–2,500 mg/m<sup>2</sup> per day orally, divided twice daily for 14 days Repeat cycles every 21 days</p>	<p><b>Gemcitabine<sup>q</sup></b> Gemcitabine 600–1,000 mg/m<sup>2</sup> per week IV, days 1, 8, and 15 Repeat cycles every 28 days (may need to hold day 15 dose based on blood counts)<sup>q</sup></p> <p><b>Liposomal doxorubicin<sup>s</sup></b> Liposomal doxorubicin 30–50 mg/m<sup>2</sup> IV over 90 minutes Repeat cycles every 28 days</p>
<b>Metastatic Combination Chemotherapy Regimens</b>	
<p><b>Docetaxel + capecitabine<sup>t</sup></b> Docetaxel 75 mg/m<sup>2</sup> IV over 1 hour, day 1 Capecitabine 2,000–2,500 mg/m<sup>2</sup> per day orally divided twice daily for 14 days Repeat cycles every 21 days</p>	<p><b>Paclitaxel + Gemcitabine<sup>w</sup></b> Paclitaxel 175 mg/m<sup>2</sup> IV over 3 hours, day 1 Gemcitabine 1,250 mg/m<sup>2</sup> IV days 1 and 8 Repeat cycles every 21 days</p>

AC, Adriamycin (doxorubicin), Cytoxan (cyclophosphamide); CAF, Cytoxan (cyclophosphamide), Adriamycin (doxorubicin), 5-fluorouracil; CEF, cyclophosphamide, epirubicin, 5-fluorouracil; CMF, cyclophosphamide, methotrexate, 5-fluorouracil; FAC, 5-fluorouracil, Adriamycin (doxorubicin), cyclophosphamide; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; TAC, Taxol (paclitaxel), Adriamycin (doxorubicin), cyclophosphamide.

<sup>o</sup>From Fisher B, Brown AM, Dimitrov NV, et al. *J Clin Oncol* 1990;8:1483.

<sup>p</sup>From Henderson CI, Berry DA, Demetri GD, et al. *J Clin Oncol* 2003;21:976.

<sup>r</sup>From Buzdar AU, Hortobagyi GN, Singletary SE, et al. In: Salmon S, ed. *Adjuvant Therapy of Cancer, VIII*. Philadelphia: Lippincott-Raven, 1997:93–100.

<sup>s</sup>From Martin M, Dienkowski T, Mackey J, et al. *NEJM* 2005;352:2302.

<sup>t</sup>From Wood WC, et al. *N Engl J Med* 1994;330:1253.

<sup>w</sup>From Green MC, Buzdar AU, Smith T, et al. *J Clin Oncol* 2005;23:5983–5992.

<sup>x</sup>French Adjuvant Study Group. *J Clin Oncol* 2001;19:602.

<sup>y</sup>From Bonadonna G, Brusamolino E, Valagussa P, et al. *N Engl J Med* 1976;294:405.

<sup>z</sup>From Fisher B, Redmond C, Dimitrov NV, et al. *N Engl J Med* 1989;32:473.

<sup>aa</sup>From Levine MN, Bramwell VH, Pritchard KI, et al. *J Clin Oncol* 1998;16:2651.

<sup>ab</sup>From Kummel S, Rezaei M, Kimmig R, et al. *Curr Opin Obstet Gynecol* 2007;19:75–81.

<sup>ac</sup>From Taxol (paclitaxel) product information. Princeton, NJ: Bristol-Myers Squibb, March 2003.

<sup>ad</sup>From Perez EA, Vogelci, Irwin DH, et al. *Clin Oncol* 2001;19:4216.

<sup>ae</sup>From Zelek L, Bartheir S, Riofrio M, et al. *Cancer* 2001;92:2267.

<sup>af</sup>From Taxotere (docetaxel) product information. Bridgewater, NJ: Sanofi-aventis, November 2007.

<sup>ag</sup>From Hainsworth JD, Burris HA 3rd, Erlaud JB, et al. *J Clin Oncol* 1998;16:2164.

<sup>ah</sup>From Carmichael J, Possinger K, Philip P, et al. *J Clin Oncol* 1995;13:2731.

<sup>ai</sup>From Gralow JR. *Breast Cancer Res Treat* 2005;89(Suppl 1):S9–S15.

<sup>aj</sup>From O'Brien ME, Wigler N, Inbar M, et al. *Ann Oncol* 2004;15:440–449.

<sup>ak</sup>From Sledge GW, Neuberg D, Bernardo P, et al. *J Clin Oncol* 2003;21:588–592.

<sup>al</sup>From O'Shaughnessy J, Miles D, Vukelja S, et al. *J Clin Oncol* 2002;20:2812–2823.

<sup>am</sup>FAC may also be given with bolus doxorubicin administration, and the fluorouracil dose is then given on days 1 and 8.

<sup>an</sup>Another way to give these agents in a dose-dense manner is A → P → C as sequential single agents, in the same doses indicated above, every 14 days for four cycles each with growth factor support (see Citron ML, Berry DA, Cirincione C, et al. *J Clin Oncol* 2003;21:1431–1439 for details).

### Adjuvant Endocrine Therapy

- **Tamoxifen** has been the gold standard for adjuvant endocrine therapy. It has both estrogenic and antiestrogenic properties, depending on the tissue and gene in question.
- Tamoxifen 20 mg daily, beginning soon after completing chemotherapy and continuing for 5 years, reduces the risk of recurrence and mortality.

Tamoxifen is usually well tolerated. Symptoms of estrogen withdrawal (hot flashes and vaginal bleeding) may occur but decrease in frequency and intensity over time. Tamoxifen increases the risks of stroke, pulmonary embolism, deep vein thrombosis, and endometrial cancer, particularly in women age 50 years or older.

- Premenopausal women benefit from ovarian ablation with luteinizing hormone-releasing hormone (LHRH) agonists (e.g., **goserelin**) in the adjuvant setting, either with or without concurrent tamoxifen. Trials are ongoing to further define the role of LHRH agonists.
- Options for adjuvant hormonal therapy in postmenopausal women include aromatase inhibitors (e.g. **anastrozole**, **letrozole**, or **exemestane**) either in place of or after tamoxifen. Adverse effects with aromatase inhibitors include hot flashes, myalgia/arthralgia, vaginal dryness/atrophy, mild headaches, and diarrhea.
- The optimal drug, dose, sequence, and duration of administration of aromatase inhibitors in the adjuvant setting are not known.

### LOCALLY ADVANCED BREAST CANCER (STAGE III)

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- Neoadjuvant or primary chemotherapy is the initial treatment of choice. Benefits include rendering inoperable tumors resectable and increasing the rate of BCT.
- Primary chemotherapy with either an anthracycline- or taxane-containing regimen is recommended. The use of trastuzumab with chemotherapy is appropriate for patients with HER2-positive tumors.
- Surgery followed by chemotherapy and adjuvant RT should be administered to minimize local recurrence.
- Cure is the primary goal of therapy for most patients with Stage III disease.

### METASTATIC BREAST CANCER (STAGE IV)

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- The choice of therapy for MBC is based on the site of disease involvement and presence or absence of certain characteristics, as described below.

#### Endocrine Therapy

- Endocrine therapy is the treatment of choice for patients who have hormone receptor-positive metastases in soft tissue, bone, pleura, or, if asymptomatic, viscera. Compared with chemotherapy, endocrine therapy has an equal probability of response and a better safety profile.
- Patients are sequentially treated with endocrine therapy until their tumors cease to respond, at which time chemotherapy can be given.
- Historically, the choice of an endocrine therapy was based primarily on toxicity and patient preference but study results have led to changes in MBC treatment (Table 61-2).
- Aromatase inhibitors reduce circulating and target organ estrogens by blocking peripheral conversion from an androgenic precursor, the primary source of estrogens in postmenopausal women. Newer agents are more selective and better tolerated than the prototype, **aminoglutethimide**. **Anastrozole**, **letrozole**, and **exemestane** are approved as second-line therapy; anastrozole and exemestane have been shown to improve OS and

**TABLE 61-2** Endocrine Therapies Used for Metastatic Breast Cancer

Class	Drug	Dose	Side Effects	
<b>Aromatase inhibitors</b>	Nonsteroidal	Anastrozole Letrozole	1 mg orally daily 2.5 mg orally daily	Hot flashes, arthralgias, myalgias, headaches, diarrhea, mild nausea
	Steroidal	Exemestane	25 mg orally daily	
	<b>Antiestrogens</b>			
SERMs	Tamoxifen Toremifene	20 mg orally daily 60 mg orally daily	Hot flashes, vaginal discharge, mild nausea, thromboembolism, endometrial cancer	
	SERDs	Fulvestrant		250 mg IM every 28 days
<b>LHRH analogs</b>	Goserelin	3.6 mg SC every 28 days	Hot flashes, amenorrhea, menopausal symptoms, injection site reactions (extended formulations are not recommended for the treatment of breast cancer)	
	Leuprolide	3.75 mg IM every 28 days		
	Triptorelin	3.75 mg IM every 28 days		
<b>Progestins</b>	Megestrol acetate	40 mg orally four times a day	Weight gain, hot flashes, vaginal bleeding, edema, thromboembolism	
	Medroxyprogesterone	400–1,000 mg IM every week		
<b>Androgens</b>	Fluoxymesterone	10 mg orally twice a day	Deepening voice, alopecia, hirsutism, facial/truncal acne, fluid retention, menstrual irregularities, cholestatic jaundice	
<b>Estrogens</b>	Diethylstilbestrol	5 mg orally three times a day	Nausea/vomiting, fluid retention, anorexia, thromboembolism, hepatic dysfunction	
	Ethinyl estradiol	1 mg orally three times a day		
	Conjugated estrogens	2.5 mg orally three times a day		

LHRH, luteinizing hormone-releasing hormone; SERD, selective estrogen receptor downregulator; SERM, selective estrogen receptor modulator.

time to progression compared with progestins. As first-line therapy, anastrozole and letrozole increase time to progression and are better tolerated compared with tamoxifen.

- **Tamoxifen** is the antiestrogen of choice in premenopausal women whose tumors are hormone-receptor positive, unless metastases occur within 1 year of adjuvant tamoxifen. Maximal beneficial effects do not occur for at least 2 months. In addition to the side effects described for adjuvant therapy, tumor flare or hypercalcemia occurs in approximately 5% of patients with MBC.
- **Toremifene** has similar efficacy and tolerability as tamoxifen and is an alternative to tamoxifen in postmenopausal patients. **Fulvestrant** is a second-line intramuscular agent with similar efficacy and safety when compared to anastrozole in patients who progressed on tamoxifen.

- Ovarian ablation (oophorectomy) is considered by some to be the endocrine therapy of choice in premenopausal women and produces similar overall response rates as tamoxifen. Medical castration with an LHRH analog, **goserelin**, **leuprolide**, or **triptorelin**, is a reversible alternative to surgery.
- Progestins are generally reserved for third-line therapy. They cause weight gain, fluid retention, and thromboembolic events.

### Chemotherapy

- Chemotherapy is preferred to endocrine therapy for women with hormone receptor-negative tumors; rapidly progressive lung, liver, or bone marrow involvement; or failure of endocrine therapy.
- The choice of treatment depends on the individual. Agents used previously as adjuvant therapy can be repeated unless the cancer recurred within 1 year. Single agents are associated with lower response rates than combination therapy, but time to progression and OS are similar. Single agents are better tolerated, an important consideration in the palliative metastatic setting.
- Combination regimens produce objective responses in approximately 60% of patients previously unexposed to chemotherapy, but complete responses occur in less than 10% of patients. The median duration of response is 5 to 12 months; the median survival is 14 to 33 months.
- **Anthracyclines** and **taxanes** produce response rates of 50% to 60% when used as first-line therapy for MBC. Single agent **capecitabine**, **vinorelbine**, or **gemcitabine** have response rates of 20% to 25% when used after an anthracycline and a taxane (see Table 61-1).
- **Ixabepilone**, a microtubule stabilizing agent, is indicated as monotherapy or in combination with capecitabine in MBC patients who have previously received an anthracycline and a taxane. Response rates and time to progression were increased with combination therapy as compared with capecitabine alone. Adverse effects include myelosuppression, peripheral neuropathy, and myalgias/arthralgias.

### Biologic Therapy

- **Trastuzumab**, a monoclonal antibody that binds to HER2, produces response rates of 15% to 20% when used as a single agent and increases response rates, time to progression, and OS when combined with chemotherapy. It has been studied in doublet (taxane-trastuzumab; vinorelbine-trastuzumab) and triplet (trastuzumab-taxane-platinum) combinations but the optimum regimen is unknown.
- Trastuzumab is well tolerated, but the risk of cardiotoxicity is 5% with single-agent trastuzumab and unacceptably high in combination with an anthracycline.
- **Lapatinib**, a tyrosine kinase inhibitor that targets both HER2 and the epidermal growth factor receptor, improved response rates and time to progression in combination with capecitabine, as compared to capecitabine alone, in patients previously treated with an anthracycline, taxane, and trastuzumab. The most common adverse events were rash and diarrhea.
- The role of **bevacizumab**, a monoclonal antibody targeted against vascular endothelial growth factor, in MBC is currently not clearly defined.

## Radiation Therapy

- Radiation is commonly used to treat painful bone metastases or other localized sites of disease including brain and spinal cord lesions. Pain relief is seen in approximately 90% of patients who receive RT.

## PREVENTION OF BREAST CANCER

- **Tamoxifen** and **raloxifene** reduce the rates of invasive breast cancer in women at high risk for developing the disease. Rates of endometrial cancer and deep vein thromboses are higher in patients receiving tamoxifen but overall quality of life is similar between the two agents.

## EVALUATION OF THERAPEUTIC OUTCOMES

### EARLY BREAST CANCER

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- The goal of adjuvant therapy in early-stage disease is cure. Because there is no clinical evidence of disease when adjuvant therapy is administered, assessment of this goal cannot be fully evaluated for years after initial diagnosis and treatment.
- Adjuvant chemotherapy can cause substantial toxicity. Because maintaining dose intensity is important in cure of disease, supportive care should be optimized with measures such as antiemetics and growth factors.

### LOCALLY ADVANCED BREAST CANCER

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- The goal of neoadjuvant chemotherapy in locally advanced breast cancer is cure. Complete pathologic response, determined at the time of surgery, is the desired end point.

### METASTATIC BREAST CANCER

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- Optimizing quality of life is the therapeutic endpoint in the treatment of patients with MBC. Many valid and reliable tools are available for objective assessment of quality of life.
- The least toxic therapies are used initially, with increasingly aggressive therapies applied in a sequential manner that does not significantly compromise quality of life.
- Tumor response is measured by clinical chemistry (e.g., liver enzyme elevation in patients with hepatic metastases) or imaging techniques (e.g., bone scans or chest x-rays).
- Assessment of the clinical status and symptom control of the patient is often adequate to evaluate response to therapy.

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*See Chap. 131, Breast Cancer, authored by Laura Boehnke Michaud, Janet L. Espirito, and Francisco J. Esteva, for a more detailed discussion of this topic.*

## DEFINITION

- Colorectal cancer is a malignant neoplasm involving the colon, rectum, and anal canal.

## PATHOPHYSIOLOGY

- Development of a colorectal neoplasm is a multistep process of genetic and phenotypic alterations of normal bowel epithelium structure and function leading to unregulated cell growth, proliferation, and tumor development.
- Sequential mutations within colonic epithelium result in cellular replication or enhanced invasiveness. Genetic changes include mutational activation of oncogenes and inactivation of tumor suppressor genes.
- Adenocarcinomas account for more than 90% of tumors of the large intestine.

## CLINICAL MANIFESTATIONS

- Signs and symptoms of colorectal cancer can be extremely varied, subtle, and nonspecific. Patients with early-stage colorectal cancer are often asymptomatic, and lesions are usually detected by screening procedures.
- Blood in the stool is the most common sign; however, any change in bowel habits, vague abdominal discomfort, or abdominal distension may be a warning sign. Less common signs and symptoms include nausea, vomiting, and, if anemia is severe, fatigue.
- Approximately 20% of patients with colorectal cancer present with metastatic disease. The most common site of metastasis is the liver, followed by the lungs, and then bones.

## PREVENTION AND SCREENING

- Primary prevention is aimed at preventing colorectal cancer in an at-risk population. To date, the only strategy shown to reduce the risk is chemoprevention with celecoxib in people with familial adenomatous polyposis.
- Secondary prevention is aimed at preventing malignancy in a population that has already manifested an initial disease process. Secondary prevention includes procedures ranging from colonoscopic removal of precancerous polyps detected during screening colonoscopy to total colectomy for high-risk individuals (e.g., familial adenomatous polyposis).
- American Cancer Society guidelines for average-risk individuals include annual occult fecal blood testing starting at age 50 years and examination of the colon every 5 or 10 years depending on the procedure.

## DIAGNOSIS

- When colorectal carcinoma is suspected, a careful personal and family history and physical examination should be performed.
- The entire large bowel should be evaluated by colonoscopy or flexible sigmoidoscopy with double-contrast barium enema.
- Baseline laboratory tests should include complete blood cell count, prothrombin time, activated partial thromboplastin time, liver and renal function tests, and serum carcinoembryonic antigen (CEA). Serum CEA can serve as a marker for monitoring colorectal cancer response to treatment, but it is too insensitive and nonspecific to be used as a screening test for early-stage colorectal cancer.
- Radiographic imaging studies may include chest x-ray, bone scan, chest and abdominal computed tomography scans, positron emission tomography, ultrasonography, and magnetic resonance imaging.
- Immunodetection of tumors using tumor-directed antibodies is an imaging technique for determining the location and extent of extrahepatic disease. These tests might also be useful for identifying metastatic or recurrent disease in patients with rising CEA levels.
- Stage of colorectal cancer should be determined at diagnosis to predict prognosis and to develop treatment options. Stage is based on the size of the primary tumor ( $T_{1-4}$ ), presence and extent of lymph node involvement ( $N_{0-2}$ ), and presence or absence of distant metastases (M).
  - ✓ Stage I disease involves tumor invasion of the submucosa ( $T_1$ ) or muscularis propria ( $T_2$ ) and negative lymph nodes.
  - ✓ Stage II disease involves tumor invasion through the muscularis propria into the subserosa, or into the nonperitonealized pericolic or perirectal tissues ( $T_3$ ) or directly invading other organs or structures and/or perforates the visceral peritoneum ( $T_4$ ) and negative lymph nodes.
  - ✓ Stage III disease includes  $T_{1-4}$  AND positive regional lymph nodes.
  - ✓ Stage IV disease includes any T, any N, AND distant metastasis.

## DESIRED OUTCOME

- The goal of treatment depends on the stage of disease. Stages I, II, and III are potentially curable; the intent is to eradicate micrometastatic disease. Twenty to thirty percent of patients with metastatic disease may be cured if their metastases are resectable. Most stage IV disease is incurable; palliative treatment is given to reduce symptoms, avoid disease-related complications, and prolong survival.

## TREATMENT

### GENERAL PRINCIPLES

- Treatment modalities are surgery, radiation therapy (RT), and chemotherapy and biomodulators. This section on treatment begins with an overview

of each modality and associated toxicities. Adjuvant therapy for early stage disease and treatment of metastatic disease will be discussed separately.

- Adjuvant therapy is administered after complete tumor resection to eliminate residual local or metastatic microscopic disease.
- Adjuvant therapy differs for colon and rectal cancer because their natural history and recurrence patterns differ. Rectal cancer is more difficult to resect with wide margins, so local recurrences are more frequent than with colon cancer. Adjuvant RT plus chemotherapy is considered standard for stage II or III rectal cancer. Adjuvant chemotherapy is standard for stage III colon cancer and can be considered for high-risk stage II colon cancer. Adjuvant therapy is not indicated for stage I colorectal cancer because most patients are cured by surgical resection alone.
- Neoadjuvant therapy is administered *before* surgery to shrink the tumor, thereby making it resectable. Neoadjuvant RT may also prevent local recurrence.
- Chemotherapy is the primary treatment modality for metastatic colorectal cancer (MCRC). Treatment options are generally similar for metastatic cancer of the colon and rectum.

## SURGERY

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- Surgical removal of the primary tumor is the treatment of choice for most patients with operable disease.
- Surgery for colon cancer generally involves complete tumor resection with an appropriate margin of tumor-free bowel and a regional lymphadenectomy.
- Surgery for rectal cancer depends on the area involved. Although less than 33% of these patients require permanent colostomy, frequent complications include urinary retention, incontinence, impotence, and locoregional recurrence.
- Common complications of surgery for both colon and rectal cancer include infection, anastomotic leakage, obstruction, adhesions, and malabsorption syndromes.
- Resection of discrete metastases in selected patients may extend disease-free survival. Resection of hepatic-limited metastases may result in cure. Adjuvant chemotherapy may be administered but the optimal regimen remains to be determined.

## RADIATION THERAPY

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- RT can be administered with curative surgical resection to prevent local recurrence of rectal cancer, before surgery to shrink a rectal tumor and make it operable, or in advanced or metastatic disease to alleviate symptoms. Adjuvant RT, however, does not have a definitive role in colon cancer because recurrences are usually extrapelvic.
- Acute adverse effects associated with RT include hematologic depression, dysuria, diarrhea, abdominal cramping, and proctitis. Chronic symptoms may persist for months after RT and may involve diarrhea, proctitis, enteritis, small-bowel obstruction, perineal tenderness, and impaired wound healing.

## CHEMOTHERAPY

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### Fluoropyrimidines

- **Fluorouracil** (5-FU) is the most widely used chemotherapeutic agent for colorectal cancer. **Leucovorin** (folinic acid) is usually added to 5-FU as a biochemical modulator to improve response rates.
- Administration method affects clinical activity and toxicity. 5-FU is administered by IV bolus once weekly or daily for 5 days each month, or by continuous IV infusion. Efficacy evaluations favor continuous infusion 5-FU but none of the combination regimens with **leucovorin** has proven superior with regard to overall patient survival.
- Continuous IV infusion of 5-FU is generally well tolerated but is associated with palmar-plantar erythrodysesthesia or hand-foot syndrome. This distinct skin toxicity can be acutely disabling, but it is reversible and not life threatening. IV bolus administration is associated with leukopenia, which is dose limiting and can be life threatening. Both methods are associated with a similar incidence of mucositis, diarrhea, nausea and vomiting, and alopecia.
- In rare cases, patients deficient in dihydropyrimidine dehydrogenase, responsible for the catabolism of 5-FU, develop severe toxicity, including death, after 5-FU administration.
- **Capecitabine**, an oral prodrug of 5-FU, has efficacy and safety profiles similar to those of IV infusion of 5-FU.

### Irinotecan

- **Irinotecan** is a topoisomerase I inhibitor. Early- and late-onset diarrhea and neutropenia are dose-limiting toxicities of irinotecan.
- Early-onset diarrhea occurs 2 to 6 hours after administration and is characterized by lacrimation, diaphoresis, abdominal cramping, flushing, and/or diarrhea. These cholinergic symptoms respond to IV or subcutaneous atropine 0.25 to 1 mg.
- Late-onset diarrhea occurs 1 to 12 days after administration, lasts 3 to 5 days, and can be fatal. Late-onset diarrhea requires aggressive, high-dose **loperamide** beginning with 4 mg after the first soft or watery stool, followed by 2 mg every 2 hours until symptom free for 12 hours.

### Oxaliplatin

- **Oxaliplatin** has a mechanism similar to that of cisplatin but, unlike other platinum drugs, is associated with minimal renal toxicity, hematologic toxicity, and nausea and vomiting.
- Oxaliplatin is associated with neuropathies. Acute neuropathy is reversible within 2 weeks, usually occurs peripherally, and is precipitated by exposure to cold. Persistent neuropathy is cumulative and is characterized by paresthesias, dysesthesias, and hypoesthesias.

### Monoclonal Antibodies

- **Bevacizumab** is a humanized monoclonal antibody directed against vascular endothelial growth factor. Bevacizumab is associated with hypertension, which is easily managed with oral antihypertensive agents.

- Bevacizumab is also associated with GI perforation. This rare, but potentially fatal, complication necessitates prompt evaluation of abdominal pain associated with vomiting or constipation.
- **Cetuximab** is a chimeric monoclonal antibody directed against epidermal growth factor receptor. Common adverse events include acne-like skin rash, asthenia, lethargy, malaise, and fatigue.
- **Panitumumab** is a human monoclonal antibody directed against epidermal growth factor receptor. Common adverse events include dermatologic toxicities, fatigue, abdominal pain, nausea, and diarrhea.

## ADJUVANT THERAPY FOR COLON CANCER

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- Results of adjuvant chemotherapy studies in patients with stage II disease are conflicting. Despite lack of consensus among practitioners, the approach to treatment of high-risk stage II and stage III disease is similar.
- Adjuvant chemotherapy significantly decreases risk of cancer recurrence and death in stage III colon cancer and is standard of care.
- Selection of an adjuvant regimen (Table 62-1) is based on patient specific factors including performance status, comorbid conditions, and patient preference based on lifestyle factors.
- Most patients with good performance status will receive oxaliplatin in combination with 5-FU and leucovorin.
- 5-FU/leucovorin regimens currently have limited use but are acceptable options in patients who cannot receive oxaliplatin and are unable to tolerate oral capecitabine.

## ADJUVANT AND NEOADJUVANT THERAPY FOR RECTAL CANCER

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- The goal of adjuvant RT for rectal cancer is to decrease local tumor recurrence after surgery, preserve the sphincter, and, with preoperative radiotherapy, improve resectability.
- 5-FU enhances the cytotoxic effects of RT. Compared with surgery alone, the combination of adjuvant 5-FU and RT reduces local and distant tumor recurrences and improves survival in stages II and III rectal cancer.
- For resectable lesions, postoperative infusional 5-FU–based chemotherapy plus RT is recommended.
- For unresectable tumors, neoadjuvant (preoperative) 5-FU or capecitabine chemoradiation followed by surgery is recommended. All patients who receive preoperative chemotherapy should receive postoperative chemotherapy, with or without RT.

## TREATMENT OF METASTATIC COLORECTAL CANCER

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- Currently, most MCRCs are incurable. Initial chemotherapy (Table 62-2) is administered with palliative intent: to reduce symptoms, improve quality-of-life, and extend survival. In general, treatment options are similar for metastatic cancer of the colon and rectum.
- Either irinotecan or oxaliplatin plus 5-FU and leucovorin is recommended as first-line therapy for MCRC. These regimens result in

**TABLE 62-1** Chemotherapy Regimens for the Adjuvant Treatment of Colorectal Cancer

Regimen	Agents	Comment
FOLFOX <sup>a</sup>	Oxaliplatin 85 mg/m <sup>2</sup> IV day 1 Folinic acid 200 mg/m <sup>2</sup> per day IV over 2 hours days 1 and 2 Fluorouracil 400 mg/m <sup>2</sup> IV bolus, after folinic acid then 600 mg/m <sup>2</sup> CIV over 22 hours days 1 and 2 • Repeat every 14 days	Improved DFS as compared to infusional fluorouracil-leucovorin-based regimens.
FLOX <sup>b</sup>	Oxaliplatin 85 mg/m <sup>2</sup> IV administered on weeks 1, 3, and 5 Fluorouracil 500 mg/m <sup>2</sup> IV bolus weekly × 6 Folinic acid 500 mg/m <sup>2</sup> IV weekly × 6 • Each cycle lasts 8 weeks and is repeated for three cycles	Improved DFS as compared to bolus fluorouracil-leucovorin-based regimens.
Capecitabine	Capecitabine 1,250 mg/m <sup>2</sup> po twice daily on days 1 through 14 every 21 days	Equivalent DFS as compared to the Mayo Clinic regimen with improved tolerability.
<b>Fluorouracil-based regimens</b>		
Roswell Park regimen <sup>c</sup>	Fluorouracil 600 mg/m <sup>2</sup> per day IV, day 1 Folinic acid 500 mg/m <sup>2</sup> per day IV over 2 hours • Repeat weekly for 6 of 8 weeks	
Mayo Clinic regimen <sup>d</sup>	Fluorouracil 425 mg/m <sup>2</sup> per day IV, days 1–5 Folinic acid 20 mg/m <sup>2</sup> per day IV, days 1–5 • Repeat every 4 to 5 weeks	
de Gramont regimen <sup>e</sup>	Fluorouracil 400 mg/m <sup>2</sup> per day IV bolus, followed by 600 mg/m <sup>2</sup> CIV over 22 hours, days 1 and 2 for 2 consecutive days Folinic acid 200 mg/m <sup>2</sup> per day IV over 2 hours days 1 and 2 • Repeat every 2 weeks	Improved safety as compared to the Mayo Clinic regimen.

CIV, continuous intravenous infusion; DFS, disease-free survival.

<sup>a</sup>Giantonio BJ, Catalano PJ, Meropol NJ, et al. *J Clin Oncol* 2007;25:1539–1544.

<sup>b</sup>Kuebler JP, Wieand HS, O'Connell MJ, et al. *J Clin Oncol* 2007;25:2198–2204.

<sup>c</sup>Wolmark N, Rockette H, Fisher B, et al. *J Clin Oncol* 1993;11:1879–1887.

<sup>d</sup>O'Connell MJ, Mailliard JA, Kahn MJ, et al. *J Clin Oncol* 1997;15:246–250.

<sup>e</sup>de Gramont A, Bosset JF, Milan C, et al. *J Clin Oncol* 1997;15:808–815.

improved response rates and progression-free survival as well as improved median survival.

- The addition of bevacizumab to 5-FU–based regimens improves efficacy compared to chemotherapy alone and the resulting four drug regimens are considered first-line therapy for MCRC.
- Capecitabine monotherapy is suitable for first-line therapy in patients not likely to tolerate IV chemotherapy. Capecitabine produced superior response rates and comparable survival compared with 5-FU and leucovorin in a pooled analysis. Capecitabine is being evaluated in combination with irinotecan or oxaliplatin.
- The most important factor in patient survival is not the initial chemotherapy regimen but ensuring that patients receive all three active drugs (5-FU, irinotecan, and oxaliplatin) at some point in their treatment course.

**TABLE 62-2** Chemotherapeutic Regimens for Metastatic Colorectal Cancer

	Regimen	Major Dose-Limiting Toxicities/Comments
<b>Initial therapy</b>		
<i>Oxaliplatin plus fluorouracil plus leucovorin</i>		
Oxaliplatin plus bimonthly infusional fluorouracil; FOLFOX4 <sup>d</sup>	Oxaliplatin 85 mg/m <sup>2</sup> IV day 1 plus bolus fluorouracil 400 mg/m <sup>2</sup> IV plus leucovorin 200 mg/m <sup>2</sup> IV followed by fluorouracil 600 mg/m <sup>2</sup> IV in 22-hour infusion on days 1 and 2, every 2 weeks	Sensory neuropathy, neutropenia
mFOLFOX6	Oxaliplatin 85 mg/m <sup>2</sup> IV day 1 plus leucovorin 400 mg/m <sup>2</sup> IV on day 1 followed by fluorouracil 400 mg/m <sup>2</sup> IV bolus on day 1, then 1,200 mg/m <sup>2</sup> /day × 2 days (total 2,400 mg/m <sup>2</sup> over 46–48 hours) continuous infusion, repeat every 2 weeks	Sensory neuropathy, neutropenia; easier administration as compared to FOLFOX4
<i>Irinotecan plus fluorouracil plus leucovorin</i>		
Irinotecan plus infusional fluorouracil; FOLFIRI <sup>e</sup>	Irinotecan 180 mg/m <sup>2</sup> IV plus leucovorin 400 mg/m <sup>2</sup> IV plus bolus fluorouracil 400 mg/m <sup>2</sup> IV, followed by fluorouracil 2,400 mg/m <sup>2</sup> continuous IV infusion over 46 hours on day 1, repeated every 2 weeks	Nausea, diarrhea, mucositis, neutropenia
Biweekly irinotecan plus infusional fluorouracil <sup>f</sup>	Irinotecan 180 mg/m <sup>2</sup> IV day 1 plus leucovorin 400 mg/m <sup>2</sup> then fluorouracil 400 mg/m <sup>2</sup> IV, followed by fluorouracil 600 mg/m <sup>2</sup> continuous IV infusion over 22 hours, days 1 and 2, repeated every 2 weeks	Neutropenia, diarrhea
Irinotecan plus bolus fluorouracil; IFL; Saltz regimen <sup>g</sup>	Irinotecan 125 mg/m <sup>2</sup> IV plus fluorouracil 500 mg/m <sup>2</sup> IV plus leucovorin 20 mg/m <sup>2</sup> IV weekly for 4 of 6 weeks	Diarrhea (increased as compared to FOLFIRI), neutropenia
<i>Bevacizumab</i>		
Bevacizumab plus fluorouracil-based regimens	Bevacizumab 5 mg/kg IV every 2 weeks plus fluorouracil and leucovorin (given in any schedule below) or IFL or FOLFOX or FOLFIRI	Hypertension, thrombosis, proteinuria from bevacizumab added to toxicities of regimen chosen

(continued)

**TABLE 62-2** Chemotherapeutic Regimens for Metastatic Colorectal Cancer (Continued)

	<b>Regimen</b>	<b>Major Dose-Limiting Toxicities/Comments</b>
<i>Capecitabine</i>		
Capecitabine monotherapy <sup>h</sup>	See Table 62-1 <sup>a</sup>	Diarrhea, hand-foot syndrome
CapOx	Oxaliplatin 130 mg/m <sup>2</sup> day 1 plus capecitabine 850 mg/m <sup>2</sup> twice a day for 14 days, repeat every 3 weeks	Diarrhea, hand-foot syndrome, neuropathies
<i>Fluorouracil plus leucovorin only</i>		
Weekly, high-dose leucovorin; Roswell Park regimen <sup>i</sup>	See Table 62-1 <sup>a</sup>	Diarrhea, mucositis
Consecutive day, low-dose leucovorin; Mayo Clinic regimen <sup>j</sup>	See Table 62-1 <sup>a</sup>	Mucositis, neutropenia
Bolus plus infusional fluorouracil; (LV5FU2); de Gramont regimen <sup>k</sup>	See Table 62-1 <sup>a</sup>	Neutropenia, mucositis
<b>Salvage therapy</b>		
<i>Irinotecan</i>		
Weekly irinotecan <sup>g</sup>	Irinotecan 125 mg/m <sup>2</sup> IV every week for 4 of 6 weeks	Neutropenia, diarrhea
Every-3-weeks irinotecan <sup>l</sup>	Irinotecan 350 mg/m <sup>2</sup> IV every 3 weeks	Neutropenia, diarrhea (less-than-weekly irinotecan)
<i>Oxaliplatin plus fluorouracil plus leucovorin</i>		
Oxaliplatin plus bimonthly infusional fluorouracil; FOLFOX4 <sup>d</sup>	Same as FOLFOX4 above	Sensory neuropathy, neutropenia
<i>Cetuximab</i>		
Cetuximab plus irinotecan <sup>b,m</sup>	Continue irinotecan as previously dosed, plus cetuximab 400 mg/m <sup>2</sup> IV loading dose, then cetuximab 250 mg/m <sup>2</sup> IV weekly thereafter	Asthenia, diarrhea, nausea, acneiform rash, vomiting
Cetuximab <sup>c,m</sup>	Cetuximab 400 mg/m <sup>2</sup> IV loading dose, then cetuximab 250 mg/m <sup>2</sup> IV weekly thereafter	Papulopustular, follicular rash, asthenia, constipation, diarrhea

<i>Fluorouracil</i>		
Protracted continuous infusion <sup>d</sup>	Fluorouracil 250–300 mg/m <sup>2</sup> per day continuous IV infusion until disease progression	Mucositis, hand–foot syndrome
<b>Investigational</b>		
CapOx <sup>e</sup>	Same as CapOx above	Diarrhea, sensory neuropathy
CapIri <sup>f</sup>	Capecitabine 1,000 mg/m <sup>2</sup> orally twice daily days 1–14 plus irinotecan 100 mg/m <sup>2</sup> IV days 1 and 8; repeat every 3 weeks	Diarrhea, neutropenia

<sup>d</sup>Doses and schedules the same as those in the adjuvant setting.

<sup>b</sup>If irinotecan-refractory disease.

<sup>c</sup>If patient cannot tolerate irinotecan.

<sup>d</sup>Giantonio BJ, Catalano PJ, Meropol NJ, et al. *J Clin Oncol* 2007;25:1539–1544.

<sup>e</sup>Tournigand C, Andre T, Achille E, et al. *J Clin Oncol* 2004;22:229–237.

<sup>f</sup>Douillard J, Cunningham D, Roth A, et al. *Lancet* 2000;355:1041–1047.

<sup>g</sup>Saltz LB, Cox JV, Blanke C, et al. *N Engl J Med* 2000;343:905–914.

<sup>h</sup>Twelves C. *Eur J Cancer* 2002;38:15–20.

<sup>i</sup>Wolmark N, Rockette H, Fisher B, et al. *J Clin Oncol* 1993;11:1879–1887

<sup>j</sup>O’Connell MJ, Mailliard JA, Kahn MJ, et al. *J Clin Oncol* 1997;15:246–250.

<sup>k</sup>de Gramont A, Bosset JF, Milan C, et al. *J Clin Oncol* 1997;15:808–815

<sup>l</sup>Cunningham D, Pyrhonen S, James R, et al. *Lancet* 1998;352:1413–1418.

<sup>m</sup>Cunningham D, Humblet Y, Siena S, et al. *N Engl J Med* 2004;351:337–345.

<sup>n</sup>Rougier P, Van Cutsem E, Bajetta E, et al. *Lancet* 1998;352:1407–1412.

<sup>o</sup>Grothey A, Jordan K, Kellner O, et al. *J Clin Oncol* 2004;22(14S)(Suppl):3534.

- Second-line or salvage therapy is based on type of and response to prior treatments, site and extent of disease, and patient factors and treatment preferences (see Table 62-2). The optimal sequence of regimens has not been established.
- If disease progressed on first-line bevacizumab, data do not support continued use.
- Cetuximab, either alone or in combination with irinotecan, can be used in patients with disease progression on irinotecan. Cetuximab monotherapy can also be considered as salvage therapy in patients with oxaliplatin-refractory disease.
- Panitumumab is approved for use in MCRC that no longer responds to previous therapy with 5-FU, irinotecan, or oxaliplatin.
- Patients who fail standard treatment for MCRC should be encouraged to participate in a clinical trial.
- Patients with hepatic-predominant disease whose disease progresses with systemic therapy may be candidates for hepatic-directed therapies such as chemoembolization, cryotherapy, or radiofrequency ablation.

## EVALUATION OF THERAPEUTIC OUTCOMES

- The goals of monitoring are to evaluate the benefit of treatment and to detect recurrence.
- Patients who undergo curative surgical resection, with or without adjuvant therapy, require routine follow-up.
- Patients should be evaluated for anticipated side effects such as loose stools or diarrhea, nausea or vomiting, mouth sores, fatigue, and fever.
- Patients should be closely monitored for side effects that require aggressive intervention such as irinotecan-induced diarrhea and bevacizumab-induced GI perforation. Patients should be evaluated for other treatment-specific side effects such as oxaliplatin-induced neuropathy, cetuximab and panitumumab-induced skin rash, and bevacizumab-induced hypertension and proteinuria.
- Less than one-half of patients develop symptoms of recurrence such as pain syndromes, changes in bowel habits, rectal or vaginal bleeding, pelvic masses, anorexia, and weight loss. CEA levels may help detect recurrences in asymptomatic patients.
- Quality of life indices should be monitored, especially in patients with metastatic disease.

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*See Chap. 133, Colorectal Cancer, authored by Patrick J. Medina, Weijing Sun, and Lisa E. Davis, for a more detailed discussion of this topic.*

## DEFINITION

- Lung cancer is a solid tumor originating from bronchial epithelial cells. This chapter distinguishes between non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) because they have different natural histories and responses to therapy.

## PATHOPHYSIOLOGY

- Lung carcinomas arise from pluripotent epithelial cells after exposure to carcinogens, which cause chronic inflammation that leads to genetic and cytologic changes and ultimately to carcinoma.
- Activation of protooncogenes, inhibition or mutation of tumor suppressor genes, and production of autocrine growth factors contribute to cellular proliferation and malignant transformation. Molecular changes, such as P53 mutations and overexpression of epidermal growth factor receptor, also affect disease prognosis and response to therapy.
- Cigarette smoking is responsible for about 80% of lung cancer cases. Other risk factors include exposure to respiratory carcinogens (e.g., asbestos, benzene), genetic risk factors, and history of other lung diseases (e.g., tuberculosis, pulmonary fibrosis).
- The major cell types are SCLC (~15% of all lung cancers), adenocarcinoma (~50%), squamous cell carcinoma (less than 30%), and large cell carcinoma. The last three types are grouped together and referred to as NSCLC.

## CLINICAL PRESENTATION

- The most common initial signs and symptoms include cough, dyspnea, chest pain, sputum production, and hemoptysis. Many patients also exhibit systemic symptoms such as anorexia, weight loss, and fatigue.
- Disseminated disease can cause neurologic deficits from CNS metastases, bone pain or pathologic fractures secondary to bone metastases, or liver dysfunction from hepatic involvement.
- Paraneoplastic syndromes commonly associated with lung cancers include cachexia, hypercalcemia, syndrome of inappropriate antidiuretic hormone secretion, and Cushing's syndrome.

## DIAGNOSIS

- Chest x-ray, computed tomography (CT) scan, and positron emission tomography (PET) scan are the most valuable diagnostic tests. Integrated CT-PET technology appears to improve diagnostic accuracy in staging NSCLC over CT or PET alone.
- Pathologic confirmation of lung cancer is established by examination of sputum cytology and/or tumor biopsy by bronchoscopy, mediastinoscopy, percutaneous needle biopsy, or open-lung biopsy.

- All patients must have a thorough history and physical examination to detect signs and symptoms of the primary tumor, regional spread of the tumor, distant metastases, paraneoplastic syndromes, and ability to withstand aggressive surgery or chemotherapy.

## STAGING

- The World Health Organization has established a TNM staging classification for lung cancer based on the primary tumor size and extent (T), regional lymph node involvement (N), and the presence or absence of distant metastases (M).
- A simpler system is commonly used to compare treatments. Stage I includes tumors confined to the lung without lymphatic spread; stage II includes large tumors with ipsilateral peribronchial or hilar lymph node involvement; stage III includes other lymph node and regional involvement; and stage IV includes any tumor with distant metastases.
- A two-stage classification is widely used for SCLC. Limited disease is confined to one hemithorax and the regional lymph nodes. All other disease is classified as extensive.

## TREATMENT

### NON-SMALL CELL LUNG CANCER

#### Desired Outcome

- The stage of NSCLC and the patient's comorbidities and performance status (i.e., the ability to perform activities of daily living) determine which treatment modalities will be used. The intent of treatment—curative or palliative—influences the aggressiveness of therapy. Favorable prognostic factors for survival include early-stage disease, good performance status, no more than 5% unintentional weight loss, and female gender.

#### Recommendations for Chemotherapy, Radiation Therapy, and Surgery

- Surgery and adjuvant (postoperative) chemotherapy (Table 63-1) are the treatments of choice for early-stage NSCLC (stage I or II); some patients benefit from postoperative radiation.
- Radiation therapy is used as primary therapy in stages I and II if the patient refuses surgery, the tumor is unresectable, or the patient is not a good surgical candidate.
- Optimal management of locally advanced NSCLC (stages IIB, IIIA, and IIIB) is controversial. **Cisplatin**-based doublet combinations are recommended for adjuvant and neoadjuvant (preoperative) chemotherapy, with or without concurrent radiation therapy.
- Four to six cycles of doublet chemotherapy with **cisplatin** or **carboplatin** plus **docetaxel**, **gemcitabine**, **paclitaxel**, or **vinorelbine** are recommended as first-line chemotherapy for patients with unresectable stage III or IV NSCLC. No combination was found to be superior; tolerance of expected toxicities may contribute to the decision.

**TABLE 63-1** Common Chemotherapy Regimens Used to Treat Lung Cancer**Non-small cell lung carcinoma<sup>a</sup>**

Cisplatin/paclitaxel	Cisplatin 75 mg/m <sup>2</sup> IV day 1 Paclitaxel 175 mg/m <sup>2</sup> over 24 hours IV day 1 Repeat cycle every 21 days <sup>b</sup> <i>or</i> Cisplatin 80 mg/m <sup>2</sup> IV day 1 Paclitaxel 175 mg/m <sup>2</sup> IV over 3 hours day 1 Repeat cycle every 21 days <sup>c</sup>
Gemcitabine/cisplatin	Gemcitabine 1,000 mg/m <sup>2</sup> IV days 1, 8, and 15 Cisplatin 100 mg/m <sup>2</sup> IV day 1 Repeat cycle every 28 days <sup>b</sup>
Gemcitabine/cisplatin	Gemcitabine 1,200 mg/m <sup>2</sup> days 1 and 8 Cisplatin 80 mg/m <sup>2</sup> IV day 1 Repeat cycle every 21 days <sup>d</sup> <i>or</i> Gemcitabine 1,250 mg/m <sup>2</sup> days 1 and 8 Cisplatin 80 mg/m <sup>2</sup> IV day 1 Repeat cycle every 21 days <sup>c</sup>
Docetaxel/cisplatin	Docetaxel 75 mg/m <sup>2</sup> IV day 1 Cisplatin 75 mg/m <sup>2</sup> IV day 1 Repeat cycle every 21 days <sup>b</sup>
Paclitaxel/carboplatin	Paclitaxel 225 mg/m <sup>2</sup> over 3 hours IV day 1 Carboplatin AUC 6 IV day 1 Repeat cycle every 21 days <sup>b,e</sup> <i>or</i> Paclitaxel 175 mg/m <sup>2</sup> IV over 3 hours day 1 Carboplatin AUC 6 IV day 1 Repeat cycle every 21 days for 6 cycles <sup>f</sup>
Vinorelbine/cisplatin	Vinorelbine 25 mg/m <sup>2</sup> IV weekly Cisplatin 100 mg/m <sup>2</sup> IV day 1 Repeat cycle every 28 days <sup>e</sup> <i>or</i> Vinorelbine 30 mg/m <sup>2</sup> IV days 1 and 8 Cisplatin 80 mg/m <sup>2</sup> IV day 1 Repeat cycle every 21 days <sup>d</sup>
Etoposide/cisplatin	Etoposide 100 mg/m <sup>2</sup> IV days 1, 2, and 3 Cisplatin 100 mg/m <sup>2</sup> IV day 1 Repeat cycle every 28 days <sup>b</sup>
Vinorelbine/gemcitabine	Vinorelbine 25 mg/m <sup>2</sup> IV days 1 and 8 Gemcitabine 1,000 mg/m <sup>2</sup> days 1 and 8 Repeat cycle every 21 days <sup>d,h</sup>
Paclitaxel/gemcitabine	Paclitaxel 175 mg/m <sup>2</sup> IV over 3 hours day 1 Gemcitabine 1,250 mg/m <sup>2</sup> days 1 and 8 Repeat cycle every 21 days <sup>c</sup>
Gemcitabine/docetaxel	Gemcitabine 1,000 mg/m <sup>2</sup> IV days 1 and 8 Docetaxel 100 mg/m <sup>2</sup> IV day 8 Repeat cycle every 21 days <sup>i</sup>
Paclitaxel/vinorelbine	Paclitaxel 135 mg/m <sup>2</sup> IV day 1 Vinorelbine 25 mg/m <sup>2</sup> IV day 1 Repeat cycle every 14 days for nine cycles <sup>f</sup>

*(continued)*

**TABLE 63-1** Common Chemotherapy Regimens Used to Treat Lung Cancer (Continued)**Small cell lung carcinoma<sup>m</sup>**

Etoposide/cisplatin	Cisplatin 80 mg/m <sup>2</sup> IV day 1 Etoposide 100 mg/m <sup>2</sup> IV days 1, 2, and 3 Repeat cycle every 3 weeks <sup>j,k</sup>
	<i>or</i>
	Cisplatin 60 mg/m <sup>2</sup> IV day 1 Etoposide 120 mg/m <sup>2</sup> IV days 1, 2, and 3 Repeat cycle every 3 weeks <sup>l</sup>
Cisplatin/irinotecan	Cisplatin 60 mg/m <sup>2</sup> IV day 1 Irinotecan 60 mg/m <sup>2</sup> IV days 1, 8, and 15 Repeat cycle every 4 weeks <sup>j,k</sup>
	<i>or</i>
	Cisplatin 30 mg/m <sup>2</sup> IV day 1 Irinotecan 65 mg/m <sup>2</sup> IV days 1 and 8 Repeat cycle every 3 weeks <sup>l</sup>

AUC, area under the curve.

<sup>a</sup>National Comprehensive Cancer Network, 2007. [http://www.nccn.org/professionals/physician\\_gls/default.asp](http://www.nccn.org/professionals/physician_gls/default.asp).

<sup>b</sup>Schiller JH, Harrington D, Belani CP, et al. *N Engl J Med* 2002;346:92–98.

<sup>c</sup>Smit EF, van Meerbeeck JP, Lianes P, et al. *J Clin Oncol* 2003;21:3909–3917.

<sup>d</sup>Gridelli C, Gallo C, Shepherd FA, et al. *J Clin Oncol* 2003;21:3025–3034.

<sup>e</sup>Kelly K, Crowley J, Bunn PA, Jr, et al. *J Clin Oncol* 2001;19:3210–3218.

<sup>f</sup>Stathopoulos GP, Veslemes M, Georgatou N, et al. *Ann Oncol* 2004;15:1048–1055.

<sup>g</sup>Kelly K, Crowley J, Bunn PA, Jr, et al. *J Clin Oncol* 2001;19:3210–3218.

<sup>h</sup>Lilenbaum RC, Chen CS, Chidiac T, et al. *Ann Oncol* 2005;16:97–101.

<sup>i</sup>Georgoulas V, Ardavanis A, Tsiafaki X, et al. *J Clin Oncol* 2005;23:2937–2945.

<sup>j</sup>Noda K, Nishiwaki Y, Kawahara M, et al. *N Engl J Med* 2002;346:85–91.

<sup>k</sup>Lara PN Jr, Gandara DR, Natale RB. *Clin Lung Cancer* 2006;7:353–356.

<sup>l</sup>Hanna N, Bunn PA Jr, Langer C, et al. *J Clin Oncol* 2006;24:2038–2043.

<sup>m</sup>National Comprehensive Cancer Network, 2007. [http://www.nccn.org/professionals/physician\\_gls/default.asp](http://www.nccn.org/professionals/physician_gls/default.asp).

- **Docetaxel, pemetrexed,** and an oral epidermal growth factor receptor inhibitor, **erlotinib,** are options for unresectable stage III or IV NSCLC patients with good performance status who progress during or after first-line therapy.
- **Bevacizumab,** a recombinant, humanized monoclonal antibody, neutralizes vascular endothelial growth factor. The addition of bevacizumab to doublet chemotherapy is recommended in advanced NSCLC of nonsquamous cell histology in patients with no history of hemoptysis and no CNS metastasis who are not receiving therapeutic anticoagulation.
- Palliative radiation therapy with chemotherapy may help control local and systemic disease and reduce disease-related symptoms. The optimal delivery method, schedule and radiation therapy dosages when used with chemotherapy are yet to be determined.

## SMALL CELL LUNG CANCER

### Desired Outcome

- The goal of treatment is cure or prolonged survival, which requires aggressive combination chemotherapy.

### Surgery and Radiation Therapy

- Surgery is almost never indicated because SCLC disseminates early in the disease.

- SCLC is very radiosensitive. Radiotherapy has been combined with chemotherapy to treat limited disease SCLC. This combined-modality therapy prevents local tumor recurrences but only modestly improves survival over chemotherapy alone.
- Radiotherapy is utilized to prevent and treat brain metastases, a frequent occurrence with SCLC. Prophylactic cranial irradiation is used in selected patients to reduce the risk of brain metastases. Neurologic and intellectual impairment are associated with prophylactic cranial irradiation, although other factors may also contribute.
- Radiotherapy followed by combination chemotherapy is recommended for patients with symptomatic brain metastases. **Dexamethasone** and **anticonvulsants** are also administered for symptom control and seizure prevention, respectively.

### Chemotherapy

- Chemotherapy with concurrent radiation is recommended for limited- and extensive-disease SCLC. Single-agent chemotherapy is inferior to doublet chemotherapy.
- The most frequently used regimen is **cisplatin** or **carboplatin** combined with **etoposide**. **Irinotecan** in combination with **cisplatin** has also been shown to be active (see Table 63-1). Overall response rates and survival durations are generally superior for patients with limited stage versus those with extensive stage disease.
- Recurrent SCLC is usually less sensitive to chemotherapy. If recurrence is more than 6 months after induction chemotherapy, the original regimen can be repeated. If recurrence occurs in less than 6 months but >3 months, treatment options include a **taxane**, **gemcitabine**, **topotecan**, irinotecan, CAV (**cyclophosphamide**, **doxorubicin**, and **vincristine**), and **vinorelbine**.
- Patients with SCLC that recurs within 3 months of first-line chemotherapy are considered refractory to chemotherapy and unlikely to respond to a second-line regimen.

## EVALUATION OF THERAPEUTIC OUTCOMES

- Efficacy of induction therapy for SCLC should be determined after two to three cycles of chemotherapy. If there is no response or progressive disease, therapy can be discontinued or changed to a non-cross-resistant regimen. If responsive to chemotherapy, the induction regimen should be administered for four to six cycles.
- Intensive therapeutic monitoring is required for all lung cancer patients to avoid drug-related and radiotherapy-related toxicities. These patients frequently have numerous concurrent medical problems requiring close attention.
- References should be consulted for management of common toxicities associated with the aggressive chemotherapy regimens used for lung cancer.

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*See Chap. 132, Lung Cancer, authored by Jeannine S. McCune and Deborah A. Frieze, for a more detailed discussion of this topic.*

## DEFINITION

- Lymphomas are a heterogeneous group of malignancies that arise from immune cells residing predominantly in lymphoid tissues. Differences in histology have led to classification as Hodgkin's and non-Hodgkin's lymphoma (HL and NHL, respectively), which are addressed separately in this chapter.

## HODGKIN'S LYMPHOMA

### PATHOPHYSIOLOGY

- Current hypotheses indicate that B-cell transcriptional processes are disrupted, which prevent expression of B-cell surface markers and production of immunoglobulin messenger RNA. Alterations in the normal apoptotic pathways favor cell survival and proliferation.
- Malignant Reed-Sternberg cells overexpress nuclear factor- $\kappa$  B, which is associated with cell proliferation and anti-apoptotic signals. Infections with viral and bacterial pathogens upregulate nuclear factor- $\kappa$  B. Epstein-Barr virus is found in many, but not all, HL tumors.

### CLINICAL PRESENTATION

- Most patients with HL present with a painless, rubbery lymph node. Adenopathy is usually localized to the cervical region but can also occur in the mediastinal, hilar, and retroperitoneal regions.
- Constitutional, or "B," symptoms (e.g., fever, night sweats, weight loss, and pruritus) are present at diagnosis in approximately 25% of patients with HL.

### DIAGNOSIS AND STAGING

- Diagnosis requires the presence of Reed-Sternberg cells in the lymph node biopsy.
- Staging is performed to provide prognostic information and to guide therapy. Clinical staging is based on noninvasive procedures such as history, physical examination, laboratory tests, and radiography. Pathologic staging is based on biopsy findings of strategic sites (e.g., muscle, bone, skin, spleen, abdominal nodes) using an invasive procedure (e.g., laparoscopy).
- Approximately half of the patients have localized disease (stages I, II, and IIE). The other half has advanced disease at diagnosis, of which 10% to 15% is stage IV.
- Prognosis predominantly depends on age and stage; patients older than 65 to 70 years are 50% as likely to be cured as younger patients. Patients with limited stage disease (stages I to II) have a 90% to 95% cure rate, whereas those with advanced disease (stages III to IV) have a 65% to 75% cure rate.

## TREATMENT SUMMARY

- The treatment goal for HL is to maximize curability while minimizing treatment-related complications.
- Treatment options include radiation therapy, chemotherapy, or both (combined-modality therapy). The therapeutic role of surgery is limited, regardless of stage.
- Combination chemotherapy is the primary treatment modality for most HL patients.
- Radiation therapy is an integral part of treatment and can be used alone for selected patients with early-stage disease, although most patients will receive chemotherapy and radiation. Involved-field radiation therapy targets a single field of HL. Extended-field or subtotal nodal radiation targets the involved field and an uninvolved area. Total nodal radiation therapy targets all areas.
- Long-term complications of radiotherapy, chemotherapy, and chemoradiotherapy include gonadal dysfunction, secondary malignancies, and cardiac disease. Patients treated for HL are at increased risk of developing leukemia, GI tumors, lung cancer, and breast cancer.

**TABLE 64-1** General Treatment Recommendations for Hodgkin's Lymphoma<sup>a,b</sup>

Early-stage disease	
Favorable prognosis (CS I or II with no risk factors)	Extended-field radiation or two cycles of Stanford V or four cycles of ABVD followed by involved-field radiation
Unfavorable prognosis (CS I or II with risk factors [e.g., B symptoms, extranodal disease, bulky disease, three or more sites of nodal involvement, or an erythrocyte sedimentation rate >50])	2–4 cycles of ABVD plus involved-field radiation
Advanced-stage disease	
Favorable prognosis (CS III or IV)	6–8 cycles of ABVD plus radiation to residual lymphoma or sites of bulky disease
Unfavorable prognosis (CS III or IV with four or more poor prognostic factors [e.g., low serum albumin, low hemoglobin, male gender, age ≥45 years, high white blood cell count])	6–8 cycles of escalated-dose BEACOPP plus radiation to residual lymphoma or sites of bulky disease
Relapsed disease	
Relapse after radiation	6–8 cycles of chemotherapy with or without radiation (treat as if this were primary advanced disease)
Relapse after primary chemotherapy <sup>c</sup>	Salvage chemotherapy at conventional doses or high-dose chemotherapy and autologous hematopoietic stem cell transplantation

ABVD, Adriamycin, bleomycin, vinblastine, and dacarbazine; BEACOPP, bleomycin, etoposide, Adriamycin, cyclophosphamide, Oncovin, procarbazine, and prednisone; CS, clinical stage.

<sup>a</sup>Patients should be considered for clinical trials when possible.

<sup>b</sup>In general, patients with large mediastinal adenopathy should be treated with chemotherapy followed by radiation to the mediastinum.

<sup>c</sup>A standard regimen or approach does not exist.

See Table 64-2 for details of chemotherapy regimens.

**Initial Chemotherapy**

- Two to 8 cycles of chemotherapy should be administered, depending on the stage of disease and presence of risk factors (Tables 64-1 and 64-2).

**Salvage Chemotherapy**

- Response to salvage therapy depends on the extent and site of recurrence, previous therapy, and duration of first remission. Choice of salvage therapy should be guided by response to initial therapy and a patient's ability to tolerate therapy.
- Patients who relapse after an initial complete response can be treated with the same regimen, a non-cross-resistant regimen, radiation therapy, or high-dose chemotherapy and autologous hematopoietic stem cell transplantation (HSCT).
- Lack of complete remission after initial therapy or relapse within one year after completing initial therapy is associated with poor prognosis. Patients with these prognostic factors are candidates for high-dose chemotherapy and HSCT.

**NON-HODGKIN'S LYMPHOMA****PATHOPHYSIOLOGY**

- Chromosomal translocations have become a hallmark of many lymphomas and are helpful in the diagnosis and classification of lymphoid malignancies. NHL often involves extranodal sites and does not spread through contiguous lymph nodes.
- NHLs are derived from monoclonal proliferation of B or, less commonly, T lymphocytes and their precursors. Two categories of B- and T-cell neoplasms are "precursor" neoplasms corresponding to the earliest stages of differentiation, and "peripheral" neoplasms corresponding to the more differentiated cell stages.

**CLINICAL PRESENTATION**

- Patients present with a variety of symptoms, which depend on the site of involvement and whether it is nodal or extranodal.
- Adenopathy can be localized or generalized. Involved nodes are painless, rubbery, and discrete and are usually located in the cervical and supraclavicular regions. Mesenteric or GI involvement can cause nausea, vomiting, obstruction, abdominal pain, palpable abdominal mass, or GI bleeding. Bone marrow involvement can cause symptoms related to anemia, neutropenia, or thrombocytopenia.
- Forty percent of patients with NHL present with B symptoms—fever, night sweats, and weight loss.

**DIAGNOSIS AND STAGING**

- Diagnosis is established by biopsy of an involved lymph node.
- Diagnostic workup of NHL is generally similar to that of HL.
- Systems for classifying NHLs continue to evolve. Lymphomas can be classified by degree of aggressiveness. Slow-growing or indolent lympho-

**TABLE 64-2** Combination Chemotherapy Regimens for Hodgkin's Lymphoma

Drug	Dosage (mg/m <sup>2</sup> )	Route	Days
<b>MOPP</b>			
Mechlorethamine	6	IV	1, 8
Vincristine	1.4	IV	1, 8
Procarbazine	100	Oral	1-14
Prednisone	40	Oral	1-14
Repeat every 21 days			
<b>ABVD</b>			
Adriamycin (doxorubicin)	25	IV	1, 15
Bleomycin	10	IV	1, 15
Vinblastine	6	IV	1, 15
Dacarbazine	375	IV	1, 15
Repeat every 28 days			
<b>MOPP/ABVD</b>			
Alternating months of MOPP and ABVD			
<b>MOPP/ABV hybrid</b>			
Mechlorethamine	6	IV	1
Vincristine	1.4	IV	1
Procarbazine	100	Oral	1-7
Prednisone	40	Oral	1-14
Doxorubicin	35	IV	8
Bleomycin	10	IV	8
Vinblastine	6	IV	8
Repeat every 28 days			
<b>Stanford V</b>			
Doxorubicin	25	IV	Weeks 1, 3, 5, 7, 9, 11
Vinblastine	6	IV	Weeks 1, 3, 5, 7, 9, 11
Mechlorethamine	6	IV	Weeks 1, 5, 9
Etoposide	60	IV	Weeks 3, 7, 11
Vincristine	1.4 <sup>a</sup>	IV	Weeks 2, 4, 6, 8, 10, 12
Bleomycin	5	IV	Weeks 2, 4, 6, 8
Prednisone	40	Oral	Every other day for 12 weeks; begin tapering at week 10
One course (12 weeks)			
<b>BEACOPP (baseline)</b>			
Bleomycin	10	IV	8
Etoposide	100	IV	1-3
Adriamycin (doxorubicin)	25	IV	1
Cyclophosphamide	650	IV	1
Oncovin (vincristine)	1.4 <sup>a</sup>	IV	8
Procarbazine	100	Oral	1-7
Prednisone	40	Oral	1-14
Repeat every 21 days			
<b>BEACOPP (escalated)</b>			
Bleomycin	10	IV	8
Etoposide	200	IV	1-3
Adriamycin (doxorubicin)	35	IV	1
Cyclophosphamide	1,250	IV	1
Oncovin (vincristine)	1.4 <sup>a</sup>	IV	8
Procarbazine	100	Oral	1-7

(continued)

**TABLE 64-2** Combination Chemotherapy Regimens for Hodgkin's Lymphoma (Continued)

Drug	Dosage (mg/m <sup>2</sup> )	Route	Days
Prednisone	40	Oral	1–14
Granulocyte colony-stimulating factor		Subcutaneously	8+
Repeat every 21 days			

<sup>a</sup>Vincristine dose capped at 2 mg.

mas are favorable (untreated survival measured in years), whereas rapid-growing or aggressive lymphomas are unfavorable (untreated survival measured in weeks to months).

- Prognosis depends on histologic subtype and clinical risk factors (e.g., age more than 60 years, performance status of 2 or more, elevated lactic dehydrogenase, extranodal involvement, and stage III or IV disease). These risk factors are used to calculate the International Prognostic Index.
- A newer prognostic index uses similar risk factors except that poor performance status is replaced with low hemoglobin (less than 12 g/dL). Current research is focused on the prognostic importance of phenotypic and molecular characteristics of NHL.

## DESIRED OUTCOME

- The primary treatment goals for NHL are to relieve symptoms and, whenever possible, cure the patient of disease without causing unacceptable toxicity.

## TREATMENT

### General Principles

- Appropriate therapy for NHL depends on many factors including patient age, histologic type, stage and site of disease, presence of adverse prognostic factors, and patient preference.
- Treatment is divided into two categories: limited disease (e.g., localized disease; Ann Arbor stages I and II) and advanced disease (e.g., Ann Arbor stage III or IV and stage II patients with poor prognostic features).
- Treatment options include radiation therapy, chemotherapy, and biologic agents.
- Radiation therapy is rarely suitable for remission induction because NHL is rarely localized at diagnosis. Radiation therapy is used more commonly in advanced disease, mainly as a palliative measure.
- Effective chemotherapy ranges from single-agent therapy for indolent lymphomas to aggressive, complex combination regimens for aggressive lymphomas. Paradoxically, indolent or favorable lymphomas are rarely curable, whereas aggressive or unfavorable lymphomas are potentially curable.
- Treatment strategies are summarized for the most common NHLs as examples of how to treat indolent (i.e., follicular) and aggressive (i.e.,

diffuse large B-cell) lymphomas. Strategies are also summarized for acquired immune deficiency syndrome (AIDS)–related lymphoma.

### Indolent Lymphomas

- Follicular lymphomas occur in older adults with a majority having advanced disease at diagnosis. The clinical course is generally indolent, with median survival of 8 to 10 years. The natural history of follicular lymphoma is unpredictable with spontaneous regression of objective disease seen in 20% to 30% of patients.

#### *Localized Follicular Lymphoma*

- Options for stage I and II follicular lymphoma include locoregional radiation therapy, chemotherapy followed by radiation therapy, and extended-field radiation therapy.
- Radiation therapy is the standard treatment and is usually curative. Chemotherapy is not recommended, unless the patient has high-risk, stage II disease.

#### *Advanced Follicular Lymphoma*

- Management of stages III and IV indolent lymphoma is controversial because standard approaches are not curative. Time to relapse is only 18 to 36 months. After relapse, response can be reinduced; however, response rates and durations decrease with each retreatment.
- Therapeutic options are diverse and include watchful waiting, single-agent therapy, combination chemotherapy, biologic therapy, radioimmunotherapy, and combined-modality therapy. Immediate aggressive therapy does not improve survival compared with conservative therapy (i.e., watchful waiting followed by single-agent chemotherapy, **rituximab** or radiation therapy, only when needed).
- Oral alkylating agents, **chlorambucil**, 0.1 to 0.2 mg/kg, or **cyclophosphamide**, 1.5 to 2.5 mg/kg (adjusted to white blood cell and platelet counts), are the mainstay of treatment. These single agents are as effective as combination regimens and produce minimal toxicity, but secondary acute myelogenous leukemia (AML) is a concern. **Fludarabine** and **cladribine** produce high response rates without secondary AML, but they are more myelosuppressive.
- **Rituximab**, a chimeric monoclonal antibody directed at the CD20 molecule on B cells, has become one of the most widely used therapies for follicular lymphoma. Rituximab is approved for first-line therapy either alone or combined with chemotherapy and as maintenance therapy for patients with stable disease or with partial or complete response following induction chemotherapy.
- The rituximab dosage is 375 mg/m<sup>2</sup> weekly for 4 weeks. Maintenance schedules include 375 mg/m<sup>2</sup> weekly for 4 weeks every 6 months for 2 years or 375 mg/m<sup>2</sup> every 2 to 3 months for 1 to 2 years. Maintenance rituximab significantly prolongs progression-free and overall survival as compared with observation or initiation of rituximab at the time of disease progression.
- Adverse effects are usually infusion related, especially after the first infusion of rituximab. Adverse effects include fever, chills, respiratory

symptoms, fatigue, headache, pruritus, and angioedema. Patients should receive **acetaminophen**, 650 mg, and **diphenhydramine**, 50 mg, 30 minutes before the infusion.

- Anti-CD20 radioimmunoconjugates are mouse antibodies linked to radioisotopes (e.g., <sup>131</sup>I-**tositumomab** and <sup>90</sup>Y-**ibritumomab tiuxetan**). They have the advantage of delivering radiation to tumor cells expressing the CD20 antigen and to adjacent tumor cells that do not express it. They have the disadvantage of damaging adjacent normal tissue (e.g., bone marrow).
- Radioimmunotherapy was initially used as salvage therapy and is being evaluated as first-line therapy in combination with CHOP (cyclophosphamids, doxorubicin, vincristine, and prednisone).
- Radioimmunotherapy is generally well tolerated. Toxicities include infusion-related reactions, myelosuppression, and possibly myelodysplastic syndrome or AML. <sup>131</sup>I-tositumomab can cause thyroid dysfunction.
- The decision to use radioimmunotherapy requires consideration of the complexity, risks, and cost. The ideal candidate has limited bone marrow involvement and adequate blood cell counts.
- High-dose chemotherapy followed by HSCT is an option for relapsed follicular lymphoma. The recurrence rate is lower after allogeneic than after autologous HSCT, but the benefit is offset by increased treatment-related mortality. The ideal candidate is young and does not have serious comorbidities.

### Aggressive Lymphomas

- Diffuse large B-cell lymphomas are the most common lymphoma in patients of all ages but most commonly seen in the seventh decade. Extranodal disease is present at diagnosis in 30% to 40% of patients. The International Prognostic Index score correlates with prognosis. Diffuse aggressive lymphomas are sensitive to chemotherapy with cure achieved in some patients.

#### Early-Stage Diffuse Large B-Cell Lymphoma

- Stage I and nonbulky stage II should be treated with three to four cycles of rituximab and CHOP (R-CHOP) (Table 64-3) followed by locoregional radiation therapy.
- Patients with at least one adverse risk factor should receive six to eight cycles of R-CHOP followed by locoregional radiation therapy.

**TABLE 64-3** Combination Chemotherapy for Non-Hodgkin's Lymphoma (CHOP)<sup>a,b</sup>

Drug	Dose (mg/m <sup>2</sup> )	Route	Days
Cyclophosphamide	750	IV	1
Doxorubicin	50	IV	1
Vincristine	1.4	IV	1
Prednisone	100	Oral	1-5

<sup>a</sup>Cycle should be repeated every 21 days.

<sup>b</sup>Rituximab 375 mg/m<sup>2</sup> on day 1 is commonly added (R-CHOP).

### Advanced Diffuse Large B-Cell Lymphoma Disease

- Bulky stage II and stages III and IV lymphoma should be treated with R-CHOP or rituximab and CHOP-like chemotherapy until achieving complete response (usually four cycles). Two or more additional cycles should be given following complete response for a total of six to eight cycles. Maintenance therapy following a complete response does not improve survival.
- High-dose chemotherapy with autologous HSCT should be considered in high-risk patients who respond to standard chemotherapy and are candidates for autologous HSCT.
- Although historically, elderly adults have lower complete response and survival rates than younger patients, full dose R-CHOP is recommended as initial treatment for aggressive lymphoma in the elderly.

### Salvage Therapy for Aggressive Lymphoma

- Approximately one-third of patients with aggressive lymphoma will require salvage therapy at some point. Salvage therapy is more likely to induce response if the response to initial chemotherapy was complete (chemosensitivity) than if it was primarily or partially resistant to chemotherapy.
- High-dose chemotherapy with autologous HSCT is the therapy of choice for younger patients with chemosensitive relapse.
- Salvage regimens incorporate drugs not used as initial therapy. Commonly used regimens include DHAP (**dexamethasone**, high-dose **cytarabine**, and **cisplatin**), ESHAP (**etoposide**, **methylprednisolone**, high-dose cytarabine, and cisplatin), and MINE (**mesna**, **ifosfamide**, **mitoxantrone**, and **etoposide**). None is clearly superior to the others.
- ICE (**ifosfamide**, **carboplatin**, and **etoposide**) appears to be better tolerated than cisplatin-containing regimens, especially in elderly adults.
- Rituximab is being evaluated in combination with many salvage regimens.

### Non-Hodgkin's Lymphoma in Acquired Immune Deficiency Syndrome

- Patients with AIDS have more than a 100-fold increased risk of developing NHL, which is usually aggressive.
- Treatment of AIDS-related lymphoma is difficult because underlying immunodeficiency increases the risk of treatment-related myelosuppression.
- Standard combination regimens (e.g., CHOP) yield disappointing results. Newer approaches including dose-adjusted EPOCH (**etoposide**, **prednisone**, **vincristine**, **cyclophosphamide**, and **doxorubicin**), and rituximab-containing combination chemotherapy are promising.
- Antiretroviral therapy and prophylactic antibiotics should be continued during chemotherapy.

## EVALUATION OF THERAPEUTIC OUTCOMES

- The primary outcome to be identified is tumor response, which is based on physical examination, radiologic evidence, and other baseline findings. Complete response is desirable because it yields the only chance for cure.

- Patients are evaluated for response at the end of four cycles or, if treatment is shorter, at the end of treatment.
- Optimal outcomes for most types of lymphoma may require delivery of full doses on time. Hematopoietic growth factors and other supportive care measures are often needed to achieve this goal.
- To optimize chemotherapy administration, the clinician must identify, monitor, treat, and prevent or minimize treatment-related toxicity. Pertinent laboratory data and other procedures should be reviewed to establish a baseline for monitoring purposes. Major organ and system toxicities to be monitored include hematologic, neurologic, skin, pulmonary, GI, renal, and cardiac.

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*See Chap. 135, Lymphomas, authored by Val R. Adams and Gary C. Yee, for a more detailed discussion of this topic.*

**DEFINITION**

- Prostate cancer is a malignant neoplasm that arises from the prostate gland. Prostate cancer has an indolent course; localized prostate cancer is curable by surgery or radiation therapy but advanced prostate cancer is not yet curable.

**PATHOPHYSIOLOGY**

- The normal prostate is composed of acinar secretory cells that are altered when invaded by cancer. The major pathologic cell type is adenocarcinoma (more than 95% of cases).
- Prostate cancer can be graded. Well-differentiated tumors grow slowly, whereas poorly differentiated tumors grow rapidly and have a poor prognosis.
- Metastatic spread can occur by local extension, lymphatic drainage, or hematogenous dissemination. Skeletal metastases from hematogenous spread are the most common sites of distant spread. The lung, liver, brain, and adrenal glands are the most common sites of visceral involvement, but these organs are not usually involved initially.

**CLINICAL PRESENTATION**

- Localized prostate cancer is usually asymptomatic.
- Locally invasive prostate cancer is associated with ureteral dysfunction or impingement, such as alterations in micturition (e.g., urinary frequency, hesitancy, dribbling).
- Patients with advanced disease commonly present with back pain and stiffness due to osseous metastases. Untreated spinal cord lesions can lead to cord compression. Lower extremity edema can occur as a result of lymphatic obstruction. Anemia and weight loss are nonspecific signs of advanced disease.

**SCREENING**

- Screening for prostate cancer is controversial. The American Cancer Society recommends baseline prostate-specific antigen (PSA) and digital rectal exam (DRE) beginning at age 50 years for men of normal risk. Earlier testing is recommended for men at higher risk for prostate cancer.
- DRE is commonly employed for screening of prostate cancer. It has the advantages of specificity, low cost, safety, and ease of performance. DRE has the disadvantages of relative insensitivity and of inter-observer variability.
- PSA is a glycoprotein produced and secreted by the epithelial cells of the prostate gland. Acute urinary retention, acute prostatitis, and benign prostatic hypertrophy (BPH) influence PSA, therefore limiting the usefulness of PSA alone for early detection. PSA is a useful marker for monitoring response to therapy.

## TREATMENT

### CHEMOPREVENTION

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- The risk of prostate cancer was reduced 25% in patients taking **finasteride** for treatment of BPH.
- Prostate cancer diagnosed in patients on finasteride is more aggressive, making its use in men without BPH controversial.

### GENERAL APPROACH TO TREATMENT

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- The initial treatment for prostate cancer depends on the disease stage, Gleason score, presence of symptoms, and patient's life expectancy. The most appropriate therapy for early-stage prostate cancer is unknown.
- Expectant management, also known as *observation* or *watchful waiting*, involves monitoring the course of the disease and initiating treatment if disease progresses or the patient becomes symptomatic. PSA and DRE are performed every 6 months.
- Radical prostatectomy and radiation therapy are generally considered equivalent for localized prostate cancer, and neither has been shown to be superior to observation alone.
- Men with disease confined to the prostate ( $T_1$  or  $T_{2a}$ ), no symptoms, Gleason score of 2 to 6, or PSA of less than 10 ng/mL are at low risk for recurrence and have a high 10-year survival rate. If life expectancy is less than 10 years, options are expectant management or radiation therapy. If life expectancy is more than 10 years, options are expectant management, radiation, or radical prostatectomy.
- Men with disease involving more than one-half of one lobe or both lobes ( $T_{2bc}$ ), Gleason score of 7, or PSA of 10 to 20 ng/mL are at intermediate risk for recurrence. If life expectancy is less than 10 years, options are expectant management, radiation therapy, or radical prostatectomy. If life expectancy is more than 10 years, options are prostatectomy or radiation therapy.
- Men with disease localized to the periprostatic area ( $T_3$ ), Gleason score of 8 to 10, or PSA of more than 20 ng/mL are at high risk for recurrence and should be treated with androgen ablation for 2 to 3 years combined with radiation therapy. Radical prostatectomy can be considered in patients with low tumor volume.
- Men with disease fixed or invading adjacent structures other than the seminal vesicles ( $T_4$ ) are at very high risk for recurrence. Androgen ablation should be initiated at diagnosis instead of waiting for the onset of symptoms.
- The major initial treatment modality for advanced prostate cancer is androgen ablation (e.g., orchiectomy or luteinizing hormone-releasing hormone [LHRH] agonists with or without antiandrogens). After disease progression, secondary hormonal manipulations, cytotoxic chemotherapy, and supportive care are used.

### SURGERY AND RADIATION THERAPY

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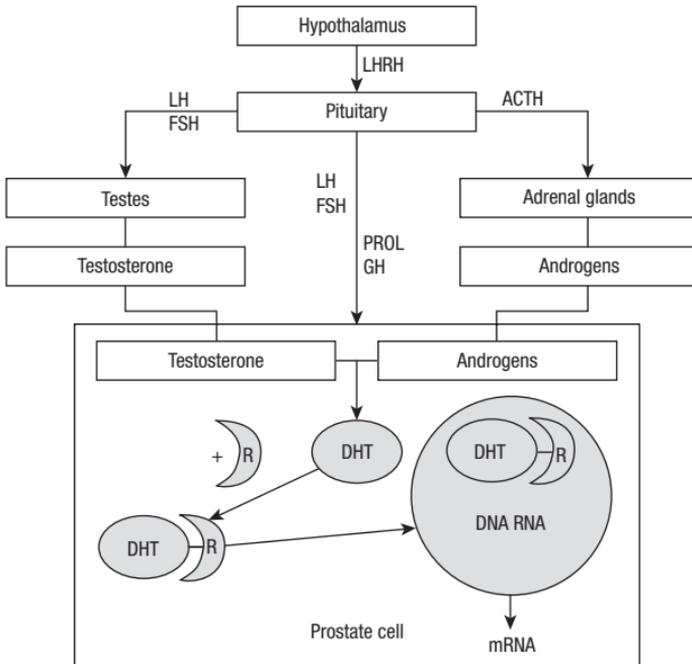
- Prostatectomy and radiation therapy are potentially curative but are associated with complications that must be weighed against expected

benefit. Consequently, many patients postpone therapy until the onset of symptoms.

- Complications of radical prostatectomy include blood loss, stricture formation, incontinence, lymphocele, fistula formation, anesthetic risk, and impotence. Nerve-sparing techniques facilitate return of sexual potency after prostatectomy.
- Acute complications of radiation therapy include cystitis, proctitis, hematuria, urinary retention, penoscrotal edema, and impotence.
- Chronic complications of radiation therapy include proctitis, diarrhea, cystitis, enteritis, impotence, urethral stricture, and incontinence.
- Bilateral orchiectomy rapidly reduces circulating androgen levels. Many patients are not surgical candidates owing to advanced age or perceived unacceptability. Nonetheless, orchiectomy is the preferred initial treatment for patients with impending spinal cord compression or ureteral obstruction.

## HORMONAL THERAPY

- The rationale for hormonal therapy is based on the effect of androgens on the growth and differentiation of the normal prostate (Fig. 65-1).



**FIGURE 65-1.** Hormonal regulation of the prostate gland. (ACTH, adrenocorticotropic hormone; DHT, dihydrotestosterone; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; LHRH, luteinizing hormone-releasing hormone; mRNA, messenger RNA; PROL, prolactin; R, receptor.)

- The testes and the adrenal glands are the major sources of androgens, specifically dihydrotestosterone (DHT).
- LHRH from the hypothalamus stimulates the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary gland.
- LH complexes with receptors on the Leydig cell testicular membrane and stimulates the production of testosterone and small amounts of estrogen.
- FSH acts on testicular Sertoli cells to promote maturation of LH receptors and produce an androgen-binding protein.
- Circulating testosterone and estradiol influence the synthesis of LHRH, LH, and FSH by a negative-feedback loop at the hypothalamic and pituitary level.
- Only 2% of total plasma testosterone is present in the active unbound state that penetrates the prostate cell, where it is converted to DHT by 5  $\alpha$ -reductase. DHT subsequently binds with a cytoplasmic receptor and is transported to the cell nucleus where transcription and translation of stored genetic material occur.

### Luteinizing Hormone-Releasing Hormone Agonists

- LHRH agonists provide response rates of approximately 80%, which is similar to that of orchiectomy, and have the advantage of being reversible.
- There are no comparative trials of LHRH agonists, so the choice is usually based on cost (Table 65-1) and on patient and physician preference. **Leuprolide acetate** is administered daily. **Leuprolide depot** and **goserelin acetate implant** can be administered monthly, or every 12 or 16 weeks.
- The most common adverse effects of LHRH agonists are disease flare-up during the first week of therapy (e.g., increased bone pain, urinary symptoms), hot flashes, erectile impotence, decreased libido, and injection-site reactions.

### Antiandrogens

- Monotherapy with **flutamide**, **bicalutamide**, and **nilutamide** is no longer recommended due to decreased survival as compared with patients treated with LHRH agonist therapy or orchiectomy. Antiandrogens are indicated for advanced prostate cancer only when combined with an LHRH agonist (flutamide and bicalutamide) or orchiectomy (nilutamide). In combination, antiandrogens can reduce the LHRH agonist-induced flare.
- The adverse effects of antiandrogens are gynecomastia, hot flashes, GI disturbances, liver function test abnormalities, and breast tenderness. GI disturbances consist of diarrhea for flutamide and bicalutamide and nausea or constipation for nilutamide. Flutamide is also associated with methemoglobinemia, whereas nilutamide causes visual disturbances (impaired dark adaptation), alcohol intolerance, and interstitial pneumonitis.

### Combined Hormonal Blockade

- The role of combined hormonal therapy, also referred to as maximal androgen deprivation or total androgen blockade, continues to be evaluated.
- Randomized trial results are mixed when candidates for second-line therapy are treated with combinations of antiandrogens plus either LHRH

**TABLE 65-1** Comparative Costs of Hormonal Therapy for Advanced Prostate Cancer

Drug	Dose	Annual Cost (Based on AWP)
Leuprolide depot	7.5 mg/mo	\$709.20/mo; \$8,510/yr
Leuprolide depot	22.5 mg/12 wks	\$2,127.59/12 wks; \$8,510/yr
Leuprolide depot	30 mg/16 wks	\$2,836.79/16 wks; \$8,510/yr
Goserelin implant	3.6 mg every 28 days	\$469.99/mo; \$5,640/yr
Goserelin implant	10.8 mg/12 wks	\$1,409.98/12 wks; \$5,640/yr
Triptorelin depot	3.75 mg q 28 day	\$582.00/mo; \$6,984/yr
Triptorelin LA depot	11.25 mg q 84 day	\$1,746.00/84; \$6,984/yr
Flutamide	750 mg/day	\$376.60/mo; \$4,519/yr
Bicalutamide	50 mg/day	\$484.44/mo; \$5,813/yr
Nilutamide	300 mg/day for first month then 150 mg/day	\$728.80 for first month, then \$364.40/mo; \$4,373.80/yr for chronic therapy
<b>Combined Androgen Blockade</b>		<b>Cost Per 3 Months of Therapy (Based on AWP)</b>
Leuprolide depot 22.5 mg/12 wks		
+ flutamide	750 mg/day	\$3,257
+ bicalutamide	50 mg/day	\$3,581
+ nilutamide	150 mg/day	\$3,221
Goserelin depot 10.8 mg/12 wks		
+ flutamide	750 mg/day	\$2,540
+ bicalutamide	50 mg/day	\$2,863
+ nilutamide	150 mg/day	\$2,503
Triptorelin LA depot 11.25 mg every 84 days		
+ flutamide	750 mg/day	\$2,876
+ bicalutamide	50 mg/day	\$3,199
+ nilutamide	150 mg/day	\$2,839

AWP, average wholesale price; LA, long-acting.

Compiled from Thomson PDR, Red Book, Montvale, NJ, 2006.

agonists or orchiectomy. The most recent metaanalysis showed only a slight survival benefit at 5 years for maximal androgen blockade with flutamide or nilutamide (27.6%) compared with conventional medical or surgical castration alone (24.7%).

- Some investigators consider combined androgen blockade to be the initial hormonal therapy of choice for newly diagnosed patients because the major benefit is seen in patients with minimal disease. Some argue that treatment should not be delayed because combined androgen deprivation trials demonstrate a survival advantage for young patients with good performance status and minimal disease who were initially treated with hormonal therapy.
- Until definitive trials are published, it is appropriate to use either LHRH agonist monotherapy or combined androgen blockade as initial therapy for metastatic prostate cancer.

## SALVAGE THERAPY

- The selection of salvage therapy depends on what was used as initial therapy. Radiotherapy can be used after radical prostatectomy. Androgen ablation can be used after radiation therapy or radical prostatectomy.

- If testosterone levels are not suppressed (i.e., greater than 20 ng/dL) after initial LHRH agonist therapy, an antiandrogen or orchiectomy may be indicated. If testosterone levels are suppressed, the disease is considered androgen independent and should be treated with palliative therapy.
- If initial therapy consisted of an LHRH agonist and antiandrogen, then androgen withdrawal should be attempted. Mutations of the androgen receptor may allow antiandrogens to become agonists. Withdrawal produces responses lasting 3 to 14 months in up to 35% of patients.
- Androgen synthesis inhibitors provide symptomatic, but brief, relief in approximately 50% of patients. **Aminoglutethimide** causes adverse effects in 50% of patients, such as lethargy, ataxia, dizziness, and self-limiting rash. The adverse effects of **ketoconazole** are GI intolerance, transient increases in liver and renal function tests, and hypoadrenalism.
- Bisphosphonates such as **pamidronate** and **zoledronic acid** may prevent skeletal morbidity, such as pathologic fractures and spinal code compression, when used for hormone-refractory prostate cancer in patients with clinically significant bone loss. Usual dosages are pamidronate, 90 mg every month, and zoledronic acid, 4 mg every 3 to 4 weeks.
- After hormonal options are exhausted, palliation can be achieved with **strontium-89** or **samarium-153 lexidronam** for bone-related pain, analgesics, glucocorticoids, local radiotherapy, or chemotherapy.

## CHEMOTHERAPY

- **Docetaxel**, 75 mg/m<sup>2</sup> every 3 weeks, combined with **prednisone**, 5 mg twice daily, has been shown to prolong survival in hormone-refractory metastatic prostate cancer. The most common adverse events were nausea, alopecia, and myelosuppression. Docetaxel can also cause fluid retention and peripheral neuropathy.
- The combination of **estramustine** 280 mg by mouth three times daily on days 1 to 5 and docetaxel 60 mg/m<sup>2</sup> on day 2 of a 21-day cycle also improves survival in hormone-refractory metastatic prostate cancer. Estramustine causes a decrease in testosterone and a corresponding increase in estrogen, which results in an increase in thromboembolic events, gynecomastia, and decreased libido.

## EVALUATION OF THERAPEUTIC OUTCOMES

- For definitive, curative therapy, objective parameters to monitor include primary tumor size, involved lymph nodes, and tumor markers such as PSA. PSA level is checked every 6 months for the first 5 years, and then annually.
- With metastatic disease, clinical benefit can be documented by evaluating performance status, weight, quality of life, analgesic requirements, and PSA or DRE at 3-month intervals.
- Patients should be monitored for treatment-related adverse events, especially events that are amenable to intervention.

*See Chap. 134, Prostate Cancer, authored by Jill M. Kolesar, for a more detailed discussion of this topic.*

## DEFINITION

- Glaucomas are ocular disorders characterized by changes in the optic nerve head (optic disk) and by loss of visual sensitivity and field.

## PATHOPHYSIOLOGY

- There are two major types of glaucoma: open-angle glaucoma, which accounts for most cases and is therefore the focus of this chapter, and closed-angle glaucoma.
- In open-angle glaucoma, the specific cause of optic neuropathy is unknown. Increased intraocular pressure (IOP) was historically considered to be the sole cause. Additional contributing factors include increased susceptibility of the optic nerve to ischemia, reduced or dysregulated blood flow, excitotoxicity, autoimmune reactions, and other abnormal physiologic processes.
- Although IOP is a poor predictor of which patients will have visual field loss, the risk of visual field loss increases with increasing IOP. IOP is not constant; it changes with pulse, blood pressure, forced expiration or coughing, neck compression, and posture.
- The balance between the inflow and outflow of aqueous humor determines IOP. Inflow is increased by  $\beta$ -adrenergic agents and decreased by  $\alpha_2$ -,  $\alpha$ -, and  $\beta$ -adrenergic blockers; dopamine blockers; carbonic anhydrase inhibitors (CAIs); and adenylate cyclase stimulators. Outflow is increased by cholinergic agents, which contract the ciliary muscle and open the trabecular meshwork, and by prostaglandin analogs and  $\beta$ - and  $\alpha_2$ -adrenergic agonists, which affect uveoscleral outflow.
- Secondary open-angle glaucoma has many causes including exfoliation syndrome, pigmentary glaucoma, systemic diseases, trauma, surgery, lens changes, ocular inflammatory diseases, and drugs. Secondary glaucoma can be classified as pretrabecular (normal meshwork is covered and prevents outflow of aqueous humor), trabecular (meshwork is altered or material accumulates in the intertrabecular spaces), or posttrabecular (episcleral venous blood pressure is increased).
- Many drugs can increase IOP (Table 66-1). The potential to induce or worsen glaucoma depends on the type of glaucoma and on whether it is adequately controlled.
- Closed-angle glaucoma occurs when there is a physical blockage of the trabecular meshwork, resulting in increased IOP.

**TABLE 66-1** Drugs That May Induce or Potentiate Increased Intraocular Pressure**Open-angle glaucoma**

Ophthalmic corticosteroids (high risk)  
 Systemic corticosteroids  
 Nasal/inhaled corticosteroids  
 Fenoldopam  
 Ophthalmic anticholinergics  
 Succinylcholine  
 Vasodilators (low risk)  
 Cimetidine (low risk)

**Closed-angle glaucoma**

Topical anticholinergics  
 Topical sympathomimetics  
 Systemic anticholinergics  
 Heterocyclic antidepressants  
 Low-potency phenothiazines  
 Antihistamines  
 Ipratropium  
 Benzodiazepines (low risk)  
 Theophylline (low risk)  
 Vasodilators (low risk)  
 Systemic sympathomimetics (low risk)  
 Central nervous system stimulants (low risk)  
 Selective serotonin reuptake inhibitors  
 Imipramine  
 Venlafaxine  
 Topiramate  
 Tetracyclines (low risk)  
 Carbonic anhydrase inhibitors (low risk)  
 Monoamine oxidase inhibitors (low risk)  
 Topical cholinergics (low risk)

**CLINICAL PRESENTATION**

- Open-angle glaucoma is slowly progressive and is usually asymptomatic until the onset of substantial visual field loss. Central visual acuity is maintained, even in late stages.
- In closed-angle glaucoma, patients typically experience intermittent prodromal symptoms (e.g., blurred or hazy vision with halos around lights and occasionally, headache). Acute episodes produce symptoms associated with a cloudy, edematous cornea; ocular pain; nausea, vomiting, and abdominal pain; and diaphoresis.

**DIAGNOSIS**

- The diagnosis of *open-angle glaucoma* is confirmed by the presence of characteristic optic disk changes and visual field loss, with or without increased IOP. *Normal tension glaucoma* refers to disk changes, visual field loss, and IOP of less than 21 mm Hg. *Ocular hypertension* refers to IOP of more than 21 mm Hg without disk changes or visual field loss.

- For *closed-angle glaucoma*, the presence of a narrow angle is usually visualized by gonioscopy. IOP is generally markedly elevated (e.g., 40 to 90 mm Hg) when symptoms are present. Additional signs include hyperemic conjunctiva, cloudy cornea, shallow anterior chamber, and occasionally edematous and hyperemic optic disk.

## DESIRED OUTCOME

- The goal of drug therapy in patients with glaucoma is to preserve visual function by reducing the IOP to a level at which no further optic nerve damage occurs.

## TREATMENT OF OCULAR HYPERTENSION AND OPEN-ANGLE GLAUCOMA

- Treatment is indicated for ocular hypertension if the patient has a significant risk factor such as IOP greater than 25 mm Hg, vertical cup-disk ratio greater than 0.5, or central corneal thickness less than 555 micrometers. Additional risk factors to be considered include family history of glaucoma, black race, severe myopia, and presence of only one eye.
- Treatment is indicated for all patients with elevated IOP and characteristic optic disk changes or visual field defects.
- Drug therapy is the most common initial treatment and is initiated in a stepwise manner, starting with a single well tolerated topical agent (Table 66-2). Historically,  $\beta$ -blockers (e.g., **timolol**) were the treatment of choice and continue to be used if there are no contraindications to potential  $\beta$ -blockade caused by systemic absorption.  $\beta$ -Blockers have the advantage of low cost owing to generic formulations.
- Newer agents are also suitable for first-line therapy. Prostaglandin analogs (e.g., **latanoprost**, **bimatoprost** and **travoprost**) have the advantage of strong potency, unique mechanism suitable for combination therapy, good safety profile, and once-a-day dosing. **Brimonidine** has the theoretical advantage of neuroprotection, which has not yet been demonstrated in humans. Topical CAIs are also suitable for first-line therapy.
- **Pilocarpine** and **dipivefrin**, a prodrug of **epinephrine**, are used as third-line therapies because of adverse events or reduced efficacy as compared with newer agents.
- **Carbachol**, topical cholinesterase inhibitors, and oral CAIs (e.g., **acetazolamide**) are used as last-resort options after failure of less toxic options.
- The optimal timing of laser or surgical trabeculectomy is controversial, ranging from initial therapy to after failure of third- or fourth-line drug therapy. Antiproliferative agents such as **fluorouracil** and **mitomycin C** are used to modify the healing process and maintain patency.

## TREATMENT OF CLOSED-ANGLE GLAUCOMA

- Acute closed-angle glaucoma with high IOP requires rapid reduction of IOP. Iridectomy is the definitive treatment, which produces a hole in the

**TABLE 66-2** Topical Drugs Used in the Treatment of Open-Angle Glaucoma

Drug	Pharmacologic Properties	Common Brand Names	Dose Form	Strength (%)	Usual Dose <sup>a</sup>	Mechanism of Action
<b><math>\beta</math>-Adrenergic blocking agents</b>						
Betaxolol	Relative $\beta_1$ -selective	Generic	Solution	0.5	1 drop twice a day	All reduce aqueous production of ciliary body
		Betoptic-S	Suspension	0.25	1 drop twice a day	
Carteolol	Nonselective, intrinsic sympathomimetic activity	Generic	Solution	1	1 drop twice a day	
Levobunolol	Nonselective	Betagan	Solution	0.25, 0.5	1 drop twice a day	
Metipranolol	Nonselective	OptiPranolol	Solution	0.3	1 drop twice a day	
Timolol	Nonselective	Timoptic, Betimol, Istalol	Solution	0.25, 0.5	1 drop one to two times a day	
		Timoptic-XE	Gelling solution	0.25, 0.5	1 drop every day <sup>a</sup>	
<b>Nonspecific adrenergic agonists</b>						
Dipivefrin	Prodrug	Propine	Solution	0.1	1 drop twice a day	Increased aqueous humor outflow
<b><math>\alpha_2</math>-Adrenergic agonists</b>						
Apraclonidine	Specific $\alpha_2$ -agonists	Iopidine	Solution	0.5, 1	1 drop two to three times a day	Both reduce aqueous humor production; brimonidine known to also increase uveoscleral outflow
Brimonidine		Alphagan P	Solution	0.15, 0.1	1 drop two to three times a day	
<b>Cholinergic agonists direct acting</b>						
Carbachol	Irreversible	Carboptic, Isopto Carbachol	Solution	1.5, 3	1 drop two to three times a day	All increase aqueous humor outflow through trabecular meshwork
Pilocarpine	Irreversible	Isopto Carpine, Pilocar	Solution	0.25, 0.5, 1, 2, 4, 6, 8, 10	1 drop two to three times a day 1 drop four times a day	
		Pilopine HS	Gel	4	Every 24 hours at bedtime	

<b>Cholinesterase inhibitors</b>							
Echothiophate		Phospholine Iodide	Solution	0.125	Once or twice a day		
<b>Carbonic anhydrase inhibitors</b>							
Topical							
Brinzolamide	Carbonic anhydrase type II inhibition	Azopt	Suspension	1	Two to three times a day	All reduce aqueous humor production of ciliary body	
Dorzolamide		Trusopt	Solution	2	Two to three times a day		
Systemic							
Acetazolamide		Generic	Tablet	125 mg, 250 mg	125–250 mg two to four times a day		
			Injection	500 mg/vial	250–500 mg		
Methazolamide		Generic	Diamox Sequels	Capsule	500 mg	500 mg twice a day	
			Tablet	25 mg, 50 mg	25–50 mg two to three times a day		
<b>Prostaglandin analogs</b>							
Latanoprost	Prostaglandin F <sub>2α</sub> analog	Xalatan	Solution	0.005	1 drop every night	Increases aqueous uveoscleral outflow and to a lesser extent trabecular outflow	
Bimatoprost	Prostamide analog	Lumigan	Solution	0.03	1 drop every night		
Travoprost		Travatan, Travatan Z	Solution	0.004	1 drop every night		
<b>Combinations</b>							
Timolol-dorzolamide		Cosopt	Solution	Timolol 0.5% dorzolamide 2%	1 drop twice daily		
Timolol-brimonidine		Combigan	Solution	Timolol 0.5% brimonide 0.2%	1 drop twice daily		

<sup>a</sup>Use of nasolacrimal occlusion will increase number of patients successfully treated with longer dosage intervals.

iris that permits aqueous flow to move directly from the posterior to the anterior chamber.

- Drug therapy of an acute attack typically consists of an osmotic agent and secretory inhibitor (e.g.,  $\beta$ -blocker,  $\alpha_2$  agonist, **latanoprost**, or CAI), with or without pilocarpine.
- Osmotic agents are used because they rapidly decrease IOP. Examples include **glycerin**, 1 to 2 g/kg orally, and **mannitol**, 1 to 2 g/kg IV.
- Although traditionally the drug of choice, pilocarpine use is controversial as initial therapy. Once IOP is controlled, pilocarpine should be given every 6 hours until iridectomy is performed.
- Topical corticosteroids can be used to reduce ocular inflammation and synechiae.
- Epinephrine should be used with caution because it can precipitate acute closed-angle glaucoma, especially when used with a  $\beta$ -blocker.

## EVALUATION OF THERAPEUTIC OUTCOMES

- Successful outcomes require identifying an effective, well-tolerated regimen; closely monitoring therapy; and patient adherence. Whenever possible, therapy for open-angle glaucoma should be started as a single agent in one eye to facilitate evaluation of drug efficacy and tolerance. Many drugs or combinations may need to be tried before the optimal regimen is identified.
- Monitoring therapy for open-angle glaucoma should be individualized. IOP response is assessed every 4 to 6 weeks initially, every 3 to 4 months after IOPs become acceptable, and more frequently after therapy is changed. The visual field and disk changes are monitored annually, unless glaucoma is unstable or worsening.
- Patients should be monitored for tachyphylaxis, especially with  $\beta$ -blockers or **apraclonidine**. Treatment can be temporarily discontinued to monitor its benefit.
- There is no specific target IOP because the correlation between IOP and optic nerve damage is poor. Typically, a 25% to 30% reduction is desired.
- The target IOP also depends on disease severity and is generally less than 21 mm Hg for early visual field loss or optic disk changes, with progressively lower targets for greater damage. Targets as low as less than 10 mm Hg are desired for very advanced disease, continued damage at higher IOPs, normal tension glaucoma, and pretreatment pressures in the low- to mid-teens.
- Using more than one drop per dose increases the risk of adverse events and cost, but not efficacy.
- Patients should be educated about possible adverse effects and methods for preventing them.
- Patients should be taught how to administer topical therapy. With a forefinger pulling down the lower eyelid to form a pocket, the patient should place the dropper over the eye, look at the tip of the bottle, and then look up and place a single drop in the eye. To maximize topical activity and minimize systemic absorption, the patient should close the lid for 1 to 3 minutes after instillation and place the index finger over the nasolacrimal drainage system in the inner corner of the eye.

- If more than one topical drug is required, instillation should be separated by 5 to 10 minutes to provide optimal ocular contact.
- Adherence to drug therapy should be monitored because it is commonly inadequate and a cause of therapy failure.

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*See Chap. 97, Glaucoma, authored by Richard G. Fiscella, Timothy S. Lesar, and Deepak P. Edward, for a more detailed discussion of this topic.*

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## DEFINITION

- Alzheimer's disease (AD) is a progressive dementia affecting cognition, behavior, and functional status with no known cause or cure. Patients eventually lose cognitive, analytical, and physical functioning, and the disease is ultimately fatal.

## PATHOPHYSIOLOGY

- The signature findings are intracellular neurofibrillary tangles (NFTs), extracellular neuritic plaques, degeneration of neurons and synapses, and cortical atrophy.
- Mechanisms proposed for these changes are:
  - ✓  $\beta$ -Amyloid protein aggregation, leading to formation of plaques
  - ✓ Hyperphosphorylation of tau protein, leading to intracellular NFT development and collapse of microtubules
  - ✓ Inflammatory processes—levels of multiple cytokines and chemokines are elevated in AD brains
  - ✓ Neurovasculature dysfunction
  - ✓ Oxidative stress
  - ✓ Mitochondrial dysfunction
- Neuritic plaques are lesions found in brain and cerebral vasculature.
- Whether genetic variations promote a primary  $\beta$ -amyloidosis in the majority of AD patients is unresolved.
- Density of NFTs correlates with severity of dementia.
- While there is a variety of neurotransmitter deficits, loss of cholinergic activity is most prominent and correlates with AD severity.
- It is clear that replacement of acetylcholine activity cannot compensate for all the changes that take place in AD.
- Deficits that exist in other pathways are:
  - ✓ Serotonergic neurons of the raphe nuclei and noradrenergic cells of the locus ceruleus are lost
  - ✓ Monoamine oxidase type B activity is increased
  - ✓ Glutamate pathways of the cortex and limbic structures are abnormal
- Excitatory neurotransmitters, including glutamate, have been implicated as potential neurotoxins in AD.
- Risk factors for AD are hypertension, elevated low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, and diabetes.

**TABLE 67-1** Stages of Alzheimer's Disease

Mild (MMSE score 26–18)	Patient has difficulty remembering recent events. Ability to manage finances, prepare food, and carry out other household activities declines. May get lost while driving. Begins to withdraw from difficult tasks and to give up hobbies. May deny memory problems.
Moderate (MMSE score 17–10)	Patient requires assistance with activities of daily living. Frequently disoriented with regard to time (date, year, season). Recall for recent events is severely impaired. May forget some details of past life and names of family and friends. Functioning may fluctuate from day to day. Patient generally denies problems. May become suspicious or tearful. Loses ability to drive safely. Agitation, paranoia, and delusions are common.
Severe (MMSE score 9–0)	Patient loses ability to speak, walk, and feed self. Incontinent of urine and feces. Requires care 24 hours a day, 7 days a week.

MMSE, Mini-Mental State Examination.

Data from Alzheimer's Association. <http://www.alz.org/>; Rubin CD. The primary care of Alzheimer's disease. *Am J Med Sci* 2006;332:314–333; and Crossberg GT, Desai AK. Management of Alzheimer's disease. *J Gerontol A Biol Sci Med Sci* 2003;58A:331–333.

## CLINICAL PRESENTATION

- The onset of AD is almost imperceptible, but deficits progress over time. Cognitive decline is gradual, and behavioral disturbances may be present in moderate stages. Table 67-1 shows the stages of AD.

## SYMPTOMS

- Table 67-2 shows the clinical presentation of AD and recommended laboratory and diagnostic tests.

## DIAGNOSIS

- The definitive diagnosis of AD is made by examining brain tissue. Useful diagnostic criteria and guidelines are provided by:
  - ✓ The *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., text revision
  - ✓ The Agency for Healthcare Research and Quality
  - ✓ The American Academy of Neurology
  - ✓ The National Institute of Neurological and Communicative Disorders and Stroke
  - ✓ Alzheimer's Disease and Related Disorders Association
- Patients with suspected AD should have a history and physical examination with appropriate laboratory and other diagnostic tests, neurologic and psychiatric examinations, standardized rating assessments, functional evaluation, and a caregiver interview.
- Information about prescription drug use; alcohol or other substance use; family medical history; and history of trauma, depression, or head injury should be obtained. It is important to rule out medication use as a contributor or cause of symptoms (e.g., anticholinergics, sedatives, hypnotics, opioids, antipsychotics, and anticonvulsants) as contributors to dementia symptoms. Other medications may contribute to delirium, e.g.,

**TABLE 67-2** Clinical Presentation of Alzheimer's Disease**General**

The patient may have vague memory complaints initially, or the patient's significant other may report that the patient is "forgetful." Cognitive decline is gradual over the course of illness. Behavioral disturbances may be present in moderate stages. Loss of daily function is common in advanced stages.

**Symptoms***Cognitive*

- Memory loss (poor recall and losing items)
- Aphasia (circumlocution and anomia)
- Apraxia
- Agnosia
- Disorientation (impaired perception of time and unable to recognize familiar people)
- Impaired executive function

*Noncognitive*

- Depression, psychotic symptoms (hallucinations and delusions)
- Behavioral disturbances (physical and verbal aggression, motor hyperactivity, uncooperativeness, wandering, repetitive mannerisms and activities, and combativeness)

*Functional*

- Inability to care for self (dressing, bathing, toileting, and eating)

**Laboratory tests**

- Rule out vitamin B<sub>12</sub> and folate deficiency
- Rule out hypothyroidism with thyroid function tests
- Blood cell counts, serum electrolytes, liver function tests

**Other diagnostic tests**

- CT or MRI scans may aid diagnosis

CT, computed tomography; MRI, magnetic resonance imaging.

digoxin, nonsteroidal antiinflammatory drugs, histamine<sub>2</sub> receptor antagonists, amiodarone, antihypertensives, and corticosteroids.

- The Folstein Mini-Mental State Examination (MMSE) can help to establish a history of deficits in two or more areas of cognition and establish a baseline against which to evaluate change in severity. The average expected decline in an untreated patient is 2 to 4 points per year.

**DESIRED OUTCOME**

- The primary goal of treatment in AD is to maintain patient functioning as long as possible. Secondary goals are to treat the psychiatric and behavioral sequelae.

**TREATMENT****NONPHARMACOLOGIC THERAPY**

- Sleep disturbances, wandering, urinary incontinence, agitation, and aggression should be managed with behavioral interventions whenever possible.
- On initial diagnosis, the patient and caregiver should be educated on the course of illness, available treatments, legal decisions, changes in lifestyle that will be necessary with disease progression, and other quality of life issues.

**TABLE 67-3** Treatment Options for Cognitive Symptoms in Alzheimer's Disease

- In mild–moderate disease, consider therapy with a cholinesterase inhibitor.
  - Donepezil, or
  - Rivastigmine, or
  - Galantamine
- Titrate to recommended maintenance dose as tolerated.
- In moderate to severe disease, consider adding antiglutamatergic therapy.
  - Memantine
- Titrate to recommended maintenance dose as tolerated.
- Alternatively, consider memantine or cholinesterase inhibitor therapy alone.
- Behavioral symptoms may require additional pharmacologic approaches.

*Data from Desai AK, Grossberg GT. Diagnosis and treatment of Alzheimer's disease. Neurology 2005;64(Suppl 3):S34–S39; Lyketsos CG, Colenda CC, Beck C, et al. Position statement of the American Association for Geriatric Psychiatry regarding principles of care for patients with dementia resulting from Alzheimer's disease. Am J Geriatr Psychiatry 2006;14:561–573; and Lleó A, Greenberg SM, Growdon JH. Current pharmacotherapy for Alzheimer's disease. Annu Rev Med 2006;57:513–533.*

- The Alzheimer's Association recommends staying physically, mentally, and socially active, adopting a low-fat/low-cholesterol diet rich in dark vegetables and fruit, and managing body weight.

## PHARMACOTHERAPY OF COGNITIVE SYMPTOMS

- Managing blood pressure, cholesterol, and blood sugar may reduce the risk of developing AD and may prevent the worsening of dementia in patients with AD.
- Current pharmacotherapeutic interventions are primarily symptomatic attempts to improve or maintain cognition. Table 67-3 may be used as an algorithm for managing cognitive symptoms in AD.
- Successful treatment reflects a decline of less than 2 points each year on the MMSE score.

### Cholinesterase Inhibitors

- Table 67-4 summarizes the clinical pharmacology of the cholinesterase inhibitors.
- No direct comparative trials have assessed the effectiveness of one agent over another. **Donepezil**, **rivastigmine**, and **galantamine** are indicated in mild to moderate AD, while donepezil is also indicated in severe AD.
- If the decline in MMSE score is more than 2 to 4 points after treatment for 1 year with the initial agent, it is reasonable to change to a different cholinesterase inhibitor. Otherwise, treatment should be continued with the initial medication throughout the course of the illness.
- The most frequent adverse effects are mild to moderate GI symptoms (nausea, vomiting, and diarrhea), urinary incontinence, dizziness, headache, syncope, bradycardia, muscle weakness, salivation, and sweating. Abrupt discontinuation can cause worsening of cognition and behavior in some patients.
- **Donepezil** (Aricept) is a piperidine derivative with specificity for inhibition of acetylcholinesterase rather than butyrylcholinesterase.

**TABLE 67-4** Clinical Pharmacology of the Cholinesterase Inhibitors

	<b>Donepezil</b>	<b>Rivastigmine</b>	<b>Galantamine</b>
Brand name	Aricept	Exelon	Razadyne
Dosage forms	Tablet Orally disintegrating tablet	Capsule Oral solution Patch	Tablet Oral solution Extended-release (ER) capsule
Starting dose	5 mg daily at bedtime	1.5 mg twice a day 4.6 mg/day (patch)	4 mg twice a day (8 mg daily for ER)
Maintenance dose	5–10 mg daily	3–6 mg twice a day 9.5 mg/day (patch)	8–12 mg twice a day (16–24 mg daily for ER)
Meals	No effect of food	Take with food	Take with food
Half-life	70 hours	1.5 hours	7 hours
Protein binding	96%	40%	18%
Metabolism	Substrate (minor) of CYP2D6 and 3A4	Cholinesterase-mediated hydrolysis	Substrate (minor) of CYP2D6 and 3A4
	Glucuronidation	—	Glucuronidation
Renal elimination	Yes	Major pathway	Yes

CYP, cytochrome P450.

Data from Namenda (memantine hydrochloride) package insert. St. Louis, MO: Forest Laboratories, 2005; Aricept (donepezil hydrochloride) package insert. Teaneck, NJ: Eisai Co, Ltd., 2006; Exelon (rivastigmine tartrate) package insert. East Hanover, NJ: Novartis Pharmaceuticals, 2006; Razadyne (galantamine hydrobromide) package insert. Titusville, NJ: Ortho-McNeil Neurologics, 2006; and Exelon (rivastigmine) Patch package insert. East Hanover, NJ: Novartis Pharmaceutical, 2007.

- **Rivastigmine** has central activity at acetylcholinesterase and butyrylcholinesterase sites, but low activity at these sites in the periphery.
- **Galantamine** is a cholinesterase inhibitor that also has activity as a nicotinic receptor agonist.
- **Tacrine** was the first cholinesterase inhibitor approved for the treatment of AD, but it has been replaced by safer drugs which are better tolerated.

### Other Drugs

- **Memantine** (Namenda) blocks glutamatergic neurotransmission by antagonizing *N*-methyl-D-aspartate receptors, which may prevent excitotoxic reactions. It is used as monotherapy, and data suggest that when it is combined with a cholinesterase inhibitor, there is improvement in cognition and activities of daily living.
  - ✓ It is indicated for treatment of moderate to severe AD.
  - ✓ It is not metabolized by the liver, but is primarily excreted unchanged in the urine (half-life of elimination = 60 to 80 hours).
  - ✓ It is usually well tolerated, and side effects include constipation, confusion, dizziness, hallucinations, headache, cough, and hypertension.
  - ✓ It is initiated at 5 mg/day and increased weekly by 5 mg/day to the effective dose of 10 mg twice daily. Dosing must be adjusted in patients with renal impairment.
- Recent trials do not support the use of **estrogen** to prevent or treat cognitive decline.
- Evidence related to the role of **vitamin E** in preventing AD is mixed, and conclusions cannot be drawn at this time.

- Because of a significant incidence of side effects and a lack of compelling evidence, **Nonsteroidal antiinflammatory drugs** are not recommended for treatment or prevention of AD.
- There is interest in the use of lipid-lowering agents, especially the 3-hydroxy-3-methylglutaryl coenzyme A–reductase inhibitors, to prevent AD. **Pravastatin** and **lovastatin**, but not **simvastatin**, were associated with a lower prevalence of AD. Further study is needed before these agents can be recommended for this use.
- A metaanalysis indicated that EGb 761 (an extract of **ginkgo biloba**) may have some therapeutic effect at doses of 120 to 240 mg of the standard leaf extract twice daily. Because of limited efficacy data, the potential for adverse effects (e.g., nausea, vomiting, diarrhea, headache, dizziness, weakness, and hemorrhage), and the poor standardization of herbal products, it is recommended that ginkgo biloba be used only with caution.
  - ✓ Ginkgo biloba should not be used in individuals taking anticoagulants or antiplatelet drugs, and should be used cautiously in those taking **nonsteroidal antiinflammatory drugs**.
- Although initial studies suggest potential effectiveness of **huperzine A**, it has not been adequately evaluated for treatment of AD.

## PHARMACOTHERAPY OF NONCOGNITIVE SYMPTOMS

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- Pharmacotherapy is aimed at treating psychotic symptoms, inappropriate or disruptive behavior, and depression. Medications and recommended doses for noncognitive symptoms are shown in Table 67-5.
- General guidelines are as follows: (1) use reduced doses, (2) monitor closely, (3) titrate dosage slowly, (4) document carefully, and (5) periodically attempt to reduce medication in minimally symptomatic patients.
- Psychotropic medications with anticholinergic effects should be avoided because they may worsen cognition.

### Cholinesterase Inhibitors and Memantine

- **Cholinesterase inhibitors** and **memantine** are first-line therapy in early management of behavioral symptoms. Modest improvement may be achieved.

### Antipsychotics

- Antipsychotic medications have traditionally been used to treat disruptive behaviors and psychosis in AD patients.
- A metaanalysis showed that 17% to 18% of dementia patients showed a modest treatment response to atypical antipsychotics. Adverse events included somnolence, extrapyramidal symptoms, abnormal gait, worsening cognition, cerebrovascular events, and increased risk of death.
- Typical antipsychotics may also be associated with a small increased risk of death, as well as more severe extrapyramidal effects and hypotension.

### Antidepressants

- Depression and dementia have many symptoms in common, and the diagnosis of depression can be difficult, especially later in the course of AD.

**TABLE 67-5** Medications Used for Noncognitive Symptoms of Dementia

Drugs	Starting Dose (mg)	Maintenance Dose in Dementia (mg/day)	Target Symptoms
<b>Antipsychotics</b>			Psychosis: hallucinations, delusions, suspiciousness Disruptive behaviors: agitation, aggression
Haloperidol	0.25	1–3	
Olanzapine	2.5	5–10	
Quetiapine	25	100–300	
Risperidone	0.25	0.75–2	
Ziprasidone	20	40–160	
<b>Antidepressants</b>			Depression: poor appetite, insomnia, hopelessness, anhedonia, withdrawal, suicidal thoughts, agitation, anxiety
Citalopram	10	10–20	
Escitalopram	5	20–40	
Fluoxetine	5	10–40	
Paroxetine	10	10–40	
Sertraline	25	75–100	
Venlafaxine	25	75–225	
Trazodone	25	75–150	
<b>Anticonvulsants</b>			Agitation or aggression
Carbamazepine	100	200–600	
Valproic acid	125	500–1,000	

Data from Lleó A, Greenberg SM, Growdon JH. Current pharmacotherapy for Alzheimer's disease. *Annu Rev Med* 2006;57:513–533; Benoit M, Arbus C, Blanchard F, et al. Professional consensus on the treatment of agitation, aggressive behavior, oppositional behavior and psychotic disturbances in dementia. *J Nutr Health Aging* 2006;10:410–415; and Grossberg GT, Desai AK. Management of Alzheimer's disease. *J Gerontol A Biol Sci Med Sci* 2003;58A:331–353.

- Treatment with a selective serotonin reuptake inhibitor is usually initiated in depressed patients with AD. **Paroxetine** causes more anticholinergic side effects than the other **selective serotonin reuptake inhibitors**. **Venlafaxine** may also be used.
- Although probably equally effective, the **tricyclic antidepressants** are usually avoided because of anticholinergic side effects.

### Miscellaneous Therapies

- **Carbamazepine**, mean dose 300 mg/day, may improve psychosis and behavioral disturbance in AD patients.
- **Oxazepam** and other benzodiazepines have been used to treat anxiety, agitation, and aggression, but they generally show inferior efficacy compared with antipsychotics. They can also worsen cognition, cause disinhibition, and increase the risk of falls.

## EVALUATION OF THERAPEUTIC OUTCOMES

- Baseline assessment should define therapeutic goals and document cognitive status, physical status, functional performance, mood, thought processes, and behavior. Both the patient and caregiver should be interviewed.
- Because target symptoms of psychiatric disorders may respond differently in demented patients, a detailed list of symptoms to be treated should be documented to aid in monitoring.

- Objective assessments, such as the MMSE for cognition and the Functional Activities Questionnaire for activities of daily living, should be used to quantify changes in symptoms and functioning.
- The patient should be observed carefully for potential side effects of drug therapy. The specific side effects to be monitored and the method and frequency of monitoring should be documented.
- Assessments for drug effectiveness, side effects, compliance, need for dosage adjustment, or change in treatment should occur at least monthly.
- A treatment period of 6 months to 1 year may be required to determine whether therapy is beneficial.

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*See Chap. 67, Alzheimer's Disease, authored by Patricia W. Slattum, Russell H. Swerdlow, and Angela Massey Hill, for a more detailed discussion of this topic.*

## DEFINITION

- Anxiety disorders include a constellation of disorders in which anxiety and associated symptoms are irrational or experienced at a level of severity that impairs functioning. The characteristic features are anxiety and avoidance.

## PATHOPHYSIOLOGY

- *Noradrenergic model.* This model suggests that the autonomic nervous system of anxious patients is hypersensitive and overreacts to various stimuli. The locus ceruleus may have a role in regulating anxiety, as it activates norepinephrine release and stimulates the sympathetic and parasympathetic nervous systems. Chronic noradrenergic overactivity down regulates  $\alpha_2$ -adrenoreceptors in patients with generalized anxiety disorder (GAD) and posttraumatic stress disorder (PTSD). Patients with social anxiety disorder (SAD) appear to have a hyperresponsive adrenocortical response to psychological stress.
- *$\gamma$ -Aminobutyric acid (GABA) receptor model.* GABA is the major inhibitory neurotransmitter in the CNS. Many antianxiety drugs target the GABA<sub>A</sub> receptor. **Benzodiazepines** (BZs) enhance the inhibitory effects of GABA, which has a strong regulatory or inhibitory effect on serotonin (5-HT), norepinephrine, and dopamine systems. Anxiety symptoms may be linked to underactivity of GABA systems or downregulated central BZ receptors. In patients with GAD, BZ binding in the left temporal lobe is reduced. Abnormal sensitivity to antagonism of the BZ binding site and decreased binding was demonstrated in panic disorder. Growth hormone response to baclofen in patients with generalized SAD suggests an abnormality of central GABA<sub>B</sub> receptor function. Abnormalities of GABA inhibition may lead to increased response to stress in PTSD patients.
- *5-HT model.* GAD symptoms may reflect excessive 5-HT transmission or overactivity of the stimulatory 5-HT pathways. Patients with SAD have greater prolactin response to **buspiron** challenge, indicating an enhanced central serotonergic response. The role of 5-HT in panic disorder is unclear, but it may have a role in development of anticipatory anxiety. Preliminary data suggest that the 5-HT and 5-HT<sub>2</sub> antagonist *meta*-chlorophenylpiperazine causes increased anxiety in PTSD patients.
- Patients with PTSD have a hypersecretion of corticotropin-releasing factor but demonstrate subnormal levels of cortisol at the time of trauma and chronically. Dysregulation of the hypothalamic-pituitary-adrenal axis may be a risk factor for eventual development of PTSD.
- Functional neuroimaging studies suggest that frontal and occipital brain areas are integral to the anxiety response. Patients with panic disorder may have abnormal activation of the parahippocampal region and prefrontal cortex at rest. Panic anxiety is associated with activation of brain stem and basal ganglia regions. GAD patients have an abnormal increase in cortical

activity and a decrease in basal ganglia activity. In patients with SAD, there may be abnormalities in the amygdala, hippocampus, and various cortical regions. Lower hippocampal volumes in patients with PTSD may be a precursor for subsequent development of PTSD.

## CLINICAL PRESENTATION

### GENERALIZED ANXIETY DISORDER

- The clinical presentation of GAD is shown in Table 68-1. The diagnostic criteria require persistent symptoms most days for at least 6 months. The anxiety or worry must be about a number of matters and is accompanied by at least three psychological or physiologic symptoms. The illness has a gradual onset at an average age of 21 years. The course of illness is chronic, with multiple spontaneous exacerbations and remissions. There is a high percentage of relapse and a low rate of recovery.

### PANIC DISORDER

- Symptoms usually begin as a series of unexpected panic attacks. These are followed by at least 1 month of persistent concern about having another panic attack.
- Symptoms of a panic attack are shown in Table 68-2. During an attack, there must be at least four physical symptoms in addition to psychological symptoms. Symptoms reach a peak within 10 minutes and usually last no more than 20 or 30 minutes.
- Many patients eventually develop agoraphobia, which is avoidance of specific situations (e.g., crowded places, bridges) where they fear a panic attack might occur. Patients may become homebound.

**TABLE 68-1** Presentation of Generalized Anxiety Disorder

#### Psychological and cognitive symptoms

- Excessive anxiety
- Worries that are difficult to control
- Feeling keyed up or on edge
- Poor concentration or mind going blank

#### Physical symptoms

- Restlessness
- Fatigue
- Muscle tension
- Sleep disturbance
- Irritability

#### Impairment

- Social, occupational, or other important functional areas
- Poor coping abilities

Data from American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, 4th ed., text revision*. Washington, DC: American Psychiatric Association, 2000:429–484; and Baldwin DS, Anderson IM, Nutt DJ, et al. Evidence-based guidelines for the pharmacological treatment of anxiety disorders: Recommendations from the British Society for Psychopharmacology. *J Psychopharmacology* 2005;19:567–596.

**TABLE 68-2** Symptoms of a Panic Attack**Psychological symptoms**

- Depersonalization
- Derealization
- Fear of losing control
- Fear of going crazy
- Fear of dying

**Physical symptoms**

- Abdominal distress
- Chest pain or discomfort
- Chills
- Dizziness or lightheadedness
- Feeling of choking
- Hot flushes
- Palpitations
- Nausea
- Paresthesias
- Shortness of breath
- Sweating
- Tachycardia
- Trembling or shaking

*Data from American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th ed., text revision. Washington, DC: American Psychiatric Association, 2000:429–484; Baldwin DS, Anderson IM, Nutt DJ, et al. Evidence-based guidelines for the pharmacological treatment of anxiety disorders: Recommendations from the British Society for Psychopharmacology. J Psychopharmacology 2005;19:567–596; and Katon WJ. Panic disorder. N Engl J Med 2006;354:2360–2367.*

## SOCIAL ANXIETY DISORDER

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- The essential feature of SAD is an intense, irrational, and persistent fear of being negatively evaluated in a social or performance situation. Exposure to the feared situation usually provokes a panic attack. Symptoms of SAD are shown in Table 68-3. The fear and avoidance of the situation must interfere with daily routine or social/occupational functioning. It is a chronic disorder with a mean age of onset in the teens.
- In the generalized subtype, fear is of many social situations where embarrassment may occur. In the discrete or specific subtype, fear is limited to one or two situations (e.g., performing, public speaking).

## POSTTRAUMATIC STRESS DISORDER

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- In PTSD, exposure to a traumatic event causes immediate intense fear, helplessness, or horror.
- The clinical presentation of PTSD is shown in Table 68-4. Patients must have at least one reexperiencing symptom, three signs or symptoms of persistent avoidance of stimuli, and at least two symptoms of increased arousal. Symptoms from each category must be present longer than 1 month and cause significant distress or impairment. PTSD can occur at any age, and the course is variable.
- One-third of patients with PTSD have a poor prognosis, and about 80% have a concurrent depression or anxiety disorder. Over half of men with

**TABLE 68-3** Presentation of Social Anxiety Disorder**Fears**

- Being scrutinized by others
- Being embarrassed
- Being humiliated

**Some feared situations**

- Addressing a group of people
- Eating or writing in front of others
- Interacting with authority figures
- Speaking in public
- Talking with strangers
- Use of public toilets

**Physical symptoms**

- Blushing
- "Butterflies in the stomach"
- Diarrhea
- Sweating
- Tachycardia
- Trembling

**Types**

- Generalized type: fear and avoidance extend to a wide range of social situations
- Nongeneralized type: fear is limited to one or two situations

Data from American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, 4th ed., text revision*. Washington, DC: American Psychiatric Association, 2000:429–484; Schneier FR. Social anxiety disorder. *N Engl J Med* 2006;355:1029–1036; and Ballenger JC, Davidson JRT, Lecrubier Y, et al. Consensus statement on social anxiety disorder from the International Consensus Group on Depression and Anxiety. *J Clin Psychiatry* 1998;59(Suppl 17):54–60.

PTSD have comorbid alcohol abuse or dependence, and about 20% of patients attempt suicide.

**DIAGNOSIS**

- Evaluation of the anxious patient requires a complete physical and mental status examination; appropriate laboratory tests; and a medical, psychiatric, and drug history.
- Anxiety symptoms may be associated with medical illnesses (Table 68-5) or drug therapy (Table 68-6). About 50% of patients with GAD have irritable bowel syndrome.
- Anxiety symptoms may be present in several major psychiatric illnesses (e.g., mood disorders, schizophrenia, organic mental syndromes, and substance withdrawal).

**DESIRED OUTCOME**

- The desired outcomes of treatment of GAD are to reduce severity, duration, and frequency of the symptoms and to improve overall functioning. The long-term goal is minimal or no anxiety or depressive symptoms, no functional impairment, and improved quality of life.
- The goals of therapy of panic disorder include a complete resolution of panic attacks, marked reduction in anticipatory anxiety and phobic fears,

**TABLE 68-4** Presentation of Posttraumatic Stress Disorder**Reexperiencing symptoms**

- Recurrent, intrusive distressing memories of the trauma
- Recurrent, disturbing dreams of the event
- Feeling that the traumatic event is recurring (e.g., dissociative flashbacks)
- Physiologic reaction to reminders of the trauma

**Avoidance symptoms**

- Avoidance of conversations about the trauma
- Avoidance of thoughts or feelings about the trauma
- Avoidance of activities that are reminders of the event
- Avoidance of people or places that arouse recollections of the trauma
- Inability to recall an important aspect of the trauma
- Anhedonia
- Estrangement from others
- Restricted affect
- Sense of a foreshortened future (e.g., does not expect to have a career, marriage)

**Hyperarousal symptoms**

- Decreased concentration
- Easily startled
- Hypervigilance
- Insomnia
- Irritability or angry outbursts

**Subtypes**

- Acute: duration of symptoms is less than 3 months
- Chronic: symptoms last for longer than 3 months
- With delayed onset: onset of symptoms is at least 6 months posttrauma

**Screening questions**

- Have you ever experienced a significant trauma in your life?
- Did this experience have a lasting negative impact or change your life?

Data from American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*. Washington, DC: American Psychiatric Association, 2000:429–484; and Ballenger JC, Davidson JRT, Lecrubier Y, et al. Consensus statement update on posttraumatic stress disorder from the International Consensus Group on Depression and Anxiety. *J Clin Psychiatry* 2004;65(Suppl 1):55–62.

**TABLE 68-5** Common Medical Illnesses Associated with Anxiety Symptoms**Cardiovascular**

Angina, arrhythmias, congestive heart failure, ischemic heart disease, myocardial infarction

**Endocrine and metabolic**

Cushing's disease, hyperparathyroidism, hyperthyroidism, hypothyroidism, hypoglycemia, hyponatremia, hyperkalemia, pheochromocytoma, vitamin B<sub>12</sub> or folate deficiencies

**Neurologic**

Dementia, migraine, Parkinson's disease, seizures, stroke, neoplasms, poor pain control

**Respiratory system**

Asthma, chronic obstructive pulmonary disease, pulmonary embolism, pneumonia

**Others**

Anemias, systemic lupus erythematosus, vestibular dysfunction

Data from Roy-Byrne PR, Wagner A. Primary care perspectives on generalized anxiety disorder. *J Clin Psychiatry* 2004;65(Suppl 13):20–26; and Chen J, Reich L, Chung H. Anxiety disorders. *West J Med* 2002;176:249–253.

**TABLE 68-6** Drugs Associated with Anxiety Symptoms

<b>Anticonvulsants:</b>	carbamazepine
<b>Antidepressants:</b>	selective serotonin reuptake inhibitors, tricyclic antidepressants
<b>Antihypertensives:</b>	felodipine
<b>Antibiotics:</b>	quinolones, isoniazid
<b>Bronchodilators:</b>	albuterol, theophylline
<b>Corticosteroids:</b>	prednisone
<b>Dopa agonists:</b>	levodopa
<b>Herbals:</b>	ma huang, ginseng, ephedra
<b>Nonsteroidal antiinflammatory drugs:</b>	ibuprofen
<b>Stimulants:</b>	amphetamines, methylphenidate, caffeine, cocaine
<b>Sympathomimetics:</b>	pseudoephedrine
<b>Thyroid hormones:</b>	levothyroxine
<b>Toxicity:</b>	anticholinergics, antihistamines, digoxin
<b>Withdrawal:</b>	alcohol, sedatives

Data from American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, 4th ed., text revision*. Washington, DC: American Psychiatric Association, 2000:429–484; and Chen J, Reich L, Chung H. *Anxiety disorders*. *West J Med* 2002;176:249–253.

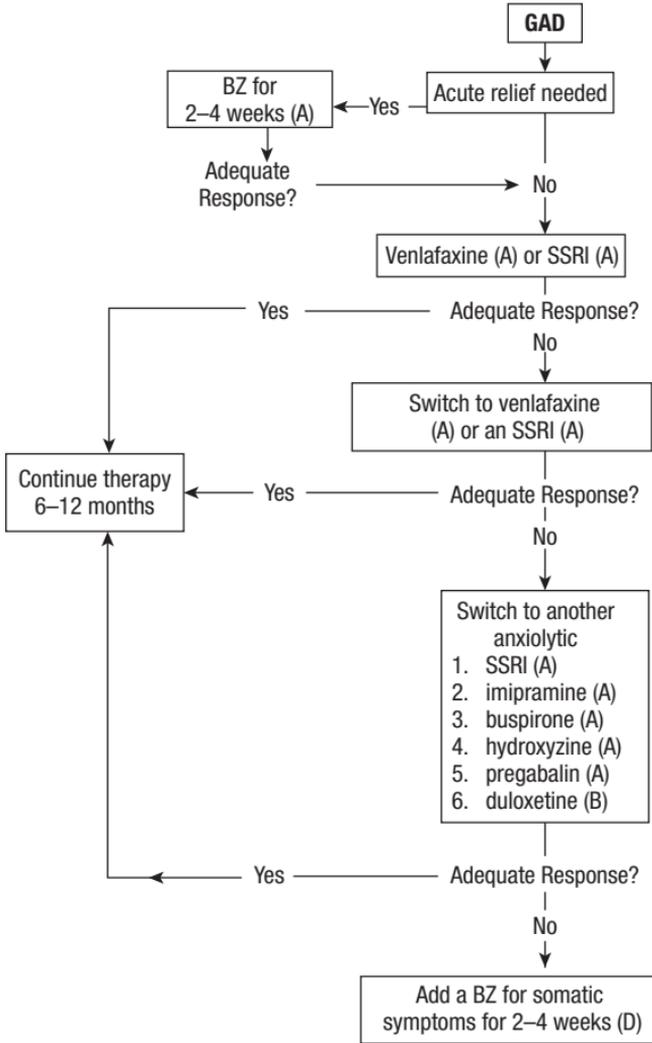
elimination of phobic avoidance, and resumption of normal activities. After treatment, 40% to 50% of patients continue to have occasional panic attacks and phobic avoidance.

- The goals of treatment of SAD are to reduce the physiologic symptoms and phobic avoidance, increase participation in desired social activities, and improve quality of life.
- The goals of therapy of PTSD are to decrease core symptoms, disability, and comorbidity and improve quality of life and resilience to stress.

## TREATMENT

### GENERALIZED ANXIETY DISORDER

- For patients with GAD, nonpharmacologic modalities include short-term counseling, stress management, cognitive therapy, meditation, supportive therapy, and exercise. GAD patients should be educated to avoid caffeine, stimulants, excessive alcohol, and diet pills. Cognitive behavioral therapy (CBT) is the most effective psychological therapy for GAD patients, and most patients with GAD should have psychological therapy, alone or in combination with antianxiety drugs.
- An algorithm for the pharmacologic management of GAD is shown in Fig. 68-1.
- Drug choices for anxiety disorders are shown in Table 68-7, and non-BZ antianxiety agents for GAD are shown in Table 68-8.
- Kava kava is not recommended as an anxiolytic because of reports of lack of efficacy and hepatotoxicity.
- **Hydroxyzine** was effective in 88% of patients for a duration of 3 months.
- **Pregabalin** produced anxiolytic effects similar to **lorazepam**, **alprazolam**, and **venlafaxine** in acute trials. Sedation and dizziness were the most common adverse effects, and the dose should be tapered over 1 week upon discontinuation.



**FIGURE 68-1.** Algorithm for the pharmacotherapy of generalized anxiety disorder (GAD). Strength of recommendations: A = directly based on category I evidence (i.e., metaanalysis of randomized clinical trials [RCT] or at least one RCT); B = directly based on category II evidence (i.e., at least one controlled study without randomization or one other type of quasi-experimental study); D = directly based on category IV evidence (i.e., expert committee reports or opinions and/or clinical experience of respected authorities). (BZ, benzodiazepine; SSRI, selective serotonin reuptake inhibitor.) (Data from Baldwin DS, Anderson IM, Nutt DJ, et al. Evidence-based guidelines for the pharmacological treatment of anxiety disorders: Recommendations from the British Society for Psychopharmacology. *J Psychopharmacology* 2005;19:567–596; and National Institute for Clinical Excellence. *The Management of Panic Disorder and Generalized Anxiety Disorder in Primary Care and Secondary Care: Clinical Guideline 22*. London: National Collaborating Centre for Mental Health, December 2004.)

**TABLE 68-7** Drug Choices for Anxiety Disorders

Anxiety Disorder	First-Line Drugs	Second-Line Drugs	Alternatives
Generalized anxiety	Duloxetine	Benzodiazepines	Hydroxyzine
	Escitalopram	Buspirone	Pregabalin
	Paroxetine	Imipramine	
	Venlafaxine XR	Sertraline	
Panic disorder	SSRIs	Alprazolam	Phenelzine
	Venlafaxine XR	Clomipramine	
		Clonazepam	
		Imipramine	
Social anxiety disorder	Escitalopram	Citalopram	Buspirone
	Fluvoxamine	Clonazepam	Gabapentin
	Paroxetine		Mirtazapine
	Sertraline		Phenelzine
	Venlafaxine XR		Pregabalin

SSRI, selective serotonin reuptake inhibitor; XR, extended-release.

Data from Schneier FR. *N Engl J Med* 2006;355:1029–1036; Baldwin DS, Anderson IM, Nutt DJ, et al. *J Psychopharmacology* 2005;19:567–596; Ballenger JC, Davidson JRT, Lecrubier Y, et al. *J Clin Psychiatry* 1998;59(Suppl 17):54–60; Bandelow B, Zohar J, Hollander E, et al. *World J Biol Psychiatry* 2002;3:171–199; and Work Group on Panic Disorder. *Am J Psychiatry* 1998;155(Suppl 5):1–34.

- The FDA has established a link between antidepressant use and suicidality (suicidal thinking and behaviors) in children, adolescents, and young adults 18 to 24 years old. All antidepressants carry a black box warning advising caution in the use of all antidepressants in this population, and the FDA also recommends specific monitoring parameters. The clinician

**TABLE 68-8** Nonbenzodiazepine Antianxiety Agents for Generalized Anxiety Disorder

Generic Name	Trade Name	Starting Dose	Dosage Range (mg/day) <sup>a</sup>
<i>Antidepressants</i>			
Duloxetine	Cymbalta	30 or 60 mg per day	60–120
Escitalopram <sup>b</sup>	Lexapro	10 mg per day	10–20
Imipramine <sup>c</sup>	Tofranil	50 mg per day	75–200
Paroxetine <sup>b,c</sup>	Paxil	20 mg per day	20–50
Venlafaxine <sup>b</sup>	Effexor XR	37.5 or 75 mg per day	75–225 <sup>d</sup>
<i>Azapirones</i>			
Buspirone <sup>b,c</sup>	BuSpar	7.5 mg twice per day	15–60 <sup>d</sup>
<i>Diphenylmethane</i>			
Hydroxyzine <sup>b,c,e</sup>	Vistaril, Atarax	25 or 50 mg four times daily	200–400
<i>Anticonvulsant</i>			
Pregabalin	Lyrica	50 mg three times daily	150–600

XR, extended-release.

<sup>a</sup>Elderly patients are usually treated with approximately one-half of the dose listed.

<sup>b</sup>FDA approved for generalized anxiety disorder.

<sup>c</sup>Available generically.

<sup>d</sup>No dosage adjustment is required in elderly patients.

<sup>e</sup>FDA approved for anxiety and tension in children in divided daily doses of 50–100 mg.

Data from Bandelow B, Zohar J, Hollander E, et al. *World J Biol Psychiatry* 2002;3:171–199; Duloxetine [package insert]. Indianapolis, IN: Eli Lilly and Company, May 2007; Lexapro [package insert]. St. Louis, MO: Forest Pharmaceuticals, Inc., September 2006; Paxil [package insert]. Research Triangle Park, NC: GlaxoSmithKline, July 2006; Effexor XR [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals, Inc., August 2006; Vistaril [package insert]. New York: Pfizer Labs, April 2004; and Kavoussi R. *Eur Neuropsychopharmacol* 2006;16:S128–S133.

should consult the FDA-approved labeling or the FDA website for additional information (see Chap. 70).

### Antidepressants

- Antidepressants are efficacious for acute and long-term management of GAD. They are considered the treatment of choice for long-term management of chronic anxiety, especially in the presence of depressive symptoms. Antianxiety response requires 2 to 4 weeks.
- **Venlafaxine extended release, duloxetine, paroxetine, and escitalopram** are FDA approved for treatment of GAD. **Sertraline** is also effective. Acute response and remission rates are approximately 65% and 30%, respectively. **Imipramine** may be used when patients fail to respond to selective serotonin reuptake inhibitors (SSRIs). In one trial, **diazepam, trazodone, and imipramine** had greater anxiolytic activity than placebo.
- Common side effects of the **SSRIs** are somnolence, nausea, ejaculation disorders, decreased libido, dry mouth, insomnia, and fatigue. **Tricyclic antidepressants (TCAs)** commonly cause sedation, orthostatic hypotension, anticholinergic effects, and weight gain. TCAs are very toxic on overdose.

### Evaluation of Therapeutic Outcomes

- Initially, anxious patients should be monitored once to twice weekly for reduction in anxiety symptoms, improvement in functioning, and side effects. The Visual Analog Scale may assist in the evaluation of drug response.

### Benzodiazepine Therapy

- The BZs are the most frequently prescribed drugs for the treatment of acute anxiety (Table 68-9). All BZs are equally effective anxiolytics, and most of the improvement occurs in the first 2 weeks of therapy. They are considered to be more effective for somatic and autonomic symptoms of GAD, while antidepressants are considered more effective for the psychic symptoms (e.g., apprehension and worry).

**TABLE 68-9** Benzodiazepine Antianxiety Agents

Generic Name	Brand Name	Approved Dosage Range (mg/day) <sup>a</sup>	Approximate Equivalent Dose (mg)
Alprazolam <sup>b</sup>	Niravam, <sup>c</sup> Xanax, Xanax XR	0.75–4 1–10 <sup>d</sup>	0.5
Chlordiazepoxide <sup>b</sup>	Librium	25–100	10
Clonazepam <sup>b</sup>	Klonopin Klonopin Wafers <sup>c</sup>	1–4 <sup>d</sup>	0.25
Clorazepate <sup>b</sup>	Tranxene	7.5–60	7.5
Diazepam <sup>b</sup>	Valium	2–40	5
Lorazepam <sup>b</sup>	Ativan	0.5–10	1
Oxazepam <sup>b</sup>	Serax	30–120	15

XR, extended-release.

<sup>a</sup>Elderly patients are usually treated with approximately one-half of the dose listed.

<sup>b</sup>Available generically.

<sup>c</sup>Orally disintegrating formulation.

<sup>d</sup>Panic disorder dose.

Equivalent doses from Chouinard G. Issues in the clinical use of benzodiazepines: Potency, withdrawal and rebound. *J Clin Psychiatry* 2004;65(Suppl 5):7–12.

- It is theorized that BZs ameliorate anxiety through potentiation of GABA activity.
- The dose must be individualized. Some patients require longer treatment.
- The elderly have an enhanced sensitivity to BZs and may experience falls when on BZ therapy.

### Pharmacokinetics

- BZ pharmacokinetic properties are shown in Table 68-10.
- **Diazepam** and **clorazepate** have high lipophilicity and are rapidly absorbed and distributed into the CNS. They have a shorter duration of effect after a single dose than would be predicted on the basis of half-life, as they are rapidly distributed to the periphery.
- **Lorazepam** and **oxazepam** are less lipophilic and have a slower onset but a longer duration of action. They are not recommended for immediate relief of anxiety.
- **IM diazepam** and **chlordiazepoxide** should be avoided because of variability in rate and extent of absorption. **IM lorazepam** provides rapid and complete absorption.
- **Clorazepate**, a prodrug, is converted to **desmethyldiazepam** in the stomach through a pH-dependent process that may be impaired by concurrent antacid use. Several other BZs are also converted to desmethyldiazepam, which has a long half-life and can accumulate, especially in the elderly and those with impaired oxidation.
- Intermediate- or short-acting BZs are preferred for chronic use in the elderly and those with liver disorders because of minimal accumulation and achievement of steady state within 1 to 3 days.

### Adverse Events

- The most common side effect of BZs is CNS depression. Tolerance usually develops to this effect. Other side effects are disorientation, psychomotor impairment, confusion, aggression, excitement, and anterograde amnesia.

**TABLE 68-10** Pharmacokinetics of Benzodiazepine Antianxiety Agents

Generic Name	Time to Peak Plasma Level (hours)	Elimination Half-Life, Parent (hours)	Metabolic Pathway	Clinically Significant Metabolites	Protein Binding (%)
Alprazolam	1–2	12–15	Oxidation	–	80
Chlordiazepoxide	1–4	5–30	<i>N</i> -Dealkylation	Desmethylchlor-diazepoxide	96
			Oxidation	Demoxepam DMDZ <sup>a</sup>	– –
Clonazepam	1–4	30–40	Nitroreduction	–	85
Clorazepate	1–2	Prodrug	Oxidation	DMDZ	97
Diazepam	0.5–2	20–80	Oxidation	DMDZ	98
				Oxazepam	–
Lorazepam	2–4	10–20	Conjugation	–	85
Oxazepam	2–4	5–20	Conjugation	–	97

<sup>a</sup>Desmethyldiazepam (DMDZ) half-life 50–100 hours.

Data from Bailey L, Ward M, Musa M. *Clinical pharmacokinetics of benzodiazepines*. *J Clin Pharmacol* 1994;34:804–811; and *Benzodiazepines. Facts and Comparisons 4.0 Online*. Wolters Kluwer Health, Inc. 2005. <http://online.factsandcomparisons.com>.

### *Abuse, Dependence, Withdrawal, and Tolerance*

- Those with a history of drug abuse are at the greatest risk for becoming BZ abusers.
- BZ dependence is defined by the appearance of a predictable withdrawal syndrome (i.e., anxiety, insomnia, agitation, muscle tension, irritability, nausea, malaise, diaphoresis, nightmares, depression, hyperreflexia, tinnitus, delusions, hallucinations, and seizures) upon abrupt discontinuation.

### *Benzodiazepine Discontinuation*

- After BZs are abruptly discontinued, three events can occur:
  - ✓ Rebound symptoms are an immediate, but transient, return of original symptoms with an increased intensity compared with baseline.
  - ✓ Recurrence or relapse is the return of original symptoms at the same intensity as before treatment.
  - ✓ Withdrawal is the emergence of new symptoms and a worsening of preexisting symptoms.
- The onset of withdrawal symptoms is within 24 to 48 hours after discontinuation of short elimination half-life BZs and 3 to 8 days after discontinuation of long elimination half-life drugs.
- Discontinuation strategies include the following:
  - ✓ A 25% per week reduction in dosage until 50% of the dose is reached, then dosage reduction by one-eighth every 4 to 7 days. If therapy exceeds 8 weeks, a taper over 2 to 3 weeks is recommended, but if duration of treatment is 6 months, a taper over 4 to 8 weeks should ensue. Longer durations of treatment may require a 2- to 4-month taper.
  - ✓ A BZ with a long elimination half-life ( $t_{1/2}$ ) (e.g., **diazepam**, **clonazepam**) may be substituted for a drug with a short  $t_{1/2}$  (e.g., **lorazepam**, **oxazepam**, **alprazolam**). The substituted drug should be given for several weeks before gradual tapering begins.
  - ✓ Adjunctive use of **imipramine**, **valproic acid**, or **bupirone** can help to reduce withdrawal symptoms during the BZ taper.

### *Drug Interactions*

- Drug interactions with the BZs are generally pharmacodynamic or pharmacokinetic (Table 68-11). The combination of **BZs** with **alcohol** or other **CNS depressants** may be fatal.
- **Alprazolam** dose should be reduced by 50% if **nefazodone** (Serzone) or **fluvoxamine** is added.

### **Dosing and Administration**

- Initial doses should be low, and dosage adjustments can be made weekly (see Table 68-9).
- Treatment of acute anxiety generally should not exceed 4 weeks. BZs can be given as needed, and if several acute courses are necessary, a BZ-free period of 2 to 4 weeks should be implemented between courses. Persistent symptoms should be managed with antidepressants.
- BZs with a long  $t_{1/2}$  may be dosed once daily at bedtime and may provide nighttime hypnotic and anxiolytic effects the next day.

**TABLE 68-11** Pharmacokinetic Drug Interactions with the Benzodiazepines

Drug	Effect
Carbamazepine	Decreased Cl of alprazolam
Ciprofloxacin	Decreased Cl of diazepam and increased $t_{1/2}$
Erythromycin	Decreased Cl of alprazolam
Fluoxetine	Decreased Cl of diazepam
Fluvoxamine	Decreased Cl of alprazolam and diazepam and prolonged $t_{1/2}$
Isoniazid	Decreased Cl of diazepam and increased $t_{1/2}$
Ketoconazole	Decreased Cl and Vd of chlordiazepoxide; increased AUC of alprazolam
Nefazodone	Decreased Cl of alprazolam, AUC doubled, and $t_{1/2}$ prolonged
Omeprazole	Decreased Cl of diazepam and prolonged $t_{1/2}$
Oral contraceptives	Decreased Cl and increased $t_{1/2}$ of diazepam and chlordiazepoxide; decreased $t_{1/2}$ of lorazepam and oxazepam
Paroxetine	Decreased Cl of alprazolam
Phenytoin	Increased Cl of clonazepam and reduced $t_{1/2}$
Propoxyphene	Decreased Cl of alprazolam and prolonged $t_{1/2}$
Propranolol	Decreased Cl of diazepam and prolonged $t_{1/2}$
Rifampin	Increased metabolism of diazepam
St. John's wort	Decreased AUC of alprazolam
Valproate	Decreased Cl of lorazepam

AUC, area under the plasma concentration curve; BZ, benzodiazepine; Cl, clearance;  $t_{1/2}$ , elimination half-life; Vd, volume of distribution. Data from Benzodiazepines. Facts and Comparisons 4.0 Online. Wolters Kluwer Health, Inc. 2005, <http://online.factsandcomparisons.com>; and Madabushi R, Frank B, Drewelow B, et al. Hyperforin in St. John's wort drug interactions. *Eur J Clin Pharmacol* 2006;62:225–233.

- In the elderly, doses should be low, and short-elimination half-life agents prescribed.

### Buspirone Therapy

- **Buspirone** is a 5-HT<sub>1A</sub> partial agonist that lacks anticonvulsant, muscle relaxant, sedative-hypnotic, motor impairment, and dependence-producing properties.
- It is considered a second-line agent for GAD because of inconsistent reports of efficacy, delayed onset of effect, and lack of efficacy for comorbid depressive and anxiety disorders (e.g., panic disorder or SAD). It is the agent of choice in patients who fail other anxiolytic therapies or in patients with a history of alcohol or substance abuse. It is not useful for situations requiring rapid antianxiety effects or as-needed therapy.
- It has a mean  $t_{1/2}$  of 2.5 hours, and it is dosed two to three times daily.
- Side effects include dizziness, nausea, and headaches.

### Drug Interactions

- **Buspirone** may increase **haloperidol** levels and elevate blood pressure in patients taking a monoamine oxidase inhibitor (MAOI).
- **Verapamil**, **itraconazole**, and **fluvoxamine** can increase buspirone levels, and **rifampin** reduces buspirone blood levels by 10-fold.

### Dosing and Administration

- Buspirone doses can be titrated in increments of 5 mg/day every 2 or 3 days as needed.

**TABLE 68-12** Drugs Used in the Treatment of Panic Disorder

Class/Generic Name	Brand Name	Starting Dose	Antipanic Dosage <sup>a</sup> Range (mg)
Selective serotonin reuptake inhibitors			
Citalopram <sup>b</sup>	Celexa	10 mg per day	20–60
Escitalopram	Lexapro	5 mg per day	10–20
Fluoxetine <sup>b</sup>	Prozac	5 mg per day	10–30
Fluvoxamine <sup>b</sup>	Luvox	25 mg per day	100–300
Paroxetine <sup>b</sup>	Paxil	10 mg per day	20–60 <sup>c</sup>
	Paxil CR	12.5 mg per day	25–75 <sup>c</sup>
Sertraline <sup>b</sup>	Zoloft	25 mg per day	50–200 <sup>c</sup>
Serotonin norepinephrine reuptake inhibitors			
Venlafaxine XR	Effexor XR	37.5 mg per day	75–225 <sup>c</sup>
Benzodiazepines			
Alprazolam <sup>b</sup>	Xanax	0.25 mg three times a day	4–10 <sup>c</sup>
	Xanax XR	0.5–1 mg per day	1–10 <sup>c</sup>
Clonazepam <sup>b</sup>	Klonopin	0.25 mg once or twice per day	1–4 <sup>c</sup>
Diazepam <sup>b</sup>	Valium	2–5 mg three times a day	5–20
Lorazepam <sup>b</sup>	Ativan	0.5–1 mg three times a day	2–8
Tricyclic antidepressant			
Imipramine <sup>b</sup>	Tofranil	10 mg per day	75–250
Monoamine oxidase inhibitor			
Phenelzine	Nardil	15 mg per day	45–90

CR, controlled-release; XR, extended-release.

<sup>a</sup>Dosage used in clinical trials but not FDA approved.

<sup>b</sup>Available generically.

<sup>c</sup>Dosage is FDA approved.

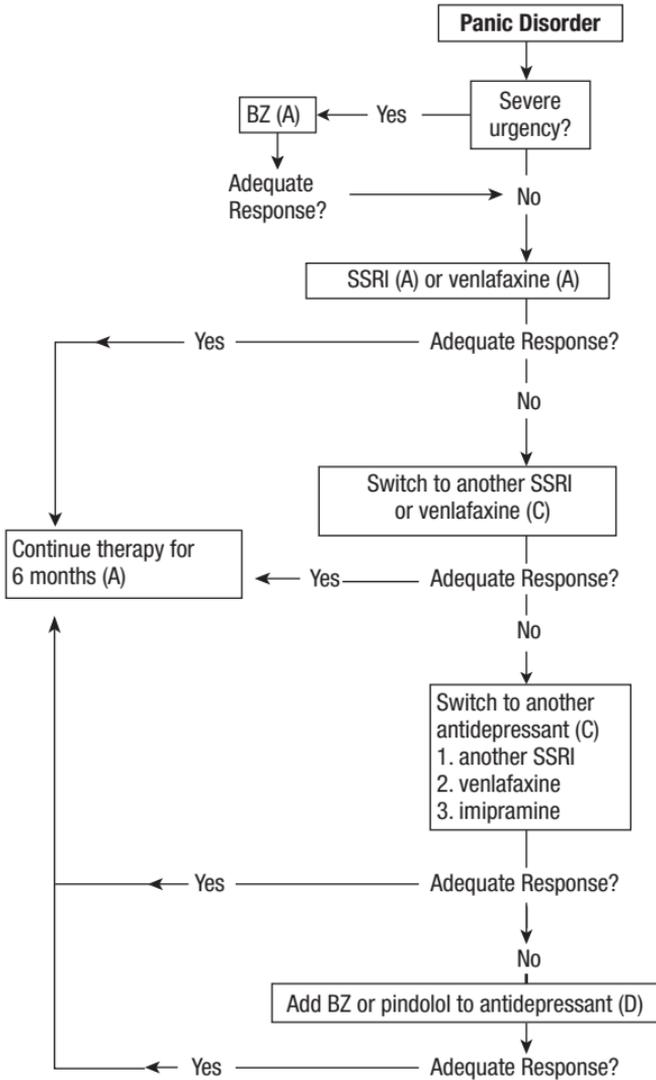
Data from Katon WJ. Panic disorder. *N Engl J Med* 2006;354:2360–2367; Bandelow B, Zohar J, Hollander E, et al. Guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and posttraumatic stress disorders. *World J Biol Psychiatry* 2002;3:171–199; Work Group on Panic Disorder. Practice guideline for the treatment of patients with panic disorder. *Am J Psychiatry* 1998;155(Suppl 5):1–34; and Effexor XR [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals, Inc., August 2006.

- The onset of anxiolytic effects requires 2 weeks or more; maximum benefit may require 4 to 6 weeks.
- When switching from a BZ to buspirone, the BZ should be tapered slowly.

## PANIC DISORDER

### General Therapeutic Principles

- Antipanic drugs are shown in Table 68-12. An algorithm for drug therapy of panic disorder is shown in Fig. 68-2.
- A metaanalysis showed that **SSRIs**, **TCAs**, and CBT are similarly effective. **Alprazolam**, **clonazepam**, **sertraline**, **paroxetine**, and **venlafaxine** are FDA approved for this indication.
- SSRIs are first-line agents, but BZs are the most commonly used drugs for panic disorder.
- Most patients without agoraphobia improve with pharmacotherapy alone, but if agoraphobia is present, CBT typically is initiated concurrently.
- Patients treated with CBT are less likely to relapse than those treated with **imipramine** alone. For patients who cannot or will not take medications,



**FIGURE 68-2.** Algorithm for the pharmacotherapy of panic disorder. Strength of recommendations: A = directly based on category I evidence (i.e., metaanalysis of randomized clinical trials [RCT] or at least one RCT); B = directly based on category II evidence (i.e., at least one controlled study without randomization or one other type of quasi-experimental study); C = directly based on category III evidence (i.e., nonexperimental descriptive studies); D = directly based on category IV evidence (i.e., expert committee reports or opinions and/or clinical experience of respected authorities). (BZ, benzodiazepine; SSRI, selective serotonin reuptake inhibitor.) (Data from Baldwin DS, Anderson IM, Nutt DJ, et al. Evidence-based guidelines for the pharmacological treatment of anxiety disorders: Recommendations from the British Society for Psychopharmacology. *J Psychopharmacology* 2005;19:567–596; and National Institute for Clinical Excellence. *The Management of Panic Disorder and Generalized Anxiety Disorder in Primary Care and Secondary Care: Clinical Guideline 22*. London: National Collaborating Centre for Mental Health, December 2004.)

CBT alone is indicated, as it is associated with improvement in 80% to 90% of patients short-term and 75% of patients at 6-month follow-up.

- Patients must be educated to avoid **caffeine**, drugs of abuse, and stimulants.
- Antidepressants, especially the SSRIs, are preferred in elderly patients and youth. The BZs are second line in these patients because of potential problems with disinhibition.

### Antidepressants

- Stimulatory side effects (e.g., anxiety, insomnia, jitteriness, irritability) can occur in **TCA**- and **SSRI**-treated patients. This may affect compliance and hinder dose increases. Low initial doses and gradual dose titration may eliminate these effects (see Table 68-12).
- **Imipramine** blocks panic attacks within 4 weeks, but maximal improvement, including reduced anticipatory anxiety and antiphobic response, requires 8 to 12 weeks.
- About 25% of panic patients discontinue **TCAs** because of side effects.
- All **SSRIs** eliminate panic attacks in 60% to 80% of patients. The antipanic effect requires 4 weeks, and some patients do not respond until 8 to 12 weeks.
- Low initial doses of **SSRIs** and gradual titration to the antipanic dose are required to avoid stimulatory side effects.
- **MAOIs** are reserved for the most difficult or refractory panic disorder patients. Side effects and dietary and drug restrictions affect patient acceptance (see Chap. 70 for food and drug restrictions). **Fluoxetine** must be stopped 5 weeks before **phenelzine** (or another MAOI) is started. Other antidepressants should be stopped 2 weeks before phenelzine is started.
- Approximately 54% to 60% of patients became panic-free on venlafaxine-extended release 75 mg or 150 mg.

### Benzodiazepines

- **BZs** are second-line agents except when rapid response is essential. They should not be used as monotherapy in panic disorder patients with a history of depression or **alcohol** or drug abuse. BZs are often used concomitantly with antidepressants in the first weeks to offset the delay in onset of antipanic effects.
- About 60% to 80% of panic patients respond to BZs, but relapse rates of 50% or higher are common despite slow drug tapering.
- **Alprazolam** and **clonazepam** are the most frequently used of the BZs and are well accepted by patients. Therapeutic response typically occurs in 1 to 2 weeks. With alprazolam, the duration of action may be as little as 4 to 6 hours with breakthrough symptoms between dosing. The use of extended-release alprazolam or clonazepam avoids this problem.

### Dosing and Administration

- The starting dose of **clonazepam** is 0.25 mg twice daily, with a dose increase to 1 mg by the third day. Increases by 0.25 to 0.5 mg every 3 days to 4 mg/day can be made if needed.
- The starting dose of **alprazolam** is 0.25 to 0.5 mg three times daily (or 0.5 mg once daily of alprazolam extended release), slowly increasing over several weeks to an ideal dose. Most patients require 3 to 6 mg/day.

- Usually patients are treated for 12 to 24 months before discontinuation (over 4 to 6 months) is attempted. Many patients require long-term therapy. Successful maintenance with single weekly doses of **fluoxetine** has been described.

### Evaluation of Therapeutic Outcomes

- Patients with panic disorder should be seen every 2 weeks during the first few weeks to adjust medication doses based on symptom improvement and to monitor side effects. Once stabilized, they can be seen every 2 months. The Hamilton Rating Scale for Anxiety (score less than or equal to 7 to 10) can be used to measure anxiety, and the Sheehan Disability Scale (with a goal of less than or equal to 1 on each item) can be used to measure for disability. During drug discontinuation, the frequency of appointments should be increased.

## SOCIAL ANXIETY DISORDER

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- SAD patients often respond more slowly and less completely than patients with other anxiety disorders.
- After improvement, at least 1 year of maintenance treatment is recommended to maintain improvement and decrease the rate of relapse. Long-term treatment may be needed for patients with unresolved symptoms, comorbidity, an early onset of disease, or a prior history of relapse.
- CBT (exposure therapy, cognitive restructuring, relaxation training, and social skills training) and pharmacotherapy are considered equally effective in SAD, but CBT can lead to a greater likelihood of maintaining response after treatment termination. Even after response, most patients continue to experience more than minimal residual symptoms.
- CBT and social skills training are effective in children with SAD. Evidence supports the efficacy of SSRIs and serotonin norepinephrine reuptake inhibitors in children 6 to 17 years of age. Individuals up to 24 years of age should be closely monitored for increased risk of suicidality.
- Drugs used in treatment of SAD are shown in Table 68-13, and an algorithm for treatment of SAD is shown in Fig. 68-3.
- Response rates of SSRIs in SAD ranged from 50% to 80% after 8 to 12 weeks of treatment. **Paroxetine**, **sertraline**, and **venlafaxine extended release** are approved for treatment of generalized SAD and are first-line agents.
- With **SSRI** treatment, the onset of effect is delayed 4 to 8 weeks, and maximum benefit is often not observed until 12 weeks or longer.
- The TCAs are not effective for SAD.
- Limited data suggest that **citalopram** is also effective for SAD, but that **fluoxetine** is not effective.
- **SSRIs** are initiated at doses similar to those used for depression (see Table 68-13). If there is comorbid panic disorder, the **SSRI** dose should be started at one-fourth to one-half the usual starting dose of antidepressants. The dose should be tapered slowly during discontinuation to decrease the risk of relapse.
- Some patients unresponsive to **SSRIs** have improved with **venlafaxine extended release**. Response has been reported by week 3.

**TABLE 68-13** Drugs Used in the Treatment of Generalized Social Anxiety Disorder

Class/Generic Name	Brand Name	Starting Dose	Dosage Range <sup>a</sup> (mg/day)
Selective serotonin reuptake inhibitors			
Citalopram <sup>b</sup>	Celexa	20 mg per day	20–40
Escitalopram	Lexapro	5 mg per day	10–20
Fluvoxamine <sup>b</sup>	Luvox	50 mg per day	150–300
Paroxetine <sup>b</sup>	Paxil	10 mg per day	10–60 <sup>c</sup>
Paroxetine CR	Paxil CR	12.5 mg per day	12.5–37.5 <sup>c</sup>
Sertraline <sup>b</sup>	Zoloft	25–50 mg per day	50–200 <sup>c</sup>
Serotonin-norepinephrine reuptake inhibitor			
Venlafaxine XR	Effexor XR	75 mg per day	75–225 <sup>c</sup>
Benzodiazepine			
Clonazepam <sup>b,d</sup>	Klonopin	0.25 mg per day	1–4
Monoamine oxidase inhibitor			
Phenelzine	Nardil	15 mg at bedtime	60–90
Alternate agents			
Bupirone <sup>b,d</sup>	BuSpar	10 mg twice per day	45–60
Gabapentin <sup>b</sup>	Neurontin	100 mg three times a day	900–3,600
Mirtazapine <sup>a,b</sup>	Remeron	15 mg at bedtime	30
Pregabalin	Lyrica	100 mg three times a day	600

CR, controlled-release; XR, extended-release.

<sup>a</sup>Dosage used in clinical trials but not FDA approved.

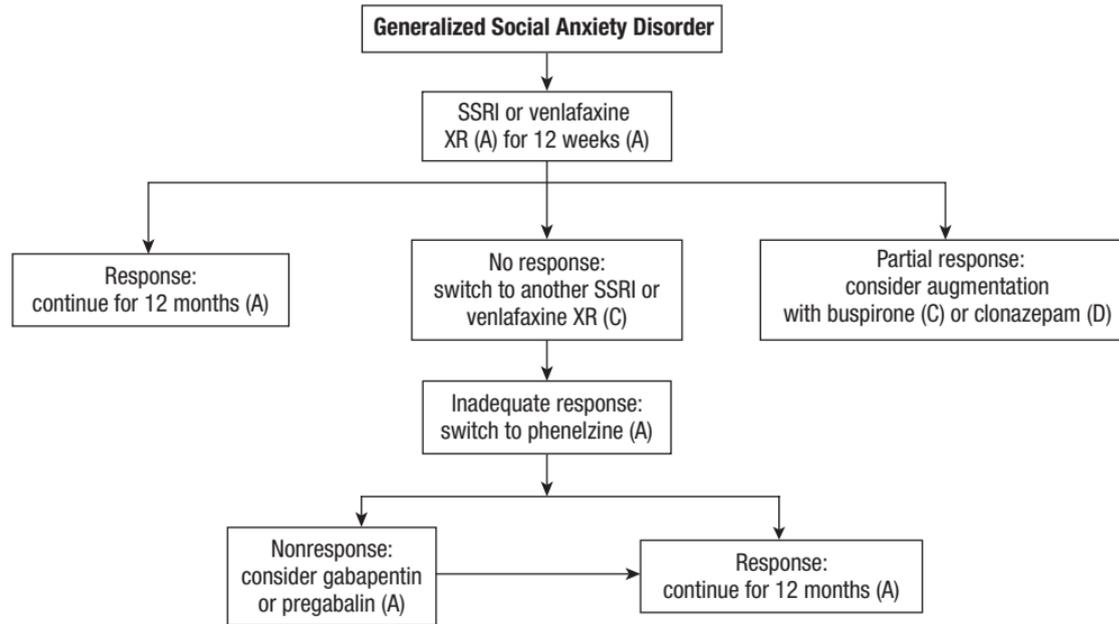
<sup>b</sup>Available generically.

<sup>c</sup>Dosage is FDA approved.

<sup>d</sup>Used as augmenting agent.

Data from Schneier FR. *N Engl J Med* 2006;355:1029–1036; Ballenger JC, Davidson JRT, Lecrubier Y, et al. *J Clin Psychiatry* 1998;59(Suppl 17):54–60; Paxil [package insert]. Research Triangle Park, NC: GlaxoSmithKline, July 2006; Effexor XR [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals, Inc., August 2006; and Blanco C, Muhammad SR, Schneier FR, et al. *Int J Neuropsychopharmacol* 2003;6:427–442.

- **BZs** should be reserved for patients at low risk of substance abuse, those who require rapid relief, or those who have not responded to other therapies.
- **Clonazepam** is the most extensively studied BZ for treatment of generalized SAD. It improved fear and phobic avoidance, interpersonal sensitivity, fears of negative evaluation, and disability measures. Adverse effects include sexual dysfunction, unsteadiness, dizziness, and poor concentration. Clonazepam should be tapered at a rate not to exceed 0.25 mg every 2 weeks.
- **Gabapentin** was effective for SAD, and onset of effect was 2 to 4 weeks.
- **$\beta$ -Blockers** blunt the peripheral autonomic symptoms of arousal (e.g., rapid heart rate, sweating, blushing, and tremor) and are often used to decrease anxiety in performance-related situations. For specific SAD, 10 to 80 mg of **propranolol** or 25 to 100 mg of **atenolol** can be taken 1 hour before the performance. A test dose should be taken at home on a day before the performance to be sure adverse effects will not be problematic.
- Incomplete response to a first-line agent may benefit from augmentation with **bupirone** or **clonazepam**.



**FIGURE 68-3.** Algorithm for the pharmacotherapy of generalized social anxiety disorder. Strength of recommendations: A = directly based on category I evidence (i.e., metaanalysis of randomized clinical trials [RCT] or at least one RCT); B = directly based on category II evidence (i.e., at least one controlled study without randomization or one other type of quasi-experimental study); C = directly based on category III evidence (i.e., nonexperimental descriptive studies); D = directly based on category IV evidence (i.e., expert committee reports or opinions and/or clinical experience of respected authorities). (SSRI, selective serotonin reuptake inhibitor; XR, extended-release.) (Data from Baldwin DS, Anderson IM, Nutt DJ, et al. Evidence-based guidelines for the pharmacological treatment of anxiety disorders: Recommendations from the British Society for Psychopharmacology. *J Psychopharmacology* 2005;19:567–596.)

- **Phenelzine**, an MAOI, is effective, but is reserved for treatment-resistant patients because of dietary restrictions, potential drug interactions, and adverse effects.
- Patients with SAD should be monitored for symptom response, adverse effects, and overall functionality and quality of life. Patients should be seen weekly during dosage titration and monthly once stabilized. Patients should be asked to keep a diary to record symptoms and their severity. The clinician-related Liebowitz Social Anxiety Scale and the patient-rated Social Phobia Inventory can be used to monitor severity of symptoms and symptom change.

## POSTTRAUMATIC STRESS DISORDER

- Immediately after the trauma, patients should receive treatment individualized to their presenting symptoms (e.g., **non-BZ hypnotic**, short courses of CBT). Brief courses of CBT in close proximity to the trauma resulted in lower rates of PTSD.
- If symptoms (e.g., hyperarousal, avoidance, dissociation, insomnia, depression) persist for 3 to 4 weeks and there is social or occupational impairment, patients should receive pharmacotherapy or psychotherapy, or both.
- Psychotherapies for PTSD include anxiety management (e.g., stress-inoculation training, relaxation training, biofeedback, distraction techniques), CBT, group therapy, hypnosis, psychodynamic therapies, and psychoeducation. Psychotherapy may be used in patients with mild symptoms, those who prefer not to use medications, or in conjunction with drugs in those with severe symptoms to improve response.
- Table 68-14 shows antidepressants used in the treatment of PTSD, and Fig. 68-4 shows an algorithm for the pharmacotherapy of PTSD.

**TABLE 68-14** Antidepressants Used in the Treatment of Posttraumatic Stress Disorder

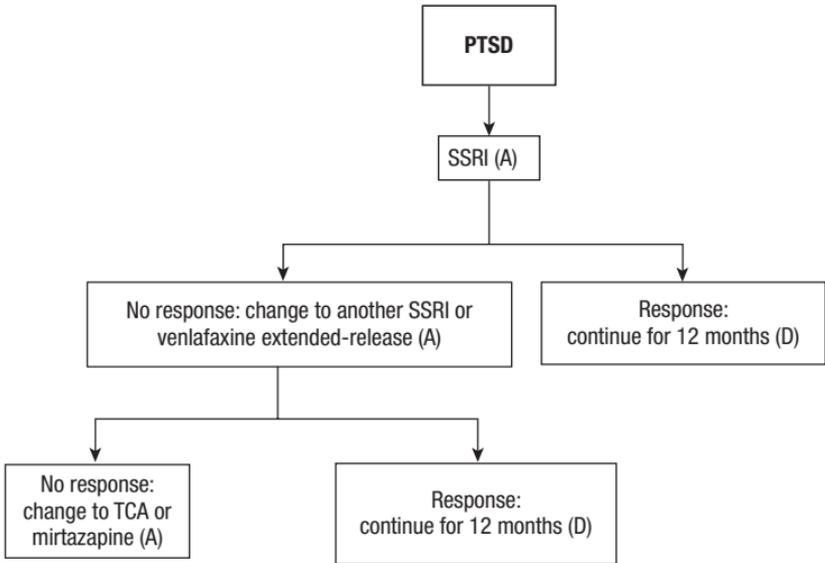
Class/Generic Name	Starting Dose	Dosage Range <sup>a</sup> (mg/day)
Selective serotonin reuptake inhibitors		
Citalopram <sup>c</sup>	20 mg per day	20–60
Escitalopram	10 mg per day	10–20
Fluoxetine <sup>c</sup>	10–20 mg per day	10–80
Fluvoxamine <sup>c</sup>	50 mg per day	100–250
Paroxetine <sup>c</sup>	10–20 mg per day	20–50 <sup>b</sup>
Sertraline <sup>c</sup>	25–50 mg per day	50–200 <sup>b</sup>
Other agents		
Amitriptyline <sup>c</sup>	25–50 mg per day	50–300
Imipramine <sup>c</sup>	25–50 mg per day	50–300
Mirtazapine <sup>c</sup>	15 mg at bedtime	15–45
Phenelzine	15 mg every night	15–90
Venlafaxine extended-release	37.5 mg per day	37.5–225

<sup>a</sup>Dosage used in clinical trials but not FDA approved.

<sup>b</sup>Doasge is FDA approved.

<sup>c</sup>Available generically.

Data from Ballenger JC, Davidson JRT, Lecrubier Y, et al. *J Clin Psychiatry* 2004;65(Suppl 1):55–62; Baldwin DS, Anderson IM, Nutt DJ, et al. *J Psychopharmacol* 2005;19:567–596; Bandelow B, Zohar J, Hollander E, et al. *World J Biol Psychiatry* 2002;3:171–199; Paxil [package insert]. Research Triangle Park, NC: GlaxoSmithKline, July 2006; Zoloft [package insert]. New York: Pfizer, September 2006; and Schoenfeld FB, Marmor CR, Neylan TC. *Psychiatr Serv* 2004;55:519–531.



**FIGURE 68-4.** Algorithm for the pharmacotherapy of posttraumatic stress disorder (PTSD). Strength of recommendations: A = directly based on category I evidence (i.e., metaanalysis of randomized clinical trials [RCT] or at least one RCT); D = directly based on category IV evidence (i.e., expert committee reports or opinions and/or clinical experience of respect authorities). (SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.) (Data from Ballenger JC, Davidson JRT, Lecrubier Y, et al. Consensus statement update on posttraumatic stress disorder from the International Consensus Group on Depression and Anxiety. *J Clin Psychiatry* 2004;65(Suppl 1):55–62; Baldwin DS, Anderson IM, Nutt DJ, et al. Evidence-based guidelines for the pharmacological treatment of anxiety disorders: Recommendations from the British Association for Pharmacology. *J Psychopharmacol* 2005;19:567–596; and Bandelow B, Zohar J, Hollander E, et al. Guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and posttraumatic stress disorders. *World J Biol Psychiatry* 2002;3:171–199.)

- The **SSRIs** are first-line pharmacotherapy for PTSD. **Venlafaxine**, the **TCAs**, and **MAOIs** may also be effective, but they have less favorable side-effect profiles.
- **Sertraline** and **paroxetine** are approved for acute treatment of PTSD, and sertraline is approved for long-term management of PTSD.
- Antiadrenergics and atypical antipsychotics can be used as augmenting agents.
- The **SSRIs** are believed to be more effective for numbing symptoms than other drugs. About 60% of **sertraline**-treated patients showed improvement in arousal and avoidance/numbing symptoms, but not reexperiencing symptoms. Similar numbers of patients have been shown to improve on **paroxetine**. **Fluoxetine** was effective in a placebo-controlled trial, and **fluvoxamine** was effective in an open trial.
- **Amitriptyline** and **imipramine**, and the **MAOI phenelzine**, can be considered second- or third-line drugs for PTSD after **SSRIs** have failed. **Mirtazapine** and **venlafaxine** may also be effective.

- If there is no improvement in the acute stress response 3 to 4 weeks post trauma, **SSRIs** should be started in a low dose with slow titration upward toward antidepressant doses. Eight to 12 weeks is an adequate duration of treatment to determine response.
- Responders to drug therapy should continue treatment for at least 12 months. When discontinued, drug therapy should be tapered slowly over a period of 1 month or more to reduce the likelihood of relapse.
- Antiadrenergic drugs (**prazosin**) can be useful in some patients with PTSD, and antipsychotics (**risperidone**, **quetiapine**, and **olanzapine**) may be used as augmenting agents in partial responders.
- Patients should be seen weekly for the first month, then biweekly through the second month. During months 3 to 6, patients can be seen monthly, then every 1 to 2 months from months 6 to 12. Responders after 1 year of pharmacotherapy can be seen every 3 months. Patients should be monitored for symptom response, side effects, and treatment adherence.
- Remission can be monitored with the Treatment Outcome PTSD Scale (score less than or equal to 5) and the Sheehan Disability Scale (score less than or equal to 1 on each item).

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*See Chap. 73, Anxiety Disorders I, authored by Cynthia K. Kirkwood and Sarah T. Melton, and Chap. 74, Anxiety Disorders II, authored by Cynthia K. Kirkwood, Eugene H. Makela, and Barbara G. Wells, for a more detailed discussion of this topic.*

## DEFINITION

- Bipolar disorder, previously known as *manic-depressive illness*, is a cyclical, lifelong disorder with recurrent extreme fluctuations in mood, energy, and behavior. Diagnosis requires the occurrence, during the course of the illness, of a manic, hypomanic, or mixed episode (not caused by any other medical condition, substance, or psychiatric disorder).

## ETIOLOGY AND PATHOPHYSIOLOGY

- Medical conditions, medications, and somatic treatments that may induce mania are shown in Table 69-1.
- See Chap. 70 for medical conditions, substance use disorders, and medications associated with depressive symptoms.
- Etiology and pathophysiology of bipolar disorder are shown in Table 69-2.

## CLINICAL PRESENTATION AND DIAGNOSIS

- The *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., text revision, classifies bipolar disorders as (1) bipolar I, (2) bipolar II, (3) cyclothymic disorder, and (4) bipolar disorder not otherwise specified. Table 69-3 defines mood disorders by type of episode. Table 69-4 describes the evaluation and diagnostic criteria for mood disorders.

## MAJOR DEPRESSIVE EPISODE

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- In bipolar depression, patients often have mood lability, hypersomnia, low energy, psychomotor retardation, cognitive impairments, anhedonia, decreased sexual activity, slowed speech, carbohydrate craving, and weight gain.
- Delusions, hallucinations, and suicide attempts are more common in bipolar depression than in unipolar depression.

## MANIC EPISODE

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- Acute mania usually begins abruptly, and symptoms increase over several days. The severe stages may include bizarre behavior, hallucinations, and paranoid or grandiose delusions. There is marked impairment in functioning or the need for hospitalization.
- Manic episodes may be precipitated by stressors, sleep deprivation, antidepressants, CNS stimulants, or bright light.

## HYPOMANIC EPISODE

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- There is no marked impairment in social or occupational functioning, no delusions, and no hallucinations.

**TABLE 69-1** Secondary Causes of Mania**Medical conditions that induce mania**

- CNS disorders (brain tumor, strokes, head injuries, subdural hematoma, multiple sclerosis, systemic lupus erythematosus, temporal lobe seizures, Huntington's disease)
- Infections (encephalitis, neurosyphilis, sepsis, human immunodeficiency virus)
- Electrolyte or metabolic abnormalities (calcium or sodium fluctuations, hyper- or hypoglycemia)
- Endocrine or hormonal dysregulation (Addison's disease, Cushing's disease, hyper- or hypothyroidism, menstrual-related or pregnancy-related or perimenopausal mood disorders)

**Medications or drugs that induce mania**

- Alcohol intoxication
- Drug withdrawal states (alcohol,  $\alpha_2$ -adrenergic agonists, antidepressants, barbiturates, benzodiazepines, opiates)
- Antidepressants (MAOIs, TCAs, 5-HT and/or NE and/or DA reuptake inhibitors, 5-HT antagonists)
- DA-augmenting agents (CNS stimulants: amphetamines, cocaine, sympathomimetics; DA agonists, releasers, and reuptake inhibitors)
- Hallucinogens (LSD, PCP)
- Marijuana intoxication precipitates psychosis, paranoid thoughts, anxiety, and restlessness
- NE-augmenting agents ( $\alpha_2$ -adrenergic antagonists,  $\beta$ -agonists, NE reuptake inhibitors)
- Steroids (anabolic, adrenocorticotropic hormone, corticosteroids)
- Thyroid preparations
- Xanthines (caffeine, theophylline)
- Nonprescription weight loss agents and decongestants (ephedra, pseudoephedrine)
- Herbal products (St. John's wort)

**Somatic therapies that induce mania**

- Bright light therapy
- Sleep deprivation

DA, dopamine; 5-HT, serotonin; LSD, lysergic acid diethylamide; MAOI, monoamine oxidase inhibitor; NE, norepinephrine; PCP, phencyclidine; TCA, tricyclic antidepressant.

Data from Torrey EF, Knable MB. New York: Basic Books, 2002; American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, 4th ed., text revision*. Washington, DC: American Psychiatric Association, 2000:382–401; American Psychiatric Association. *Am J Psychiatry* 2002;159:1–50; and Goodnick PJ, ed. Washington, DC: American Psychiatric Press, 1998.

- During a hypomanic episode, some patients may be more productive and creative than usual, but 5% to 15% of patients may rapidly switch to a manic episode.

**MIXED EPISODE**

- Mixed episodes occur in up to 40% of all episodes, are often difficult to diagnose and treat, and are more common in younger and older patients and females.
- Patients with mixed states often have comorbid alcohol and substance abuse, severe anxiety symptoms, a higher suicide rate, and a poorer prognosis.

**COURSE OF ILLNESS**

- The average age of onset of a first manic episode is 21 years. More than 80% of bipolar patients have more than four episodes during their lifetime. Usually there is normal functioning between episodes.
- Rapid cyclers (10% to 20% of bipolar patients) have four or more episodes per year (major depressive, manic, mixed, or hypomanic). Rapid-cycling

**TABLE 69-2** Etiologic and Pathophysiologic Theories of Bipolar Disorder**Genetic factors**

80–90% of patients with bipolar disorder have a biologic relative with a mood disorder (e.g., bipolar disorder, major depression, cyclothymia, or dysthymia).

First-degree relatives of bipolar patients have a 15–35% lifetime risk of developing any mood disorder and a 5–10% lifetime risk for developing bipolar disorder.

The concordance rate of mood disorders is 60–80% for monozygotic twins and 14–20% for dizygotic twins. Linkage studies suggest that certain loci on genes and the X chromosome may contribute to genetic susceptibility of bipolar disorder.

**Nongenetic factors***Perinatal insult**Head trauma**Environmental factors*

Dysynchronization of circadian or seasonal rhythms cause diurnal variations in mood and sleep patterns and can result in seasonal recurrences of mood episodes.

Changes in the sleep-wake cycle or light-dark cycle can precipitate episodes of mania or depression.

Bright light therapy can be used for the treatment of winter depression and can precipitate hypomania, mania, or mixed episodes.

*Psychosocial or physical stressors*

Stressful life events often precede mood episodes and can increase recurrence rates and prolong time to recovery from mood episodes.

*Nutritional factors*

Deficiency of essential amino acid precursors in the diet can cause a dysregulation of neurotransmitter activity (e.g., L-tryptophan deficiency causes a decrease in 5-HT and melatonin synthesis and activity).

Deficiency in essential fatty acids (e.g., omega-3 fatty acids) can cause a dysregulation of neurotransmitter activity.

*Neurotransmitter/neuroendocrine/hormonal theories*

Dysregulation between excitatory and inhibitory neurotransmitter systems; excitatory: NE, DA, glutamate, and aspartate; inhibitory: 5-HT and GABA.

*Monoamine hypothesis*

An excess of catecholamines (primarily NE and DA) causes mania.

Agents that decrease catecholamines are used for the treatment of mania (e.g., DA antagonists and  $\alpha_2$ -adrenergic agonists).

Deficit of neurotransmitters (primarily NE, DA, and/or 5-HT) causes depression.

Agents that increase neurotransmitter activity are used for the treatment of depression (e.g., 5-HT and NE/DA reuptake inhibitors and MAOIs).

*Dysregulation of amino acid neurotransmitters*

Deficiency of GABA or excessive glutamate activity causes dysregulation of neurotransmitters (e.g., increased DA and NE activity).

Agents that increase GABA activity or decrease glutamate activity are used for the treatment of mania and for mood stabilization (e.g., benzodiazepines, lamotrigine, lithium, or valproic acid).

*Cholinergic hypothesis*

Deficiency of acetylcholine causes an imbalance in cholinergic-adrenergic activity and can increase the risk of manic episodes.

Agents that increase acetylcholine activity can decrease manic symptoms (e.g., use of cholinesterase inhibitors or augmentation of muscarinic cholinergic activity).

Increased central acetylcholine levels can increase the risk of depressive episodes.

Agents that decrease acetylcholine activity can alleviate depressive symptoms (i.e., anticholinergic agents).

*Secondary messenger system dysregulation*

Abnormal G protein functioning dysregulates adenylate cyclase activity, phosphoinositide responses, sodium/potassium/calcium channel exchange, and activity of phospholipases. Abnormal cyclic adenosine monophosphate and phosphoinositide secondary messenger system activity.

Abnormal protein kinase C activity and signaling pathways.

*(continued)*

**TABLE 69-2** Etiologic and Pathophysiologic Theories of Bipolar Disorder (Continued)*Hypothalamic-pituitary-thyroid axis dysregulation*

Hyperthyroidism can precipitate manic-like symptoms.

Hypothyroidism can precipitate a depression and be a risk factor for rapid cycling; thyroid supplementation can be used for refractory rapid cycling and augmentation of antidepressants in unipolar depression.

Positive antithyroid antibody titers reported in patients with bipolar disorder.

Hormonal changes during the female life cycle can cause dysregulation of neurotransmitters (e.g., premenstrual, postpartum, and perimenopause).

*Membrane and cation theories*

Abnormal neuronal calcium and sodium activity and homeostasis cause neurotransmitter dysregulation.

Hypocalcemia has been associated with causing anxiety, mood irritability, mania, psychosis, and delirium.

Hypercalcemia has been associated with causing depression, stupor, and coma.

Extracellular and intracellular calcium concentrations may affect the synthesis and release of NE, DA, and 5-HT, as well as the excitability of neuronal firing.

*Sensitization and kindling theories*

Recurrences of mood episodes causes behavioral sensitivity and electrophysiologic kindling (similar to the amygdala-kindling models for seizures in animals) and can result in rapid or continuous mood cycling.

DA, dopamine; GABA,  $\gamma$ -aminobutyric acid; 5-HT, serotonin; MAOI, monoamine oxidase inhibitor; NE, norepinephrine.

Data from Torrey EF, Knable MB. *New York: Basic Books, 2002*; Goldberg JF, Harrow M, eds. *Washington, DC: American Psychiatric Press, 1999*; Kelso JR. *J Affect Disord* 2003;73:183–197; Manji HK, Bowden CL, Belmaker RH, eds. *Washington, DC: American Psychiatric Press, 2000*; Lenox RH, Gould TD, Manji HK. *Am J Med Genet* 2002;114:391–406; Baron M. *Mol Psychiatry* 2002;7:342–358; Bezchlibnyk Y, Young LT. *Can J Psychiatry* 2002;47:135–148; Goodnick PJ, ed. *Washington, DC: American Psychiatric Press, 1998*; Soares JC. *Mol Psychiatry* 2002;7(Suppl 1):S64–S70; Manji HK, Moore GJ, Chen G. *Br J Psychiatry Suppl* 2001;41:S107–S119; Gould TD, Manji HK. *J Psychosom Res* 2002;53:687–697; Sobczak S, Honig A, van Duinen MA, Riedel WJ. *Bipolar Disord* 2002;4:347–356; Freeman MP, Wosnitzer Smith K, Freeman SA, et al. *J Clin Psychiatry* 2002;63:284–287; Ketter TA, Wang PW. *J Clin Psychiatry* 2003;64(Suppl 3):15–20; White HS. *J Clin Psychiatry* 2003;64(Suppl 8):5–8; Rasgon N, Bauer M, Glenn T, et al. *Bipolar Disord* 2003;5:48–52; and Mahmood T, Silverstone T. *J Affect Disord* 2001;66:1–11.

**TABLE 69-3** Mood Disorders Defined by Episodes

Disorder Subtype	Episode(s) <sup>a</sup>
Major depressive disorder, single episode	Major depressive episode
Major depressive disorder, recurrent	Two or more major depressive episodes
Bipolar disorder, type I <sup>b</sup>	Manic episode $\pm$ major depressive or mixed episode
Bipolar disorder, type II <sup>c</sup>	Major depressive episode + hypomanic episode
Dysthymic disorder	Chronic subsyndromal depressive episodes
Cyclothymic disorder <sup>d</sup>	Chronic fluctuations between subsyndromal depressive and hypomanic episodes (2 years for adults and 1 year for children and adolescents)
Bipolar disorder not otherwise specified	Mood states do not meet criteria for any specific bipolar disorder

<sup>a</sup>The length and severity of a mood episode and the interval between episodes vary from patient to patient. Manic episodes are usually briefer and end more abruptly than major depressive episodes. The average length of untreated manic episodes ranges from 4 to 13 months. Episodes can occur regularly (at the same time or season of the year) and often cluster at 12-month intervals. Women have more depressive episodes than manic episodes, whereas men have a more even distribution of episodes.

<sup>b</sup>For bipolar I disorder, 90% of individuals who experience a manic episode later have multiple recurrent major depressive, manic, hypomanic, or mixed episodes alternating with a normal mood state.

<sup>c</sup>Approximately 5–15% of patients with bipolar II disorder will develop a manic episode over a 5-year period. If a manic or mixed episode develops in a patient with bipolar II disorder, the diagnosis is changed to bipolar I disorder.

<sup>d</sup>Patients with cyclothymic disorder have a 15–50% risk of later developing a bipolar I or II disorder.

Data from American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Text Revision.*

*Washington, DC: American Psychiatric Association, 2000:382–401*; Goldberg JF, Harrow M, eds. *Bipolar Disorders: Clinical Course and Outcome.* Washington, DC: American Psychiatric Press, 1999; and Goodnick PJ, ed. *Mania: Clinical and Research Perspectives.* Washington, DC: American Psychiatric Press, 1998.

**TABLE 69-4** Evaluation and Diagnostic Criteria of Mood Episodes

Diagnostic workup depends on clinical presentation and findings

- Mental status examination
- Psychiatric, medical, and medication history
- Physical and neurologic examination
- Basic laboratory tests: complete blood count, blood chemistry screen, thyroid function, urinalysis, urine drug screen
- Psychological testing
- Brain imaging: magnetic resonance imaging and functional scan; alternative: computed tomography scan, positron emission tomography scan
- Lumbar puncture
- Electroencephalogram

<b>Diagnosis Episode</b>	<b>Impairment of Functioning or Need for Hospitalization<sup>a</sup></b>	<b>DSM-IV-TR Criteria<sup>b</sup></b>
Major depressive	Yes	<p>&gt;2-Week period of either depressed mood or loss of interest or pleasure in normal activities, associated with at least five of the following symptoms:</p> <ul style="list-style-type: none"> <li>• Depressed, sad mood (adults); can be irritable mood in children</li> <li>• Decreased interest and pleasure in normal activities</li> <li>• Decreased appetite, weight loss</li> <li>• Insomnia or hypersomnia</li> <li>• Psychomotor retardation or agitation</li> <li>• Decreased energy or fatigue</li> <li>• Feelings of guilt or worthlessness</li> <li>• Impaired concentration and decision making</li> <li>• Suicidal thoughts or attempts</li> </ul>
Manic	Yes	<p>&gt;1-Week period of abnormal and persistent elevated mood (expansive or irritable), associated with at least three of the following symptoms (four if the mood is only irritable):</p> <ul style="list-style-type: none"> <li>• Inflated self-esteem (grandiosity)</li> <li>• Decreased need for sleep</li> <li>• Increased talking (pressure of speech)</li> <li>• Racing thoughts (flight of ideas)</li> <li>• Distractible (poor attention)</li> <li>• Increased activity (either socially, at work, or sexually) or increased motor activity or agitation</li> <li>• Excessive involvement in activities that are pleasurable but have a high risk for serious consequences (buying sprees, sexual indiscretions, poor judgment in business ventures)</li> </ul>
Hypomanic	No	<p>At least 4 days of abnormal and persistent elevated mood (expansive or irritable); associated with at least three of the following symptoms (four if the mood is only irritable):</p> <ul style="list-style-type: none"> <li>• Inflated self-esteem (grandiosity)</li> <li>• Decreased need for sleep</li> <li>• Increased talking (pressure of speech)</li> <li>• Racing thoughts (flight of ideas)</li> <li>• Increased activity (either socially, at work, or sexually) or increased motor activity or agitation</li> <li>• Excessive involvement in activities that are pleasurable but have a high risk for serious consequences (buying sprees, sexual indiscretions, poor judgment in business ventures)</li> </ul>

(continued)

**TABLE 69-4** Evaluation and Diagnostic Criteria of Mood Episodes (Continued)

Mixed	Yes	Criteria for both a major depressive episode and manic episode (except for duration) occur nearly every day for at least a 1-week period
Rapid cycling	Yes	>Four major depressive or manic episodes (manic, mixed, or hypomanic) in 12 months

DSM-IV-TR, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., text revision.

<sup>a</sup>Impairment in social or occupational functioning; need for hospitalization because of potential self-harm, harm to others, or psychotic symptoms.

<sup>b</sup>The disorder is not caused by a medical condition (e.g., hypothyroidism) or substance-induced disorder (e.g., antidepressant treatment, medications, electroconvulsive therapy).

Data from Torrey EF, Knable MB. *Surviving Manic Depression: A Manual on Bipolar Disorder for Patients, Families, and Providers*. New York: Basic Books, 2002; American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Text Revision*. Washington, DC: American Psychiatric Association, 2000:382–401; and American Psychiatric Association. *Practice guideline for the treatment of patients with bipolar disorder (revision)*. *Am J Psychiatry* 2002;159:1–50.

and mixed states are associated with a poorer prognosis and nonresponse to antimanic agents. Risk factors for rapid cycling include biologic rhythm dysregulation, antidepressant or stimulant use, hypothyroidism, and premenstrual and postpartum states.

- Women are more likely to have mixed states, depressive episodes, and rapid cycling than men.
- Suicide attempts occur in up to 50% of patients with bipolar disorder, and approximately 10% to 19% of individuals with bipolar I disorder commit suicide. Bipolar II patients may be more likely than bipolar I patients to attempt suicide.
- Bipolar patients with substance abuse disorders are more likely to have an earlier onset of illness, mixed states, higher relapse rates, poorer response to treatment, higher suicide risk, and more hospitalizations.
- Approximately 10% to 15% of adolescents with recurrent major depressive episodes subsequently have an episode of mania or hypomania.
- Episodes may become longer in duration and more frequent with aging.

## DESIRED OUTCOME

- The goals of treatment are shown in Table 69-5.

## TREATMENT

### GENERAL APPROACH

- The general approach to treatment is shown in Table 69-5.

### NONPHARMACOLOGIC THERAPY

- Psychoeducation for the patient and family includes:
  - ✓ Early signs and symptoms of mania and depression and how to chart mood changes
  - ✓ Importance of compliance with therapy

**TABLE 69-5** General Principles for the Management of Bipolar Disorder**Goals of treatment**

- Eliminate mood episode with complete remission of symptoms (i.e., acute treatment)
- Prevent recurrences or relapses of mood episodes (i.e., continuation phase treatment)
- Return to complete psychosocial functioning
- Maximize adherence with therapy
- Minimize adverse effects
- Use medications with the best tolerability and fewest drug interactions
- Treat comorbid substance use and abuse
- Eliminate alcohol, marijuana, cocaine, amphetamines, and hallucinogens
- Minimize nicotine use and stop caffeine intake at least 8 hours prior to bedtime
- Avoidance of stressors or substances that precipitate an acute episode

**Monitor for**

- Mood episodes: document symptoms on a daily mood chart (document life stressors, type of episode, length of episode, and treatment outcome); monthly and yearly life charts are valuable for documenting patterns of mood cycles
- Medication adherence (missing doses of medications is a primary reason for nonresponse and recurrence of episodes)
- Adverse effects, especially sedation and weight gain (manage rapidly and vigorously to avoid noncompliance)
- Suicidal ideation or attempts (suicide completion rates with bipolar I disorder are 10–15%; suicide attempts are primarily associated with depressive episodes, mixed episodes with severe depression or presence of psychosis)

**Frequency of visits**

- Severely ill patients should be seen more often (i.e., weekly) compared with less ill patients who are symptomatic (i.e., every 2 weeks)
- When starting new medications or switching therapies, frequent monitoring is recommended (e.g., every 2 weeks) to assess adherence, efficacy, dosing, and adverse effects
- When a patient is stabilized on medication, less frequent monitoring is possible during the continuation phase (e.g., every month for the first 3 months, then every 2–3 months)
- Patients should be encouraged to call their clinician if any problems or adverse events occur or if mood episodes occur between scheduled appointments; rapidly identifying and correcting potential problems or making dosage adjustments is essential in achieving mood stabilization

Data from Torrey EF, Knable MB. *New York: Basic Books, 2002; American Psychiatric Association. Am J Psychiatry 2002;159:1–50; Goodnick PJ, ed. Washington, DC: American Psychiatric Press, 1998; and Suppes T, Denney EB, Swann AC, et al. J Clin Psychiatry 2002;63:288–299.*

- ✓ Psychosocial or physical stressors that may precipitate an episode and strategies for coping with stressful life events
- ✓ Limiting substances and drugs that can trigger mood episodes
- ✓ Development of a crisis intervention plan
- Other nonpharmacologic approaches include:
  - ✓ Psychotherapy (e.g., individual, group, and family), interpersonal therapy, and/or cognitive behavioral therapy
  - ✓ Stress reduction techniques, relaxation therapy, massage, yoga, etc.
  - ✓ Sleep (regular bedtime and awake schedule; avoid alcohol or caffeine intake prior to bedtime)
  - ✓ Nutrition (regular intake of protein-rich foods or drinks and essential fatty acids; supplemental vitamins and minerals)
  - ✓ Exercise (regular aerobic and weight training at least three times a week)
  - ✓ The use of electroconvulsive therapy for severe mania or mixed episodes, psychotic depression, or rapid cycling is still considered the best

acute treatment approach for those patients who do not respond to first-line mood stabilizers, such as **lithium** and **valproate**

## PHARMACOLOGIC THERAPY

- An example treatment algorithm for the acute treatment of mood episodes in patients with bipolar I disorder is shown in Table 69-6.

### Treatments of First Choice

- **Lithium, divalproex sodium (valproate), aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone** are currently approved by the FDA for treatment of acute mania in bipolar disorder. **Lithium, olanzapine, and lamotrigine** are approved for maintenance treatment of bipolar disorder. **Quetiapine** is the only antipsychotic that is FDA approved for bipolar depression.
- **Lithium** is the drug of choice for bipolar disorder with euphoric mania, whereas valproate has better efficacy for mixed states, irritable/dysphoric mania, and rapid cycling compared with lithium.
- Combination therapies (e.g., lithium plus **valproate** or **carbamazepine**; lithium or valproate plus an atypical antipsychotic) may provide better acute response and prevention of relapse and recurrence than monotherapy in some bipolar patients, especially those with mixed states or rapid cycling.
- Useful guidelines include the following: Practice Guideline for the Treatment of Patients with Bipolar Disorder (Revision) published by the American Psychiatric Association; Texas Medication Algorithm Project developed by the Texas Department of Mental Health and Mental Retardation; World Federation of Societies of Biological Psychiatry guideline; Practice Parameters for the Assessment and Treatment of Children and Adolescents with Bipolar Disorder developed by the American Academy of Child and Adolescent Psychiatry; and the Treatment Guidelines for Children and Adolescents with Bipolar Disorder: Child Psychiatric Workgroup on Bipolar Disorder.
- Lithium was the first established mood stabilizer and is still considered a first-line agent for acute mania and maintenance treatment of both bipolar I and II disorders. It is the only bipolar medication approved for adults and children 12 years and older. Long-term use of lithium reduces suicide risk. Patients with rapid cycling or mixed states may not respond as well to lithium monotherapy as to some anticonvulsants.
- **Divalproex sodium (sodium valproate)** is now the most prescribed mood stabilizer in the United States. It is FDA approved only for the treatment of acute manic or mixed episodes, but it is often used as maintenance monotherapy for bipolar disorder.
- **Carbamazepine** is also commonly used for acute and maintenance therapy, but it is not FDA approved for bipolar disorder. Some data support the efficacy of oxcarbazepine, but it is also not FDA approved for bipolar disorder in the United States.
- **Lamotrigine** is approved for the maintenance treatment of bipolar I disorder. It has been used as monotherapy or add-on therapy for refractory bipolar depression.

**TABLE 69-6** Algorithm and Guidelines for the Acute Treatment of Mood Episodes in Patients with Bipolar I Disorder

<b>Acute Manic or Mixed Episode</b>		<b>Acute Depressive Episode</b>	
<p><b>General guidelines</b></p> <p>Assess for secondary causes of mania or mixed states (e.g., alcohol or drug use)</p> <p>Taper off antidepressants, stimulants, and caffeine if possible</p> <p>Treat substance abuse</p> <p>Encourage good nutrition (with regular protein and essential fatty acid intake), exercise, adequate sleep, stress reduction, and psychosocial therapy</p> <p>Optimize the dose of mood stabilizing medication(s) before adding on benzodiazepines; if psychotic features are present, add on antipsychotic; ECT used for severe or treatment-resistant manic/mixed episodes or psychotic features</p>		<p><b>General guidelines</b></p> <p>Assess for secondary causes of depression (e.g., alcohol or drug use)</p> <p>Taper off antipsychotics, benzodiazepines, or sedative-hypnotic agents if possible</p> <p>Treat substance abuse</p> <p>Encourage good nutrition (with regular protein and essential fatty acid intake), exercise, adequate sleep, stress reduction, and psychosocial therapy</p> <p>Optimize the dose of mood stabilizing medication(s) before adding on lithium, lamotrigine, or antidepressant (e.g., bupropion or an SSRI); if psychotic features are present, add on an antipsychotic; ECT used for severe or treatment-resistant depressive episodes or for psychosis or catatonia</p>	
<p><b>Hypomania</b></p> <p>First, optimize current mood stabilizer or initiate mood-stabilizing medication: lithium,<sup>a</sup> valproate,<sup>a</sup> or carbamazepine.<sup>a</sup> Consider adding a benzodiazepine (lorazepam or clonazepam) for short-term adjunctive treatment of agitation or insomnia if needed</p> <p>Alternative medication treatment options: carbamazepine<sup>a</sup>; if patient does not respond or tolerate, consider atypical antipsychotic (e.g., olanzapine, quetiapine, risperidone) or oxcarbazepine.</p>	<p><b>Mania</b></p> <p>First, two or three drug combinations: lithium<sup>a</sup> or valproate<sup>a</sup> <b>plus</b> a benzodiazepine (lorazepam or clonazepam) for short-term adjunctive treatment of agitation or insomnia; lorazepam is recommended for catatonia. If psychosis is present, initiate atypical antipsychotic in combination with above.</p> <p>Alternative medication treatment options: carbamazepine<sup>a</sup>; if patient does not respond or tolerate, consider oxcarbazepine.</p>	<p><b>Mild to Moderate Depressive Episode</b></p> <p>First, initiate and/or optimize mood-stabilizing medication: lithium<sup>a</sup> or lamotrigine.<sup>b</sup></p> <p>Alternative anticonvulsants: valproate,<sup>a</sup> carbamazepine,<sup>a</sup> or oxcarbazepine.</p>	<p><b>Severe Depressive Episode</b></p> <p>First, two or three drug combinations: lithium<sup>a</sup> or lamotrigine<sup>b</sup> <b>plus</b> an antidepressant<sup>c</sup>; lithium <b>plus</b> lamotrigine. If psychosis is present, initiate atypical antipsychotic in combination with above.</p> <p>Alternative anticonvulsants: valproate,<sup>a</sup> carbamazepine,<sup>a</sup> or oxcarbazepine.</p> <p>Second, if response is inadequate, consider adding an atypical antipsychotic (quetiapine).</p>

Second, if response is inadequate, consider a two-drug combination:

- Lithium<sup>a</sup> **plus** an anticonvulsant or an atypical antipsychotic
- Anticonvulsant plus an anticonvulsant or atypical antipsychotic

Second, if response is inadequate, consider a three-drug combination:

- Lithium<sup>a</sup> **plus** an anticonvulsant **plus** an atypical antipsychotic
- Anticonvulsant **plus** an anticonvulsant **plus** an atypical antipsychotic

Third, if response is inadequate, consider ECT for mania with psychosis or catatonia<sup>d</sup>; or add clozapine for treatment-refractory illness

Third, if response is inadequate, consider a three-drug combination:

- Lamotrigine<sup>b</sup> **plus** an anticonvulsant **plus** an antidepressant
- Lamotrigine<sup>b</sup> **plus** lithium<sup>a</sup> **plus** an antidepressant

Fourth, if response is inadequate, consider ECT for treatment-refractory illness and depression with psychosis or catatonia<sup>d</sup>

ECT, electroconvulsive therapy; MAOI, monoamine oxidase inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

<sup>a</sup>Use standard therapeutic serum concentration ranges if clinically indicated; if partial response or breakthrough episode, adjust dose to achieve higher serum concentrations without causing intolerable adverse effects; valproate is preferred over lithium for mixed episodes and rapid cycling; lithium and/or lamotrigine is preferred over valproate for bipolar depression.

<sup>b</sup>Lamotrigine is not approved for the acute treatment of depression, and the dose must be started low and slowly titrated up to decrease adverse effects if used for maintenance therapy of bipolar I disorder. A drug interaction and a severe dermatologic rash can occur when lamotrigine is combined with valproate (i.e., lamotrigine doses must be halved from standard dosing titration).

<sup>c</sup>Antidepressant monotherapy is not recommended for bipolar depression. Bupropion, SSRIs, (e.g., citalopram, escitalopram, or sertraline), and SNRIs (e.g., venlafaxine) have shown good efficacy and fewer adverse effects in the treatment of unipolar depression; MAOIs and TCAs have more adverse effects (e.g., weight gain) and can have a higher risk of causing antidepressant-induced mania; fluoxetine, fluvoxamine, nefazodone, and paroxetine inhibit liver metabolism and should be used with caution in patients on concomitant medications that require cytochrome P450 clearance; paroxetine and venlafaxine have a higher risk for causing a discontinuation syndrome.

<sup>d</sup>ECT is used for severe mania or depression during pregnancy and for mixed episodes; prior to treatment, anticonvulsants, lithium, and benzodiazepines should be tapered off to maximize therapy and minimize adverse effects.

Data from American Psychiatric Association. *Am J Psychiatry* 2002;159:1–50; *Suppes T, Dennehy EB, Swann AC, et al. J Clin Psychiatry* 2002;63:288–299; *Sachs GS. J Clin Psychiatry* 2003;64(Suppl 80):35–40; *Keck PE Jr, McElroy SL. J Affect Disord* 2003;73:163–169; and *Kusmakar V. J Clin Psychiatry* 2002;63(Suppl 10):23–28.

- **Aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone** are effective as monotherapy or as add-on therapy to lithium or valproate for acute mania. Prophylactic use of antipsychotics can be needed for some patients with recurrent mania or mixed states, but the risks versus benefits must be weighed in view of long-term side effects (e.g., obesity, type 2 diabetes, hyperlipidemia, hyperprolactinemia, cardiac disease, and tardive dyskinesia).

### Alternative Treatments

- High-potency benzodiazepines (e.g., **clonazepam** and **lorazepam**) are common alternatives to or in combination with antipsychotics for acute mania, agitation, anxiety, panic, and insomnia or in those who cannot take mood stabilizers. **Lorazepam IM** may be used for acute agitation. A relative contraindication for long-term benzodiazepines is a history of drug or alcohol abuse or dependency.
- Antidepressants are routinely added for the treatment of acute depression, but **tricyclic antidepressants** are associated with an increased risk of inducing mania in bipolar I disorder and possibly cause rapid cycling. Some guidelines recommend avoiding antidepressants in the treatment of bipolar depression or limiting their use to brief intervals, but evidence suggests that coadministration of therapeutic doses of mood stabilizers can reduce the risk of antidepressant-induced switching. Generally the antidepressant should be withdrawn 2 to 6 months after remission and the patients maintained on a mood stabilizer. Long-term antidepressants are required in some patients.
- **Nimodipine** may be more effective than **verapamil** for rapid-cycling bipolar disorder because of its anticonvulsant properties, high lipid solubility, and good penetration into the brain.

### Special Populations

- Approximately 20% to 50% of women with bipolar disorder relapse postpartum; prophylaxis with mood stabilizers (e.g., **lithium** or **valproate**) is recommended immediately postpartum to decrease the risk of relapse.
- Current estimates of the rate of occurrence of Epstein anomaly in infants exposed to lithium during the first trimester is between 1:1,000 and 1:2,000.
- When **lithium** is to be used during pregnancy, it should be used at the lowest effective dose in order to avoid “floppy” infant syndrome, hypothyroidism, and nontoxic goiter in the infant.
- Serum concentrations in the nursing infant are 10% to 50% of the mother’s serum concentration, thus breast-feeding is usually discouraged for women taking lithium.
- When **valproate** is taken during the first trimester, the risk of neural tube defect is 5% to 9%. For **carbamazepine**, the risk is estimated to be 0.5% to 1%.
- Administration of folic acid can reduce the risk of neural tube defects.
- Women taking valproate may breast-feed, but mother and infant should have identical laboratory monitoring.

### Drug Class Information

- Product information, dosing and administration, clinical use, and proposed mechanisms of action for agents used for bipolar disorder are shown in Table 69-7.

**TABLE 69-7** Product Formulations, Dosage and Administration, Clinical Use, and Proposed Mechanism of Action of Agents Used in the Treatment of Bipolar Disorder

Generic Name	Trade Name	Formulations	Dosage and Administration	Clinical Use	Proposed Mechanism of Action
<i>Lithium salts: FDA approved for bipolar disorder</i>					
Lithium carbonate	Eskalith	Capsule: 300 mg	900–2,400 mg/day in 2–4 divided doses, preferably with meals. There is wide variation in the dosage needed to achieve therapeutic response and trough serum lithium concentration (i.e., 0.6–1.2 mEq/L for maintenance therapy and 1.0–1.2 mEq/L for acute mood episodes taken 8–12 hours after the last dose).	Use alone or in combination with other drugs (e.g., valproate, carbamazepine, antipsychotics) for the acute treatment of mania and for maintenance treatment.	Normalizes or inhibits secondary messenger systems (e.g., inhibits phosphoinositide and adenylate cyclase signaling; normalizes guanine nucleotide-binding protein [G protein] signal transduction system); Decreases 5-HT reuptake and increases postsynaptic 5-HT receptor sensitivity; Inhibits the synthesis of DA, decreases the number of $\beta$ -adrenergic receptors and inhibits DA <sub>2</sub> and $\beta$ -adrenergic receptor supersensitivity; Enhances GABAergic activity and normalizes GABA levels; Reduces glutamatergic activity (e.g., increases glutamate uptake) with chronic therapy.
	Eskalith CR	Extended-release tablet: 450 mg			
	Lithobid	Extended-release tablet: 300 mg			
Lithium citrate	Generic	Tablet: 300 mg (scored) Capsule: 150, 300, 600 mg			
	Cibalith-S	8 mEq/5 mL			Decreases Ca <sup>+</sup> transport into cells, interferes with Ca <sup>+</sup> -Na <sup>+</sup> active transport system, increases renal tubular reabsorption of Ca <sup>+</sup> and increases serum Ca <sup>+</sup> and parathyroid concentrations; Increases choline in red blood cells and potentiates the cholinergic secondary messenger system.
<i>Anticonvulsants: FDA approved for bipolar disorder</i>					
Divalproex sodium	Depakote	Enteric-coated, delayed-release tablet: 125, 250, 500 mg	750–3,000 mg/day (20–60 mg/kg per day) given once daily or in divided doses for delayed-release divalproex or valproic acid. Extended-release divalproex can be given once daily at bedtime after stabilization. A loading dose of divalproex (20–30 mg/kg per day) can be given, then 20 mg/kg per day and titrated to a serum concentration of 50–125 mcg/mL or clinical response.	Use alone or in combination with other drugs (e.g., lithium, carbamazepine, antipsychotics) for the acute treatment of mania and for maintenance treatment. Use caution when combining with lamotrigine because of potential drug interaction.	Increases GABA levels in plasma and CNS; inhibits GABA catabolism, increases synthesis, and release; can prevent GABA reuptake; enhances the action of GABA at the GABA <sub>A</sub> receptor; Normalizes Na <sup>+</sup> and Ca <sup>+</sup> channels; Reduces intracellular inositol and protein kinase C isozymes; Can modulate gene expression. Antikindling properties can decrease rapid cycling and mixed states.
		Sprinkle capsule: 125 mg			
	Depakote ER	Enteric-coated, extended release tablet: 250, 500 mg			

*(continued)*

**TABLE 69-7** Product Formulations, Dosage and Administration, Clinical Use, and Proposed Mechanism of Action of Agents Used in the Treatment of Bipolar Disorder (Continued)

Generic Name	Trade Name	Formulations	Dosage and Administration	Clinical Use	Proposed Mechanism of Action
Valproic acid	Depakene	Capsule: 250 mg	—	—	—
Valproate sodium	Depakene	Syrup: 250 mg/5 mL	—	—	—
Lamotrigine	Lamictal	Tablet: 25, 100, 150, 200 mg Chewable tablet: 2, 5, 25 mg	50–400 mg/day in divided doses. Dosage should be slowly increased (e.g., 25 mg/day for 2 weeks, then 50 mg/day for weeks 3 and 4, then 50-mg/day increments at weekly intervals up to 200 mg/day). When combined with valproate, initial and titration dosing should be decreased by 50% to minimize the risk of a serious rash.	Use alone or in combination with other drugs (e.g., lithium, carbamazepine) for long-term maintenance treatment for bipolar I disorder. Lamotrigine can have efficacy for prevention of bipolar depression.	Blocks voltage-sensitive Na <sup>+</sup> and Ca <sup>+</sup> channels; Modulates or decreases presynaptic aspartate and glutamate release; Antikindling properties may decrease rapid cycling and mixed states.
<i>Anticonvulsants: Not FDA approved for bipolar disorder</i>					
Carbamazepine	Tegretol,	Tablet: 200 mg	200–1,800 mg/day in 2–4 divided doses.	Use alone or in combination with other medications (e.g., lithium, valproate, antipsychotics) for the acute and long-term maintenance treatment of mania or mixed episodes for bipolar I disorder. APA guidelines recommend reserving it for patients unable to tolerate or who have inadequate response to lithium or valproate.	Blocks voltage-sensitive Na <sup>+</sup> channels; Stimulates the release of antidiuretic hormone and decreases Na <sup>+</sup> serum concentrations; Blocks Ca <sup>+</sup> influx through the NMDA glutamate receptor and decreases Ca <sup>+</sup> serum concentrations; Modulates presynaptic aspartate and glutamate release; Antikindling properties may decrease rapid cycling and mixed states.
	Epitol	Chewable tablet: 100 mg	Dosage should be slowly increased according to response and adverse effects (e.g., 100–200 mg twice daily and increase by 200 mg/day at weekly intervals). Dose can be increased rapidly for inpatients.		
	Tegretol	Suspension: 100 mg/5 mL			
	Tegretol-XR	Extended-release tablet: 100, 200, 400 mg	Administer conventional tablets and suspension with meals. Extended-release tablets should be swallowed whole and not be broken or chewed.		
	Carbatrol	Extended-release capsule: 200, 300 mg	Carbatrol capsules can be opened and contents sprinkled over food.		
	Equetro	Extended-release capsule: 100, 200, 300 mg			

Oxcarbazepine	Trileptal	Tablet: 150, 300, 600 mg Suspension: 300 mg/5 mL	300–1,200 mg/day in two divided doses. Dosage should be slowly adjusted up and down according to response and adverse effects (e.g., 150–300 mg twice daily and increase by 300–600 mg/day at weekly intervals). Dose can be increased rapidly for inpatients.	Can have fewer adverse effects and be better tolerated than carbamazepine	Oxcarbazepine and its monohydroxy metabolite increase K <sup>+</sup> conductance; modulates the activity of high-voltage activated Ca <sup>+</sup> channels; and blocks Na <sup>+</sup> channels.
Clonazepam	Klonopin	Tablet: 0.5, 1, 2 mg	0.5–20 mg/day in divided doses or one dose at bedtime. Dosage should be slowly adjusted up and down according to response and adverse effects.	Use in combination with other drugs (e.g., antipsychotics, lithium, valproate) for the acute treatment of mania or mixed episodes. Use as a short-term adjunctive sedative-hypnotic agent.	Binds to the benzodiazepine site and augments the action of GABA <sub>A</sub> by increasing the frequency of Cl <sup>-</sup> channel opening, which causes hyperpolarization (a less excitable state) and inhibits neuronal firing.
Lorazepam	Ativan	Tablet: 0.5, 1, 2 mg Oral solution: 2 mg/mL Injection: 2, 4 mg/mL	2–40 mg/day in divided doses or one dose at bedtime. Dosage should be slowly adjusted up and down according to response and adverse effects.		
<i>Atypical antipsychotics: FDA approved for bipolar disorder</i>					
Aripiprazole	Abilify	Tablet: 5, 10, 15, 20, 30 mg	10–30 mg/day once daily	Use in combination with lithium or valproate for the acute treatment of mania or mixed states (primarily with psychotic features) for bipolar I disorder. Only olanzapine is FDA approved at this time for maintenance treatment and only quetiapine for bipolar depression.	Antagonist of postsynaptic DA <sub>2</sub> receptors; atypical agents also block 5-HT <sub>2A</sub> receptors that increase the presynaptic release of DA, thus lowering the risk of extrapyramidal symptoms and prolactin release
Olanzapine	Zyprexa	Tablet: 2.5, 5, 7.5, 10, 15, 20 mg	5–20 mg/day once daily or in divided doses		
	Zyprexa Zydis	Tablet, orally disintegrating: 5, 10, 15, 20 mg			
Quetiapine	Seroquel	Tablet: 25, 50, 100, 200, 300, 400 mg	50–800 mg/day in divided doses or once daily when stabilized		Receptor blockade varies by agent: DA <sub>4</sub> , 5-HT <sub>2A-2C</sub> , α <sub>1-2</sub> -adrenergic, muscarinic, and histamine <sub>1</sub> .
Risperidone	Risperdal	Tablet: 0.25, 0.5, 1, 2, 3, 4 mg Oral solution: 1 mg/mL	0.5–6 mg/day once daily or in divided doses		

(continued)

**TABLE 69-7** Product Formulations, Dosage and Administration, Clinical Use, and Proposed Mechanism of Action of Agents Used in the Treatment of Bipolar Disorder (Continued)

Generic Name	Trade Name	Formulations	Dosage and Administration	Clinical Use	Proposed Mechanism of Action
	Risperdal M-Tab	0.5, 1, 2, 3, 4 mg			
Ziprasidone	Geodon	Capsule: 20, 40, 60, 80 mg	40–160 mg/day in divided doses	–	–
<i>Calcium channel blockers: Not FDA approved for bipolar disorder</i>					
Nimodipine	Nimotop	Capsule: 30 mg	30–120 mg/day	Use as third-line agent for combination with other drugs (e.g., carbamazepine, valproate, antipsychotics).	Blocks Ca <sup>+</sup> influx through L-type Ca <sup>+</sup> channels Alters Ca <sup>+</sup> -Na <sup>+</sup> exchange Decreases 5-HT, DA, and endorphin activity
Verapamil	Verelan	Capsule: 120, 180, 240, 360 mg	80–480 mg/day		
	Calan, Isoptin	Film-coated tablet: 40, 80, 120 mg Extended-release tablet: 120, 180, 240 mg			

APA, American Psychiatric Association; Ca<sup>+</sup>, calcium; Cl<sup>-</sup>, chloride; DA, dopamine; GABA,  $\gamma$ -aminobutyric acid; 5-HT, serotonin; K<sup>+</sup>, potassium; Na<sup>+</sup>, sodium; NMDA, *N*-methyl-D-aspartate; NE, norepinephrine.

Compiled data from Torrey EF, Knable MB. *New York: Basic Books, 2002; American Psychiatric Association. Am J Psychiatry 2002;159:1–50; Goldberg JF, Harrow M, eds. Washington, DC: American Psychiatric Press, 1999; Manji HK, Bowden CL, Belmaker RH, eds. Washington, DC: American Psychiatric Press, 2000; Baron M. Mol Psychiatry 2002;7:342–358; Goodnick PJ, ed. Washington, DC: American Psychiatric Press, 1998; Freeman MP, Wosnitzer Smith K, Freeman SA, et al. J Clin Psychiatry 2002;63:284–287; White HS. J Clin Psychiatry 2003;64(Suppl 8):5–8; and Calabrese JR, Shelton MD, Rappaport DJ, et al. J Affect Disord 2001;67:241–255.*

- Guidelines for baseline and routine laboratory monitoring of mood stabilizers are shown in Table 69-8.
- For more information on the side effects, pharmacokinetics, and drug interactions of specific agents, refer to Chap. 71 on Schizophrenia, Chap. 70 on Major Depressive Disorder, and Chap. 52 on Epilepsy.

### *Antipsychotics*

- Both typical and atypical antipsychotics are effective in approximately 70% of patients with acute mania associated with agitation, aggression, and psychosis, and atypical antipsychotics are better tolerated.
- **Aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone** are FDA approved for the treatment of acute manic episodes in bipolar I disorder.
- Depot antipsychotics (e.g., **haloperidol decanoate, fluphenazine decanoate, and risperidone long-acting injection**) can be used for maintenance therapy of bipolar disorder with noncompliance or treatment resistance.
- **Lithium** plus an antipsychotic and **valproate** plus an antipsychotic may be more effective than any of these agents alone.
- Adjunctive atypical antipsychotics can be beneficial for breakthrough manic episodes or if there is incomplete response to lithium or valproate monotherapy.
- Only **olanzapine** is FDA approved for maintenance treatment, and only **quetiapine** is FDA approved for bipolar depression.
- **Clozapine** monotherapy has acute and long-term mood stabilizing effects in refractory bipolar disorder, including mixed mania and rapid cycling, but requires regular white blood cell monitoring for agranulocytosis.
- Higher initial doses of antipsychotics (e.g., 20 mg/day of **olanzapine**) are required for acute mania, but once mania is controlled (usually 7 to 28 days), the antipsychotic can be gradually tapered and discontinued, and the patient maintained on the mood stabilizer alone.

### *Carbamazepine*

- **Carbamazepine** is usually reserved for lithium-refractory patients, rapid cyclers, or mixed states. It has some acute antimanic effects, but its long-term effectiveness is unclear.
- The combination of carbamazepine with **lithium, valproate**, and antipsychotics is often used for manic episodes in treatment-resistant patients.
- Carbamazepine induces the metabolism of antidepressants, anticonvulsants, and antipsychotics, thus, dosage adjustments may be required.
- Acute overdoses of carbamazepine are potentially lethal.
- Women who receive carbamazepine require higher doses of **oral contraceptives** or alternative contraceptive methods.
- Certain medications (e.g., **cimetidine, diltiazem, erythromycin, fluoxetine, fluvoxamine, isoniazid, itraconazole, ketoconazole, nefazodone, propoxyphene, and verapamil**) added to carbamazepine therapy may cause carbamazepine toxicity.
- Doses can be started at 400 mg to 600 mg/day in divided doses, and increased by 200 mg/day every 2 to 4 days up to 10 to 15 mg/kg/day. Outpatients should be titrated upward more slowly to avoid side effects. Many patients are able to tolerate once daily dosing once their mood episode has stabilized.

**TABLE 69-8** Guidelines for Baseline and Routine Laboratory Tests and Monitoring for Agents Used in the Treatment of Bipolar Disorder

	Baseline: Physical Examination & General Chemistry <sup>a</sup>	Hematologic Tests <sup>b</sup>		Metabolic Tests <sup>c</sup>		Liver Function Tests <sup>d</sup>		Renal Function Tests <sup>e</sup>		Thyroid Function Tests <sup>f</sup>		Serum Electrolytes <sup>g</sup>		Dermatologic <sup>h</sup>	
		Baseline	6-12 months	Baseline	6-12 months	Baseline	6-12 months	Baseline	6-12 months	Baseline	6-12 months	Baseline	6-12 months	Baseline	3-6 months
Atypical antipsychotics <sup>i</sup>	X			X	X										
Carbamazepine <sup>j</sup>	X	X	X			X	X	X				X	X	X	X
Lamotrigine <sup>k</sup>	X													X	X
Lithium <sup>l</sup>	X	X	X	X	X			X	X	X	X	X	X	X	X
Oxcarbazepine <sup>m</sup>	X											X	X		
Valproate <sup>n</sup>	X	X	X	X	X	X	X							X	X

<sup>a</sup> Screen for drug abuse and serum pregnancy.

<sup>b</sup> Complete blood cell count (CBC) with differential and platelets.

<sup>c</sup> Fasting glucose, serum lipids, weight.

<sup>d</sup> Lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, alkaline phosphatase.

<sup>e</sup>Serum creatinine, blood urea nitrogen, urinalysis, urine osmolality, specific gravity.

<sup>f</sup>Triiodothyronine, total thyroxine, thyroxine uptake, and thyroid-stimulating hormone.

<sup>g</sup>Serum sodium.

<sup>h</sup>Rashes, hair thinning, alopecia.

<sup>i</sup>Atypical antipsychotics: Monitor for increased appetite with weight gain (primarily in patients with initial low or normal body mass index); monitor closely if rapid or significant weight gain occurs during early therapy; cases of hyperlipidemia and diabetes reported.

<sup>j</sup>Carbamazepine: Manufacturer recommends CBC and platelets (and possibly reticulocyte counts and serum iron) at baseline, and that subsequent monitoring be individualized by the clinician (e.g., CBC, platelet counts, and liver function tests every 2 weeks during the first 2 months of treatment, then every 3 months if normal). Monitor more closely if patient exhibits hematologic or hepatic abnormalities or if the patient is receiving a myelotoxic drug; discontinue if platelets are  $<100,000/\text{mm}^3$ , if white blood cell (WBC) count is  $<3,000/\text{mm}^3$  or if there is evidence of bone marrow suppression or liver dysfunction. Serum electrolyte levels should be monitored in the elderly or those at risk for hyponatremia. Carbamazepine interferes with some pregnancy tests.

<sup>k</sup>Lamotrigine: If renal or hepatic impairment, monitor closely and adjust dosage according to manufacturer's guidelines. Serious dermatologic reactions have occurred within 2–8 weeks of initiating treatment and are more likely to occur in patients receiving concomitant valproate, with rapid dosage escalation, or using doses exceeding the recommended titration schedule.

<sup>l</sup>Lithium: Obtain baseline electrocardiogram for patients older than 40 years or if preexisting cardiac disease (benign, reversible T-wave depression can occur). Renal function tests should be obtained every 2–3 months during the first 6 months, then every 6–12 months; if impaired renal function, monitor 24-hour urine volume and creatinine every 3 months; if urine volume  $>3 \text{ L/day}$ , monitor urinalysis, osmolality, and specific gravity every 3 months. Thyroid function tests should be obtained once or twice during the first 6 months, then every 6–12 months; monitor for signs and symptoms of hypothyroidism; if supplemental thyroid therapy is required, monitor thyroid function tests and adjust thyroid dose every 1–2 months until thyroid function indices are within normal range, then monitor every 3–6 months.

<sup>m</sup>Oxcarbazepine: Hyponatremia (serum sodium concentrations  $<125 \text{ mEq/L}$ ) has been reported and occurs more frequently during the first 3 months of therapy; serum sodium concentrations should be monitored in patients receiving drugs that lower serum sodium concentrations (e.g., diuretics or drugs that cause inappropriate antidiuretic hormone secretion) or in patients with symptoms of hyponatremia (e.g., confusion, headache, lethargy, and malaise). Hypersensitivity reactions have occurred in approximately 25–30% of patients with a history of carbamazepine hypersensitivity and requires immediate discontinuation.

<sup>n</sup>Valproate: Weight gain reported in patients with low or normal body mass index. Monitor platelets and liver function during first 3–6 months if evidence of increased bruising or bleeding. Monitor closely if patients exhibit hematologic or hepatic abnormalities or in patients receiving drugs that affect coagulation, such as aspirin or warfarin; discontinue if platelets are  $<100,000/\text{mm}^3/\text{L}$  or if prolonged bleeding time. Pancreatitis, hyperammonemic encephalopathy, polycystic ovary syndrome, increased testosterone, and menstrual irregularities have been reported; not recommended during first trimester of pregnancy due to risk of neural tube defects.

*Data from American Psychiatric Association. Am J Psychiatry 2002;159:1–50; Goodnick PJ, ed. Washington, DC: American Psychiatric Press, 1998; McEvoy GK, Miller J, Snow EK, et al. Bethesda, MD: American Society of Health-System Pharmacists, 2004:2425–2434; McEvoy GK, Miller J, Snow EK, et al. Bethesda, MD: American Society of Health-System Pharmacists, 2004:2152–2158; McEvoy GK, Miller J, Snow EK, et al. Bethesda, MD: American Society of Health-System Pharmacists, 2004:2122–2127; McEvoy GK, Miller J, Snow EK, et al. Bethesda, MD: American Society of Health-System Pharmacists, 2004:2134–2140; and McEvoy GK, Miller J, Snow EK, et al. Bethesda, MD: American Society of Health-System Pharmacists, 2004:2146–2147.*

- During the first month of therapy, serum concentrations can decrease because of autoinduction of metabolizing enzymes, requiring a dose increase.
- Carbamazepine serum levels are usually obtained every 1 or 2 weeks during the first 2 months, and then every 3 to 6 months during maintenance therapy. Serum samples are drawn 10 to 12 hours after the dose and at least 4 to 7 days after dosage initiation or change. Most clinicians attempt to maintain levels between 6 and 10 mcg/mL, but some patients may require up to 14 mcg/mL.

### *Lamotrigine*

- **Lamotrigine** is effective for the maintenance treatment of bipolar I disorder in adults. It has both antidepressant and mood-stabilizing effects, and it may have augmenting properties when combined with lithium or valproate. It has low rates of switching patients to mania. Although it is less effective for acute mania compared to **lithium** and **valproate**, it may be beneficial for the maintenance therapy of treatment-resistant bipolar I and II disorders, rapid-cycling, and mixed states. It is often used for bipolar II patients.
- Common adverse effects include headache, nausea, dizziness, ataxia, diplopia, drowsiness, tremor, rash, and pruritus. Although most rashes resolve with continued therapy, some progress to life-threatening conditions, such as Stevens-Johnson syndrome. The incidence of rash appears to be greatest with concomitant administration of **valproate**, rapid dose escalation of lamotrigine, and higher than recommended lamotrigine initial doses. In patients taking valproate, lamotrigine dose should be about one-half the standard dose, and upward titration must be slower than usual.
- For maintenance treatment of bipolar disorder, the usual dosage range of lamotrigine is 50 to 300 mg/day. The target dose is generally 200 mg/day (100 mg/day when combined with valproate, which decreases the clearance of lamotrigine), and 400 mg/day when combined with **carbamazepine**). For patients NOT taking medications that affect lamotrigine's clearance, the dose is 25 mg/day for the first 2 weeks, then 50 mg/day for 2 weeks, then 100 mg/day for the next week, then 200 mg/day.

### *Lithium*

- Lithium is rapidly absorbed; it is not protein bound, not metabolized, and is excreted unchanged in the urine and other body fluids.
- Lithium is effective for acute mania, but it may require 6 to 8 weeks to show antidepressant efficacy. It may be more effective for elated mania and less effective for mania with psychotic features, mixed episodes, rapid cycling, and when alcohol and drug abuse is present. Maintenance therapy is more effective in patients with fewer episodes, good functioning between episodes, and when there is a family history of good response to lithium. It produces a prophylactic response in up to two-thirds of patients and reduces suicide risk by eight- to 10-fold.
- Patients with serum concentrations between 0.8 mEq/L and 1 mEq/L may have fewer relapses than those with lower serum concentrations.
- Lithium augmentation of antidepressants, carbamazepine, lamotrigine, and valproate can improve response, but it may increase the risk of sedation, weight gain, GI complaints, and tremor.

- Combining lithium with **typical antipsychotics** may cause neurotoxicity (e.g., delirium, cerebellar dysfunction, extrapyramidal symptoms). Lithium should be withdrawn and discontinued at least 2 days before electroconvulsive therapy.
- Initial side effects are often dose related and are worse at peak serum concentrations (1 to 2 hours postdose). Lowering the dose, taking smaller doses with food, using extended-release products, and once-daily dosing at bedtime may help.
- GI distress may be minimized by standard approaches or by adding antacids or antidiarrheals.
- Muscle weakness and transient lethargy occur in about 30% of patients. Polydipsia with polyuria and nocturia occurs in up to 70% of patients and is managed by changing to once-daily dosing at bedtime.
- Up to 40% of patients complain of headache, memory impairment, confusion, poor concentration, and impaired motor performance. A fine hand tremor may occur in up to 50% of patients. Hand tremor may be treated with **propranolol** 20 to 120 mg/day.
- Lithium reduces the kidney's ability to concentrate urine and may cause a nephrogenic diabetes insipidus with low urine specific gravity and low osmolality polyuria (urine volume greater than 3 L/day). This may be treated with **loop diuretics, thiazide diuretics, or triamterene**. If a thiazide diuretic is used, lithium doses should be decreased by 50% and lithium and potassium levels monitored.
- Long-term lithium therapy is associated with a 10% to 20% risk of morphologic renal changes (e.g., glomerular sclerosis, tubular atrophy, and interstitial nephritis).
- Lithium-induced nephrotoxicity is rare if patients are maintained on the lowest effective dose, if once-daily dosing is used, if good hydration is maintained, and if toxicity is avoided.
- Up to 30% of patients on maintenance lithium therapy develop transiently elevated serum concentrations of thyroid-stimulating hormone, and 5% to 35% of patients develop a goiter and/or hypothyroidism, which is dose-related and more likely to occur in women. This is managed by adding **levothyroxine** to the regimen.
- Lithium may cause cardiac effects including T-wave flattening or inversion (up to 30% of patients), atrioventricular block, and bradycardia. If a patient has preexisting cardiac disease, a cardiologist should be consulted and an electrocardiogram obtained at baseline and regularly during therapy.
- Other late-appearing lithium side effects include benign reversible leukocytosis, acne, alopecia, exacerbation of psoriasis, pruritic dermatitis, maculopapular rash, folliculitis, and weight gain.
- Lithium toxicity can occur with serum levels greater than 1.5 mEq/L, but the elderly may have toxic symptoms at therapeutic levels. Severe toxic symptoms may occur with serum concentrations above 2 mEq/L, including vomiting, diarrhea, incontinence, incoordination, impaired cognition, arrhythmias, and seizures. Permanent neurologic impairment and kidney damage may occur as a result of toxicity.

- Several factors predispose to lithium toxicity, including sodium restriction, dehydration, vomiting, diarrhea, drug interactions that decrease lithium clearance, heavy exercise, sauna baths, hot weather, and fever. Patients should be told to maintain adequate sodium and fluid intake and to avoid excessive coffee, tea, cola, and other caffeine-containing beverages and alcohol.
- If lithium toxicity is suspected, the patient should discontinue lithium and go immediately to the emergency room. Hemodialysis is generally required when serum lithium levels are above 4 mEq/L for patients on long-term treatment, or greater than 6 to 8 mEq/L after acute poisoning.
- Lithium is usually initiated with low to moderate doses (600 mg/day divided into two to three doses) for prophylaxis, and higher doses (900 to 1,200 mg/day, divided into two to three doses) for acute mania. Immediate-release preparations should be given two to three times daily, whereas extended-release products can be given once or twice daily. After patients are stabilized, many patients can be switched to once-daily dosing.
- Initially, serum lithium concentrations are checked once or twice weekly. After a desired serum concentration is achieved, levels should be drawn in 2 weeks, and if stable, they can be drawn every 3 to 6 months.
- Lithium clearance increases by 50% to 100% during pregnancy. Serum levels should be monitored monthly during pregnancy and weekly the week before delivery. At delivery, a dose reduction to prepregnancy doses and adequate hydration are recommended.
- For bipolar prophylaxis in elderly patients, serum concentrations of 0.4 to 0.6 mEq/L are recommended.

### *Oxcarbazepine*

- **Oxcarbazepine** has mood-stabilizing effects similar to those of carbamazepine, but with milder side effects, no autoinduction of metabolizing enzymes, and potentially fewer drug interactions. There are fewer data supporting its efficacy than there are for **carbamazepine's** efficacy.
- Dose-related side effects include dizziness, sedation, headache, ataxia, fatigue, vertigo, abnormal vision, diplopia, nausea, vomiting, and abdominal pain. It causes more hyponatremia than carbamazepine.
- It induces the metabolism of **oral contraceptives**, and alternative contraception measures are required.

### *Valproate Sodium and Valproic Acid*

- **Valproate** is as effective as **lithium** and **olanzapine** for pure mania, and it can be more effective than lithium for rapid cycling, mixed states, and bipolar disorder with substance abuse. It reduces the frequency of recurrent manic, depressive, and mixed episodes.
- **Lithium, carbamazepine, antipsychotics, or benzodiazepines** can augment the antimanic effects of valproate. Valproate can be added to lithium or carbamazepine to achieve synergistic effects. **Atypical antipsychotics** can be added to valproate for breakthrough mania or if there is partial response to antipsychotic monotherapy.
- The most frequent dose-related side effects of valproate are GI complaints, fine hand tremor, and sedation. A  $\beta$ -blocker may alleviate tremors. Other

side effects include ataxia, lethargy, alopecia, pruritus, prolonged bleeding, transient increases in liver enzymes, weight gain, and hyperammonemia.

- For outpatients who are hypomanic, euthymic, or for elderly patients, the starting dose is generally 5 to 10 mg/kg/day in divided doses. This is gradually increased to the optimal dose. After establishing the optimal dose, the dose can be given twice daily or at bedtime if tolerated.
- Extended-release divalproex can be given once daily, but bioavailability can be 15% lower than that of immediate-release.

## EVALUATION OF THERAPEUTIC OUTCOMES

- Monitoring parameters are discussed in Table 69-5.
- Patients who have a partial response or nonresponse to therapy should be reassessed for an accurate diagnosis, concomitant medical or psychiatric conditions, and medications or substances that exacerbate mood symptoms.
- Patients and family members should be actively involved in treatment to monitor target symptoms, response, and side effects.

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*See Chap. 72, Bipolar Disorder, authored by Shannon J. Drayton and Benjamin Weinstein, for a more detailed discussion of this topic.*

## DEFINITION

- The essential feature of major depressive disorder is a clinical course that is characterized by one or more major depressive episodes without a history of manic, mixed, or hypomanic episodes. Dysthymic disorder is a chronic disturbance of mood involving depressed mood and at least two other symptoms, and it is generally less severe than major depressive disorder. This chapter focuses exclusively on the diagnosis and treatment of major depressive disorder.

## PATHOPHYSIOLOGY

- *Biogenic amine hypothesis.* Depression may be caused by decreased brain levels of the neurotransmitters norepinephrine (NE), serotonin (5-HT), and dopamine (DA).
- *Postsynaptic changes in receptor sensitivity.* Studies of many antidepressants have demonstrated that desensitization or downregulation of NE or 5-HT<sub>1A</sub> receptors may relate to onset of antidepressant effects.
- *Dysregulation hypothesis.* This theory emphasizes a failure of homeostatic regulation of neurotransmitter systems, rather than absolute increases or decreases in their activities. Effective antidepressants are theorized to restore efficient regulation to these systems.
- *5-HT/NE link hypothesis.* This theory suggests that there is a link between 5-HT and NE activity, and that both the serotonergic and noradrenergic systems are involved in the antidepressant response.
- *The role of DA.* Several reviews suggest that increased DA neurotransmission in the mesolimbic pathway may be related to the mechanism of action of antidepressants.

## CLINICAL PRESENTATION

- Emotional symptoms may include diminished ability to experience pleasure, loss of interest in usual activities, sadness, pessimistic outlook, crying spells, hopelessness, anxiety (present in almost 90% of depressed outpatients), feelings of guilt, and psychotic features (e.g., auditory hallucinations, delusions).
- Physical symptoms may include fatigue, pain (especially headache), sleep disturbance, appetite disturbance (decreased or increased), loss of sexual interest, and GI and cardiovascular complaints (especially palpitations).
- Intellectual or cognitive symptoms may include decreased ability to concentrate or slowed thinking, poor memory for recent events, confusion, and indecisiveness.
- Psychomotor disturbances may include psychomotor retardation (slowed physical movements, thought processes, and speech) or psychomotor agitation.

**TABLE 70-1** DSM-IV-TR Criteria for Major Depressive Episode

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

**Note:** Do not include symptoms that are clearly caused by a general medical condition or mood-incongruent delusions or hallucinations.

1. Depressed mood most of the day nearly every day
  2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day nearly every day
  3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day
  4. Insomnia or hypersomnia nearly every day
  5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
  6. Fatigue or loss of energy nearly every day
  7. Feelings of worthlessness or excessive or inappropriate guilt nearly every day
  8. Diminished ability to think or concentrate, or indecisiveness, nearly every day
  9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
- B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- C. The symptoms are not due to the direct physiologic effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).
- D. The symptoms are not better accounted for by bereavement (i.e., after the loss of a loved one), the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

Data from American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, 4th ed., text revision.* Washington, DC: American Psychiatric Association, 2000.

## DIAGNOSIS

- Major depression is characterized by one or more episodes of major depression, as defined by the *Diagnostic and Statistical Manual of Mental Disorders, 4th ed., text revision* (Table 70-1). Symptoms must have been present nearly every day for at least 2 weeks. Patients with major depressive disorder may have one or more recurrent episodes of major depression during their lifetime.
- When a patient presents with depressive symptoms, it is necessary to investigate the possibility of a medical-, psychiatric-, and/or drug-induced cause (Table 70-2).
- Depressed patients should have a medication review, physical examination, mental status examination, a complete blood count with differential, thyroid function tests, and electrolyte determinations.

## DESIRED OUTCOME

- The goals of treatment of the acute depressive episode are to eliminate or reduce the symptoms of depression, minimize adverse effects, ensure compliance with the therapeutic regimen, facilitate a return to a premorbid level of functioning, and prevent further episodes of depression.

**TABLE 70-2** Common Medical Conditions, Substance Use Disorders, and Medications Associated with Depressive Symptoms

<b>General medical conditions</b>	Cardiovascular disease	<b>Drug therapy</b>
Endocrine diseases	Coronary artery disease	Antihypertensives
Hypothyroidism	Congestive heart failure	Clonidine
Addison's or Cushing's disease	Myocardial infarction	Diuretics
Deficiency states	Neurologic disorders	Guanethidine sulfate
Pernicious anemia	Alzheimer's disease	Hydralazine hydrochloride
Wernicke encephalopathy	Epilepsy	Methyldopa
Severe anemia	Huntington's disease	Propranolol
Infections	Multiple sclerosis	Reserpine
AIDS	Pain	<b>Hormonal therapy</b>
Encephalitis	Parkinson's disease	Oral contraceptives
Human immunodeficiency virus	Poststroke	Steroids/adrenocorticotropic hormone
Mononucleosis	Malignant disease	<b>Acne therapy</b>
Sexually transmitted diseases	<b>Substance use disorders (including intoxication and withdrawal)</b>	Isotretinoin
Tuberculosis	Alcoholism	Other
Collagen disorder	Marijuana abuse and dependence	Interferon- $\beta_{1a}$
Systemic lupus erythematosus	Nicotine dependence	
Metabolic disorders	Opiate abuse and dependence (e.g., heroin)	
Electrolyte imbalance	Psychostimulant abuse and dependence (e.g., cocaine)	
Hypokalemia		
Hyponatremia		
Hepatic encephalopathy		

AIDS, acquired immune deficiency syndrome.

Modified and reprinted with permission from American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, 4th ed., text revision*. Washington, DC: American Psychiatric Association, 2000; Sofuoglu M, Dudish-Poulsen S, Poling J, et al. The effect of individual cocaine withdrawal symptoms on outcomes in cocaine users. *Addict Behav* 2005;30:1125–1134; and Patten SB, Barbui C. Drug-induced depression: a systematic review to inform clinical practice. *Psychoth Psychosom* 2004;73:207–215.

## TREATMENT

### NONPHARMACOLOGIC TREATMENT

- The efficacy of psychotherapy and antidepressants is considered to be additive. Psychotherapy alone is not recommended for the acute treatment of patients with severe and/or psychotic major depressive disorders. For uncomplicated nonchronic major depressive disorder, combined treatment may provide no unique advantage. Cognitive therapy, behavioral therapy, and interpersonal psychotherapy appear to be equal in efficacy.
- Electroconvulsive therapy (ECT) is a safe and effective treatment for major depressive disorder. It is considered when a rapid response is needed, risks of other treatments outweigh potential benefits, there has been a poor response to drugs, and the patient expresses a preference for ECT. A rapid therapeutic response (10 to 14 days) has been reported. Relative contraindications include increased intracranial pressure, cerebral lesions, recent myocardial infarction, recent intracerebral hemorrhage, bleeding, and otherwise unstable vascular conditions. Adverse effects of ECT include confusion, memory impairment (retrograde and anterograde), prolonged

apnea, treatment emergent mania, headache, nausea, muscle aches, and cardiovascular dysfunction. Relapse rates during the year following ECT are high unless maintenance antidepressants are prescribed.

- Bright light therapy (i.e., the patient looking into a 10,000-lux intensity light box for about 30 min/day) may be used for patients with seasonal affective disorder and as adjunctive use for major depression.

## PHARMACOLOGIC THERAPY—GENERAL THERAPEUTIC PRINCIPLES

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- Table 70-3 shows adult doses of antidepressants.
- In general, antidepressants are equal in efficacy in groups of patients when administered in comparable doses.
- Factors that influence the choice of antidepressant include the patient's history of response, history of familial response, concurrent medical conditions, presenting symptoms, potential for drug–drug interactions, comparative side-effect profiles of various drugs, patient preference, and drug cost.
- Between 65% and 70% of patients with major depression improve with drug therapy.
- Psychotically depressed individuals generally require either ECT or combination therapy with an antidepressant and an antipsychotic agent.
- The acute phase of treatment lasts 6 to 10 weeks, and the goal is remission (i.e., absence of symptoms).
- The continuation phase lasts 4 to 9 months after remission. The goal is to eliminate residual symptoms or prevent relapse.
- The maintenance phase lasts at least 12 to 36 months, and the goal is to prevent recurrence of a separate episode of depression.
- Some clinicians recommend lifelong maintenance therapy for persons at greatest risk for recurrence (i.e., persons younger than 40 years with two or more prior episodes and persons of any age with three or more prior episodes).
- Educating the patients and their support systems regarding the delay in antidepressant effects (typically 2 to 4 weeks) and the importance of adherence should occur before therapy is started and throughout treatment.

## DRUG CLASSIFICATION

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- Table 70-3 shows the commonly accepted classification of available antidepressants.
- Table 70-4 shows the relative potency and selectivity of the antidepressants for inhibition of NE and 5-HT reuptake and relative side-effect profiles.
- The **selective serotonin reuptake inhibitors** (SSRIs) inhibit the reuptake of 5-HT into the presynaptic neuron. They are generally chosen as first-line antidepressants because of their safety in overdose and improved tolerability compared to earlier agents.
- **Tricyclic antidepressants** (TCAs) are effective for all depressive subtypes, but their use has diminished because of the availability of equally effective therapies that are safer on overdose and better tolerated. In addition to inhibiting the reuptake of NE and 5-HT, they also block adrenergic, cholinergic, and histaminergic receptors.

**TABLE 70-3** Adult Dosages for Currently Available Antidepressant Medications<sup>a</sup>

Generic Name	Trade Name	Suggested Therapeutic Plasma Concentration (ng/mL)	Initial Dose (mg/day)	Usual Dosage Range (mg/day)
<b>Selective serotonin reuptake inhibitors</b>				
Citalopram	Celexa		20	20–60
Escitalopram	Lexapro		10	10–20
Fluoxetine	Prozac		20	20–60
Fluvoxamine	Luvox		50	50–300
Paroxetine	Paxil		20	20–60
Sertraline	Zoloft		50	50–200
<b>Serotonin/norepinephrine reuptake inhibitors</b>				
Venlafaxine	Effexor		37.5–75	75–225
Duloxetine	Cymbalta		30	30–90
<b>Aminoketone</b>				
Bupropion	Wellbutrin		150	150–300
<b>Triazolopyridines</b>				
Nefazodone	Serzone		100	200–600
Trazodone	Desyrel		50	150–300
<b>Tetracyclics</b>				
Mirtazapine	Remeron		15	15–45
<b>Tricyclics</b>				
<i>Tertiary amines</i>				
Amitriptyline	Elavil	120–250 <sup>b</sup>	25	100–300
Clomipramine	Anafranil		25	100–250
Doxepin	Sinequan		25	100–300
Imipramine	Tofranil	200–350 <sup>c</sup>	25	100–300
<i>Secondary amines</i>				
Desipramine	Norpramin	100–300 <sup>c</sup>	25	100–300
Nortriptyline	Pamelor	50–150	25	50–200
<b>Monoamine oxidase inhibitors</b>				
Phenelzine	Nardil		15	30–90
Selegiline (transdermal)	Emsam		6 <sup>d</sup>	6–12 <sup>d</sup>
Tranylcypromine	Parnate		10	20–60

<sup>a</sup>Doses listed are total daily doses; elderly patients are usually treated with approximately one-half of the dose listed.

<sup>b</sup>Parent drug plus metabolite.

<sup>c</sup>It has been suggested that combined imipramine + desipramine concentrations should fall between 150–240 ng/mL.

<sup>d</sup>Transdermal delivery system designed to deliver stated dose continuously over a 24-hour period.

Data from American Psychiatric Association. *Am J Psychiatry* 2000;157(4 Suppl):1–45; Baldessarini RI. In: Hardman JG, Limbird LE, Goodman A, et al. eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 10th ed. New York: McGraw-Hill, 2000:447–484; Mann JJ. *N Engl J Med* 2005;353:1819–1834; Patkar AA, Pae C-U, Masand PS. *CNS Spectr* 2006;11:363–375; and Watanabe MD, Winter ME. In: Winter ME, ed. *Basic Clinical Pharmacokinetics*, 4th ed. Baltimore, MD: Lippincott Williams & Wilkins, 2004:423–437.

- The monoamine oxidase inhibitors (MAOIs) **phenelzine** and **tranylcypromine** increase the concentrations of NE, 5-HT, and DA within the neuronal synapse through inhibition of the monoamine oxidase (MAO) enzyme system. Both drugs are nonselective inhibitors of MAO-A and MAO-B. **Selegiline** is available as a transdermal patch for treatment of major depression. It inhibits MAO-A and MAO-B in the brain, but has reduced effects on MAO-A in the gut.

**TABLE 70-4** Relative Potencies of Norepinephrine and Serotonin Reuptake Blockade and Side-Effect Profile of Antidepressant Drugs

	Reuptake Antagonism		Anticholinergic Effects	Sedation	Orthostatic Hypotension	Seizures <sup>a</sup>	Conduction Abnormalities <sup>a</sup>
	Norepinephrine	Serotonin					
<b>Selective serotonin reuptake inhibitors</b>							
Citalopram	0	++++	0	+	0	++	0
Escitalopram	0	++++	0	0	0	0	0
Fluoxetine	0	+++	0	0	0	++	0
Fluvoxamine	0	++++	0	0	0	++	0
Paroxetine	0	++++	+	+	0	++	0
Sertraline	0	++++	0	0	0	++	0
<b>Serotonin/norepinephrine reuptake inhibitors</b>							
Venlafaxine <sup>b</sup>	++++	++++	+	+	0	++	+
Duloxetine <sup>c</sup>	++++	++++	+	0	+	0	0
<b>Aminoketone</b>							
Bupropion <sup>d</sup>	+	0	+	0	0	++++	+
<b>Triazolopyridines</b>							
Nefazodone	0	++	0	+++	+++	++	+
Trazodone	0	++	0	++++	+++	++	+
<b>Tetracyclics</b>							
Mirtazapine	0	0	+	++	++	0	+

*(continued)*

**TABLE 70-4** Relative Potencies of Norepinephrine and Serotonin Reuptake Blockade and Side-Effect Profile of Antidepressant Drugs (Continued)

	Reuptake Antagonism		Anticholinergic Effects	Sedation	Orthostatic Hypotension	Seizures <sup>a</sup>	Conduction Abnormalities <sup>a</sup>
	Norepinephrine	Serotonin					
<b>Tricyclics</b>							
<i>Tertiary amines</i>							
Amitriptyline	++	++++	++++	++++	+++	+++	+++
Clomipramine	++	+++	++++	++++	++	++++	+++
Doxepin	++	++	+++	++++	++	+++	++
Imipramine	+++	+++	+++	+++	++++	+++	+++
<i>Secondary amines</i>							
Desipramine	++++	+	++	++	++	++	++
Nortriptyline	+++	++	++	++	+	++	++
<b>Monoamine oxidase inhibitors</b>							
Phenelzine	++	++	+	++	++	+	
Selegiline	0	0	0	+	++	0	0
Tranylcypromine	++	+	+	+	++	+	+

++++, high; +++, moderate; ++, low; +, very low; 0, absent.

<sup>a</sup>These are uncommon side effects of antidepressant drugs, particularly when used at normal therapeutic doses.

<sup>b</sup>Primarily serotonin (5-HT) at lower doses, norepinephrine (NE) at higher doses, and dopamine at very high doses.

<sup>c</sup>Balanced 5-HT and NE reuptake inhibition.

<sup>d</sup>Also blocks dopamine reuptake.

Data from Baldessarini RJ. In: Hardman JG, Limbird LE, Goodman A, et al. eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 10th ed. New York: McGraw-Hill, 2000:447-484; Mann JJ. *N Engl J Med* 2005;353:1819-1834; Stahl SM, Grady MM, Moret C, Briley M. *SNRIs: CNS Spectr* 2005;10:732-747; Horst WD, Preskorn SH. *J Affect Disord* 1998;51:237-254; and Patkar AA, Pae C-U, Masand PS. *CNS Spectr* 2006;11:363-375.

- The triazolopyridines **trazodone** and **nefazodone** are antagonists at the 5-HT<sub>2</sub> receptor and inhibit the reuptake of 5-HT. They can also enhance 5-HT<sub>1A</sub> neurotransmission. They have negligible affinity for cholinergic and histaminergic receptors.
- **Bupropion's** most potent neurochemical action is blockade of DA reuptake; it blocks the reuptake of NE to a lesser extent.
- The serotonin-norepinephrine reuptake inhibitors include **venlafaxine** and **duloxetine**. Venlafaxine is an inhibitor of 5-HT and NE reuptake and a weak inhibitor of DA reuptake. **Desvenlafaxine** (Pristiq) was recently approved by the FDA. The dose is 50 mg once daily.
- **Maprotiline** and **amoxapine** are inhibitors of NE reuptake, with less effect on 5-HT reuptake.
- **Mirtazapine** enhances central noradrenergic and serotonergic activity through the antagonism of central presynaptic  $\alpha_2$ -adrenergic autoreceptors and heteroreceptors. It also antagonizes 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptors. It also blocks histamine receptors.
- **St. John's wort**, an herbal nonprescription medication containing hypericum, may be effective for mild to moderate depression, but it is associated with several drug-drug interactions. Its potency, purity, and manufacture are not regulated by the FDA. As depression is a potentially life-threatening disease, all antidepressant treatments should be overseen by a trained healthcare professional.

## ADVERSE EFFECTS

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- Adverse-effect profiles of the various antidepressants are summarized in Table 70-4.

### Tricyclic Antidepressants and Other Heterocyclics

- Anticholinergic side effects (e.g., dry mouth, blurred vision, constipation, urinary retention, tachycardia, memory impairment, and delirium) and sedation are more likely to occur with the tertiary amine TCAs than with the secondary amine TCAs.
- Orthostatic hypotension and resultant syncope, a common and potentially serious adverse effect of the TCAs, occurs as a result of  $\alpha_1$ -adrenergic antagonism. Additional side effects include cardiac conduction delays and heart block, especially in patients with preexisting conduction disease.
- Other side effects that may lead to noncompliance include weight gain and sexual dysfunction.
- Abrupt withdrawal of TCAs (especially high doses) may result in symptoms of cholinergic rebound (e.g., dizziness, nausea, diarrhea, insomnia, restlessness).
- **Amoxapine** is a demethylated metabolite of loxapine and, as a result of its postsynaptic receptor DA-blocking effects, may be associated with extrapyramidal side effects.
- **Maprotiline**, a tetracyclic drug, causes seizures at a higher incidence than do standard TCAs and is contraindicated in patients with a history of seizure disorder. The ceiling dose is considered to be 225 mg/day.

**Venlafaxine**

- **Venlafaxine** may cause a dose-related increase in diastolic blood pressure. Dosage reduction or discontinuation may be necessary if sustained hypertension occurs. Other side effects are similar to those associated with the SSRIs (e.g., nausea and sexual dysfunction).

**Duloxetine**

- The most common side effects are nausea, dry mouth, constipation, decreased appetite, insomnia, and increased sweating.

**Selective Serotonin Reuptake Inhibitors**

- The SSRIs produce fewer sedative, anticholinergic, and cardiovascular adverse effects than the TCAs and are less likely to cause weight gain than the TCAs. The primary adverse effects include nausea, vomiting, diarrhea, headache, insomnia, fatigue, and sexual dysfunction. A few patients have anxiety symptoms early in treatment.

**Triazolopyridines**

- **Trazodone** and **nefazodone** cause minimal anticholinergic effects. Sedation, dizziness, and orthostatic hypotension are the most frequent dose-limiting side effects.
- Priapism occurs rarely with trazodone use (1 in 6,000 male patients). Surgical intervention may be required, and impotence may result.
- A black box warning for life-threatening liver failure was added to the prescribing information for nefazodone. Treatment with nefazodone should not be initiated in individuals with active liver disease or with elevated baseline serum transaminases.

**Aminoketone**

- The occurrence of seizures with **bupropion** is dose related and may be increased by predisposing factors (e.g., history of head trauma or CNS tumor). At the ceiling dose (450 mg/day), the incidence of seizures is 0.4%. Other side effects include nausea, vomiting, tremor, insomnia, dry mouth, and skin reactions. It is contraindicated in patients with bulimia or anorexia nervosa.

**Mixed Serotonin-Norepinephrine Effects**

- **Mirtazapine's** most common adverse effects are somnolence, weight gain, dry mouth, and constipation.

**Monoamine Oxidase Inhibitors**

- The most common adverse effect of MAOIs is postural hypotension (more likely with **phenelzine** than **tranylcypromine**), which can be minimized by divided-daily dosing. Anticholinergic side effects are common but less severe than with the TCAs. Phenelzine causes mild to moderate sedating effects, but tranylcypromine is often stimulating, and the last dose of the day is administered in early afternoon. Sexual dysfunction in both genders is common. Phenelzine has been associated with hepatocellular damage and weight gain.
- Hypertensive crisis is a potentially fatal adverse reaction that can occur when MAOIs are taken concurrently with certain foods, especially those high in

**TABLE 70-5** Dietary Restrictions for Patients Taking Monoamine Oxidase Inhibitors<sup>a</sup>

Aged cheeses <sup>b</sup>
Sour cream <sup>c</sup>
Yogurt <sup>c</sup>
Cottage cheese <sup>c</sup>
American cheese <sup>c</sup>
Mild Swiss cheese <sup>c</sup>
Wine <sup>d</sup> (especially Chianti and sherry)
Beer
Herring (pickled, salted, dry)
Sardines
Snails
Anchovies
Canned, aged, or processed meats
Monosodium glutamate
Liver (chicken or beef, more than 2 days old)
Fermented foods
Canned figs
Raisins
Pods of broad beans (fava beans)
Yeast extract and other yeast products
Meat extract (Marmite)
Soy sauce
Chocolate <sup>e</sup>
Coffee <sup>e</sup>
Ripe avocado
Sauerkraut
Licorice

<sup>a</sup>According to the FDA-approved prescribing information for the transdermal selegiline patch, patients receiving the 6 mg/24 hour dose are not required to modify their diet. However, patients receiving the 9 or 12 mg/24 hour dose are still required to follow the dietary restrictions similar to the other monoamine oxidase inhibitors (MAOIs).

<sup>b</sup>Clearly warrants absolute prohibition (e.g., English Stilton, blue, Camembert, cheddar).

<sup>c</sup>Up to 56 g (2 oz) daily is acceptable.

<sup>d</sup>An 88 mL (3 oz) white wine or a single cocktail is acceptable.

<sup>e</sup>Up to 56 g (2 oz) daily is acceptable; larger amounts of decaffeinated coffee are acceptable.

Recommended first-line drug and food interaction search engines: Lexi-Comp, Inc. Lexi-Comp Online. <http://online.lexi.com> and Thomson MICROMEDEX Healthcare Series. <https://www.thomsonhc.com>.

tyramine (Table 70-5), and with certain drugs (Table 70-6). Symptoms of hypertensive crisis include occipital headache, stiff neck, nausea, vomiting, sweating, and sharply elevated blood pressure. Hypertensive crisis may be treated with agents, such as captopril. Education of patients taking MAOIs regarding dietary and medication restrictions is critical.

## PHARMACOKINETICS

- The pharmacokinetics of the antidepressants is summarized in Table 70-7.
- The major metabolic pathways of the TCAs are demethylation, hydroxylation, and glucuronide conjugation. Metabolism of the TCAs appears to be linear within the usual dosage range, but dose-related kinetics cannot be ruled out in the elderly.

**TABLE 70-6** Medication Restrictions for Patients Taking Monoamine Oxidase Inhibitors (MAOIs)

Amphetamines	Levodopa
Appetite suppressants	Local anesthetics containing sympathomimetic vasoconstrictors
Asthma inhalants	Meperidine
Bupirone	Methyldopa
Carbamazepine	Methylphenidate
Cocaine	Other antidepressants <sup>a</sup>
Cyclobenzaprine	Other MAOIs
Decongestants (topical and systemic)	Reserpine
Dextromethorphan	Rizatriptan
Dopamine	Stimulants
Ephedrine	Sumatriptan
Epinephrine	Sympathomimetics
Guanethidine	Tryptophan

<sup>a</sup>Tricyclic antidepressants can be used with caution by experienced clinicians in treatment-resistant populations.

Recommended first-line drug interaction search engines: Lexi-Comp, Inc. Lexi-Comp Online. <http://online.lexi.com> and Thomson MICROMEDEX Healthcare Series. <https://www.thomsonhc.com>.

- The SSRIs, with the possible exception of **citalopram** and **sertraline**, may have a nonlinear pattern of drug accumulation with chronic dosing.
- **Mirtazapine** is primarily eliminated in the urine.
- Factors reported to influence **TCA** plasma concentrations include disease states (e.g., renal or hepatic dysfunction), genetics, age, cigarette smoking, and concurrent drug administration. Similarly, hepatic impairment, renal impairment, and age have been reported to influence the pharmacokinetics of **SSRIs**.
- In acutely depressed patients, there is a correlation between antidepressant effect and plasma concentrations for some **TCAs**. Table 70-3 shows suggested therapeutic plasma concentration ranges. The best-established therapeutic range is for **nortriptyline**, and data suggest a therapeutic window.
- Some indications for plasma level monitoring include inadequate response, relapse, serious or persistent adverse effects, use of higher than standard doses, suspected toxicity, elderly patients, children and adolescents, pregnant patients, patients of African or Asian descent (because of slower metabolism), cardiac disease, suspected noncompliance, suspected pharmacokinetic drug interactions, and changing brands.
- Plasma concentrations should be obtained at steady state, usually after a minimum of 1 week at constant dosage. Sampling should be done during the elimination phase, usually in the morning, 12 hours after the last dose. Samples collected in this manner are comparable for patients on once-daily, twice-daily, or thrice-daily regimens.

## DRUG-DRUG INTERACTIONS

- Drug interactions of the **TCAs** are summarized in Tables 70-8 and 70-9. Table 70-10 summarizes the drug interactions of non-**TCAs**.
- The very slow elimination of **fluoxetine** and **norfluoxetine** makes it critical to ensure a 5-week washout after fluoxetine discontinuation before

**TABLE 70-7** Pharmacokinetic Properties of Antidepressants

Generic Name	Elimination Half-Life (hours) <sup>a</sup>	Time of Peak Plasma Concentration (hours)	Plasma Protein Binding (%)	Percentage Bioavailable	Clinically Important Metabolites
<b>Selective serotonin reuptake inhibitors</b>					
Citalopram	33	2–4	80	≥80	None
Escitalopram	27–32	5	56	80	None
Fluoxetine	4–6 days <sup>b</sup>	4–8	94	95	Norfluoxetine
Fluvoxamine	15–26	2–8	77	53	None
Paroxetine	24–31	5–7	95	<sup>d</sup>	None
Sertraline	27	6–8	99	36 <sup>c</sup>	None
<b>Serotonin/norepinephrine reuptake inhibitor</b>					
Venlafaxine	5	2	27–30	45	<i>O</i> -Desmethylvenlafaxine
Duloxetine	12	6	90	50	None
<b>Aminoketone</b>					
Bupropion	10–21	3	82–88	<sup>d</sup>	Hydroxybupropion Threohydrobupropion Erythrohydrobupropion
<b>Triazolopyridines</b>					
Nefazodone	2–4	1	99	20	<i>Meta</i> -chlorophenylpiperazine
Trazodone	6–11	1–2	92	<sup>d</sup>	<i>Meta</i> -chlorophenylpiperazine (continued)

**TABLE 70-7** Pharmacokinetic Properties of Antidepressants (Continued)

Generic Name	Elimination Half-Life (hours) <sup>a</sup>	Time of Peak Plasma Concentration (hours)	Plasma Protein Binding (%)	Percentage Bioavailable	Clinically Important Metabolites
<b>Tetracyclics</b>					
Mirtazapine	20–40	2	85	50	None
<b>Tricyclics</b>					
<i>Tertiary amines</i>					
Amitriptyline	9–46	1–5	90–97	30–60	Nortriptyline
Clomipramine	20–24	2–6	97	36–62	Desmethyldomipramine
Doxepin	8–36	1–4	68–82	13–45	Desmethyldoxepin
Imipramine	6–34	1.5–3	63–96	22–77	Desipramine
<i>Secondary amines</i>					
Desipramine	11–46	3–6	73–92	33–51	2-Hydroxydesipramine
Nortriptyline	16–88	3–12	87–95	46–70	10-Hydroxynortriptyline

<sup>a</sup>Biologic half-life in slowest phase of elimination.

<sup>b</sup>4–6 days with chronic dosing; norfluoxetine, 4–16 days.

<sup>c</sup>Increases 30–40% when taken with food.

<sup>d</sup>No data available.

Data from Stahl SM, Grady MM, Moret C, Briley M. SNRIs. *CNS Spectr* 2005;10:732–747; Hemeryck A, Belpaire FM. *Curr Drug Metab* 2002;3:13–37; Kent JM. *Lancet* 2000;355:911–918; and DeVane CL. *J Clin Psychiatry* 1998;59(Suppl 20):85–93.

**TABLE 70-8** Pharmacokinetic Drug Interactions Involving Tricyclic Antidepressants (TCAs)**Elevates plasma concentrations of TCAs**

Cimetidine  
 Diltiazem  
 Ethanol, acute ingestion  
 SSRIs  
 Haloperidol  
 Labetalol  
 Methylphenidate  
 Oral contraceptives  
 Phenothiazines  
 Propoxyphene  
 Quinidine  
 Verapamil

**Lowers plasma concentrations of TCAs**

Barbiturates  
 Carbamazepine  
 Ethanol, chronic ingestion  
 Phenytoin

**Elevates plasma concentrations of interacting drug**

Hydantoins  
 Oral anticoagulants

**Lowers plasma concentrations of interacting drug**

Levodopa

SSRI, selective serotonin reuptake inhibitor.

Recommended first-line drug interaction search engines: Lexi-Comp, Inc. Lexi-Comp Online. <http://online.lexi.com> and Thomson MICROMEDEX Healthcare Series. <https://www.thomsonhc.com>.

starting an MAOI. Potentially fatal reactions may occur when any SSRI or TCA is coadministered with an MAOI.

- Increased plasma concentrations of TCAs and symptoms of toxicity may occur when **fluoxetine** and **paroxetine** are added to a TCA regimen.
- The combination of an SSRI with another 5-HT augmenting agent can lead to the serotonin syndrome, which is characterized by symptoms such as clonus, hyperthermia, and mental status changes.
- The ability of an SSRI, or any antidepressant, to inhibit or induce the activity of the cytochrome P450 (CYP450) enzymes can be a significant contributory factor in determining its capability to cause a pharmacokinetic drug–drug interaction.
- Table 70-11 compares second- and third-generation antidepressants for their effects on the enzymes of the CYP450 system.
- The drug interaction literature should be consulted for detailed information concerning any real or potential drug interaction involving any psychotherapeutic agent.

## SPECIAL POPULATIONS

### Elderly Patients

- Prominent symptoms of depression in the elderly are loss of appetite, cognitive impairment, sleeplessness, anergia, fatigue, and loss of interest in and enjoyment of the normal pursuits of life.

**TABLE 70-9** Pharmacodynamic Drug Interactions Involving Tricyclic Antidepressants

Interacting Drug	Effect
Alcohol	Increased CNS depressant effects
Amphetamines	Increased effect of amphetamines
Androgens	Delusions, hostility
Anticholinergic agents	Excessive anticholinergic effects
Bepidil	Increased antiarrhythmic effect
Clonidine	Decreased antihypertensive efficacy
Disulfiram	Acute organic brain syndrome
Estrogens	Increased or decreased antidepressant response; increased toxicity
Guanadrel	Decreased antihypertensive efficacy
Guanethidine	Decreased antihypertensive efficacy
Insulin	Increased hypoglycemic effects
Lithium	Possible additive lowering of seizure threshold
Methyldopa	Decreased antihypertensive efficacy; tachycardia; CNS stimulation
Monoamine oxidase inhibitors	Increased therapeutic and possibly toxic effects of both drugs; hypertensive crisis; delirium; seizures; hyperpyrexia; serotonin syndrome
Oral hypoglycemics	Increased hypoglycemic effects
Phenytoin	Possible lowering of seizure threshold and reduced antidepressant response
Sedatives	Increased CNS depressant effects
Sympathomimetics	Increased pharmacologic effects of direct-acting sympathomimetics; decreased effects of indirect-acting sympathomimetics
Thyroid hormones	Increased therapeutic and possibly toxic effects of both drugs; CNS stimulation; tachycardia

Recommended first-line drug interaction search engines: Lexi-Comp, Inc. Lexi-Comp Online. <http://online.lexi.com> and Thomson MICROMEDEX Healthcare Series. <https://www.thomsonhc.com>.

- The **SSRIs** are often selected as first-choice antidepressants in elderly patients.
- In healthy elderly patients, cautious use of a secondary amine **TCA** (**desipramine** or **nortriptyline**) may be appropriate because of their defined therapeutic plasma concentration ranges, well-established efficacy, and well-known adverse-effect profiles.
- **Bupropion** and **venlafaxine** may also be chosen because of their milder anticholinergic and less frequent cardiovascular side effects.

### Children and Adolescents

- Symptoms of depression in childhood include boredom, anxiety, failing adjustment, and sleep disturbance.
- Data supporting efficacy of antidepressants in children and adolescents are sparse. **Fluoxetine** is the only antidepressant that is FDA approved for treatment of depression in patients less than 18 years of age.
- The FDA has established a link between antidepressant use and suicidality (suicidal thinking and behaviors) in children, adolescents, and young adults 18 to 24 years old. All antidepressants carry a black box warning providing cautions in the use of all antidepressants in this population, and the FDA also recommends specific monitoring parameters. The clinician should consult the FDA-approved labeling or the FDA website for additional information. However, several retrospective longitudinal reviews of

**TABLE 70-10** Selected Drug Interactions of Newer-Generation Antidepressants

Antidepressant	Interacting Drug/ Drug Class	Effect
<b>Serotonin/norepinephrine reuptake inhibitors</b>		
Venlafaxine	MAOIs	Potential for hypertensive crisis, serotonin syndrome, delirium
	Sibutramine	Serotonin syndrome
Duloxetine	Triptans	Serotonin syndrome
	MAOIs	Potential for hypertensive crisis, serotonin syndrome, delirium
	Sibutramine	Serotonin syndrome
	Thioridazine	Thioridazine $C_{max}$ increased; prolonged QTc interval
	Triptans	Serotonin syndrome
<b>Selective serotonin reuptake inhibitors</b>		
Citalopram & escitalopram	MAOIs	Potential for hypertensive crisis, serotonin syndrome, delirium
	Linezolid ( <i>MAOI effects</i> )	Serotonin syndrome
	Sibutramine	Serotonin syndrome
Fluoxetine	Triptans	Serotonin syndrome
	Alprazolam	Increased plasma concentrations and half-life of alprazolam; increased psychomotor impairment
	Antipsychotics (e.g., haloperidol and risperidone)	Increased antipsychotic concentrations; increased extrapyramidal side effects
	$\beta$ -Adrenergic blockers	Increased metoprolol serum concentrations; increased bradycardia; possible heart block
	Carbamazepine	Increased plasma concentrations of carbamazepine; symptoms of carbamazepine toxicity
	Linezolid ( <i>MAOI effects</i> )	Serotonin syndrome
	MAOIs	Potential for hypertensive crisis, serotonin syndrome, delirium
	Phenytoin	Increased plasma concentrations of phenytoin; symptoms of phenytoin toxicity
	TCA	Markedly increased TCA plasma concentrations; symptoms of TCA toxicity
		Sibutramine
Fluvoxamine	Triptans	Serotonin syndrome
	Thioridazine	Thioridazine $C_{max}$ increased; prolonged QTc interval
	Alosetron	Increased alosetron AUC (sixfold) and half-life (threefold)
	Alprazolam	Increased AUC of alprazolam by 96%; increased alprazolam half-life by 71%; increased psychomotor impairment
	$\beta$ -Adrenergic blockers	Fivefold increase in propranolol serum concentration; bradycardia and hypotension
	Carbamazepine	Increased plasma concentrations of carbamazepine; symptoms of carbamazepine toxicity
	Clozapine	Increased clozapine serum concentrations; increased risk for seizures and orthostatic hypotension
	Diltiazem	Bradycardia
	MAOIs	Potential for hypertensive crisis, serotonin syndrome, delirium
	Methadone	Increased methadone plasma concentrations; symptoms of methadone toxicity
	Ramelteon	Increased AUC (190-fold) and $C_{max}$ (70-fold)

*(continued)*

**TABLE 70-10** Selected Drug Interactions of Newer-Generation Antidepressants (Continued)

Antidepressant	Interacting Drug/ Drug Class	Effect
Fluvoxamine ( <i>cont'd</i> )	Sibutramine	Serotonin syndrome
	TCA	Increased TCA plasma concentration; symptoms of TCA toxicity
	Theophylline & caffeine	Increased serum concentrations of theophylline or caffeine; symptoms of theophylline or caffeine toxicity
Paroxetine	Thioridazine	Thioridazine $C_{max}$ increased; prolonged QTc interval
	Warfarin	Increased hypoprothrombinemic response to warfarin
	Antipsychotics (e.g., haloperidol, perphenazine, and risperidone)	Increased antipsychotic concentrations; increased CNS and extrapyramidal side effects
	$\beta$ -Adrenergic blockers	Increased metoprolol serum concentrations; increased bradycardia; possible heart block
	Linezolid (MAOI effects)	Serotonin syndrome
Sertraline	MAOIs	Potential for hypertensive crisis, serotonin syndrome, delirium
	TCA	Markedly increased TCA plasma concentrations; symptoms of TCA toxicity
	Sibutramine	Serotonin syndrome
	Triptans	Serotonin syndrome
	Thioridazine	Thioridazine $C_{max}$ increased; prolonged QTc interval
	Linezolid (MAOI effects)	Serotonin syndrome
	MAOIs	Potential for hypertensive crisis, serotonin syndrome, delirium
Tetracyclics		
Mirtazapine	Sibutramine	Serotonin syndrome
	Triptans	Serotonin syndrome
Aminoketone	Sibutramine	Serotonin syndrome
	Triptans	Serotonin syndrome
Mirtazapine	Carbamazepine	Mirtazapine concentration decrease (60%)
	MAOIs	Theoretically central serotonin syndrome could occur
Bupropion	MAOIs	Potential for hypertensive crisis
	Medications that lower seizure threshold	Increased incidence of seizures

AUC, area under the curve,  $C_{max}$ , maximum concentration; MAOI, monoamine oxidase inhibitor; TCA, tricyclic antidepressant. Recommended first-line drug interaction search engines: Lexi-Comp, Inc. Lexi-Comp Online. <http://online.lexi.com> and Thomson MICROMEDEX Healthcare Series. <https://www.thomsonhc.com>.

the use of antidepressants in children found no significant increase in the risk of suicide attempts or deaths.

- Several cases of sudden death have been reported in children and adolescents taking **desipramine**. A baseline electrocardiogram (ECG) is recommended before initiating a TCA in children and adolescents, and an additional ECG is advised when steady-state plasma concentrations are achieved. TCA plasma concentration monitoring is critical to ensure safety.

### Pregnancy

- As a general rule, if effective, nondrug approaches are preferred when treating depressed pregnant patients.

**TABLE 70-11** Second- and Third-Generation Antidepressants and Cytochrome (CYP) P450 Enzyme Inhibitory Potential

Drug	CYP Enzyme			
	1A2	2C	2D6	3A4
Bupropion	0	0	+	0
Citalopram	0	0	+	0
Escitalopram	0	0	+	0
Fluoxetine	0	++	++++	++
Fluvoxamine	++++	++	0	+++
Mirtazapine	0	0	0	0
Nefazodone	0	0	0	++++
Paroxetine	0	0	++++	0
Sertraline	0	++	+	+
Venlafaxine	0	0	0/+	0

++++, high; +++, moderate; ++, low; +, very low; 0, absent.

Data from Preskorn SH. *Clin Pharmacokinet* 1997;32(Suppl 1):1-21; Hemeryck A, Belpaire FM. *Curr Drug Metab* 2002;3:13-37; Kent JM. *Lancet* 2000;355:911-918; and DeVane CL. *J Clin Psychiatry* 1998;59(Suppl 20):85-93.

- One study showed that pregnant women who discontinued antidepressants were five times more likely to relapse during their pregnancy than were women who continued treatment.
- No major teratogenic effects have been identified with the **SSRIs** or **TCAs**. However, evaluations to date suggest a possible association of **fluoxetine** with low birth weight and respiratory distress. Another study reported a sixfold greater likelihood of the occurrence of persistent pulmonary hypertension of newborn infants exposed to an SSRI after the twentieth week of gestation.
- The risks of untreated depression in pregnancy should be considered. These included low birth weight, maternal suicidality, potential for hospitalization or marital discord, poor prenatal care, and difficulty caring for other children.

## REFRACTORY PATIENTS

- Most “treatment-resistant” depressed patients have received inadequate therapy. Issues to be considered in patients who have not responded to treatment include the following: (1) Is the diagnosis correct? (2) Does the patient have a psychotic depression? (3) Has the patient received an adequate dose and duration of treatment? (4) Do adverse effects preclude adequate dosing? (5) Has the patient been compliant with the prescribed regimen? (6) Was treatment outcome measured adequately? (7) Is there a coexisting or preexisting medical or psychiatric disorder? (8) Was a stepwise approach to treatment used? (9) Are there other factors that interfere with treatment?
- The STAR\*D study showed that one in three depressed patients who previously did not achieve remission with an antidepressant became symptom-free with the help of an additional medication (e.g., **bupropion sustained release**), and one in four achieved remission after switching to a different antidepressant (e.g., **venlafaxine XR**).

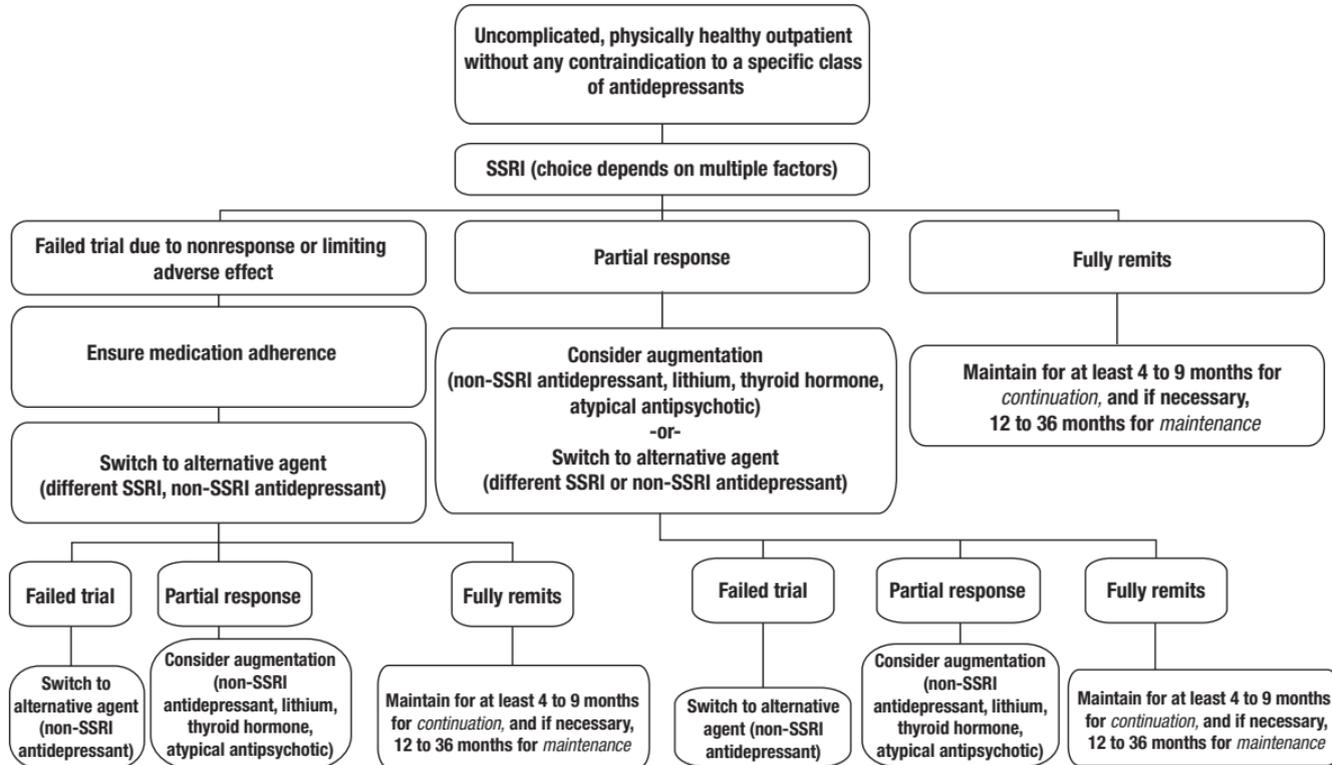
- The current antidepressant may be stopped, and a trial initiated with an agent of unrelated chemical structure (e.g., **mirtazapine** or **nortriptyline**).
- Alternatively, the current antidepressant may be augmented (potentiated) by the addition of another agent (e.g., **lithium**, **T<sub>3</sub>**), or an **atypical antipsychotic** (e.g., **risperidone**). Risperidone has been shown to be effective in combination with **fluvoxamine**, **paroxetine**, or **citalopram** in treatment-resistant depression. **Olanzapine** and **fluoxetine** have been found to be safe and effective in treatment-resistant depression.
- The practice guideline of the American Psychiatric Association recommends that after 6 to 8 weeks of antidepressant treatment, partial responders should consider changing the dose, augmenting the antidepressant, or adding psychotherapy or ECT. For those with no response, options include changing to another antidepressant or the addition of psychotherapy or ECT.
- An algorithm for treatment of depression including refractory patients is shown in Fig. 70-1.

## DOSING

- The usual initial adult dose of most **TCAs** is 50 mg at bedtime, and the dose may be increased by 25 to 50 mg every third day (see Table 70-3).
- **Bupropion** is usually initiated at 100 mg twice daily, and this dose may be increased to 100 mg three times daily after 3 days. An increase to 450 mg/day (the ceiling dose), given as 150 mg three times daily, may be considered in patients with no clinical response after several weeks at 300 mg/day.
- A 6-week antidepressant trial at a maximum dosage is considered an adequate trial. Patients must be told about the expected lag time of 2 to 4 weeks before the onset of antidepressant effect.
- Elderly patients should receive one-half the initial dose given to younger adults, and the dose is increased at a slower rate. The elderly may require 6 to 12 weeks of treatment to achieve the desired antidepressant response.
- To prevent relapse, antidepressants should be continued at full therapeutic doses for 4 to 9 months after remission.

## EVALUATION OF THERAPEUTIC OUTCOMES

- Several monitoring parameters, in addition to plasma concentrations, are useful in managing patients. Patients must be monitored for adverse effects, remission of previously documented target symptoms, and changes in social or occupational functioning. Regular monitoring should be assured for several months after antidepressant therapy is discontinued.
- Patients given **venlafaxine** should have blood pressure monitored regularly.
- Patients older than age 40 years should receive a pretreatment ECG before starting TCA therapy, and follow-up ECGs should be performed periodically.
- Patients should be monitored for emergence of suicidal ideation after initiation of any antidepressant, especially in the first few weeks of treatment.



**FIGURE 70-1.** Algorithm for treatment of uncomplicated major depression. (SSRI, selective serotonin reuptake inhibitor.)

- In addition to the clinical interview, psychometric rating instruments allow for rapid and reliable measurement of the nature and severity of depressive and associated symptoms.

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*See Chap. 71, Depressive Disorders, authored by Christian J. Teter, Judith C. Kando, Barbara G. Wells, and Peggy E. Hayes, for a more detailed discussion of this topic.*

## DEFINITION

- Schizophrenia is a chronic heterogeneous syndrome of disorganized and bizarre thoughts, delusions, hallucinations, inappropriate affect, cognitive deficits, and impaired psychosocial functioning.

## PATHOPHYSIOLOGY

- Multiple etiologies likely exist.
- Increased ventricular size, decreased brain size, and brain asymmetry have been reported. Lower hippocampal volume may correspond to impairment in neuropsychological testing and poorer response to first-generation antipsychotics (FGAs).
- *Dopaminergic hypothesis*. Psychosis may result from hyper- or hypoactivity of dopaminergic processes in specific brain regions. This may include the presence of a dopamine (DA) receptor defect.
- Positive symptoms (see Diagnosis section below) may be more closely associated with DA receptor hyperactivity in the mesocaudate, while negative symptoms (see Diagnosis section below) and cognitive symptoms (see Diagnosis section below) may be most closely related to DA receptor hypofunction in the prefrontal cortex.
- *Glutamatergic dysfunction*. A deficiency of glutamatergic activity produces symptoms similar to those of dopaminergic hyperactivity and possibly symptoms seen in schizophrenia.
- *Serotonin (5-HT) abnormalities*. Schizophrenic patients with abnormal brain scans have higher whole blood 5-HT concentrations, and these concentrations correlate with increased ventricular size.

## CLINICAL PRESENTATION

- Symptoms of the acute episode may include the following: being out of touch with reality; hallucinations (especially hearing voices); delusions (fixed false beliefs); ideas of influence (actions controlled by external influences); disconnected thought processes (loose associations); ambivalence (contradictory thoughts); flat, inappropriate, or labile affect; autism (withdrawn and inwardly directed thinking); uncooperativeness, hostility, and verbal or physical aggression; impaired self-care skills; and disturbed sleep and appetite.
- After the acute psychotic episode has resolved, the patient typically has residual features (e.g., anxiety, suspiciousness, lack of volition, lack of motivation, poor insight, impaired judgment, social withdrawal, difficulty in learning from experience, and poor self-care skills). Patients often have comorbid substance abuse and are nonadherent with medications.

## DIAGNOSIS

- The *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., text revision, specifies the following criteria for the diagnosis of schizophrenia:
  - ✓ Persistent dysfunction lasting longer than 6 months
  - ✓ Two or more symptoms (present for at least 1 month), including hallucinations, delusions, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms
  - ✓ Significantly impaired functioning (work, interpersonal, or self-care)
- The *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., text revision, classifies symptoms as positive or negative.
- Positive symptoms (the ones most affected by antipsychotic drugs) include delusions, disorganized speech (association disturbance), hallucinations, behavior disturbance (disorganized or catatonic), and illusions.
- Negative symptoms include alogia (poverty of speech), avolition, affective flattening, anhedonia, and social isolation.
- Cognitive dysfunction is another symptom category that includes impaired attention, working memory, and executive function.

## DESIRED OUTCOME

- The goals of treatment include the following: alleviation of target symptoms, avoidance of side effects, improvement in psychosocial functioning and productivity, compliance with the prescribed regimen, and involvement of the patient in treatment planning.

## TREATMENT

- A thorough mental status examination, physical and neurologic examination, a complete family and social history, vital signs and laboratory workup (complete blood count, electrolytes, hepatic function, renal function, electrocardiogram [ECG], fasting serum glucose, serum lipids, thyroid function, and urine drug screen) should be performed prior to treatment.

## GENERAL THERAPEUTIC PRINCIPLES

- Second-generation antipsychotics (SGAs) (also known as *atypical antipsychotics*), except **clozapine**, are the agents of first choice in treatment of schizophrenia. Growing, but still controversial, evidence supports that the SGAs (e.g., **clozapine**, **olanzapine**, **risperidone**, **quetiapine**, **ziprasidone**, and **aripiprazole**) have superior efficacy for treatment of negative symptoms, cognition, and mood.
- SGAs cause few or no acutely occurring extrapyramidal side effects. Other attributes ascribed include minimal or no propensity to cause tardive dyskinesia (TD) and less effect on serum prolactin than the FGAs. **Clozapine** is the only SGA that fulfills all these criteria.
- The Clinical Antipsychotic Trials of Intervention Effectiveness study showed that olanzapine, compared with quetiapine, risperidone, ziprasidone,

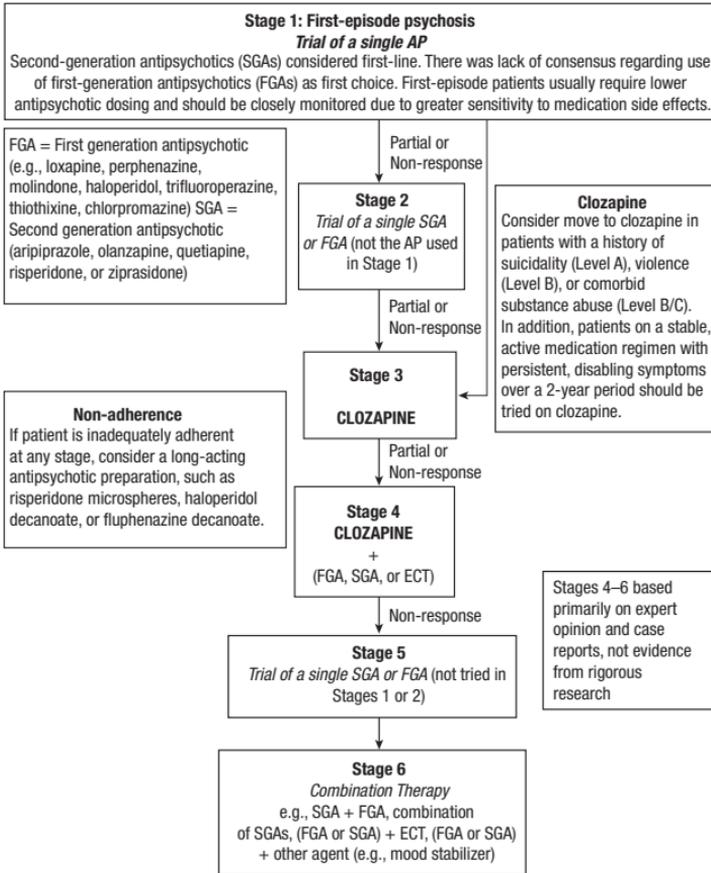
done, and perphenazine, has modest superiority in persistence of maintenance therapy, but olanzapine had more metabolic side effects.

- Selection of an antipsychotic should be based on (1) the need to avoid certain side effects, (2) concurrent medical or psychiatric disorders, and (3) patient or family history of response. Fig. 71-1 is an algorithm for management of first episode psychosis.
- All FGAs are equal in efficacy in groups of patients when used in equipotent doses.
- Dosage equivalents (expressed as chlorpromazine [CPZ]-equivalent dosages—the equipotent dosage of an FGA compared with 100 mg of CPZ) may be useful when switching from one FGA to another FGA drug (Table 71-1).
- Predictors of good antipsychotic response include a prior good response to the drug selected, absence of alcohol or drug abuse, acute onset and short duration of illness, acute stressors or precipitating factors, later age of onset, affective symptoms, family history of affective illness, compliance with the prescribed regimen, and good premorbid adjustment. Negative symptoms are generally less responsive to antipsychotic therapy.
- An initial dysphoric response, demonstrated by a dislike of the medication or feeling worse, combined with anxiety or akathisia, is associated with a poor drug response, adverse effects, and nonadherence.
- If partial or poor adherence is an issue, a long-acting or depot injectable antipsychotic should be considered (e.g., risperidone microspheres, haloperidol decanoate, fluphenazine decanoate).

## PHARMACOKINETICS

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- Pharmacokinetic parameters and major metabolic pathways of antipsychotics are summarized in Table 71-2.
- Antipsychotics are highly lipophilic and highly bound to membranes and plasma proteins.
- They have large volumes of distribution and are largely metabolized through the cytochrome P450 pathways (except ziprasidone).
- **Risperidone** and its active metabolite 9-OH-risperidone are metabolized by CYP2D6. Polymorphic metabolism should be considered in those with side effects at low doses (approximately 40% of African Americans and Asians can have increased side effects from risperidone and other drugs metabolized through CYP2D6).
- Most antipsychotics have half-lives of elimination in the range of 20 to 40 hours. After dosage stabilization, most antipsychotics (except **quetiapine** and **ziprasidone**) can be dosed once daily. It may be possible to dose SGAs less often than their plasma kinetics would suggest.
- A 12-hour postdose **clozapine** serum concentration of at least 250 ng/mL is recommended for patients taking divided doses of clozapine, or 350 ng/mL if the patient is taking once-daily dosing.
- Serum concentration monitoring of clozapine should be done before exceeding 600 mg daily in patients who develop unusual or severe adverse side effects, in those taking concomitant medications that might cause drug interactions, in those with age or pathophysiologic changes suggesting altered kinetics, and in those suspected of being nonadherent to their regimens.



**FIGURE 71-1.** Patient entry into the algorithm is determined by individual patient history and clinical presentation. Only new-onset patients with no history of antipsychotic treatment failure are treated at stage 1. Algorithm stages can be skipped if clinically appropriate, and one can go back stages if indicated. In general, inadequately responding patients should not remain in stages 1 or 2 longer than 12 weeks at therapeutic doses. Stage 3 can be up to 6 months. In stages 4, 5, and 6, a 12-week trial is recommended, and if there is greater than or equal to 20% improvement in positive symptoms at week 12, the medication trial warrants extension for an additional 12 weeks with dose titration as clinically warranted. The levels of evidence for algorithm recommendations are as follows: stage 1, level A for efficacy for both first-generation antipsychotics and second-generation antipsychotics; level C for second-generation antipsychotics as first choice; stage 2, level A; stage 3, level A; stage 4, level C; stage 5, level C; stage 6, level C. Level A is supported by one or more randomized controlled trials. Level B is supported by large cohort studies, epidemiologic studies, and so on. Level C is supported by case series, case reports, or expert opinion. (AP, antipsychotic; ECT, electroconvulsive therapy.) (*This figure is copyrighted by the Texas Department of State Health Services and may be reproduced with appropriate citation of the authors and source. Algorithm updates and user manuals can be obtained at <http://www.dshs.state.tx.us/mhprograms/pdf/timasczman.pdf>. Data from Moore TA, Buchanan RW, Buckley PF, et al. The Texas Medication Algorithm Project antipsychotic algorithm for schizophrenia: 2006 update. *J Clin Psychiatry* 2007;68:1751–1762.*)

**TABLE 71-1** Available Antipsychotics: Doses and Dosage Forms

Generic Name	Trade Name	Traditional Equivalent Dose (mg)	Usual Dosage Range (mg/day)	Manufacturer's Maximum Dose (mg/day) <sup>a</sup>	Dosage Forms <sup>b</sup>
<b>Traditional antipsychotics (first-generation antipsychotics)</b>					
chlorpromazine	Thorazine	100	100–800	2,000	T,L,LC,I,C-ER,S
fluphenazine	Prolixin	2	2–20	40	T,L,LC,I,LAI
haloperidol	Haldol	2	2–20	100	T,LC,I,LAI
loxapine	Loxitane	10	10–80	250	C,LC
molindone	Moban	10	10–100	225	T,LC
perphenazine	Trilafon	10	10–64	64	T,LC,I
thioridazine	Mellaril	100	100–800	800	T,LC
thiothixene	Navane	4	4–40	60	C,LC
trifluoperazine	Stelazine	5	5–40	80	T,LC,I
<b>Atypical antipsychotics (second-generation antipsychotics)</b>					
aripiprazole	Abilify	NA	15–30	30	T,O,L
clozapine	Clozaril	NA	50–500	900	T,O
olanzapine	Zyprexa	NA	10–20	20	T,I,O
paliperidone	Invega	NA	3–9	12	ER
quetiapine	Seroquel	NA	250–500	800	T
risperidone	Risperdal	NA	2–8	16	T,O,L
risperidone	Risperdal Consta	NA	25–50 mg every 2 weeks	50	LAI
ziprasidone	Geodon	NA	40–160	200	C,I

<sup>a</sup>NA. This parameter does not apply to atypical antipsychotics.

<sup>b</sup>C, capsule; ER or SR, extended- or sustained-release; I, injection; L, liquid solution, elixir, or suspension; LC, liquid concentrate; LAI, long-acting injectable; O, orally disintegrating tablets; R, rectal suppositories; T, tablet.

## INITIAL THERAPY

- The goals during the first 7 days are decreased agitation, hostility, anxiety, and aggression and normalization of sleep and eating patterns.
- In general, titrate over the first few days to an average effective dose. After 1 week at a stable dose, a modest dosage increase may be considered. If there is no improvement within 3 to 4 weeks at therapeutic doses, then an alternative antipsychotic should be considered (i.e., move to the next treatment stage in the algorithm; see Fig. 71-1).
- In partial responders who are tolerating the antipsychotic well, it may be reasonable to titrate above the usual dose range.
- In general, rapid titration of antipsychotic dose is not recommended.
- IM antipsychotic administration (e.g., ziprasidone 10 to 20 mg, olanzapine 2.5 to 10 mg, or haloperidol 2 to 5 mg) can be used to calm agitated patients. However, this approach does not improve the extent of response, time to remission, or length of hospitalization.
- Intramuscular (IM) **lorazepam**, 2 mg, as needed in combination with the maintenance antipsychotic may actually be more effective in controlling agitation than using additional doses of the antipsychotic.

**TABLE 71-2** Pharmacokinetic Parameters of Selected Antipsychotics

Drug	Bioavailability (%)	Half-Life (hours)	Major Metabolic Pathways	Active Metabolites
<b>Selected first-generation antipsychotics (FGAs)</b>				
Chlorpromazine	10–30	8–35	FMO3, CYP3A4	7-hydroxy, others
Fluphenazine	20–50	14–24	CYP2D6	?
Fluphenazine decanoate		14.2 ± 2.2 <sup>a</sup> days		
Haloperidol	40–70	12–36	CYP1A2, CYP2D6, CYP3A4	Reduced haloperidol
Haloperidol decanoate		21 days		
Perphenazine	20–25	8.1–12.3	CYP2D6	7-OH-perphenazine
<b>Second-generation antipsychotics (SGAs)</b>				
Aripiprazole	87	48–68	CYP3A4, CYP2D6	Dehydroaripiprazole
Clozapine	12–81	11–105	CYP1A2, CYP3A4, CYP2C19	Desmethylclozapine
Olanzapine	80	20–70	CYP1A2, CYP3A4, FMO3	<i>N</i> -glucuronide; 2-OH-methyl; 4-N-oxide
Paliperidone ER	28	23	Renal unchanged (59%) Multiple pathways	None known
Quetiapine	9 ± 4	6.88	CYP3A4	7-OH-quetiapine
Risperidone	68	3–24	CYP2D6	9-OH-risperidone
Risperidone Consta		3–6 days	CYP2D6	9-OH-risperidone
Ziprasidone	59	4–10	Aldehyde oxidase, CYP3A4	None

<sup>a</sup>Based on multiple dose data. Single dose data indicate a  $\beta$ -half-life of 6–10 days.

Data from De Leon A, Patel NC, Crismon ML. *Clin Ther* 2004;26:649–666; Harrison TS, Goa KL. *CNS Drugs* 2004;18:113–132; Ereshefsky L, Saklad SR, Jann MW, et al. *J Clin Psychiatry* 1984;45(5 pt 2):50–59; Ereshefsky L, Toney G, Saklad SR, Seidel DR. *Hosp Community Psychiatry* 1993;44:1155–1161; Mauri MC, Volonteri LS, Colasanti A, et al. *Clin Pharmacokinet* 2007;46:359–388; and Spina E, de Leon J. *Basic Clin Pharmacol Toxicol* 2007;100:4–22.

## STABILIZATION THERAPY

- During weeks 2 and 3, the goals should be to improve socialization, self-care habits, and mood. Improvement in formal thought disorder may require an additional 6 to 8 weeks.
- Most patients require a dose of 300 to 1,000 mg of CPZ equivalents (of FGAs) daily or SGAs in usual labeled doses. Dose titration may continue every 1 to 2 weeks as long as the patient has no side effects.
- If symptom improvement is not satisfactory after 8 to 12 weeks, a different strategy (see Fig. 71-1) should be tried.

## MAINTENANCE THERAPY

- Medication should be continued for at least 12 months after remission of the first psychotic episode. Continuous treatment is necessary in most patients at the lowest effective dose.
- Antipsychotics (especially FGAs and **clozapine**) should be tapered slowly before discontinuation to avoid rebound cholinergic withdrawal symptoms.

- In general, when switching from one antipsychotic to another, the first should be tapered and discontinued over 1 to 2 weeks after the second antipsychotic is initiated.

### Depot Antipsychotic Medications

- The principle for conversion from oral antipsychotics to depot formulations is as follows:
  - ✓ Stabilize on an oral dosage form of the same agent (or at least a short trial of 3 to 7 days) to be sure the medication is tolerated adequately.
- **Risperidone Consta** is the first SGA to be available as a long-acting injectable. The recommended starting dose is 25 mg. Usual dosing range is 25 to 50 mg deep IM every 2 weeks. It is a suspension of drug in glycolic acid-lactate copolymer microspheres. Significant risperidone serum concentrations are measurable about 3 weeks after single-dose administration. Thus oral medication must be administered for at least 3 weeks after beginning injections. Dose adjustments should be made no more often than every 4 weeks.
- For **fluphenazine decanoate**, an esterified formulation in sesame seed oil, the simplest conversion is the Stimmel method, which uses 1.2 times the oral daily dose for stabilized patients, rounding up to the nearest 12.5-mg interval, administered IM in weekly doses for the first 4 to 6 weeks (1.6 times the oral daily dose for patients who are more acutely ill). Subsequently, fluphenazine decanoate may be administered once every 2 to 3 weeks. Oral fluphenazine may be overlapped for 1 week.
- For **haloperidol decanoate**, an esterified formulation in sesame seed oil, a factor of 10 to 15 times the oral daily dose is commonly recommended, rounding up to the nearest 50-mg interval, administered IM in a once-monthly dose with oral haloperidol overlap for 1 month.
- Haloperidol and fluphenazine decanoate should be administered by a deep, “Z-track” IM method. Long-acting risperidone is injected by deep IM injection in the gluteus maximus, but Z-tracking is not necessary.
- In patients previously unexposed to the drug, an oral test dose of the medication is recommended before long-acting antipsychotics are given.

### MANAGEMENT OF TREATMENT-RESISTANT SCHIZOPHRENIA

- Only **clozapine** has shown superiority over other antipsychotics in randomized clinical trials for the management of treatment-resistant schizophrenia.
- Symptomatic improvement with clozapine often occurs slowly in resistant patients, and as many as 60% of patients may improve if clozapine is used for up to 6 months.
- Because of the risk of orthostatic hypotension, clozapine is usually titrated more slowly than other antipsychotics. If a 12.5-mg test dose does not produce hypotension, then 25 mg of clozapine at bedtime is recommended, increased to 25 mg twice daily after 3 days, and then increased in 25- to 50-mg/day increments every 3 days until a dose of at least 300 mg/day is reached.
- Augmentation therapy involves the addition of a non-antipsychotic drug to an antipsychotic in a poorly responsive patient, while combination treatment involves using two antipsychotics simultaneously.

- Responders to augmentation therapy usually improve rapidly. If there is no improvement, the augmenting agent should be discontinued.
- Mood stabilizers (e.g., **lithium**, **valproic acid**, and **carbamazepine**) used as augmentation agents may improve labile affect and agitated behavior. A placebo-controlled trial supports fast symptom improvement when **divalproex** is combined with either olanzapine or **risperidone**.
- **Selective serotonin reuptake inhibitors** have been used with FGAs with improvement of negative symptoms. Selective serotonin reuptake inhibitors have been used for obsessive-compulsive symptoms that worsen or arise during **clozapine** treatment.
- **Propranolol**, **pindolol**, and **nadolol** have been used for antiaggressive effects, especially in organic aggressive syndrome. If propranolol is used, a 20-mg test dose should be given to assess tolerability. If well tolerated, it can be initiated at 20 mg three times daily. Increments can then be 60 mg/day every 3 days. Six to 8 weeks may be needed to evaluate response.
- Combining an FGA and an SGA and combining different SGAs have been suggested, but no data exist to support or refute these strategies. If a series of antipsychotic monotherapies fails, a time-limited combination trial may be attempted. If there is no improvement within 6 to 12 weeks, one of the drugs should be tapered and discontinued.

## ADVERSE EFFECTS

- Table 71-3 presents the relative incidence of common categories of antipsychotic side effects.

### Autonomic Nervous System

- Anticholinergic (ACh) side effects include impaired memory, dry mouth, constipation, tachycardia, blurred vision, inhibition of ejaculation, and

**TABLE 71-3** Relative Side-Effect Incidence of Commonly Used Antipsychotics<sup>a,b</sup>

	Sedation	EPS	Anticholinergic	Orthostasis	Weight Gain	Prolactin
Aripiprazole	+	+	+	+	+	+
Chlorpromazine	++++	+++	+++	++++	++	+++
Clozapine	++++	+	++++	++++	++++	+
Fluphenazine	+	++++	+	+	+	++++
Haloperidol	+	++++	+	+	+	++++
Olanzapine	++	++	++	++	++++	+
Perphenazine	++	++++	++	+	+	++++
Quetiapine	++	+	+	++	++	+
Risperidone	+	++	+	++	++	++++
Thioridazine	++++	+++	++++	++++	+	+++
Thiothixene	+	++++	+	+	+	++++
Ziprasidone	++	++	+	+	+	+

EPS, extrapyramidal side effects. Relative side-effect risk: ±, negligible; +, low; ++, moderate; +++, moderately high; +++++, high.

<sup>a</sup>Side effects shown are relative risk based on doses within the recommended therapeutic range.

<sup>b</sup>Individual patient risk varies depending on patient-specific factors.

urinary retention. Elderly patients are especially sensitive to these side effects. Low potency FGAs, clozapine, and olanzapine are most likely to cause ACh effects.

- Dry mouth can be managed with increased intake of fluids, oral lubricants (Xerolube), ice chips, or use of sugarless chewing gum or hard candy.
- Constipation can be treated with increases in exercise, fluid, and dietary fiber intake.

## Central Nervous System

### Extrapyramidal System

#### Dystonia

- Dystonias are prolonged tonic muscle contractions, with rapid onset (usually within 24 to 96 hours of dosage initiation or dosage increase); they may be life threatening (e.g., pharyngeal-laryngeal dystonias). Dystonic reactions occur primarily with FGAs. Risk factors include younger patients (especially males), use of high-potency agents, and high dose.
- Treatment includes IM or IV AChs (Table 71-4) or **benzodiazepines**. **Benzotropine mesylate**, 2 mg, or **diphenhydramine**, 50 mg, may be given IM or IV, or **diazepam**, 5 to 10 mg slow IV push, or **lorazepam**, 1 to 2 mg IM, may be given. Relief usually occurs within 15 to 20 minutes of IM injection or within 5 minutes of IV administration. The dose should be repeated if no response is seen within 15 minutes of IV injection or 30 minutes of IM injection.
- Prophylactic ACh medications (but not amantadine) are reasonable when using high-potency FGAs (e.g., **haloperidol**, **fluphenazine**), in young men, and in patients with a history of dystonia.
- Dystonias can be minimized through the use of lower initial doses of FGAs and by using SGAs instead of FGAs.

**TABLE 71-4** Agents to Treat Extrapyramidal Side Effects

Generic Name	Equivalent Dose (mg)	Daily Dosage Range (mg)
Antimuscarinics		
Benzotropine <sup>a</sup>	1	1–8 <sup>b</sup>
Biperiden <sup>a</sup>	2	2–8
Trihexyphenidyl	2	2–15
Antihistaminic		
Diphenhydramine <sup>a</sup>	50	50–400
Dopamine agonist		
Amantadine	NA	100–400
Benzodiazepines		
Lorazepam <sup>a</sup>	NA	1–8
Diazepam	NA	2–20
Clonazepam	NA	2–8
$\beta$ -Blockers		
Propranolol	NA	20–160

NA, not applicable.

<sup>a</sup>Injectable dosage form can be given intramuscularly for relief of acute dystonia.

<sup>b</sup>Dosage can be titrated to 12 mg/day with careful monitoring; nonlinear pharmacokinetics have been demonstrated.

*Akathisia*

- Symptoms include subjective complaints (feelings of inner restlessness) and/or objective symptoms (pacing, shuffling, or tapping feet).
- Treatment with AChs is disappointing, and reduction in antipsychotic dose may be the best intervention. Another alternative is to switch to an SGA, although akathisia occasionally occurs with the SGAs. **Quetiapine** and **clozapine** appear to have the lowest risk for causing akathisia.
- **Diazepam** may be used (5 mg three times daily), but efficacy data are conflicting.
- **Propranolol** (up to 160 mg/day) and **metoprolol** (up to 100 mg/day) are reported to be effective.

*Pseudoparkinsonism*

- Patients with pseudoparkinsonism may have any of four cardinal symptoms:
  - ✓ Symptoms are (1) akinesia, bradykinesia, or decreased motor activity, including mask-like facial expression, micrographia, slowed speech, and decreased arm swing; (2) tremor (predominantly at rest and decreasing with movement); (3) rigidity, which may present as stiffness; cogwheel rigidity is seen as the patient's limbs yield in jerky, ratchet-like fashion when moved passively by the examiner; and (4) postural abnormalities, including stooped, unstable posture and slow, shuffling, or festinating gait.
- Risk factors are FGAs (especially in high dose), increasing age, and possibly female gender.
- Accessory symptoms include seborrhea, sialorrhea, hyperhidrosis, fatigue, dysphagia, and dysarthria. A variant is rabbit syndrome, a perioral tremor.
- The onset of symptoms is usually 1 to 2 weeks after initiation of antipsychotic therapy or dose increase. The risk of pseudoparkinsonism with SGAs is low except in the case of **risperidone** in doses greater than 6 mg/day.
- AChs are an effective treatment (see Table 71-4). **Benztropine** has a half-life that allows once- to twice-daily dosing. Dose increases above 6 mg/day must be slow because of nonlinear pharmacokinetics. **Trihexyphenidyl**, **diphenhydramine**, and **biperiden** usually require three-times-daily dosing. Diphenhydramine produces more sedation, but all of the AChs have been abused for euphoriant effects.
- **Amantadine** is as efficacious as AChs and has less effect on memory.
- An attempt should be made to taper and discontinue these agents 6 weeks to 3 months after symptoms resolve.

*Tardive Dyskinesia*

- TD is sometimes irreversible and is characterized by abnormal involuntary movements occurring with chronic antipsychotic therapy.
- The classic presentation is buccolingual-masticatory movements (BLM). Symptoms may become severe enough to interfere with chewing, wearing dentures, speech, respiration, or swallowing. Facial movements include frequent blinking, brow arching, grimacing, upward deviation of the eyes, and lip smacking. Involvement of the extremities occurs in later stages (restless choreiform and athetotic movements of limbs). Truncal move-

ments are classically reported in young adults. Movements may worsen with stress, decrease with sedation, and disappear with sleep.

- The Abnormal Involuntary Movement Scale (AIMS) and the Dyskinesia Identification System: Condensed User Scale (DISCUS) should be used to screen (at baseline and at least quarterly) and can facilitate early detection of TD, but neither scale is diagnostic.
- Dosage reduction or discontinuation may have significant effect on outcome, with a complete disappearance of symptoms in some patients (especially if implemented early in the course of TD).
- Prevention of TD is best accomplished by (1) using antipsychotics only when there is a clear indication and at the lowest effective dose for the shortest duration possible; (2) using SGAs as first-line agents; (3) using the DISCUS or other scales to assess for early signs of TD at least quarterly; (4) discontinuing antipsychotics or switching to SGAs (e.g., **risperidone** or **olanzapine**) at the earliest symptoms of TD, if possible; and (5) using antipsychotics only short term to abort aggressive behavior in nonpsychotic patients.
- Risk factors for TD include duration of antipsychotic therapy, higher dose, possibly cumulative dose, increasing age, occurrence of acute extrapyramidal symptoms, poor antipsychotic response, diagnosis of organic mental disorder, diabetes mellitus, mood disorders, and possibly female gender.
- To date, there are no reports of TD with **clozapine** monotherapy. Switching the patient with TD to clozapine is a first-line strategy, especially in patients with moderate to severe dyskinesias.

### *Sedation and Cognition*

- Administration of most or all of the daily dose at bedtime can decrease daytime sedation and may eliminate the need for hypnotics.
- The SGAs as first-line treatment have been shown to improve cognition (attention to tasks and improved working memory) over a 9-month period.

### *Seizures*

- There is an increased risk of drug-induced seizures in all patients treated with antipsychotics. The highest risk for antipsychotic-induced seizures is with the use of **CPZ** or **clozapine**. Seizures are more likely with initiation of treatment and with the use of higher doses and rapid dose increases.
- When an isolated seizure occurs, a dosage decrease is recommended, and anticonvulsant therapy is usually not recommended.
- If a change in antipsychotic therapy is required, **risperidone**, **molindone**, **thioridazine**, **haloperidol**, **pimozide**, **trifluoperazine**, and **fluphenazine** may be considered.

### *Thermoregulation*

- In temperature extremes, patients taking antipsychotics may experience their body temperature adjusting to ambient temperature (poikilothermia). Hyperpyrexia can lead to heat stroke. Hypothermia is also a risk, particularly in elderly patients. These problems are more common with the use of low-potency FGAs.

### Neuroleptic Malignant Syndrome

- Neuroleptic malignant syndrome occurs in 0.5% to 1% of patients taking FGAs. It may be more frequent with high-potency FGAs, injectable, or depot antipsychotics; in dehydrated patients; or in those with organic mental disorders. It has been reported with the SGAs, including **clozapine**, but is less frequent than with the FGAs.
- Symptoms develop rapidly over 24 to 72 hours and include body temperature exceeding 38°C (100.4°F), altered level of consciousness, autonomic dysfunction (tachycardia, labile blood pressure, diaphoresis, tachypnea, urinary or fecal incontinence), and rigidity.
- Laboratory evaluation frequently shows leukocytosis, increases in creatine kinase (CK), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), and myoglobinuria.
- Treatment should begin with antipsychotic discontinuation and supportive care.
- **Bromocriptine**, used in theory to reverse DA blockade, reduces rigidity, fever, or CK levels in up to 94% of patients. **Amantadine** has been used successfully in up to 63% of patients. **Dantrolene** has been used as a skeletal muscle relaxant, with favorable effects on temperature, respiratory rate, and CK in up to 81% of patients.
- Rechallenge with the lowest effective dose of SGA may be considered only for patients in need of reinstatement of antipsychotics following observation for at least 2 weeks without antipsychotics. There must be careful monitoring and slow-dose titration.

### Endocrine System

- Antipsychotic-induced elevations in prolactin levels with associated galactorrhea and menstrual irregularities are common. These effects may be dose related and are more common with the use of FGAs and risperidone.
- Possible management strategies for galactorrhea include switching to an SGA (e.g., **olanzapine**, **quetiapine**, **aripiprazole**, or **ziprasidone**).
- Weight gain is frequent with antipsychotic therapy including SGAs, especially **olanzapine** and **clozapine**. Weight gain may also occur with **risperidone** and **quetiapine**, but **ziprasidone** and **aripiprazole** are associated with minimal weight gain.
- Schizophrenics have a higher prevalence of type 2 diabetes than nonschizophrenics. Antipsychotics may adversely affect glucose levels in diabetic patients. New onset diabetes has been reported with use of the SGAs. Clozapine and olanzapine may be more likely, and aripiprazole may be less likely to cause this.

### Cardiovascular System

- The incidence of orthostatic hypotension (defined as a greater than 20-mm Hg drop in systolic pressure upon standing) is greatest with low-potency FGAs, especially with IM or IV administration. Diabetics with cardiovascular disease and the elderly are predisposed.
- Tolerance to this effect usually occurs within 2 to 3 months. Reducing the dose or changing to an antipsychotic with less  $\alpha$ -adrenergic blockade may also help.

- Low-potency piperidine phenothiazines (e.g., **thioridazine**), **clozapine**, and **ziprasidone** are more likely to cause ECG changes.
- ECG changes include increased heart rate, flattened T waves, ST-segment depression, prolongation of QT and PR intervals, and torsade de pointes. Torsade de pointes has been reported with **thioridazine**, which may be a cause of cardiac sudden death.
- Ziprasidone prolonged the QTc interval about one-half as much as thioridazine. Ziprasidone's effect on the ECG is probably without clinical sequelae except in patients with baseline risk factors.
- It has been recommended to discontinue a medication associated with QTc prolongation if the interval consistently exceeds 500 msec.
- In patients older than 50 years, pretreatment ECG and serum potassium and magnesium levels are recommended.

### Lipid Effects

- Some SGAs and phenothiazines cause elevations in serum triglycerides and cholesterol. The risk for this effect may be less with risperidone, ziprasidone, and aripiprazole.
- Metabolic syndrome consists of raised triglycerides (greater than or equal to 150 mg/dL), low high-density lipoprotein cholesterol (less than or equal to 40 mg/dL for males, less than or equal to 50 mg/dL for females), elevated fasting glucose (greater than or equal to 100 mg/dL), blood pressure elevation (greater than or equal to 130/85 mm Hg), and weight gain (abdominal circumference greater than 102 cm (40 inches) for males, greater than 88 cm (34 inches) for females).

### Psychiatric Side Effects

- Akathisia, akinesia, and dysphoria can result in behavioral toxicity. Symptoms may include apathy and withdrawal, and patients may appear depressed.
- Chronic confusion and disorientation can occur in the elderly.
- Delirium and psychosis may occur with high doses of FGAs or combinations of FGAs with AChs.

### Ophthalmologic Effects

- Impairment in visual accommodation results from paresis of ciliary muscles. Photophobia may also result. If severe, **pilocarpine** ophthalmic solution may be necessary.
- Exacerbation of narrow-angle glaucoma can occur with use of antipsychotics or AChs.
- Opaque deposits in the cornea and lens may occur with chronic phenothiazine treatment, especially with **CPZ**. Although visual acuity is not usually affected, periodic slit-lamp examinations are recommended with use of long-term phenothiazines. Baseline and periodic slit-lamp examinations are also recommended for **quetiapine**-treated patients because of cataract development and lenticular changes in animal studies.
- Retinitis pigmentosa can result from **thioridazine** doses greater than 800 mg daily (the recommended maximum dose) and can cause permanent visual impairment or blindness.

### Hepatic System

- Liver function test abnormalities are common. If aminotransferases are greater than three times the upper limit of normal, the antipsychotic should be changed to a chemically unrelated antipsychotic. These changes are less common with the SGAs but are reported with **risperidone** and **clozapine**.
- Cholestatic hepatocanalicular jaundice can occur in up to 2% of patients receiving phenothiazines.
- Cholestatic hepatitis has been reported with risperidone, and liver function test abnormalities (mostly transient) have been reported with olanzapine and clozapine.

### Genitourinary System

- Urinary hesitancy and retention are commonly reported, especially with low-potency FGAs and **clozapine**, and men with benign prostatic hypertrophy are especially prone.
- Urinary incontinence is especially problematic with **clozapine**.
- Risperidone produces at least as much sexual dysfunction as FGAs, but other SGAs (which have a weaker effect of prolactin) are less likely to have this effect.

### Hematologic System

- Transient leukopenia may occur with antipsychotic therapy, but it typically does not progress to clinically significant parameters.
- If the white blood cell (WBC) count is less than  $3,000/\text{mm}^3$  or the absolute neutrophil count (ANC) is less than  $1,000/\text{mm}^3$ , the antipsychotic should be discontinued, and the WBC count monitored closely until it returns to normal.
- Agranulocytosis reportedly occurs in 0.01% of patients receiving FGAs, and it may occur more frequently with **CPZ** and **thioridazine**. The onset is usually within the first 8 weeks of therapy. It may initially manifest as a local infection (e.g., sore throat, leukoplakia, and erythema and ulcerations of the pharynx). These symptoms should trigger an immediate WBC.
- The 18-month treatment risk of developing agranulocytosis with **clozapine** is approximately 0.91%. Increasing age and female gender are associated with greater risk. The greatest risk appears to be between months 1 and 6 of treatment. WBC monitoring is required weekly for the first 6 months, every 2 weeks for months 7 through 12, and then monthly if all WBCs are normal (as mandated by the product labeling). If the WBC drops to less than  $2,000/\text{mm}^3$  or the ANC is less than  $1,000/\text{mm}^3$ , clozapine should be discontinued. In cases of mild to moderate neutropenia (granulocytes between 2,000 and  $3,000/\text{mm}^3$  or ANC between 1,000 and  $1,500/\text{mm}^3$ ), which occurs in up to 2% of patients, clozapine should be discontinued, with daily monitoring of complete blood counts until values return to normal.

### Dermatologic System

- Allergic reactions are rare and usually occur within 8 weeks of initiating therapy. They manifest as maculopapular, erythematous, or pruritic rashes. Drug discontinuation and topical steroids are recommended when they occur.

- Contact dermatitis, including on the oral mucosa, may occur. Swallowing of the oral concentrate quickly may decrease problems.
- Both FGAs and SGAs can cause photosensitivity. Erythema and severe sunburns can occur. Patients should be educated to use maximal blocking sunscreens, hats, protective clothing, and sunglasses when in the sun.
- Blue-gray or purplish discoloration of skin exposed to sunlight may occur with higher doses of low-potency phenothiazines (especially CPZ) long term.

## USE IN PREGNANCY AND LACTATION

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- There is a slightly increased risk of birth defects with low-potency FGAs.
- There is no relationship between **haloperidol** use and teratogenicity.
- Concern has been expressed over the use of SGAs in pregnancy because of the risk for weight gain and potential risk for gestational diabetes.
- Antipsychotics appear in breast milk with milk-to-plasma ratios of 0.5 to 1, however, 1-week post-delivery, clozapine milk concentrations were found to be 279% of serum concentrations. Use of clozapine during breast-feeding is not recommended.

## DRUG INTERACTIONS

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- Most antipsychotic drug interactions are relatively minor and often involve additive CNS, ACh, or sedative effects.
- Antipsychotic pharmacokinetics can be significantly affected by concomitantly administered enzyme inducers or inhibitors. Smoking is a potent inducer of hepatic enzymes and may increase antipsychotic clearance by as much as 50%. The published literature may be consulted for a listing of antipsychotic drug interactions.

## EVALUATION OF THERAPEUTIC OUTCOMES

- Clinicians should use standardized psychiatric rating scales to rate response objectively. The four-item Positive Symptom Rating Scale and the Brief Negative Symptom Assessment are scales that are brief enough to be useful in the outpatient setting.
- Patient-rated self-assessments can also be useful, as they engage the patient in treatment and can open the door for patient education and addressing patient misconceptions.
- A brief cognitive battery has recently been validated that can be completed in 15 to 20 minutes.
- Weight should be monitored monthly for 3 months, then quarterly. Body mass index, waist circumference, blood pressure, fasting plasma glucose, and fasting lipid profile should be monitored at the end of 3 months, then annually. The use of patient self-assessments are encouraged.

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*See Chap. 70, Schizophrenia, authored by M. Lynn Crismon, Tami R. Argo, and Peter F. Buckley, for a more detailed discussion of this topic.*

## DEFINITION

- The *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., text revision, classifies sleep disorders as shown in Table 72-1. One month of symptoms is required before a sleep disorder is diagnosed.

## SLEEP PHYSIOLOGY

- Humans typically have four to six cycles of non-rapid eye movement (NREM) and rapid eye movement (REM) sleep each night, each cycle lasting 70 to 120 minutes. Usually there is progression through the four stages of NREM sleep before the first REM period.
- Stage 1 of NREM is the stage between wakefulness and sleep. Stage 3 and 4 sleep is called *delta sleep* (i.e., slow-wave sleep).
- In REM sleep, there is a low-amplitude, mixed-frequency electroencephalogram, increased electric and metabolic activity, increased cerebral blood flow, muscle atonia, poikilothermia, vivid dreaming, and fluctuations in respiratory and cardiac rate.
- In the elderly, sleep is lighter and more fragmented with more arousals and a gradual reduction in slow-wave sleep.
- Sleep is reduced when there is decreased serotonin activity or destruction of the dorsal raphe nucleus.
- REM sleep is turned on by cholinergic cells.
- Dopamine has an alerting effect. Neurochemicals involved in wakefulness include norepinephrine and acetylcholine in the cortex and histamine and neuropeptides (e.g., substance P and corticotropin-releasing factor) in the hypothalamus.
- Polysomnography (PSG) is a procedure that measures multiple electrophysiologic parameters simultaneously during sleep (e.g., electroencephalogram, electrooculogram, and electromyogram) to characterize sleep and diagnose sleep disorders.

## INSOMNIA

## CLINICAL PRESENTATION

- Patients with insomnia complain of difficulty falling asleep, maintaining sleep, or not feeling rested in spite of a sufficient opportunity to sleep.
- Transient (two to three nights) and short-term (less than 3 weeks) insomnia is common and is usually related to a precipitating factor. Chronic insomnia (greater than 1 month) may be related to medical or psychiatric disorders or medication, or it may be psychophysiologic.

**TABLE 72-1** DSM-IV-TR Classification of Sleep Disorders**Primary sleep disorders****Dyssomnias—abnormality in the amount, quality, or timing of sleep**

Primary insomnia  
 Primary hypersomnia  
 Narcolepsy  
 Breathing-related sleep disorder  
 Circadian rhythm sleep disorder  
   Delayed sleep phase type  
     Jet lag type  
     Shift work type  
     Unspecified type  
 Dyssomnia not otherwise specified

**Parasomnias—abnormal behavioral or physiologic events associated with sleep**

Nightmare disorder  
 Sleep terror disorder  
 Sleepwalking disorder  
 Parasomnia not otherwise specified

**Sleep disorders related to another mental disorder**

Insomnia or hypersomnia related to another mental disorder

Data from American Psychiatric Association. *Sleep disorders*. In: *Diagnostic and Statistical Manual of Mental Disorders, 4th ed., text revision*. Washington, DC: American Psychiatric Press, 2000:597–644, with permission.

## DIAGNOSIS

- Common causes of insomnia are shown in Table 72-2. In patients with chronic disturbances, a diagnostic evaluation includes physical and mental status examinations, routine laboratory tests, and medication and substance abuse histories.
- Management includes identifying the cause of insomnia, education on sleep hygiene, stress management, monitoring for mood symptoms, and elimination of unnecessary pharmacotherapy.
- Transient and short-term insomnia should be treated with good sleep hygiene and careful use of sedative-hypnotics if necessary.
- Chronic insomnia calls for careful assessment for a medical cause, non-pharmacologic treatment, and careful use of sedative-hypnotics (intermittently to prevent tolerance and dependence).

## NONPHARMACOLOGIC THERAPY

- Behavioral and educational interventions that may help include short-term cognitive behavioral therapy, relaxation therapy, stimulus control therapy, cognitive therapy, sleep restriction, paradoxical intention, and sleep hygiene education (Table 72-3).

## PHARMACOLOGIC THERAPY

### Nonbenzodiazepine Hypnotics

- Antihistamines (e.g., **diphenhydramine**, **doxylamine**, and **pyrilamine**) are less effective than benzodiazepines, but side effects are usually minimal. Their anticholinergic side effects may be problematic, especially in the elderly.

**TABLE 72-2** Common Etiologies of Insomnia**Situational**

Work or financial stress, major life events, interpersonal conflicts  
Jet lag or shift work

**Medical**

Cardiovascular (angina, arrhythmias, heart failure)  
Respiratory (asthma, sleep apnea)  
Chronic pain  
Endocrine disorders (diabetes, hyperthyroidism)  
GI (gastroesophageal reflux disease, ulcers)  
Neurologic (delirium, epilepsy, Parkinson's disease)  
Pregnancy

**Psychiatric**

Mood disorders (depression, mania)  
Anxiety disorders (e.g., generalized anxiety disorder, obsessive-compulsive disorder)  
Substance abuse (alcohol or sedative-hypnotic withdrawal)

**Pharmacologically induced**

Anticonvulsants  
Central adrenergic blockers  
Diuretics  
Selective serotonin reuptake inhibitors  
Steroids  
Stimulants

- The antidepressants are good alternatives for patients with poor sleep who should not receive benzodiazepines, especially those with depression or a history of substance abuse.
- **Amitriptyline, doxepin, and nortriptyline** are effective, but side effects include anticholinergic effects, adrenergic blockade, and cardiac conduction prolongation.

**TABLE 72-3** Nonpharmacologic Recommendations for Insomnia**Stimulus control procedures**

1. Establish regular times to wake up and to go to sleep (including weekends).
2. Sleep only as much as necessary to feel rested.
3. Go to bed only when sleepy. Avoid long periods of wakefulness in bed. Use the bed only for sleep or intimacy; do not read or watch television in bed.
4. Avoid trying to force sleep; if you do not fall asleep within 20–30 minutes, leave the bed and perform a relaxing activity (e.g., read, listen to music, or watch television) until drowsy. Repeat this as often as necessary.
5. Avoid daytime naps.
6. Schedule worry time during the day. Do not take your troubles to bed.

**Sleep hygiene recommendations**

1. Exercise routinely (three to four times weekly) but not close to bedtime because this can increase wakefulness.
2. Create a comfortable sleep environment by avoiding temperature extremes, loud noises, and illuminated clocks in the bedroom.
3. Discontinue or reduce the use of alcohol, caffeine, and nicotine.
4. Avoid drinking large quantities of liquids in the evening to prevent nighttime trips to the restroom.
5. Do something relaxing and enjoyable before bedtime.

- **Trazodone**, 25 to 100 mg, is often used for insomnia induced by selective serotonin reuptake inhibitors or bupropion. Side effects include serotonin syndrome (when used with other serotonergic drugs), oversedation,  $\alpha$ -adrenergic blockade, dizziness, and rarely priapism.
- **Ramelteon** is a melatonin receptor agonist selective for the  $MT_1$  and  $MT_2$  receptors. The dose is 8 mg at bedtime. It is well tolerated, but side effects include headache, dizziness, and somnolence. It is not a controlled substance.
- **Zolpidem**, chemically unrelated to benzodiazepines or barbiturates, acts selectively at the  $\gamma$ -aminobutyric acid<sub>A</sub> ( $GABA_A$ )-receptor and has minimal anxiolytic and no muscle relaxant or anticonvulsant effects. It is comparable in effectiveness to benzodiazepine hypnotics, and it has little effect on sleep stages. Its duration is approximately 6 to 8 hours, and it is metabolized to inactive metabolites. Common side effects are drowsiness, amnesia, dizziness, headache, and GI complaints. Rebound effects when discontinued and tolerance with prolonged use are minimal, but theoretical concerns about abuse exist. It appears to have minimal effects on next-day psychomotor performance. The usual dose is 10 mg (5 mg in the elderly or those with liver impairment), which can be increased up to 20 mg nightly. Cases of psychotic reactions and sleep-eating have been reported.
- **Zaleplon** also binds to the  $GABA_A$  receptor. It has a rapid onset, a half-life of about 1 hour, and no active metabolites. It does not reduce nighttime awakenings or increase the total sleep time. It may be best used for middle-of-the-night awakenings. It does not appear to cause significant rebound insomnia or next-day psychomotor impairment. The most common side effects are dizziness, headache, and somnolence. The recommended dose is 10 mg (5 mg in the elderly).
- **Eszopiclone** has a rapid onset and a duration of action of up to 6 hours. The most common adverse effects are somnolence, unpleasant taste, headache, and dry mouth. It may be taken nightly for up to 6 months.
- **Valerian**, an herbal product, is also available without a prescription. The recommended dose is 300 to 600 mg. Purity and potency concerns are an issue. It may cause daytime sedation.

### Benzodiazepine Hypnotics

- The pharmacokinetic properties of benzodiazepine hypnotics are summarized in Table 72-4.
- Benzodiazepines bind to  $GABA_A$  receptors, and they have sedative, anxiolytic, muscle relaxant, and anticonvulsant properties. They increase stage 2 sleep and decrease REM and delta sleep.
- Overdose fatalities are rare unless benzodiazepines are taken with other CNS depressants.
- **Triazolam** is distributed quickly because of its high lipophilicity, and thus it has a short duration of effect. **Erythromycin**, **nefazodone**, **fluvoxamine**, and **ketconazole** reduce the clearance of triazolam and increase plasma concentrations.
- **Estazolam** and **temazepam** are intermediate in their duration of action.
- The effects of **flurazepam** and **quazepam** are long because of active metabolites.

**TABLE 72-4** Pharmacokinetics of Selected Hypnotics

Generic Name (Brand Name)	$t_{max}$ (hours) <sup>a</sup>	Half-Life <sup>b</sup> (hours)	Daily Dose Range (mg)	Metabolic Pathway	Clinically Significant Metabolites
Estazolam (ProSom)	2	12–15	1–2	Oxidation	–
Eszopiclone (Lunesta)	1–1.5	6	2–3	Oxidation Demethylation	–
Flurazepam (Dalmane)	1	8	15–30	Oxidation <i>N</i> -dealkylation	Hydroxyethylflurazepam, flurazepam aldehyde <i>N</i> -desalkylflurazepam <sup>c</sup>
Quazepam (Doral)	2	39	7.5–15	Oxidation, <i>N</i> - dealkylation	2-Oxo-quazepam, <i>N</i> - desalkylflurazepam <sup>c</sup>
Temazepam (Restoril)	1.5	10–15	15–30	Conjugation	–
Triazolam (Halcion)	1	2	0.125–0.25	Oxidation	–
Zaleplon (Sonata)	1	1	5–10	Oxidation	–
Zolpidem (Ambien)	1.6	2–2.6	5–10	Oxidation	–

<sup>a</sup>Time to peak plasma concentration.<sup>b</sup>Half-life of parent drug.<sup>c</sup>*N*-desalkylflurazepam, mean half-life 47 to 100 hours.

- With the exception of **temazepam**, which is eliminated by conjugation, all benzodiazepine hypnotics are metabolized by microsomal oxidation followed by glucuronide conjugation.
- ***N*-desalkylflurazepam** accounts for most of **flurazepam**'s pharmacologic effects. This metabolite may help when daytime anxiety or early morning awakening is present, but daytime sedation with impaired psychomotor performance may occur.

### Benzodiazepine Adverse Effects

- Side effects include drowsiness, psychomotor incoordination, decreased concentration, and cognitive deficits.
- Tolerance to the daytime CNS effects (e.g., drowsiness, psychomotor impairment, decreased concentration) may develop in some individuals.
- Tolerance to hypnotic effects develops after 2 weeks of continuous use of **triazolam**. Efficacy of **flurazepam**, **quazepam**, and **temazepam** lasts for at least 1 month of continuous nightly use. **Estazolam** reportedly maintains efficacy at maximum dosage (2 mg nightly) for up to 12 weeks.
- Anterograde amnesia has been reported with most benzodiazepines. Using the lowest dose possible minimizes amnesia.
- Rebound insomnia occurs frequently with high doses of **triazolam**, even when used intermittently.
- Rebound insomnia can be minimized by utilizing the lowest effective dose and tapering the dose upon discontinuation.
- There is an association between falls and hip fractures and the use of long-elimination half-life benzodiazepines; thus, **flurazepam** and **quazepam** should be avoided in the elderly.

## SLEEP APNEA

- Apnea is repetitive episodes of cessation of breathing during sleep. The goals of therapy are to alleviate sleep disordered breathing (Fig. 72-1).

### OBSTRUCTIVE SLEEP APNEA

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- Obstructive sleep apnea (OSA) is potentially life threatening and characterized by repeated episodes of nocturnal breathing cessation. It is caused by occlusion of the upper airway, and blood oxygen ( $O_2$ ) desaturation can occur. In severe episodes, there is heavy snoring, severe gas exchange disturbances, and respiratory failure, causing gasping. These episodes may occur up to 600 times/night.
- Episodes may be caused by obesity or fixed upper airway lesions, enlarged tonsils, amyloidosis, and hypothyroidism. Complications include arrhythmias, hypertension, cor pulmonale, and sudden death.
- The apneic episode is terminated by a reflex action in response to the fall in blood  $O_2$  saturation that causes a brief arousal during which breathing resumes.
- OSA patients usually complain of excessive daytime sleepiness. Other symptoms are morning headache, poor memory, and irritability.

#### Treatment

- Patients with severe apnea (greater than 20 apneas per hour on PSG) and moderate apnea (five to 20 apneas per hour on PSG) have shown significant improvement and reduction in mortality with treatment.
- Nonpharmacologic approaches are the treatments of choice (e.g., weight loss [which should be implemented for all overweight patients], tonsillectomy, nasal septal repair, and nasal positive airway pressure [PAP], which may be continuous or bilevel PAP). Other surgical therapies, uvulopalatopharyngoplasty and tracheostomy, may be necessary in severe cases.
- The most important pharmacologic intervention is avoidance of all CNS depressants, which can be lethal.
- Modafinil is approved by the FDA to improve wakefulness in those who have residual daytime sleepiness while treated with PAP. It should be used only after patients are using optimal PAP therapy to alleviate sleep-disordered breathing.

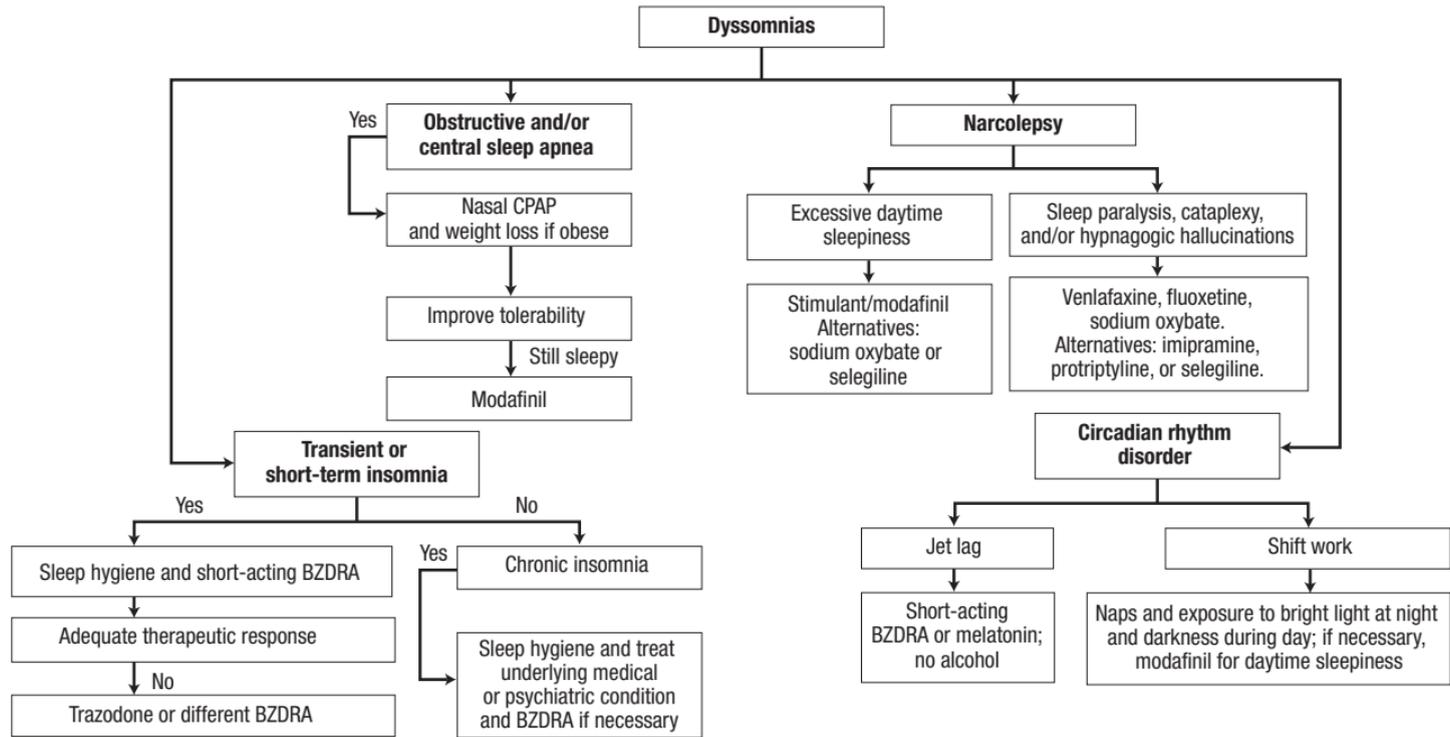
### CENTRAL SLEEP APNEA

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- Central sleep apnea (CSA; less than 10% of all apneas) is characterized by repeated episodes of apnea caused by temporary loss of respiratory effort during sleep. It may be caused by autonomic nervous system lesions, neurologic diseases, high altitudes, and congestive heart failure.

#### Treatment

- The primary treatment approach for CSA is PAP therapy with or without supplemental  $O_2$ .
- **Acetazolamide** causes a metabolic acidosis that stimulates respiratory drive and may be beneficial for high altitude, heart failure, and idiopathic CSA.



**FIGURE 72-1.** Algorithm for treatment of dyssomnias. (BZDRA, benzodiazepine receptor agonist; CPAP, continuous positive airway pressure.) (Adapted and reprinted with permission from Jermain DM, Sleep disorders. In: Jann M, ed. *Pharmacotherapy Self-Assessment Program*, 2nd ed. Kansas City, MO, American College of Clinical Pharmacy, 1995:139–154.)

## NARCOLEPSY

- The essential features are sleep attacks, cataplexy, hypnagogic hallucinations, and sleep paralysis. Individuals with narcolepsy complain of excessive daytime sleepiness, sleep attacks that last up to 30 minutes, fatigue, impaired performance, and disturbed nighttime sleep. They have multiple arousals during the night.
- Cataplexy is sudden bilateral loss of muscle tone with collapse, which is often precipitated by highly emotional situations.
- The hypocretin/orexin neurotransmitter system may play a central role in narcolepsy. An autoimmune process may cause destruction of hypocretin-producing cells.

## TREATMENT

- The goal of therapy is to maximize alertness during waking hours and improve quality of life (see Fig. 72-1).
- Good sleep hygiene, as well as two or more brief daytime naps daily (as little as 15 minutes), should be encouraged.
- Medications used to treat narcolepsy are shown in Table 72-5. Pharmacotherapy focuses on excessive daytime sleepiness and cataplexy.
- **Modafinil** is considered the standard for treatment of excessive daytime sleepiness. Plasma concentrations peak in 2 to 4 hours, and the half-life is 15 hours. Preliminary evidence suggests no tolerance or withdrawal after abrupt discontinuation and no risk of abuse.
- Side effects of modafinil include headache, nausea, nervousness, and insomnia.
- **Amphetamines** and **methylphenidate** have a fast onset of effect and durations of 3 to 4 hours and 6 to 10 hours, respectively, for excessive

**TABLE 72-5** Drugs Used to Treat Narcolepsy

Generic Name	Trade Name	Daily Dosage Range (mg)
<b>Excessive daytime somnolence</b>		
Dextroamphetamine	Dexedrine	5–60
Dextroamphetamine/Amphetamine salts <sup>a</sup>	Adderall	5–60
Methamphetamine <sup>b</sup>	Desoxyn	5–15
Methylphenidate	Ritalin	30–80
Modafinil	Provigil	200–400
Sodium oxybate <sup>c</sup>	Xyrem	4.5–9 g per night
<b>Adjunct agents for cataplexy</b>		
Fluoxetine	Prozac	20–80
Imipramine	Tofranil	50–250
Nortriptyline	Aventyl, Pamelor	50–200
Protriptyline	Vivactil	5–30
Selegiline	Eldepryl	20–40

<sup>a</sup>Dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate, and amphetamine sulfate.

<sup>b</sup>Not available in some states.

<sup>c</sup>Also is effective at treating cataplexy.

Compiled from U.S. Modafinil in Narcolepsy Multicenter Study Group and Standard of Practice Committee of the American Sleep Disorders Association. Practice parameters for the use of stimulants in the treatment of narcolepsy. *Sleep* 1994;17:348–351.

daytime sleepiness. Divided daily doses are recommended, but sustained-release formulations are available. Amphetamines are associated with more likelihood of abuse and tolerance. Side effects include insomnia, hypertension, palpitations, and irritability.

- The most effective treatment for cataplexy is the **tricyclic antidepressants, fluoxetine, or venlafaxine**. **Imipramine, protriptyline, clomipramine, fluoxetine, and nortriptyline** are effective in about 80% of patients.
- **Sodium oxybate ( $\gamma$ -hydroxybutyrate;** a potent sedative-hypnotic) improves excessive daytime sleepiness and decreases episodes of sleep paralysis, cataplexy, and hypnagogic hallucinations. It is taken at bedtime and repeated 2.5 to 4 hours later. Side effects include nausea, somnolence, confusion, dizziness, and incontinence.

## EVALUATION OF THERAPEUTIC OUTCOMES

- Patients with short-term or chronic insomnia should be evaluated after 1 week of therapy to assess for drug effectiveness, adverse events, and compliance with nonpharmacologic recommendations. Patients should be instructed to maintain a sleep diary, including a daily recording of awakenings, medications taken, naps, and an index of sleep quality.
- Patients with OSA should be evaluated after 1 to 3 months of treatment for improvement in alertness, daytime symptoms, and weight reduction. The bed partner can report on snoring and gasping.
- Monitoring parameters for pharmacotherapy of narcolepsy include reduction in daytime sleepiness, cataplexy, hypnagogic and hypnopompic hallucinations, and sleep paralysis. Patients should be evaluated regularly during medication titration, then every 6 to 12 months to assess adverse drug events (e.g., mood changes, sleep disturbances, and cardiovascular abnormalities). If symptoms increase during therapy, PSG should be done.

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*See Chap. 75, Sleep Disorders, authored by John M. Dopp and Bradley G. Phillips, for a more detailed discussion of this topic.*

## DEFINITION

- The substance-related disorders include disorders of intoxication, dependence, and withdrawal. Substance dependence or addiction can be viewed as a chronic illness that can be successfully controlled with treatment, but cannot be cured, and is associated with a high relapse rate.
- *Addiction*: A primary chronic neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following 5Cs: chronicity, impaired control over drug use, compulsive use, continued use despite harm, and craving.
- *Intoxication*: Development of a substance-specific syndrome after recent ingestion and presence in the body of a substance, and it is associated with maladaptive behavior during the waking state caused by the effect of the substance on the CNS.
- *Physical dependence*: A state of adaptation that is manifested by a drug class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.
- *Substance abuse*: A maladaptive pattern of substance use characterized by repeated adverse consequences related to the repeated use of the substance.
- *Substance dependence*: The characteristic feature is a continued maladaptive pattern of substance use in spite of repeated adverse consequences related to the repeated use.
- *Tolerance*: A state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time.
- *Withdrawal*: The development of a substance-specific syndrome after cessation of or reduction in intake of a substance that was used regularly.

## CENTRAL NERVOUS SYSTEM DEPRESSANTS

## ALCOHOL

- Table 73-1 relates the effects of **alcohol** to the blood alcohol concentration (BAC).
- Signs and symptoms of alcohol intoxication are slurred speech, ataxia, sedation, nystagmus, unconsciousness, nausea, vomiting, hallucinations, delirium, and seizures. Signs and symptoms of alcohol withdrawal are tachycardia, diaphoresis, and hyperthermia.
- There is 14 g of alcohol in 12 oz of beer, 4 oz of wine, or 1.5 oz (one shot) of 80-proof whiskey. This amount will increase the BAC by about 25 mg/dL in a healthy 70-kg male. Deaths generally occur when BACs are greater than 500 mg/dL.

**TABLE 73-1** Specific Effects of Alcohol Related to Blood Alcohol Concentration (BAC)

BAC (%) <sup>a</sup>	Effect
0.02–0.03	No loss of coordination, slight euphoria, and loss of shyness.
0.04–0.06	Feeling of well-being, relaxation, lower inhibitions, sensation of warmth. Euphoria. Some minor impairment of reasoning and memory, lowering of caution.
0.07–0.09	Slight impairment of balance, speech, vision, reaction time, and hearing. Euphoria. Judgment and self-control are reduced, and caution, reason, and memory are impaired. It is illegal to operate a motor vehicle in some states at this level.
0.10–0.125	Significant impairment of motor coordination and loss of good judgment. Speech can be slurred; balance, vision, reaction time, and hearing impaired. Euphoria. It is illegal to operate a motor vehicle at this level of intoxication.
0.13–0.15	Gross motor impairment and lack of physical control. Blurred vision and major loss of balance. Euphoria is reduced, and dysphoria is beginning to appear.
0.16–0.2	Dysphoria (anxiety, restlessness) predominates, nausea can appear. The drinker has the appearance of a “sloppy drunk.”
0.25	Needs assistance in walking; total mental confusion. Dysphoria with nausea and some vomiting.
0.3	Loss of consciousness.
≥0.4	Onset of coma, possible death caused by respiratory arrest.

<sup>a</sup>Grams of ethyl alcohol per 100 mL of whole blood.

Data from Mayo-Smith MF. *JAMA* 1997;278:144–151; Federal Aviation Administration. *Alcohol and Flying: Deadly Combination*. 2006. <http://www.faa.gov/pilots/safety/pilotsafetybrochures/media/alcohol.pdf>; Brunton LL, Lazo JS, Parker KL, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 11th ed. [electronic version]. 2006. Access-Medicine. <http://www.accessmedicine.com/resourceTOC.aspx?resourceID=28>; Goldman HH. *Review of General Psychiatry*, 5th ed. [electronic version]. 2000. StatRef. <http://onlinestatref.com>; Alcohol and Substance Awareness Program. *Blood alcohol level*. 2006. <http://www.barnard.columbia.edu/asap/bal.html>; and Garriot JC, ed. *Medical-Legal Aspects of Alcohol*. Tucson, AZ: Lawyers and Judges Publishing, 2003:27.

- Absorption of alcohol begins in the stomach within 5 to 10 minutes of ingestion. Peak concentrations are usually achieved 30 to 90 minutes after finishing the last drink.
- Alcohol is metabolized by alcohol dehydrogenase (a zero-order process except at very high and very low concentrations) to acetaldehyde, which is metabolized to carbon dioxide and water by aldehyde dehydrogenase. Catalase and the microsomal alcohol oxidase system are also involved.
- Most clinical labs report BAC in milligrams per deciliter. In legal cases, results are reported in percentage (grams of alcohol per 100 mL of whole blood). Thus, a BAC of 150 mg/dL = 0.15%.
- Alcohol withdrawal includes two main components: (1) history of cessation or reduction in heavy and prolonged alcohol use, and (2) presence of two or more of the symptoms of alcohol withdrawal.

## BENZODIAZEPINES AND OTHER SEDATIVE-HYPNOTICS

- The most commonly ingested BZs by individuals seen in emergency rooms are alprazolam and clonazepam, but lorazepam and diazepam are also commonly abused.
- Flunitrazepam (Rohypnol) is most commonly ingested orally, frequently in conjunction with alcohol or other drugs. It is often taken with other CNS depressants and has been given to women (without their knowledge) to lower their inhibitions. Thus it has been called a date-rape drug.

- Benzodiazepine (BZ) intoxication is manifested as slurred speech, poor coordination, swaying, drowsiness, hypotension, nystagmus, and confusion.
- Signs and symptoms of BZ withdrawal are similar to those of alcohol withdrawal, including muscle pain, anxiety, restlessness, confusion, irritability, hallucinations, delirium, seizures, and cardiovascular collapse. Withdrawal from short-acting BZs (e.g., **oxazepam**, **lorazepam**, **alprazolam**) has an onset within 12 to 24 hours of the last dose. **Diazepam**, **chlordiazepoxide**, and **clorazepate** have elimination half-lives (or active metabolites with elimination half-lives) of 24 to greater than 100 hours. So, withdrawal may be delayed for several days after their discontinuation.
- Sedative-hypnotic dependence is summarized in Table 73-2.
- Likelihood and severity of withdrawal are a function of dose and duration of exposure. Gradual tapering of dosage is necessary to minimize withdrawal and rebound anxiety.

### $\gamma$ -HYDROXYBUTYRATE

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- **$\gamma$ -Hydroxybutyrate** is also called a “date-rape drug.” It is sold as a liquid or powder, and effects include amnesia, hypotonia, abnormal sequence of rapid eye movement and non-rapid eye movement sleep, and anesthesia.
- Toxic effects include decreased cardiac output, coma, seizures, vomiting, and respiratory depression. Treatment is nonspecific supportive care.
- Withdrawal symptoms include mental status changes, tremors, elevated blood pressure, tachycardia, tremors, and severe agitation. BZs may be useful to control agitation.

### OPIATES

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- Signs and symptoms of opioid intoxication are euphoria, dysphoria, apathy, sedation, and attention impairment. Signs and symptoms of withdrawal are lacrimation, rhinorrhea, mydriasis, piloerection, diaphoresis, diarrhea, yawning, fever, insomnia, and muscle aches. The onset of withdrawal ranges from a few hours after stopping heroin to 3 to 5 days after stopping methadone. Duration of withdrawal ranges from 3 to 14 days. Occurrence of delirium suggests withdrawal from another drug (e.g., **alcohol**).
- **Heroin** can be snorted, smoked, and given intravenously. Complications of heroin use include overdoses, anaphylactic reactions to impurities, nephrotic syndrome, septicemia, endocarditis, and acquired immunodeficiency.
- Oxycodone, a controlled-release dosage form, is sometimes crushed by abusers to get the full 12-hour effect almost immediately. Snorting or injecting the crushed tablet can lead to overdose and death.
- **Opiates** are commonly combined with stimulants (e.g., cocaine [speedball]) or alcohol.

## CENTRAL NERVOUS SYSTEM STIMULANTS

### COCAINE

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- **Cocaine** may be the most behaviorally reinforcing of all drugs. Ten percent of people who begin to use the drug “recreationally” go on to heavy use.

**TABLE 73-2** Dependence on Sedative-Hypnotics

Generic Name	Common Trade Names	Oral Sedating Dose (mg)	Physical Dependence Daily Dose and Time Needed to Produce Dependence	Time Before Onset of Withdrawal (hours)	Peak Withdrawal Symptoms (days) <sup>a</sup>
<b>Benzodiazepines</b>					
Alprazolam	Xanax	0.25–8	8–16 mg × 42 days (est.)	8–24	2–3
Clorazepate	Tranxene	7.5–15	45–180 mg × 42–120 days (est.)	12–24	5–8
Diazepam	Valium	5–10	40–100 mg × 42–120 days	12–24	5–8
Flunitrazepam	Rohypnol	1–2	8–10 mg × 42 days (est.)	24–36	2–3
<b>Barbiturates</b>					
Amobarbital	Amytal	65–100	Same	8–12	2–5
Secobarbital	Seconal, Seco-8	100	800–2,200 mg × 35–37 days	6–12	2–3
Equal parts of secobarbital and amobarbital	Tuinal	100	Same	6–12	2–3
Pentobarbital	Nembutal	100	Same	6–12	2–3
<b>Nonbarbiturate sedative-hypnotics</b>					
Chloral hydrate	Noctec	250	Exact dose unknown; 12 g/day chronically has led to delirium upon sudden withdrawal	6–12	2–3
Meprobamate	Equanil, Miltown, Mepro tabs	400	1.6–3.2 g × 270 days	8–12	3–8

<sup>a</sup>Withdrawal symptoms are tremor, tachycardia, diaphoresis, nausea, vomiting, elevated blood pressure, delirium, seizures, and hallucinations.

- It blocks reuptake of catecholamine neurotransmitters and causes a depletion of brain dopamine.
- The hydrochloride salt is inhaled or injected. It can be converted to cocaine base (crack or rock) and smoked to achieve almost instant absorption and intense euphoria. Tolerance to the “high” develops quickly. The high from snorting can last 15 to 30 minutes; the high from smoking can last 5 to 10 minutes.
- In the presence of alcohol, cocaine is metabolized to cocaethylene, a longer-acting compound than cocaine with a greater risk for causing death.
- The elimination half-life of cocaine is 1 hour.
- Adverse events include ulceration of nasal mucosa and nasal septal collapse, tachycardia, heart failure, hyperthermia, shock, seizures, psychosis (similar to paranoid schizophrenia), and sudden death.
- Signs and symptoms of cocaine intoxication are agitation, elation, euphoria, grandiosity, loquacity, hypervigilance, sweating or chills, nausea, vomiting, tachycardia, arrhythmias, respiratory depression, mydriasis, altered blood pressure, and seizures. Signs and symptoms of withdrawal are fatigue, sleep disturbances, nightmares, depression, changes in appetite, bradyarrhythmias, myocardial infarction, and tremors.
- Withdrawal symptoms begin within hours of discontinuation and last up to several days.

## METHAMPHETAMINE

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- **Methamphetamine** (speed, meth, crank) can be taken orally, rectally, intranasally, by IV injection, and by smoking. The hydrochloride salt (ice, crystal, glass) is a clear crystal.
- Systemic effects of methamphetamine are similar to those of cocaine. Inhalation or IV injection results in an intense rush that lasts a few minutes. Methamphetamine has a longer duration of effect than cocaine. Pharmacologic effects include increased wakefulness, increased physical activity, decreased appetite, increased respiration, hyperthermia, euphoria, irritability, insomnia, confusion, tremors, anxiety, paranoia, aggressiveness, convulsions, increased heart rate and blood pressure, stroke, and death.
- Methamphetamine intoxication is an acute condition that may result in death; pharmacotherapy may be indicated for seizures.
- Symptoms of withdrawal include depression, altered mental status, drug craving, dysomnia, and fatigue. Duration of withdrawal from methamphetamine ranges from 3 to 24 days, but these individuals are usually not in acute distress. Occurrence of delirium suggests withdrawal from another drug (e.g., alcohol).
- **Ephedrine** and **pseudoephedrine** can be extracted from cold and allergy tablets and converted in illegal labs to methamphetamine.

## OTHER DRUGS OF ABUSE

### NICOTINE

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- More than 440,000 deaths annually, or 20% of the total deaths in the United States, are caused by smoking.

- **Nicotine** is a ganglionic cholinergic-receptor agonist with pharmacologic effects that are dose dependent. Effects include CNS and peripheral nervous system stimulation and depression; respiratory stimulation; skeletal muscle relaxation; catecholamine release by the adrenal medulla; peripheral vasoconstriction; and increased blood pressure, heart rate, cardiac output, and oxygen consumption. Low doses of nicotine produce increased alertness and improved cognitive functioning. Higher doses stimulate the “reward” center in the limbic system.
- Abrupt cessation results in onset of withdrawal symptoms usually within 24 hours, which include anxiety, cravings, difficulty concentrating, frustration, irritability, hostility, insomnia, and restlessness.

### METHAMPHETAMINE ANALOGS

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- The analogs of current concern include 3,4-methylenedioxy-amphetamine (**MDA**) and 3,4-methylenedioxy-methamphetamine (**MDMA**, ecstasy, Adam, X, Stacy).
- MDMA is usually taken by mouth as a tablet, capsule, or powder, but it can also be smoked, snorted, or injected. Taken by mouth, effects last 4 to 6 hours.
- MDMA stimulates the CNS, causes euphoria and relaxation, and produces a mild hallucinogenic effect. It can cause muscle tension, nausea, faintness, chills, sweating, panic, anxiety, depression, hallucinations, and paranoid thinking. It increases heart rate and blood pressure and destroys serotonin (5-HT)-producing neurons in animals. It is considered to be neurotoxic in humans.

### MARIJUANA

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- **Marijuana** (reefer, pot, grass, weed) is the most commonly used illicit drug. The principal psychoactive component is  $\Delta^9$ -**tetrahydrocannabinol (THC)**. **Hashish**, the dried resin of the top of the plant, is more potent than the plant itself. Pharmacologic effects begin immediately and last 1 to 3 hours.
- Chronic exposure is not usually associated with a withdrawal syndrome, but sudden discontinuation by heavy users can cause a withdrawal syndrome.
- Initial effects of marijuana use include increased heart rate, dilated bronchial passages, and bloodshot eyes. Subsequent effects include euphoria, dry mouth, hunger, tremor, sleepiness, anxiety, fear, distrust, panic, incoordination, poor recall, amotivation, and toxic psychosis. Other physiologic effects include sedation, difficulty in performing complex tasks, and disinhibition. Endocrine effects include amenorrhea, decreased testosterone production, and inhibition of spermatogenesis. Signs and symptoms of marijuana intoxication are tachycardia, conjunctival congestion, increased appetite, dry mouth, euphoria, apathy, and hallucinations.
- THC is detectable on toxicologic screening for up to 4 to 5 weeks in chronic users.
- Daily use of one to three joints appears to produce about the same lung damage and potential cancer risk as smoking five times as many tobacco cigarettes.

## PHENCYCLIDINE AND KETAMINE

- **Phencyclidine (PCP)** (angel dust, crystal) is often misrepresented as **lysergic acid diethylamide (LSD)** or THC. It is commonly smoked with marijuana (crystal joint) but can be taken orally or IV.
  - ✓ Signs and symptoms of PCP intoxication include very unpredictable behavior, increased blood pressure, tachycardia, ataxia, slurred speech, euphoria, agitation, anxiety, hostility, and psychosis. At toxic doses, coma, seizures, and respiratory and cardiac arrest may occur.
- **Ketamine** (special K, jet, green), chemically related to PCP, is a veterinary anesthetic that can cause hallucinations, delirium, and vivid dreams.
  - ✓ It is usually injected but can be evaporated to crystals, powdered, and smoked, snorted, or swallowed. Marijuana cigarettes can be soaked in ketamine solution.
  - ✓ Side effects are increased blood pressure and heart rate, respiratory depression, apnea, muscular hypertonus, and dystonic reactions. In overdose, seizures, polyneuropathy, increased intracranial pressure, and respiratory and cardiac arrest may occur.

## LYSERGIC ACID DIETHYLAMIDE

- Physical signs and symptoms of **LSD** intoxication include mydriasis, tachycardia, diaphoresis, palpitations, blurred vision, tremor, incoordination, dizziness, weakness, and drowsiness; psychiatric signs and symptoms include perceptual intensification, depersonalization, derealization, illusions, psychosis, and synesthesia. There is no withdrawal syndrome after discontinuation.
- LSD and similar drugs stimulate presynaptic 5-HT<sub>1A</sub> and 5-HT<sub>1B</sub>, as well as postsynaptic 5-HT<sub>2</sub> receptors in the brain.
- Flashbacks may occur, especially in chronic users. It produces tolerance but is not addictive.
- LSD is sold as tablets, capsules, and a liquid. It is also added to absorbent paper and divided into small decorated squares, each square being one dose.

## INHALANTS

- Organic solvents inhaled by abusers include **gasoline, glue, aerosols, amyl nitrite, butyl nitrite, typewriter correction fluid, lighter fluid, cleaning fluids, paint products, nail polish remover, waxes, and varnishes**. Chemicals in these products include **nitrous oxide, toluene, benzene, methanol, methylene chloride, acetone, methyl ethyl ketone, methyl butyl ketone, trichloroethylene, and trichloroethane**.
- Physiologic effects include CNS depression, headache, nausea, anxiety, hallucinations, and delusions. With chronic use, the drugs are toxic to virtually all organ systems. Death may occur from arrhythmias or suffocation by plastic bags.

## DESIRED OUTCOME

- The goals of treatment are cessation of use of the drug, termination of associated drug-seeking behaviors, and return to normal functioning. The

goals of treatment of the withdrawal syndrome are prevention of progression of withdrawal to life-threatening severity, thus enabling the patient to be sufficiently comfortable and functional in order to participate in a treatment program.

## TREATMENT

### INTOXICATION

- When possible, drug therapy should be avoided, but it may be indicated if patients are agitated, combative, or psychotic (Table 73-3).
- When toxicology screens are desired, blood or urine should be collected immediately when the patient presents for treatment.
- **Flumazenil** is not indicated in all cases of suspected BZ overdose, and it is contraindicated when cyclic antidepressant involvement is known or suspected because of the risk of seizures. It should be used with caution when BZ physical dependence is suspected, as it may precipitate BZ withdrawal.

**TABLE 73-3** Pharmacologic Treatment of Substance Intoxication

Drug Class	Nonpharmacologic Therapy	Pharmacologic Therapy	Level of Evidence <sup>a,b</sup>
Benzodiazepines	Support vital functions	Flumazenil 0.2 mg/min IV initially, repeat up to 3 mg maximum	A1
Alcohol, barbiturates, and sedative-hypnotics (nonbenzodiazepines)	Support vital functions	None	B3
Opiates	Support vital functions	Naloxone 0.4–2 mg IV every 3 minutes	A1
Cocaine and other CNS stimulants	Monitor cardiac function	Lorazepam 2–4 mg IM every 30 minutes to 6 hours as needed for agitation Haloperidol 2–5 mg (or other antipsychotic agent) every 30 minutes to 6 hours as needed for psychotic behavior	B2 B3
Hallucinogens, marijuana, and inhalants	Reassurance; “talk-down therapy”; support vital functions	Lorazepam and/or haloperidol as above	B3
Phencyclidine	Minimize sensory input	Lorazepam and/or haloperidol as above	B3

<sup>a</sup>Strength of recommendations, evidence to support recommendation, A, good; B, moderate; C, poor.

<sup>b</sup>Quality of evidence: 1, evidence from more than one properly randomized, controlled trial; 2, evidence from more than one well-designed clinical trial with randomization, from cohort or case-controlled analytic studies or multiple time series; or dramatic results from uncontrolled experiments; 3, evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert communities.

Data from O'Brien CP. In: Brunton LL, Lazo JS, Parker KL, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 11th ed. New York: McGraw-Hill, 2006:625–626; Fudala PJ, Greenstein RA, O'Brien CP. In: Lowinson JH, Ruiz P, Millman RB, Langrod JG, eds. *Substance Abuse: A Comprehensive Textbook*, 4th ed. Baltimore: Williams & Wilkins, 2005:641–653; Smith DE, Seymour RB. In: Galanter M, Kleber HD, eds. *Textbook of Substance Abuse Treatment*. Washington, DC: American Psychiatric Press, 1994:179–186; and Knapp CM, Ciraulo DA, Jaffe J. In: Lowinson JH, Ruiz P, Millman RB, Langrod JG, eds. *Substance Abuse: A Comprehensive Textbook*, 4th ed. Baltimore: Williams & Wilkins, 2005:180–195.

- In opiate intoxication, **naloxone** may revive unconscious patients with respiratory depression. However, it may also precipitate physical withdrawal in dependent patients.
- **Cocaine** intoxication is treated pharmacologically only if the patient is agitated and psychotic. Low-dose antipsychotics can be used short-term if necessary for psychotic symptoms.
- Many patients with **hallucinogen**, **marijuana**, or **inhalant** intoxication respond to reassurance, but short-term antianxiety and/or antipsychotic therapy can be used.
- **PCP** intoxication is unpredictable, and “talk-down therapy” is not recommended. Sensory input should be minimized. Antianxiety and/or **antipsychotic** drug therapy may be necessary if behavior is uncontrollable.

## WITHDRAWAL

- Treatment of withdrawal from some common drugs of abuse is summarized in Table 73-4.

**TABLE 73-4** Treatment of Withdrawal from Some Common Drugs of Abuse

Drug or Drug Class	Pharmacologic Therapy	Level of Evidence <sup>a,b</sup>
Benzodiazepines		
Short- to intermediate-acting	Lorazepam 2 mg three to four times a day; taper over 5–7 days	A1
Long-acting	Lorazepam 2 mg three to four times a day; taper over additional 5–7 days	A1
Barbiturates	Pentobarbital tolerance test; initial detoxification at upper limit of tolerance test; decrease dosage by 100 mg every 2–3 days	B3
Opiates	Methadone 20–80 mg orally daily; taper by 5–10 mg daily or buprenorphine 4–32 mg orally daily, or clonidine 2 mcg/kg three times a day × 7 days; taper over additional 3 days	A1 (methadone and buprenorphine) B1 (clonidine)
Mixed-substance withdrawal		
Drugs are cross-tolerant	Detoxify according to treatment for longer-acting drug used	B3
Drugs are not cross-tolerant	Detoxify from one drug while maintaining second drug (cross-tolerant drugs), then detoxify from second drug	B3
CNS stimulants	Supportive treatment only; pharmacotherapy often not used; bromocriptine 2.5 mg three times a day or higher may be used for severe craving associated with cocaine withdrawal	B2

<sup>a</sup>Strength of recommendations, evidence to support recommendation, A, good; B, moderate; C, poor.

<sup>b</sup>Quality of evidence: 1, evidence from more than one properly randomized, controlled trial; 2, evidence from more than one well-designed clinical trial with randomization, from cohort or case-controlled analytic studies or multiple time series; or dramatic results from uncontrolled experiments; 3, evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert communities.

Data from Hajak G, Muller WE, Wittchen HU, et al. Abuse and dependence potential for the non-benzodiazepine hypnotics zolpidem and zopiclone: A review of case reports and epidemiological data. *Addiction* 2003;98:1371–1378; O'Brien CP. Drug addiction and drug abuse. In: Brunton LL, Lazo JS, Parker KL, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 11th ed. New York: McGraw-Hill, 2006:614–615; and Kosten TR, O'Connor PG. Management of drug and alcohol withdrawal. *N Engl J Med* 2003;348:1786–1795.

## Alcohol

- Most clinicians agree that the **BZs** are the drugs of choice in treatment of **alcohol** withdrawal.
- Lorazepam is preferred by many clinicians because it can be administered intravenously, intramuscularly, or orally with predictable results. (Table 73-5)
- Agents with rapid onset of action (e.g., diazepam, alprazolam) have higher abuse potential because of their reinforcing effects. Chlordiazepoxide or oxazepam are less likely to be abused.
- With symptom-triggered therapy, medication is given only if symptoms emerge, resulting in shorter treatment duration, and avoidance of over sedation. A typical regimen would be lorazepam 2 mg administered every hour as needed when a structured assessment scale (e.g., Clinical Institute Withdrawal Assessment-Alcohol, Revised) indicates that symptoms are moderate to severe. Current guidelines recommend such individualized therapy over fixed-schedule therapy.
- Alcohol withdrawal seizures do not require anticonvulsant drug treatment unless they progress to status epilepticus. Patients with seizures should be treated supportively. An increase in the dosage and slowing of the tapering schedule of the **BZ** used for detoxification or a single injection of a **BZ** may be necessary to prevent further seizure activity.

## Benzodiazepines

- For **BZ** withdrawal, the same drugs and dosages that are used for alcohol withdrawal are used (see Table 73-5).
- The onset of withdrawal from long-acting **BZs** may be up to 7 days after discontinuation of the drug. Detoxification is approached by initiating treatment at usual doses and maintaining this dose for 5 days. The dose is then tapered over 5 days. Alprazolam withdrawal may require a more gradual taper.

## Opiates

- Unnecessary detoxification with drugs should be avoided if possible (e.g., if symptoms are tolerable). **Heroin** withdrawal reaches a peak within 36 to 72 hours, and **methadone** withdrawal peak is reached at 72 hours.
- Conventional drug therapy for opiate withdrawal has been **methadone**, a synthetic opiate. Usual starting doses have been 20 to 40 mg/day. The dosage can be tapered in decrements of 5 to 10 mg/day until discontinued. Some clinicians use discontinuation schedules over 30 days or over 180 days.
- **Buprenorphine** in two formulations (both assigned to schedule III) was recently made available for office-based management of opioid dependence by qualified physicians. Once-daily dosage is titrated to a target of 16 mg/day (range, 4 to 24 mg/day).
- **Subutex (buprenorphine)** is used at the beginning of treatment for opiate abuse.
- **Suboxone (buprenorphine and naloxone)**, is used in maintenance treatment of opiate addiction.
- If **L-methadyl acetate hydrochloride** is used instead of methadone; dosing is three times weekly.

**TABLE 73-5** Pharmacologic Agents Used in the Treatment of Alcohol Withdrawal

<b>Drug</b>	<b>Dose per Day (Unless Otherwise Stated)</b>	<b>Indication</b>	<b>Monitoring</b>	<b>Duration of Dosing</b>	<b>Level of Evidence<sup>a</sup></b>
Multivitamin	1 tablet	Malnutrition	Diet	At least until eating a balanced diet at caloric goal	B3
Thiamine	50–100 mg	Deficiency	CBC, WBC, nystagmus	Empiric × 5 days. More if evidence of deficiency	B2
Crystalloid fluids (typically D5-0.45 NS with 20 mEq of KCl per liter)	50–100 mL/hour	Dehydration	Weight, electrolytes, urine output, nystagmus if dextrose	Until intake and outputs stabilize and oral intake is adequate	A3
Clonidine oral	0.05–0.3 mg	Autonomic tone rebound and hyperactivity	Shaking, tremor, sweating, blood pressure	3 days or less	B2
Clonidine transdermal	TTS-1 to TTS-3	Autonomic tone rebound and hyperactivity	Shaking, tremor, sweating, blood pressure	1 week or less. One patch only	B3
Labetalol	20 mg IV every 2 hours as needed	Hypertensive urgencies and above	Blood pressure target	Individual doses as needed	B3
Antipsychotics, Haloperidol	2.5–5 mg q 4 h	Agitation unresponsive to benzodiazepines, hallucinations (tactile, visual, auditory or otherwise) or delusions	Subjective response plus rating scale (CIWA-Ar or equivalent)	Individual doses as needed	B1
Antipsychotics, atypical Quetiapine Aripiprazole	25–200 mg 5–15 mg	Agitation unresponsive to benzodiazepines, hallucinations, or delusions in patients intolerant of conventional antipsychotics	Subjective response plus rating scale (CIWA-Ar or equivalent)	Individual doses as needed in addition to scheduled antipsychotic	C3

*(continued)*

**TABLE 73-5** Pharmacologic Agents Used in the Treatment of Alcohol Withdrawal (Continued)

Drug	Dose per Day (Unless Otherwise Stated)	Indication	Monitoring	Duration of Dosing	Level of Evidence <sup>a</sup>
Benzodiazepines		Tremor, anxiety, diaphoresis, tachypnea, dyspnea, seizures	Subjective response plus rating scale (CIWA-Ar or equivalent)	Individual doses as needed. Underdosing is more common than overdosing	A2
Lorazepam	0.5–2 mg				
Chlordiazepoxide	5–25 mg				
Clonazepam	0.5–2 mg				
Diazepam	2.5–10 mg				
Alcohol oral		Prevent withdrawal	Subjective signs of withdrawal	Wide variation	C3
Alcohol IV		Prevent withdrawal	Subjective signs of withdrawal	Wide variation	C3

CBC, complete blood cell count; CIWA-Ar, Clinical Institute Withdrawal Assessment for Alcohol, revised; D5, dextrose 5%; KCl, potassium chloride; NS, normal saline; WBC, white blood cell count.

<sup>a</sup>Strength of recommendations, evidence to support recommendation: A, good; B, moderate; C, poor.

Quality of evidence: 1, evidence from more than one properly randomized, controlled trial; 2, evidence from more than one well-designed clinical trial with randomization, from cohort or case-controlled analytic studies or multiple time series; or dramatic results from uncontrolled experiments; 3, evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert communities.

Data from Mayo-Smith MF. Pharmacological management of alcohol withdrawal. A meta-analysis and evidence-based practice guideline. *American Society of Addiction Medicine Working Group on Pharmacological Management of Alcohol Withdrawal. JAMA* 1997;278:144–151; Mayo-Smith MF, Beecher LH, Fischer TL, et al. Working Group on the Management of Alcohol Withdrawal Delirium, Practice Guidelines Committee, American Society of Addiction Medicine. Management of alcohol withdrawal delirium. An evidence-based practice guideline [erratum *Arch Intern Med* 2004;164:2068]. *Arch Intern Med* 2004;164:1405–1412; and Hillbom M, Pieninkeroinen L, Leone M. Seizures in alcohol-dependent patients. *CNS Drugs* 2003;17:1013–1030.

- **Clonidine** can attenuate the noradrenergic hyperactivity of opiate withdrawal without interfering significantly with activity at the opiate receptors. Monitoring should include blood pressure checks, supine and standing, at least daily.

## SUBSTANCE DEPENDENCE

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- The treatment of drug dependence or addiction is primarily behavioral. The goal of treatment is complete abstinence, and treatment is a lifelong process. Most drug-dependence treatment programs embrace a treatment approach based on Alcoholics Anonymous.

### Alcohol

- **Disulfiram** deters a patient from drinking by producing an aversive-reaction if the patient drinks. It inhibits aldehyde dehydrogenase in the pathway for alcohol metabolism, allowing acetaldehyde to accumulate, resulting in flushing, vomiting, headache, palpitations, tachycardia, fever, and hypotension. Severe reactions include respiratory depression, arrhythmias, myocardial infarction, seizures, and death. Inhibition of the enzyme continues for as long as 2 weeks after stopping disulfiram. Disulfiram reactions have occurred with the use of alcohol-containing mouthwashes and after-shaves. Usual dosage is 250 to 500 mg/day.
- Prior to starting disulfiram, baseline liver function tests (LFTs) should be obtained, and patients should be monitored for hepatotoxicity. LFTs should be repeated at 2 weeks, 3 months, and 6 months, then twice yearly. The prescriber should wait at least 24 hours after the last drink before starting disulfiram, usually at a dose of 250 mg/day.
- **Naltrexone**, 50 to 100 mg/day, has been associated with reduced craving and fewer drinking days. It should not be given to patients currently dependent on opiates as it can precipitate a severe withdrawal syndrome. A new depot formulation allows monthly administration in a usual dose of 380 mg intramuscularly.
- Naltrexone is hepatotoxic and contraindicated in patients with hepatitis or liver failure. LFTs should be monitored monthly for the first 3 months, then every 3 months. Side effects include nausea, headache, dizziness, nervousness, insomnia, and somnolence.
- Acamprosate-treated patients (999 to 1,998 mg/day and higher) have less craving and more success in maintaining abstinence than placebo-treated patients. The combination of acamprosate and naltrexone with psychosocial intervention may be more effective than acamprosate alone.
- The most common acamprosate side effects are GI.

### Nicotine

- Every patient who uses tobacco should be offered at least brief treatment. All patients attempting tobacco cessation should be offered practical counseling (problem-solving/skills training), social support, stress management, and relapse prevention.
- First-line pharmacotherapies for smoking cessation are **bupropion sustained release, nicotine gum, nicotine inhaler, nicotine nasal spray**, and

**nicotine patch.** Second-line pharmacotherapies include **clonidine** and **nortriptyline** and should be considered if first-line therapy fails.

- **Varenicline** was approved by the FDA in May 2006, and its place in therapy has not yet been determined.
- Interventions are more effective when they last greater than 10 minutes, involve contact with a professional, provide at least four to seven sessions, and provide **nicotine-replacement therapy (NRT)**. Group and individual counseling is effective, and interventions are more successful when they include social support and training in problem-solving, stress management, and relapse prevention.

### *Nicotine-Replacement Therapy*

- The role of pharmacotherapy in smoking cessation is summarized in Table 73-6. In general, use of NRT doubles the odds of successfully quitting compared to placebo.
- NRT should be used with caution in patients within 2 weeks post-myocardial infarction, those with serious arrhythmias, and those with serious or worsening angina.
- The **2-mg gum** is recommended for those smoking less than 25 cigarettes a day, and the 4-mg gum for those smoking more than 25 cigarettes a day. Generally, the gum should be used for up to 12 weeks at doses of no more than 24 pieces per day. It should be chewed slowly until a peppery or minty taste emerges and then parked for about 30 minutes or until the taste dissipates. A fixed schedule may be more efficacious than as-needed use.
- The **patch** is available as a prescription and nonprescription medication. Treatment of 8 weeks or less is as effective as longer treatments. The 16- and 24-hour patches have comparable efficacy. A new patch should be placed on a relatively hairless location each morning.
- **Nicotine nasal spray** requires a prescription. Recommended duration of therapy is 3 to 6 months at no more than 40 doses per day. A dose is one 0.5-mg delivery to each nostril (1 mg total). Initial doses are gradually increased as needed for symptom relief.
- NRT products have few side effects. Nausea and lightheadedness may indicate nicotine overdose. The patch site may be rotated to minimize skin irritation, and nonprescription **hydrocortisone** or **triamcinolone** cream may improve skin irritation. Sleep disturbances are reported in 23% of patients using the patch.

### *Bupropion*

- **Bupropion sustained release (SR)** is an effective smoking-cessation treatment. It is contraindicated in patients with a seizure disorder, a current or prior diagnosis of bulimia or anorexia nervosa, and use of a **monoamine oxidase inhibitor** within the previous 14 days. It can be used in combination with NRT.
- Insomnia and dry mouth are the most frequent side effects. Other side effects were tremor, rash, and anaphylactoid reactions.
- Bupropion SR should be dosed at 150 mg once daily for 3 days, then twice daily for 7 to 12 weeks or longer, with or without NRT. Patients should stop

**TABLE 73-6 Pharmacologic Agents Used for Smoking Cessation**

Drug	Place in Therapy	Dosage Range	Duration	Comments/Monitoring Parameters	LOE <sup>d</sup>
Bupropion SR <sup>a,b</sup>	First-line	Titrate up to 150 mg orally twice daily	3–6 months	Patients receiving both bupropion and a nicotine patch should be monitored for hypertension.	A1
Clonidine <sup>b,c</sup>	Second-line	Titrate to response: 0.2–0.75 mg per day	6–12 months	Monitor baseline electrolyte and lipid profiles, renal function, uric acid, complete blood count, and blood pressure.	B2
Nicotine polacrilex (gum) <sup>d</sup>	First-line	Initial dose depends on smoking history: 2–4 mg every 1–8 hours	12 weeks (taper down over time)	Heart rate and blood pressure should be monitored periodically during nicotine replacement therapy.	A1
Nicotine inhaler <sup>d</sup>	First-line	24–64 mg per day (total daily dose)	3–6 months (taper down over time)	Heart rate and blood pressure should be monitored periodically during nicotine replacement therapy.	A1
Nicotine nasal spray <sup>d</sup>	First-line	8–40 mg per day (total daily dose)	14 weeks (taper down over time)	Heart rate and blood pressure should be monitored periodically during nicotine replacement therapy.	A1
Nicotine patch <sup>d</sup>	First-line	Initial dose depends on smoking history: 7–21 mg topically once daily	6 weeks (taper down over time)	Heart rate and blood pressure should be monitored periodically during nicotine replacement therapy.	A1
Nortriptyline <sup>b,c</sup>	Second-line	Titrate up to 75–100 mg orally daily	6–12 months	Dry mouth, blurred vision, and constipation are dose-dependent adverse effects.	B2
Varenicline <sup>b</sup>	FDA approved in 2006	Titrate up to 1 mg orally twice daily	3–6 months	Monitor renal function, especially in elderly patients. Nausea, headache, insomnia are dose-dependent adverse effects.	A1

LOE, level of evidence.

<sup>a</sup>Nicotine replacement therapies can be combined with each other and/or bupropion to increase long-term abstinence rates.

<sup>b</sup>Do not abruptly discontinue. Taper up initially, and taper off once therapy is complete.

<sup>c</sup>Clonidine and nortriptyline are not FDA approved for smoking cessation.

<sup>d</sup>Strength of recommendations, evidence to support recommendation: A, good; B, moderate; C, poor.

Quality of evidence: 1, evidence from more than one properly randomized, controlled trial; 2, evidence from more than one well-designed clinical trial with randomization, from cohort or case-controlled analytic studies or multiple time series; or dramatic results from uncontrolled experiments; 3, evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert communities.

Data from Goldstein MG, Niaura R, Willey-Lessne C, et al. Physicians counseling smokers. A population-based survey of patients' perceptions of health care provider-delivered smoking cessation interventions. *Arch Intern Med* 1997;157:1313–1319; Goldstein MG, Niaura R, Willey C, et al. An academic detailing intervention to disseminate physician-delivered smoking cessation counseling: Smoking cessation outcomes of the Physicians Counseling Smokers Project. *Prev Med* 2003;36:185–196; and U.S. Department of Health and Human Services. *Healthy People 2010, 2nd ed. Understanding and Improving Health and Objectives for Improving Health (2 vols)*. Washington, DC: U.S. Department of Health and Human Services, 2000.

smoking during the second week of treatment. For maintenance treatment, bupropion SR 150 mg twice daily for up to 6 months can be given.

### *Second-Line Medications*

- **Clonidine**, delivered transdermally or orally, is an effective smoking-cessation treatment. It is given for 3 to 10 weeks and should not be discontinued abruptly. Abrupt discontinuation may cause nervousness, agitation, headache, tremor, and rapid rise in blood pressure.
- Dosing of clonidine initially is 0.1 mg orally twice daily or 0.1 mg/day transdermally, increasing by 0.1 mg/day each week if needed.
- The most common clonidine side effects are dry mouth, dizziness, sedation, and constipation. Blood pressure should be monitored.
- **Nortriptyline** is initiated 10 to 28 days before the quit date. The dose is initiated at 25 mg/day, gradually increasing to 75 to 100 mg/day. Treatment duration is commonly 12 weeks in trials, and common side effects were sedation, dry mouth, blurred vision, urinary retention, and lightheadedness.
- **Varenicline** is a partial agonist that binds selectively to nicotinic acetylcholine receptors with a greater affinity than nicotine, thus producing an attenuated response compared to that of nicotine. Its place in therapy has not been established.

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*See Chap. 68, Substance-Related Disorders: Overview and Depressants, Stimulants, and Hallucinogens, authored by Paul L. Doering and Lisa Boothby, and Chap. 69, Substance-Related Disorders: Alcohol, Nicotine, and Caffeine, authored by Paul L. Doering, W. Klugh Kennedy, and Lisa A. Boothby, for a more detailed discussion of the topic.*

## DEFINITION

- Acid–base disorders are caused by disturbances in hydrogen ion ( $H^+$ ) homeostasis, which is ordinarily maintained by extracellular buffering, renal regulation of hydrogen ion and bicarbonate, and ventilatory regulation of carbon dioxide ( $CO_2$ ) elimination.

## GENERAL PRINCIPLES

- General principles that are common to all types of acid–base disturbances are addressed first, followed by separate discussions of each type of acid–base disturbance.
- Buffering refers to the ability of a solution to resist change in pH after the addition of a strong acid or base. The body's principal buffer system is the carbonic acid/bicarbonate ( $H_2CO_3/HCO_3^-$ ) system.
- Most of the body's acid production is in the form of  $CO_2$  and is produced from catabolism of carbohydrates, proteins, and lipids.
- There are four primary types of acid–base disturbances, which can occur independently or together as a compensatory response.
- Metabolic acidosis is characterized by decreased plasma bicarbonate concentrations ( $HCO_3^-$ ), whereas metabolic alkalosis is characterized by increased  $HCO_3^-$ .
- Respiratory acid–base disorders are caused by altered alveolar ventilation producing changes in arterial carbon dioxide tension ( $PaCO_2$ ). Respiratory acidosis is characterized by increased  $PaCO_2$ , whereas respiratory alkalosis is characterized by decreased  $PaCO_2$ .

## DIAGNOSIS

- Blood gases (Table 74-1), serum electrolytes, medical history, and clinical condition are the primary tools for determining the cause of acid–base disorders and for designing therapy.
- Arterial blood gases are measured to determine oxygenation and acid–base status (Fig. 74-1). Low pH values (less than 7.35) indicate acidemia, whereas high values (greater than 7.45) indicate alkalemia. The  $PaCO_2$  value helps to determine if there is a primary respiratory abnormality, whereas the  $HCO_3^-$  concentration helps to determine if there is a primary metabolic abnormality. Steps in acid–base interpretation are described in Table 74-2.

**TABLE 74-1** Normal Blood Gas Values

	Arterial Blood	Mixed Venous Blood
pH	7.40 (7.35–7.45)	7.38 (7.33–7.43)
PO <sub>2</sub>	80–100 mm Hg	35–40 mm Hg
SaO <sub>2</sub>	95%	70–75%
PCO <sub>2</sub>	35–45 mm Hg	45–51 mm Hg
HCO <sub>3</sub> <sup>-</sup>	22–26 mEq/L (22–26 mmol/L)	24–28 mEq/L (24–28 mmol/L)

HCO<sub>3</sub><sup>-</sup>, bicarbonate; PCO<sub>2</sub>, partial pressure of carbon dioxide; PO<sub>2</sub>, partial pressure of oxygen; SaO<sub>2</sub>, saturation of arterial oxygen.

## DESIRED OUTCOME

- Initial treatment is aimed at stabilizing the acute condition, followed by identifying and correcting the underlying cause(s) of the acid–base disturbance. Additional treatment may be needed depending on the severity of symptoms and likelihood of recurrence, especially in patients with ongoing initiating events.

## METABOLIC ACIDOSIS

### PATHOPHYSIOLOGY

- Metabolic acidosis is characterized by decreased pH and serum HCO<sub>3</sub><sup>-</sup> concentrations, which can result from adding organic acid to extracellular fluid (e.g., lactic acid, ketoacids), loss of HCO<sub>3</sub><sup>-</sup> stores (e.g., diarrhea), or accumulation of endogenous acids due to impaired renal function (e.g., phosphates, sulfates).
- Anion gap can be calculated to elucidate the cause of metabolic acidosis (Table 74-3). The anion gap is calculated as follows:

$$\text{Anion gap} = [\text{Na}^+] - [\text{Cl}^-] - [\text{HCO}_3^-]$$

The normal anion gap is approximately 9 mEq/L, with a range of 3 to 11 mEq/L. ).

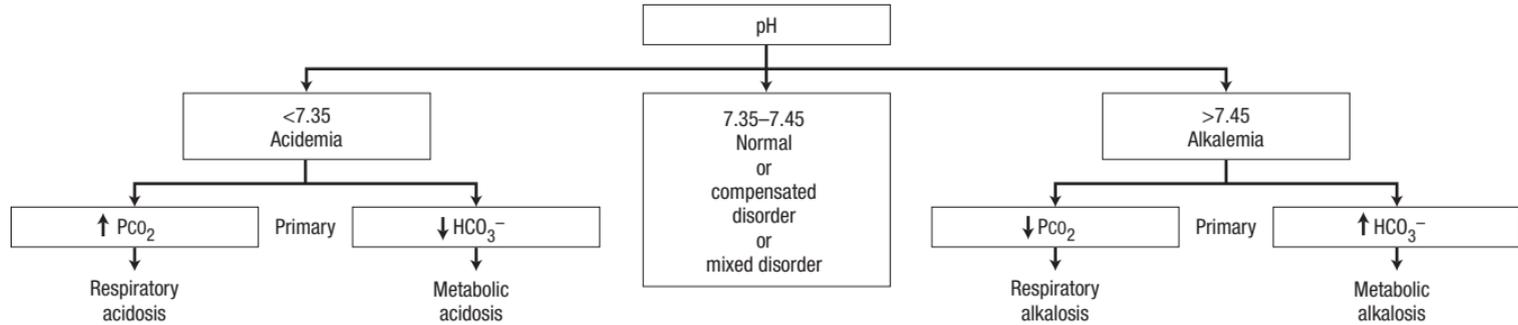
- The primary compensatory mechanism is to decrease PaCO<sub>2</sub> by increasing the respiratory rate.

### CLINICAL PRESENTATION

- The major manifestation of chronic metabolic acidosis is bone demineralization with the development of rickets in children and osteomalacia and osteopenia in adults.
- The manifestations of acute severe metabolic acidemia (pH less than 7.15 to 7.20) involve the cardiovascular, respiratory, and central nervous systems. Hyperventilation is often the first sign of metabolic acidosis. Respiratory compensation may occur as Kussmaul's respirations (i.e., deep, rapid respirations characteristic of diabetic ketoacidosis).

### TREATMENT

- The primary treatment of metabolic acidosis is to correct the underlying disorder. Additional treatment depends on the severity and onset of acidosis.



**FIGURE 74-1.** Analysis of arterial blood gases. ( $HCO_3^-$ , bicarbonate;  $PCO_2$ , partial pressure of carbon dioxide.)

**TABLE 74-2** Steps in Acid–Base Diagnosis

1. Obtain arterial blood gases (ABGs) and electrolytes simultaneously.
2. Compare  $[\text{HCO}_3^-]$  on ABG and electrolytes to verify accuracy.
3. Calculate anion gap (AG).
4. Is acidemia ( $\text{pH} < 7.35$ ) or alkalemia ( $\text{pH} > 7.45$ ) present?
5. Is the primary abnormality respiratory (alteration in  $\text{PaCO}_2$ ) or metabolic (alteration in  $[\text{HCO}_3^-]$ )?
6. Estimate compensatory response (see Table 55-7 in *Pharmacotherapy: A Pathophysiologic Approach*, seventh edition).
7. Compare change in  $[\text{Cl}^-]$  with change in  $[\text{Na}^+]$ .

$[\text{Cl}^-]$ , chloride ion;  $[\text{HCO}_3^-]$ , bicarbonate;  $[\text{Na}^+]$ , sodium ion;  $\text{PaCO}_2$ , partial pressure of carbon dioxide from arterial blood.

- Asymptomatic patients with mild to moderate acidemia ( $\text{HCO}_3^-$ , 12 to 20 mEq/L;  $\text{pH}$ , 7.2 to 7.4) can usually be managed with gradual correction of the acidemia over days to weeks using oral **sodium bicarbonate** or other alkali preparations (Table 74-4). The dose of bicarbonate can be calculated as follows:

**TABLE 74-3** Common Causes of Metabolic Acidosis**Increased Serum Anion Gap**

Lactic acidosis  
 Diabetic ketoacidosis  
 Lactic acidosis  
 Renal failure (acute or chronic)  
 Methanol ingestion  
 Ethylene glycol ingestion  
 Salicylate overdosage  
 Starvation

**Normal Serum Anion Gap/Hyperchloremic States****GI bicarbonate loss**

Diarrhea  
 External pancreatic or small bowel drainage (fistula)  
 Ureterosigmoidostomy, ileostomy

**Drugs**

Cholestyramine (bile acid diarrhea)  
 Magnesium sulfate (diarrhea)  
 Calcium chloride (acidifying agent)

**Renal tubular acidosis**

Hypokalemia  
 Proximal renal tubular acidosis (type II)  
 Distal renal tubular acidosis (type I)  
 Carbonic anhydrase inhibitors (e.g., acetazolamide)

**Hyperkalemia**

Generalized distal nephron dysfunction (type IV)  
 Mineralocorticoid deficiency or resistance  
 Tubulointerstitial disease  
 Drug-induced hyperkalemia  
 Potassium-sparing diuretics (amiloride, spironolactone, triamterene)  
 Trimethoprim  
 Pentamidine  
 Heparin  
 Angiotensin-converting enzyme inhibitors and receptor blockers  
 Nonsteroidal antiinflammatory drugs  
 Cyclosporin A

**Other**

Acid ingestion (ammonium chloride, hydrochloric acid, hyperalimentation)  
 Expansion acidosis (rapid saline administration)

**TABLE 74-4 Therapeutic Alternatives for Oral Alkali Replacement**

Generic Name	Trade Name(s)	Milliequivalents of Alkali	Dosage Form(s)	Comment
Shohl solution Sodium citrate/citric acid	Bicitra (Willen)	1 mEq Na/mL; equivalent to 1 mEq bicarbonate	Solution (500 mg Na citrate, 334 mg citric acid/5 mL)	Citrate preparations increase absorption of aluminum
Sodium bicarbonate	Various (e.g., Sodamint)	3.9 mEq bicarbonate/tablet (325 mg)	325 mg tablet	Bicarbonate preparations can cause bloating because of carbon dioxide production
Potassium citrate	Baking soda (various)	7.8 mEq bicarbonate/tablet (650 mg)	650 mg tablet	
Potassium bicarbonate/potassium citrate	Urocit-K (Mission)	60 mEq bicarbonate/tsp (5 g/tsp)	Powder	
	K-Lyte (Bristol)	5 mEq citrate/tablet	5 mEq tablet	See above
	K-Lyte DS (Bristol)	25 mEq bicarbonate/tablet	25 mEq tablet (effervescent)	
	K-Lyte DS (Bristol)	50 mEq bicarbonate/tablet (double strength)	50 mEq tablet (effervescent)	See above
Potassium citrate/citric acid	Polycitra-K (Willen)	2 mEq K/mL; equivalent to 2 mEq bicarbonate	Solution (1,100 mg K citrate, 334 mg citric acid/5 mL)	See above
		30 mEq bicarbonate/unit dose packet	Crystals for reconstitution (3,300 mg K citrate, 1,002 mg citric acid/unit dose packet)	
Sodium citrate/potassium citrate/citric acid	Polycitra (Willen), Polycitra-LC (Willen)	1 mEq K, 1 mEq Na/mL; equivalent to 2 mEq bicarbonate	Syrup (Polycitra) solution (Polycitra-LC) (Both contain 550 mg K citrate, 500 mg Na citrate, 334 mg citric acid/5 mL)	See above

$$\text{Loading dose (mEq)} = (\text{Vd HCO}_3^- \times \text{body weight}) \times (\text{desired [HCO}_3^-] - \text{current [HCO}_3^-])$$

where Vd  $\text{HCO}_3^-$  is the volume of distribution of  $\text{HCO}_3^-$  (0.5 L/kg).

- Alkali therapy can be used to treat patients with acute severe metabolic acidosis due to hyperchloremic acidosis, but its role is controversial in patients with lactic acidosis. Therapeutic options include **sodium bicarbonate** and **tromethamine**.
  - ✓ Sodium bicarbonate has been recommended to raise arterial pH to 7.15 to 7.20. However, no controlled clinical studies have demonstrated reduced morbidity and mortality compared with general supportive care. If IV sodium bicarbonate is administered, the goal is to increase, not normalize, pH to 7.20 and  $\text{HCO}_3^-$  to 8 to 10 mEq/L.
  - ✓ Tromethamine, a highly alkaline solution, is a sodium-free organic amine that acts as a proton acceptor to prevent or correct acidosis. However, no evidence exists that tromethamine is beneficial or more efficacious than sodium bicarbonate. The usual empiric dosage for tromethamine is 1 to 5 mmol/kg administered IV over 1 hour and an individualized dose can be calculated as follows:

$$\text{Dose of tromethamine (in mL)} = 1.1 \times \text{body weight (in kg)} \times (\text{normal [HCO}_3^-] - \text{current [HCO}_3^-])$$

## METABOLIC ALKALOSIS

### PATHOPHYSIOLOGY

- Metabolic alkalosis is *initiated* by increased pH and  $\text{HCO}_3^-$ , which can result from loss of  $\text{H}^+$  via the GI tract (e.g., nasogastric suctioning, vomiting) or kidneys (e.g., diuretics, Cushing's syndrome), or from gain of bicarbonate (e.g., administration of bicarbonate, acetate, lactate, or citrate).
- Metabolic alkalosis is *maintained* by abnormal renal function that prevents the kidneys from excreting excess bicarbonate.
- The respiratory response to metabolic alkalosis is to increase  $\text{PaCO}_2$  by hypoventilation.

### CLINICAL PRESENTATION

- No unique signs or symptoms are associated with mild to moderate metabolic alkalosis. Some patients complain of symptoms related to the underlying disorder (e.g., muscle weakness with hypokalemia or postural dizziness with volume depletion) or have a history of vomiting, gastric drainage, or diuretic use.
- Severe alkalemia (pH greater than 7.60) can be associated with cardiac arrhythmias and neuromuscular irritability.

### TREATMENT

- Treatment of metabolic alkalosis should be aimed at correcting the factor(s) responsible for maintaining the alkalosis.

- Treatment depends on whether the disorder is sodium chloride responsive or resistant (Fig. 74-2).

## RESPIRATORY ALKALOSIS

### PATHOPHYSIOLOGY

- Respiratory alkalosis is characterized by a decrease in  $\text{PaCO}_2$  and an increase in pH.
- $\text{PaCO}_2$  decreases when ventilatory excretion exceeds metabolic production, usually because of hyperventilation.
- Causes of respiratory alkalosis include increases in neurochemical stimulation via central or peripheral mechanisms, or physical increases in ventilation via voluntary or artificial means (e.g., mechanical ventilation).
- The earliest compensatory response is to chemically buffer excess bicarbonate by releasing hydrogen ions from intracellular proteins, phosphates, and hemoglobin. If respiratory alkalosis is prolonged (more than 6 hours), the kidneys attempt to further compensate by increasing bicarbonate elimination.

### CLINICAL PRESENTATION

- Although usually asymptomatic, respiratory alkalosis can cause adverse neuromuscular, cardiovascular, and GI effects.
- Lightheadedness, confusion, decreased intellectual functioning, syncope, and seizures can be caused by decreased cerebral blood flow.
- Nausea and vomiting can occur, probably due to cerebral hypoxia.
- Serum electrolytes can be altered secondary to respiratory alkalosis. Serum chloride is usually increased; serum potassium, phosphorus, and ionized calcium are usually decreased.

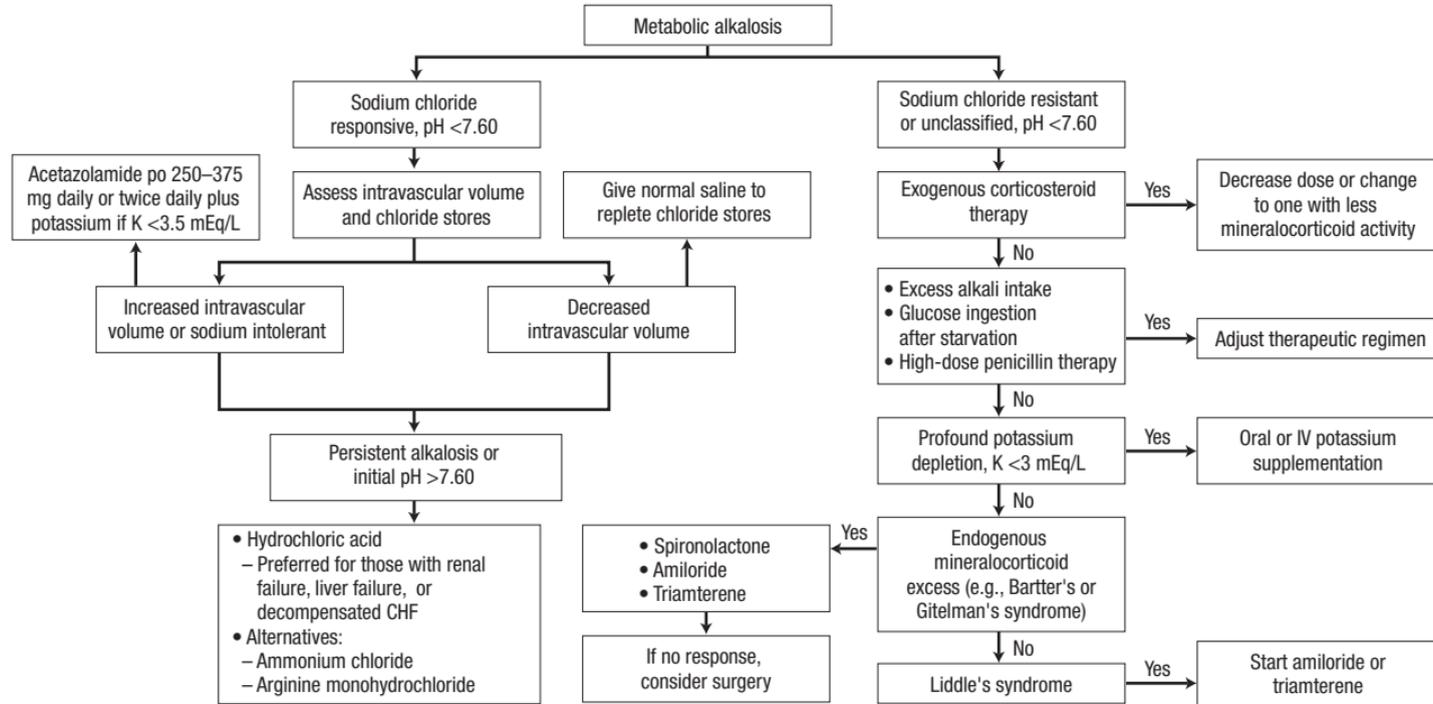
### TREATMENT

- Treatment is often unnecessary because most patients have few symptoms and only mild pH alterations (i.e., pH less than 7.50).
- Direct measures (e.g., treatment of pain, hypovolemia, fever, infection, or salicylate overdose) can be effective. A rebreathing device (e.g., paper bag) can help control hyperventilation.
- Respiratory alkalosis associated with mechanical ventilation can often be corrected by decreasing the number of mechanical breaths per minute, using a capnograph and spirometer to adjust ventilator settings more precisely, or increasing dead space in the ventilator circuit.

## RESPIRATORY ACIDOSIS

### PATHOPHYSIOLOGY

- Respiratory acidosis is characterized by an increase in  $\text{PaCO}_2$  and a decrease in pH.



**FIGURE 74-2.** Treatment algorithm for patients with primary metabolic alkalosis. (CHF, congestive heart failure; K, potassium.)

- Respiratory acidosis results from disorders that restrict ventilation or increase CO<sub>2</sub> production, airway and pulmonary abnormalities, neuromuscular abnormalities, or mechanical ventilator problems.
- The early compensatory response to acute respiratory acidosis is chemical buffering. If respiratory acidosis is prolonged (more than 12 to 24 hours), renal excretion of H<sup>+</sup> increases, which generates new bicarbonate.

## CLINICAL PRESENTATION

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- Neuromuscular symptoms include altered mental status, abnormal behavior, seizures, stupor, and coma. Hypercapnia can mimic a stroke or CNS tumor by producing headache, papilledema, focal paresis, and abnormal reflexes. CNS symptoms are caused by increased cerebral blood flow and are variable, depending in part on the acuity of onset.

## TREATMENT

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- Adequate ventilation should be provided if carbon dioxide excretion is acutely and severely impaired (PaCO<sub>2</sub> more than 80 mm Hg) or if life-threatening hypoxia is present (arterial oxygen tension [PaO<sub>2</sub>] less than 40 mm Hg). Ventilation can include maintaining a patent airway (e.g., emergency tracheostomy, bronchoscopy, or intubation), clearing excessive secretions, administering oxygen, and providing mechanical ventilation.
- The underlying cause of acute acidosis should be treated aggressively (e.g., administration of bronchodilators for bronchospasm or discontinuation of respiratory depressants such as narcotics and benzodiazepines). Bicarbonate administration is rarely necessary and is potentially harmful.
- In a patient with chronic respiratory acidosis (e.g., chronic obstructive pulmonary disease), treatment is essentially similar to that for acute respiratory acidosis with a few important exceptions. Oxygen therapy should be initiated carefully and only if the PaO<sub>2</sub> is less than 50 mm Hg because the drive to breathe depends on hypoxemia rather than hypercarbia.
- For information on chronic respiratory acidosis, see Chap. 81.

## MIXED ACID–BASE DISORDERS

### PATHOPHYSIOLOGY

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- Failure of compensation is responsible for mixed acid–base disorders such as respiratory acidosis and metabolic acidosis, or respiratory alkalosis and metabolic alkalosis. In contrast, excess compensation is responsible for metabolic acidosis and respiratory alkalosis, or metabolic alkalosis and respiratory acidosis.
- Respiratory and metabolic acidosis can develop in patients with cardiorespiratory arrest, with chronic lung disease and shock, and with metabolic acidosis and respiratory failure.
- The most common mixed acid–base disorder is respiratory and metabolic alkalosis, which occurs in critically ill surgical patients with respiratory alkalosis caused by mechanical ventilation, hypoxia, sepsis, hypotension,

neurologic damage, pain, or drugs; and with metabolic alkalosis caused by vomiting or nasogastric suctioning and massive blood transfusions.

- Mixed metabolic acidosis and respiratory alkalosis occur in patients with advanced liver disease, salicylate intoxication, and pulmonary-renal syndromes.
- Metabolic alkalosis and respiratory acidosis can occur in patients with chronic obstructive pulmonary disease and respiratory acidosis who are treated with salt restriction, diuretics, and possibly glucocorticoids.

## TREATMENT

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- Mixed respiratory and metabolic acidosis should be treated by responding to both the respiratory and metabolic acidosis. Improved oxygen delivery must be initiated to improve hypercarbia and hypoxia. Mechanical ventilation can be needed to reduce  $\text{PaCO}_2$ . During initial therapy, appropriate amounts of alkali should be given to reverse the metabolic acidosis.
- The metabolic component of mixed respiratory and metabolic alkalosis should be corrected by administering **sodium** and **potassium chloride solutions**. The respiratory component should be treated by readjusting the ventilator or by treating the underlying disorder causing hyperventilation.
- Treatment of mixed metabolic acidosis and respiratory alkalosis should be directed at the underlying cause.
- In metabolic alkalosis and respiratory acidosis, pH does not usually deviate significantly from normal, but treatment can be required to maintain  $\text{PaO}_2$  and  $\text{PaCO}_2$  at acceptable levels. Treatment should be aimed at decreasing plasma bicarbonate with **sodium** and **potassium chloride** therapy, allowing renal excretion of retained bicarbonate from diuretic-induced metabolic alkalosis.

## EVALUATION OF THERAPEUTIC OUTCOMES

- Patients should be monitored closely because acid–base disorders can be serious and even life threatening.
- Arterial blood gases are the primary tools for evaluation of therapeutic outcome. They should be monitored closely to ensure resolution of simple acid–base disorders without deterioration to mixed disorders due to compensatory mechanisms. For example, arterial blood gases should be obtained every 2 to 4 hours during the acute phase of respiratory acidosis and then every 12 to 24 hours as acidosis improves.

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See Chap. 55, *Acid–Base Disorders*, authored by John W. Devlin, Gary R. Matzke, and Paul M. Palevsky, for a more detailed discussion of this topic.

## DEFINITIONS

- Acute renal failure (ARF) is broadly defined as a decrease in glomerular filtration rate (GFR) occurring over hours to weeks that is associated with an accumulation of waste products, including urea and creatinine. Clinicians use a combination of the serum creatinine ( $S_{cr}$ ) value with change in either  $S_{cr}$  or urine output (UOP) as the primary criteria for diagnosing ARF.
- A consensus-derived definition and classification system for ARF has been proposed and is being validated (Fig. 75-1). Components of the system include both GFR and UOP plus two clinical outcomes. Definitions of risk of dysfunction, injury to and failure of the kidney, loss of function, and end-stage kidney disease are included in the RIFLE acronym.

## PATHOPHYSIOLOGY

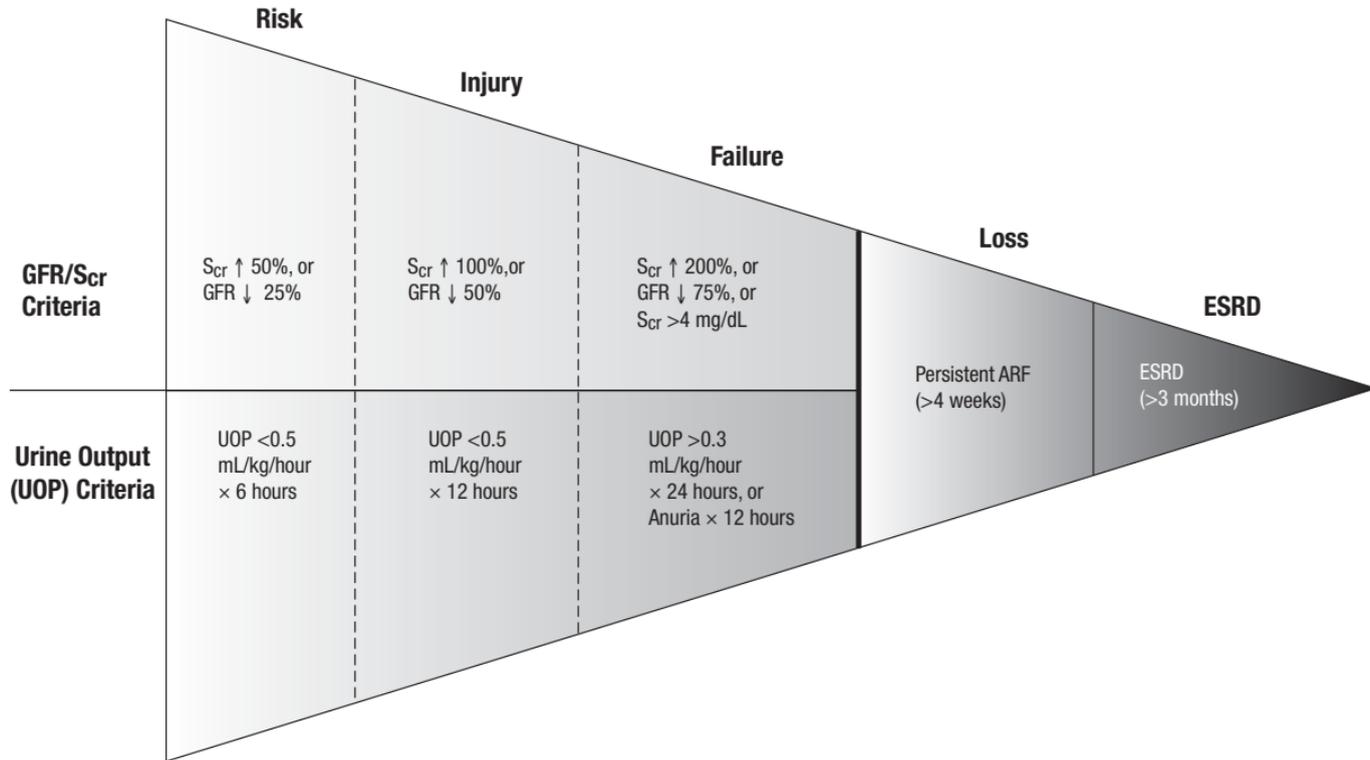
- ARF can be categorized as prerenal (resulting from decreased renal perfusion), intrinsic (resulting from structural damage to the kidney), postrenal (resulting from obstruction of urine flow from the renal tubule to the urethra), and functional (resulting from hemodynamic changes at the glomerulus independent of decreased perfusion or structural damage) (Table 75-1).

## CLINICAL PRESENTATION

- The presentation can be subtle and depends on the setting. Outpatients often are not in acute distress; hospitalized patients may develop ARF after a catastrophic event.
- Symptoms in the outpatient setting include change in urinary habits, weight gain, or flank pain. Clinicians typically notice symptoms of ARF before they are detected by inpatients.
- Signs include edema, colored or foamy urine, and, in volume-depleted patients, orthostatic hypotension.

## DIAGNOSIS

- Thorough medical and medication histories, physical examination, assessment of laboratory values and if needed, imaging studies, are important in the diagnosis of ARF.
- $S_{cr}$  and blood urea nitrogen cannot be used alone to diagnose ARF because they are insensitive to rapid changes in GFR and therefore may not reflect current renal function.
- Monitoring changes in UOP can help diagnose the cause of ARF. Acute anuria (less than 50 mL urine/day) is secondary to complete urinary obstruction or a catastrophic event (e.g., shock). Oliguria (400 to 500 mL urine/day) suggests prerenal azotemia. Nonoliguric renal failure (more



**FIGURE 75-1.** RIFLE classification for acute renal failure (ARF). (ESRD, end-stage renal disease; GFR, glomerular filtration rate;  $S_{cr}$ , serum creatinine.) (Reprinted and adapted from *Crit Care Clin*, Vol. 21, Bellomo R. Defining, quantifying, and classifying acute renal failure, pages 223–237, Copyright ©2005, with permission from Elsevier.)

**TABLE 75-1** Classification of Acute Renal Failure

Category	Abnormality Causing Acute Renal Failure	Possible Causes
<b>Prerenal</b>	Intravascular volume depletion resulting in arterial hypotension	Dehydration Inadequate fluid intake Excessive vomiting, diarrhea, or gastric suctioning Increased insensible losses (e.g., fever, burns) Diabetes insipidus High-serum glucose (glucosuria) Overdiuresis
	Arterial hypotension (regardless of volume status)	Hemorrhage Decreased cardiac output Hypoalbuminemia Liver disease Nephrotic syndrome
	Decreased cardiac output	Anaphylaxis Sepsis Excessive antihypertensive use Heart failure Sepsis Pulmonary hypertension Aortic stenosis (and other valvular abnormalities) Anesthetics
	Isolated renal hypoperfusion	Bilateral renal artery stenosis (unilateral renal artery stenosis in solitary kidney) Emboli Cholesterol Thrombotic Medications Cyclosporine Angiotensin-converting enzyme inhibitors Nonsteroidal antiinflammatory drugs Radiocontrast media Hypercalcemia Hepatorenal syndrome
<b>Intrinsic</b>	Vascular damage	Vasculitis Polyarteritis nodosa Hemolytic uremic syndrome/thrombotic thrombocytopenic purpura Emboli Atherosclerotic Thrombotic
	Glomerular damage	Accelerated hypertension Systemic lupus erythematosus Poststreptococcal glomerulonephritis Antiglomerular basement membrane disease
	Acute tubular necrosis	Ischemic Hypotension Vasoconstriction Exogenous toxins Contrast dye Heavy metals Drugs (amphotericin B, aminoglycosides, etc.)

*(continued)*

**TABLE 75-1** Classification of Acute Renal Failure (Continued)

Category	Abnormality Causing Acute Renal Failure	Possible Causes
	Acute interstitial nephritis	Endogenous toxins Myoglobin Hemoglobin Drugs Penicillins Ciprofloxacin Sulfonamides Infection Viral Bacterial
<b>Postrenal</b>	Bladder outlet obstruction	Prostatic hypertrophy, infection, cancer Improperly placed bladder catheter Anticholinergic medication
	Ureteral	Cancer with abdominal mass Retroperitoneal fibrosis Nephrolithiasis
	Renal pelvis or tubules	Nephrolithiasis Oxalate Indinavir Sulfonamides Acyclovir Uric acid

than 400 to 500 mL urine/day) usually results from acute intrinsic renal failure or incomplete urinary obstruction.

- Urinalysis can help clarify the cause of ARF. Certain laboratory parameters are helpful in the assessment of renal function with ARF (Table 75-2). Urine microscopy gives further information to assist with determination of the etiology of the ARF (Table 75-3).

**TABLE 75-2** Diagnostic Parameters for Differentiating Causes of Acute Renal Failure

Laboratory Test	Prerenal Azotemia	Acute Intrinsic Renal Failure	Postrenal Obstruction
Urine sediment	Normal	Casts, cellular debris	Cellular debris
Urinary RBC	None	2–4+	Variable
Urinary WBC	None	2–4+	1+
Urine sodium	<20	>40	>40
FE <sub>Na</sub> (%)	<1	>2	Variable
Urine/serum osmolality	>1.5	<1.3	<1.5
Urine/S <sub>Cr</sub>	>40:1	<20:1	<20:1
BUN/S <sub>Cr</sub>	>20	~15	~15

ARF, acute renal failure; BUN, blood urea nitrogen; FE<sub>Na</sub>, fractional excretion of sodium; S<sub>Cr</sub>, serum creatinine; RBC, red blood cell; WBC, white blood cell.

Common laboratory tests are used to classify the cause of ARF. Functional ARF, which is not included in this table, would have laboratory values similar to those seen in prerenal azotemia. However, the urine osmolality-to-plasma osmolality ratios may not exceed 1.5, depending on the circulating levels of antidiuretic hormone. The laboratory results listed under acute intrinsic renal failure are those seen in acute tubular necrosis, the most common cause of acute intrinsic renal failure.

**TABLE 75-3** Differential Diagnosis of Acute Renal Failure on the Basis of Urine Microscopic Examination Findings

Urine Sediment	Suggestive of
<b>Cells</b>	
Microorganisms	Pyelonephritis
Red blood cells	Glomerulonephritis, pyelonephritis, renal infarction, papillary necrosis, renal tumors, kidney stones
White blood cells	Pyelonephritis, interstitial nephritis
Eosinophils	Drug-induced allergic interstitial nephritis, renal transplant rejection
Epithelial cells	Tubular necrosis
<b>Casts</b>	
Granular casts	Tubular necrosis
White blood cell casts	Pyelonephritis, interstitial nephritis
Red blood cell casts	Glomerulonephritis, renal infarct, lupus nephritis, vasculitis
<b>Crystals</b>	
Urate	Postrenal obstruction
Phosphate	Alkaline urine, possibly secondary to <i>Proteus</i> sp. infection, postrenal obstruction

- Simultaneous measurement of urine and serum chemistries and calculation of the fractional excretion of sodium ( $FE_{Na}$ ) can help determine the etiology of ARF (see Table 75-2). The  $FE_{Na}$  is calculated as:

$$FE_{Na} = (U_{Na} \times P_{Cr} \times 100) / (U_{Cr} \times P_{Na})$$

where  $U_{Na}$  = urine sodium,  $P_{Cr}$  = plasma creatinine,  $U_{Cr}$  = urine creatinine, and  $P_{Na}$  = plasma sodium.

## DESIRED OUTCOME

- The primary goal of therapy is to prevent ARF. If ARF develops, the goals are to avoid or minimize further renal insults that would delay recovery and to provide supportive measures until kidney function returns.

## TREATMENT

### PREVENTION OF ACUTE RENAL FAILURE

- Risk factors for ARF include advanced age, acute infection, preexisting chronic respiratory or cardiovascular disease, dehydration, and chronic kidney disease (CKD). Decreased renal perfusion secondary to abdominal or coronary bypass surgery, acute blood loss in trauma, and uric acid nephropathy also increase risk.
- Nephrotoxin administration (e.g., radiocontrast dye) should be avoided whenever possible. When patients require contrast dye and are at risk of contrast dye-induced nephropathy, renal perfusion should be maximized through strategies such as assuring adequate hydration with normal saline or sodium bicarbonate solutions and administration of **oral acetylcysteine** 600 mg every 12 hours for four doses. Strict glycemc control with **insulin** in diabetics has also reduced the development of ARF.

- **Amphotericin B** nephrotoxicity can be reduced by slowing the infusion rate to 24 hours or, in at-risk patients, substituting **liposomal amphotericin B**.
- Many other strategies are popular but *lack* supportive evidence, including **mannitol, loop diuretics, dopamine, and fenoldopam**.

## MANAGEMENT OF ESTABLISHED ACUTE RENAL FAILURE

- No drugs have been found to accelerate ARF recovery. Therefore, patients with established ARF should be supported with nonpharmacologic and pharmacologic approaches through the period of ARF.

### Nonpharmacologic Approaches

- Supportive care goals include maintenance of adequate cardiac output and blood pressure to optimize tissue perfusion while restoring renal function to pre-ARF baseline.
- Medications associated with diminished renal blood flow should be stopped. Appropriate fluid replacement should be initiated. Avoidance of nephrotoxins is essential in the management of patients with ARF.
- Renal replacement therapy (RRT), such as hemodialysis and peritoneal dialysis, maintains fluid and electrolyte balance while removing waste products. See Table 75-4 for indications for RRT in ARF. Intermittent and continuous options have different advantages (and disadvantages) but, after correcting for severity of illness, have similar outcomes. Consequently, hybrid approaches (e.g., sustained low-efficiency dialysis and extended daily dialysis) are being developed to provide the advantages of both.
- Intermittent RRT (e.g., hemodialysis) has the advantage of widespread availability and the convenience of lasting only 3 to 4 hours. Disadvantages include difficult venous dialysis access in hypotensive patients and hypotension due to rapid removal of large amounts of fluid.
- Several continuous renal replacement therapy (CRRT) variants have been developed. CRRT, performed as continuous hemodialysis, continuous hemofiltration, or both, is becoming increasingly popular. CRRT gradually removes solute resulting in better tolerability by critically ill patients. Disadvantages include limited availability, need for 24-hour nursing care, high expense, and incomplete guidelines for drug dosing (see Chap. 77).

**TABLE 75-4** The AEIOUs That Describe the Indications for Renal Replacement Therapy

Indication for Renal Replacement Therapy	Clinical Setting
<b>A</b> Acid-base abnormalities	Metabolic acidosis resulting from the accumulation of organic and inorganic acids
<b>E</b> Electrolyte imbalance	Hyperkalemia, hypermagnesemia
<b>I</b> Intoxications	Salicylates, lithium, methanol, ethylene glycol, theophylline, phenobarbital
<b>O</b> fluid Overload	Postoperative fluid gain
<b>U</b> Uremia	High catabolism of acute renal failure

## Pharmacologic Approaches

- Loop diuretics have not been shown to accelerate ARF recovery or improve patient outcome; however, diuretics can facilitate management of fluid overload. The most effective diuretics are mannitol and loop diuretics.
- **Mannitol** 20% is typically started at a dose of 12.5 to 25 g IV over 3 to 5 minutes. Disadvantages include IV administration, hyperosmolality risk, and need for monitoring because mannitol can contribute to ARF.
- Equipotent doses of loop diuretics (**furosemide, bumetanide, torsemide, ethacrynic acid**) have similar efficacy. Ethacrynic acid is reserved for sulfallergic patients. Continuous infusions of loop diuretics appear to be more effective and to have fewer adverse effects than intermittent boluses. An initial IV loading dose (equivalent to furosemide 40 to 80 mg) should be administered before starting a continuous infusion (equivalent to furosemide 10 to 20 mg/hour).
- Strategies are available to overcome diuretic resistance (Table 75-5), a common problem in patients with ARF. Agents from different pharmacologic classes, such as diuretics that work at the distal convoluted tubule (thiazides) or the collecting duct (**amiloride, triamterene, spironolactone**), may be synergistic when combined with loop diuretics. **Metolazone** is commonly used because, unlike other thiazides, it produces effective diuresis at GFR less than 20 mL/min.

**TABLE 75-5** Common Causes of Diuretic Resistance in Patients with Acute Renal Failure

Causes of Diuretic Resistance	Potential Therapeutic Solutions
Excessive sodium intake (sources may be dietary, IV fluids, and drugs)	Remove sodium from nutritional sources and medications
Inadequate diuretic dose or inappropriate regimen	Increase dose, use continuous infusion or combination therapy
Reduced oral bioavailability (usually furosemide)	Use parenteral therapy; switch to oral torsemide or bumetanide
Nephrotic syndrome (loop diuretic protein binding in tubule lumen)	Increase dose, switch diuretics, use combination therapy
Reduced renal blood flow Drugs (NSAIDs ACEIs, vasodilators) Hypotension	Discontinue these drugs if possible Intravascular volume expansion and/or vasopressors
Intravascular depletion	Intravascular volume expansion
Increased sodium resorption Nephron adaptation to chronic diuretic therapy NSAID use Heart failure	Combination diuretic therapy, sodium restriction Discontinue NSAID Treat the heart failure, increase diuretic dose, switch to better-absorbed loop diuretic
Cirrhosis	High-volume paracentesis
Acute tubular necrosis	Higher dose of diuretic, diuretic combination therapy, add low-dose dopamine

ACEIs, angiotensin-converting enzyme inhibitors; NSAIDs, nonsteroidal antiinflammatory drugs.

**TABLE 75-6** Key Monitoring Parameters for Patients with Established Acute Renal Failure

Parameter	Frequency
Fluid ins/outs	Every shift
Patient weight	Daily
Hemodynamics (blood pressure, heart rate, mean arterial pressure, etc.)	Every shift
Blood chemistries	
Sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium	Daily
Blood urea nitrogen/serum creatinine	Daily
Drugs and their dosing regimens	Daily
Nutritional regimen	Daily
Blood glucose	Daily (minimum)
Serum concentration data for drugs	After regimen changes and after renal replacement therapy has been instituted
Times of administered doses	Daily
Doses relative to administration of renal replacement therapy	Daily
Urinalysis	
Calculate measured creatinine clearance	Every time measured urine collection performed
Calculate fractional excretion of sodium	Every time measured urine collection performed
Plans for renal replacement	Daily

## ELECTROLYTE MANAGEMENT AND NUTRITION THERAPY

- Hyperkalemia is the most common and serious electrolyte abnormality in ARF. Typically, potassium must be restricted to less than 3 g/day and monitored daily.
- Hyponatremia and fluid retention commonly occur, necessitating restricting daily sodium intake to no more than 3 g. All sources of sodium, including antibiotics, need to be considered when calculating daily sodium intake.
- Phosphorus and magnesium should be monitored; neither is efficiently removed by dialysis.
- Enteral (see Chap. 58), but not parenteral, nutrition has been shown to improve patient outcomes.

## DRUG-DOSING CONSIDERATIONS

- Drug therapy optimization in ARF is a challenge. Confounding variables include residual drug clearance, fluid accumulation, and use of RRTs.
- Volume of distribution for water-soluble drugs is significantly increased due to edema. Use of dosing guidelines for CKD does not reflect the clearance and volume of distribution in critically ill ARF patients.
- ARF patients may have a higher residual nonrenal clearance than CKD patients with similar creatinine clearances; this complicates drug therapy individualization, especially with RRTs.
- The mode of CRRT determines the rate of drug removal, further complicating individualization of drug therapy. The rates of ultrafiltration, blood flow, and dialysate flow influence drug clearance during CRRT.

**EVALUATION OF THERAPEUTIC OUTCOMES**

- Vigilant monitoring of patient status is essential (Table 75-6).
- Drug concentrations should be monitored frequently because of changing volume status, changing renal function, and RRTs in patients with ARF.

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*See Chap. 45, Acute Renal Failure, authored by William Dager and Anne Spencer, for a more detailed discussion of this topic.*

## DEFINITION

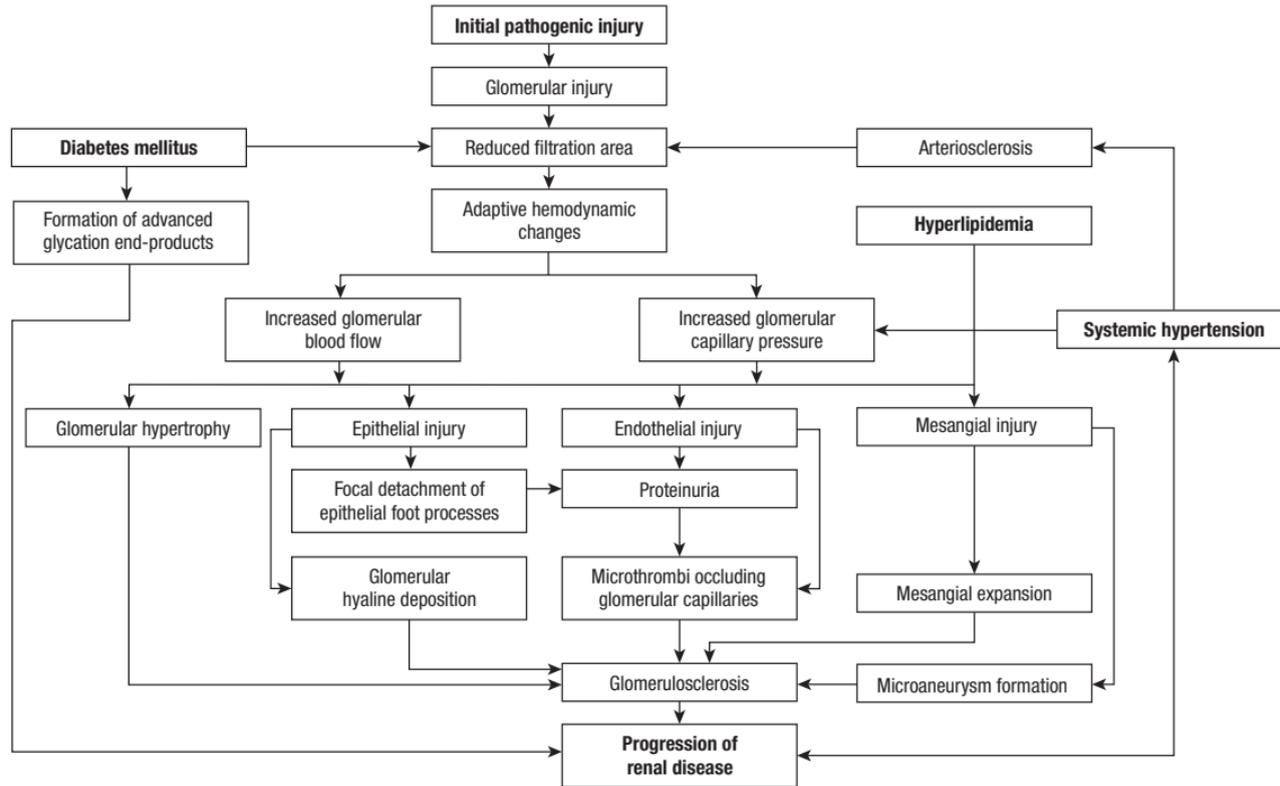
- Chronic kidney disease (CKD) is a progressive loss of function over several months to years, characterized by gradual replacement of normal kidney architecture with interstitial fibrosis.
- CKD is categorized by the level of kidney function, based on glomerular filtration rate (GFR), into stages 1 to 5, with each increasing number indicating a more advanced stage of the disease, as defined by a declining GFR. This classification system from the National Kidney Foundation's Kidney Dialysis Outcomes and Quality Initiative (K/DOQI) also accounts for structural evidence of kidney damage.
- CKD stage 5, previously referred to as end-stage renal disease (ESRD), occurs when the GFR falls below 15 mL/min per 1.73 m<sup>2</sup> body surface area. The patient with stage 5 CKD requiring chronic dialysis or renal transplantation for relief of uremic symptoms is said to have ESRD.

## PATHOPHYSIOLOGY

- *Susceptibility factors* increase the risk for kidney disease but do not directly cause kidney damage. Susceptibility factors include advanced age, reduced kidney mass and low birth weight, racial or ethnic minority, family history, low income or education, systemic inflammation, and dyslipidemia.
- *Initiation factors* initiate kidney damage and can be modified by drug therapy. Initiation factors include diabetes mellitus, hypertension, autoimmune disease, polycystic kidney disease, and drug toxicity.
- *Progression factors* hasten decline in kidney function after initiation of kidney damage. Progression factors include glycemia in diabetics, hypertension, proteinuria, and smoking.
- Most progressive nephropathies share a final common pathway to irreversible renal parenchymal damage and ESRD (Fig. 76-1). Key pathway elements are loss of nephron mass, glomerular capillary hypertension, and proteinuria.

## CLINICAL PRESENTATION

- CKD development and progression is insidious. Patients with stage 1 or 2 CKD usually do not have symptoms or metabolic derangements seen with stages 3 to 5, such as anemia, secondary hyperparathyroidism, cardiovascular disease, malnutrition, and fluid and electrolyte abnormalities that are more common as kidney function deteriorates.
- Uremic symptoms (fatigue, weakness, shortness of breath, mental confusion, nausea, vomiting, bleeding, and anorexia) are generally absent in stages 1 and 2, minimal during stages 3 and 4, and common in patients with stage 5 CKD who may also experience itching, cold intolerance, weight gain, and peripheral neuropathies.



**FIGURE 76-1.** Proposed mechanisms for progression of renal disease.

- Signs and symptoms of uremia are foundational to the decision to implement kidney replacement therapy.

## DESIRED OUTCOME

- The goal is to delay the progression of CKD, minimizing the development or severity of complications.

## TREATMENT: PROGRESSION-MODIFYING THERAPIES

- The treatment of CKD includes nonpharmacologic and pharmacologic strategies. Strategies differ depending on the presence (Fig. 76-2) or absence of diabetes (Fig. 76-3).

### NONPHARMACOLOGIC THERAPY

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- A low-protein diet (0.6 to 0.75 g/kg/day) can delay progression of CKD in patients with or without diabetes, although the benefit is relatively small.

### PHARMACOLOGIC THERAPY

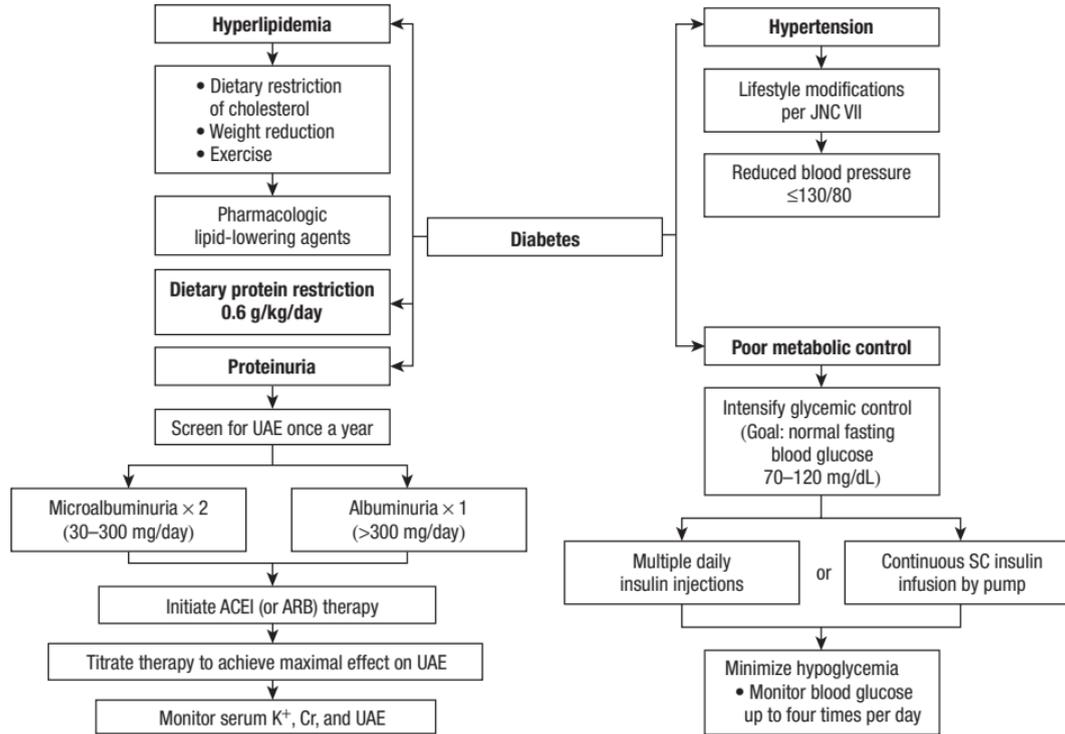
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#### Hyperglycemia

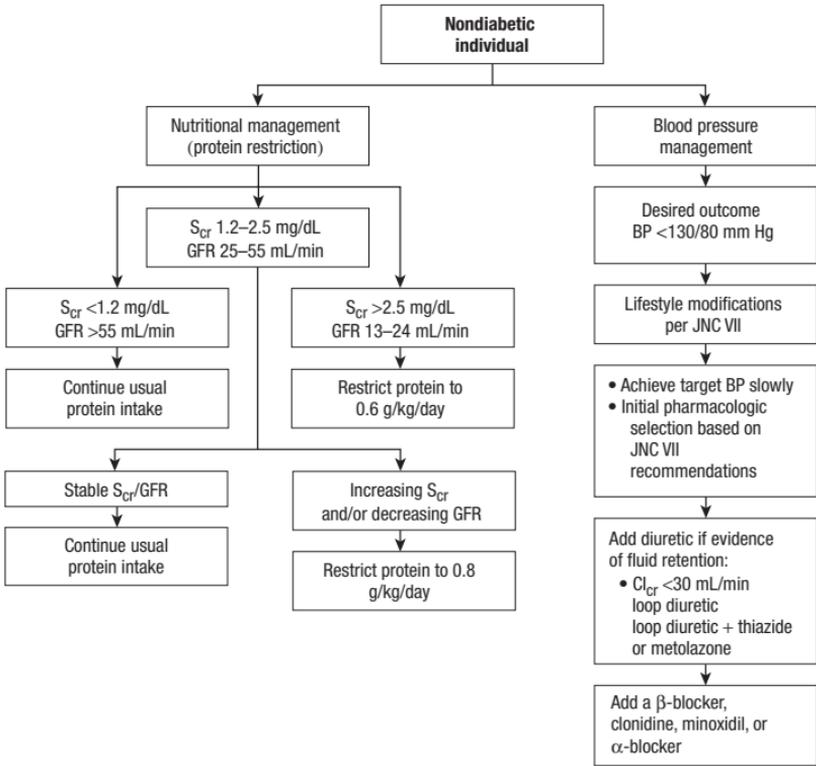
- Intensive therapy in patients with type 1 and type 2 diabetes reduces microvascular complications, including nephropathy. Intensive therapy can include insulin or oral drugs and involves blood sugar testing at least three times daily.
- The progression of CKD can be limited by optimal control of hyperglycemia and hypertension.
- For more information on diabetes, see Chap. 19.

#### Hypertension

- Adequate blood pressure control (Fig. 76-4, see Figs. 76-2 and 76-3) can reduce the rate of decline in GFR and albuminuria in patients with or without diabetes.
- Antihypertensive therapy should be initiated in diabetic or nondiabetic CKD patients with an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin II receptor blocker. Nondihydropyridine calcium channel blockers are generally used as second-line antiproteinuric drugs when ACEIs or angiotensin II receptor blockers are not tolerated.
- ACEI clearance is reduced in CKD, therefore treatment should begin with the lowest possible dose followed by gradual titration to achieve target blood pressure and, secondarily, to minimize proteinuria. No individual ACEI is superior to another.
- GFR typically decreases 25% to 30% within 3 to 7 days after starting ACEIs because this class reduces intraglomerular pressure. Sustained increases in the serum creatinine by more than 30% after starting ACEIs may be due to the ACEI and discontinuation should be strongly considered. Serum potassium should also be monitored to detect development of hyperkalemia after initiating or increasing the dose of an ACEI.



**FIGURE 76-2.** Therapeutic strategies to prevent progression of renal disease in diabetic individuals. (ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; JNC VII, the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; UAE, urinary albumin excretion.)



**FIGURE 76-3.** Therapeutic strategies to prevent progression of renal disease in nondiabetic individuals. (ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure;  $CL_{cr}$ , creatinine clearance; GFR, glomerular filtration rate; JNC VII, the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure;  $S_{cr}$ , serum creatinine.)

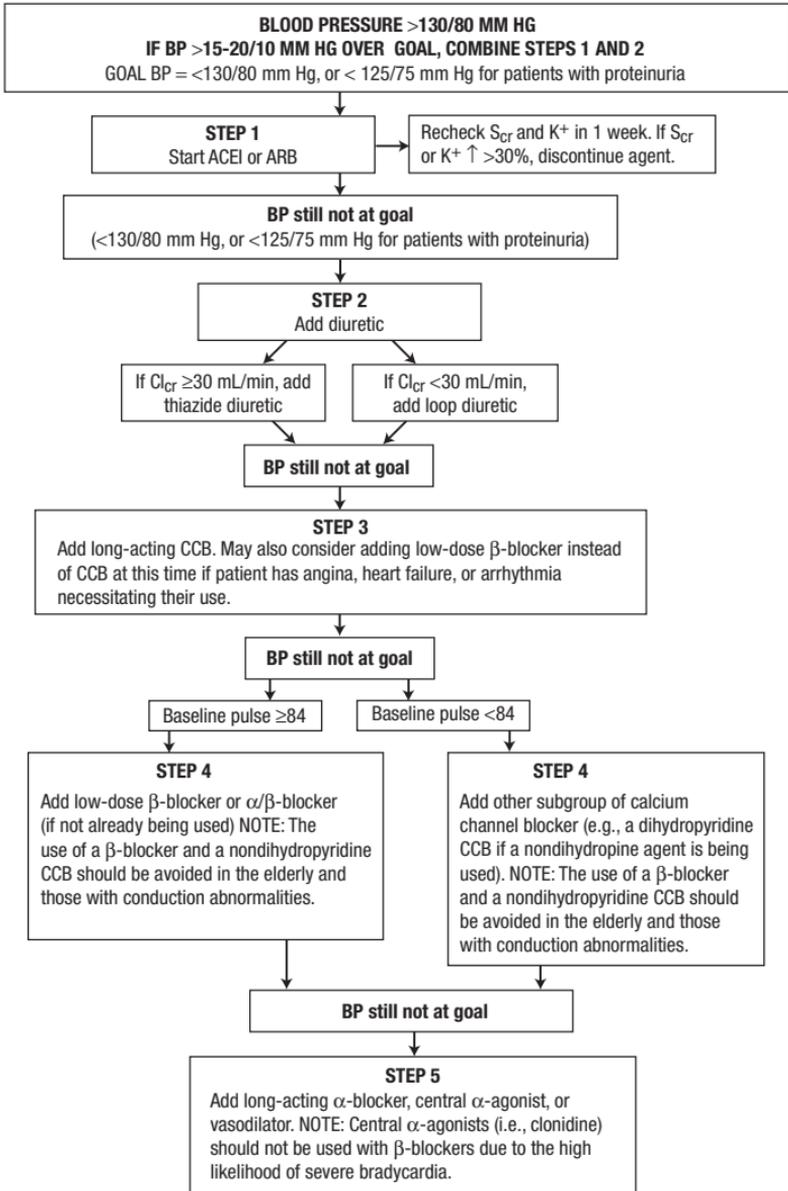
- For more information on hypertension, see Chap. 10.

### Supportive Therapies

- Dietary protein restriction (see Fig. 76-3), lipid-lowering medications, smoking cessation, and anemia management may help slow the rate of CKD progression.
- The primary goal of lipid-lowering therapies in CKD is to decrease the risk for progressive atherosclerotic cardiovascular disease (Table 76-1).
- A secondary goal is to reduce proteinuria and renal function decline seen with administration of statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors).
- For more information on hyperlipidemia, see Chap. 9.

## TREATMENT: MANAGEMENT OF COMPLICATIONS

- Progression of CKD to ESRD can occur over years to decades, with the mechanism of kidney damage dependent on the etiology of the disease;



**FIGURE 76-4.** Hypertension management algorithm for patients with chronic kidney disease. Dosage adjustments should be made every 2 to 4 weeks as needed. The dose of one agent should be maximized before another is added. (ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker;  $Cl_{cr}$ , creatinine clearance;  $S_{cr}$ , serum creatinine.) (Adapted from Bakris GL, Williams M, Dworkin L, et al. Preserving renal function in adults with hypertension and diabetes: A consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. *Am J Kidney Dis* 2000; 36:646–661, with permission.)

**TABLE 76-1** Management of Dyslipidemia in Patients with Chronic Kidney Disease

Dyslipidemia	Goal	Initial Therapy	Modification in Therapy <sup>a</sup>	Alternative <sup>a</sup>
TG ≥500 mg/dL	TG <500 mg/dL	TLC	TLC + fibrate or niacin	Fibrate or niacin
LDL 100–129 mg/dL	LDL <100 mg/dL	TLC	TLC + low-dose statin	Bile acid sequestrant or niacin
LDL ≥130 mg/dL	LDL <100 mg/dL	TLC + low-dose statin	TLC + maximum-dose statin	Bile acid sequestrant or niacin
TG ≥200 mg/dL and non-HDL ≥130 mg/dL	Non-HDL <130 mg/dL	TLC + low-dose statin	TLC + maximum-dose statin	Fibrate or niacin

HDL, high-density lipoprotein; LDL, low-density lipoprotein; Non-HDL, total cholesterol minus HDL cholesterol; TG, triglycerides; TLC, therapeutic lifestyle changes.

<sup>a</sup>Dosing of selected agents by class: fibrate (gemfibrozil 600 mg twice a day); niacin (1.5–3 g/day of immediate-release product); statin (simvastatin 10–40 mg/day if glomerular filtration rate [GFR] <30 mL/min, 20–80 mg/day if GFR >30 mL/min); bile acid sequestrant (cholestyramine 4–16 g/day).

See Chap. 23 in *Pharmacotherapy: A Pathophysiologic Approach*, seventh edition, for more complete dosing information.

From *K/DOQI Clinical Practice Guidelines for managing dyslipidemias in patients with chronic kidney disease. Am J Kidney Dis* 2003;41:S1–S91.

however, the consequences and complications of marked reductions in kidney function are fairly uniform irrespective of the underlying etiology.

- No single toxin is responsible for all of the signs and symptoms of uremia observed in stage 4 or 5 CKD. Toxins accumulate as a result of increased secretion, decreased clearance secondary to reduced metabolism within the kidney, and/or decreased renal clearance of by-products of protein metabolism.
- The overall goal of therapy is to optimize the patient's duration and quality of life. Patients who reach CKD stage 4 almost inevitably progress to ESRD, requiring dialysis to sustain life.
- The most common complications associated with a decline in GFR are discussed below.

## FLUID AND ELECTROLYTE ABNORMALITIES

- Serum sodium concentration is generally maintained by an increase in fractional excretion of sodium, resulting in a volume-expanded state. The most common manifestation of increased intravascular volume is systemic hypertension.
- The kidney's ability to adjust to abrupt changes in sodium intake is diminished in patients with ESRD. Sodium restriction beyond a no-added-salt diet is not recommended unless hypertension or edema is present. A negative sodium balance can decrease renal perfusion and cause a further decline in GFR.
- Diuretic therapy or dialysis may be necessary to control edema or blood pressure.
- Loop diuretics, particularly when administered by continuous infusion, increase urine volume and renal sodium excretion. Although thiazide

diuretics are ineffective when creatinine clearance is less than 30 mL/min, adding them to loop diuretics can enhance excretion of sodium and water.

## POTASSIUM HOMEOSTASIS

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- Serum potassium concentration is usually maintained in the normal range until the GFR is less than 20 mL/min per  $1.73 \text{ m}^2$ , when mild hyperkalemia is likely to develop.
- The definitive treatment of severe hyperkalemia in ESRD is hemodialysis. Temporary measures include **calcium gluconate**, **insulin and glucose**, **nebulized albuterol**, and **sodium polystyrene sulfonate**.
- For more information on potassium homeostasis, see Chap. 78.

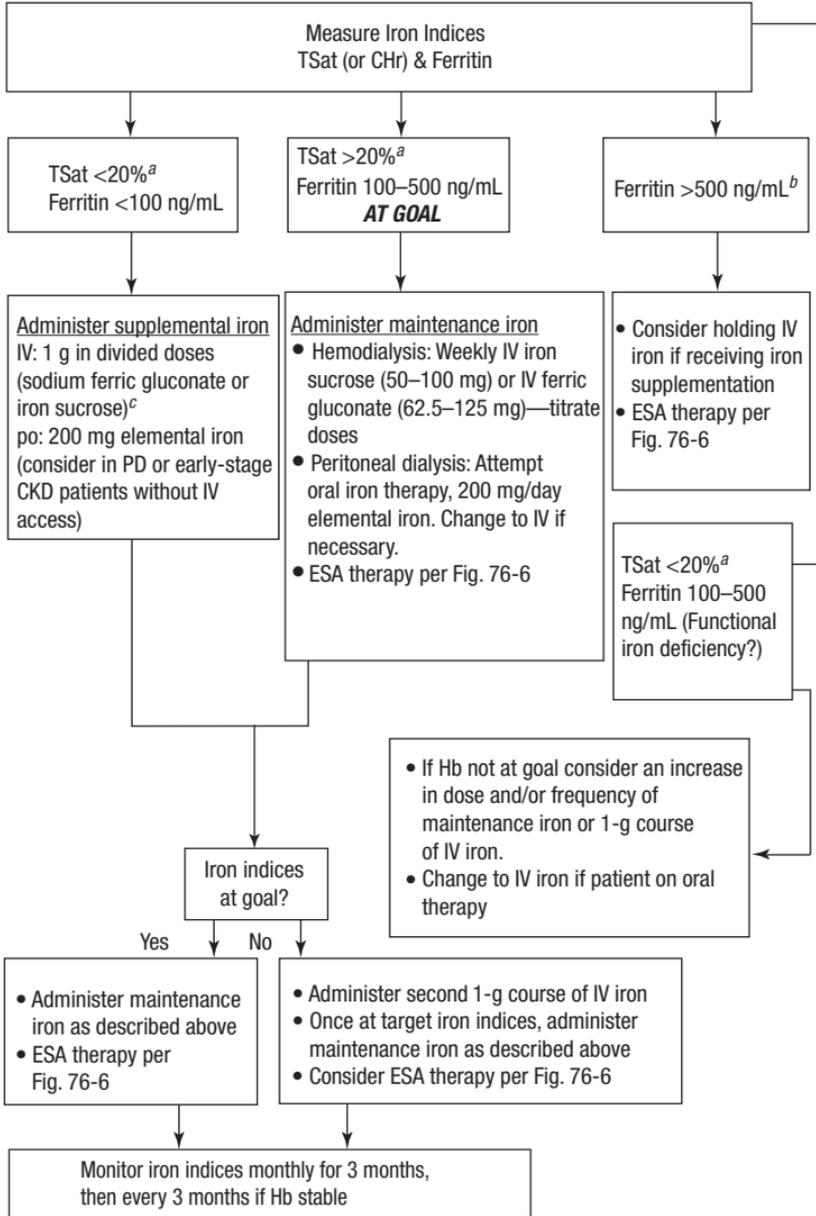
## ANEMIA

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- The primary cause of anemia in patients with CKD or ESRD is erythropoietin deficiency. Other contributing factors include decreased lifespan of red blood cells, blood loss, and iron deficiency.
- **Iron** supplementation is necessary to replete iron stores (Fig. 76-5). Parenteral iron therapy improves response to erythropoietic therapy and reduces the dose required to achieve and maintain target indices. In contrast, oral therapy is often inadequate.
- IV iron preparations have different pharmacokinetic profiles, which do not correlate with pharmacodynamic effect.
- Adverse effects of IV iron include allergic reactions, hypotension, dizziness, dyspnea, headaches, lower back pain, arthralgia, syncope, and arthritis. Some of these reactions can be minimized by decreasing the dose or rate of infusion. Sodium ferric gluconate and iron sucrose have better safety records than iron dextran. Iron dextran requires a test dose to reduce the risk of anaphylactic reactions.
- Subcutaneous (SC) administration of **epoetin alfa** is preferred because IV access is not required, and the SC dose that maintains target indices is 15% to 50% lower than the IV dose (Fig. 76-6).
- **Darbepoetin alfa** has a longer half-life than epoetin alfa and prolonged biologic activity. Doses are administered less frequently, starting at once a week when administered IV or SC.
- Erythropoietic agents are well tolerated. Hypertension is the most common adverse event.

## Evaluation of Therapeutic Outcomes

- Iron indices (transferrin saturation [TSat]; ferritin) should be evaluated before initiating an erythropoietic agent (see Fig. 76-5). To avoid errors, clinicians should wait at least 2 weeks after a loading dose of IV iron to reassess iron indices.
- For monitoring purposes, hemoglobin is preferred to hematocrit because the latter fluctuates with volume status. The target hemoglobin is 12 g/dL.
- After an erythropoietic agent is initiated, hemoglobin response is typically delayed. Steady-state hemoglobin levels do not occur until after the life span of a red blood cell (mean 2 months; range 1 to 4 months). To avoid

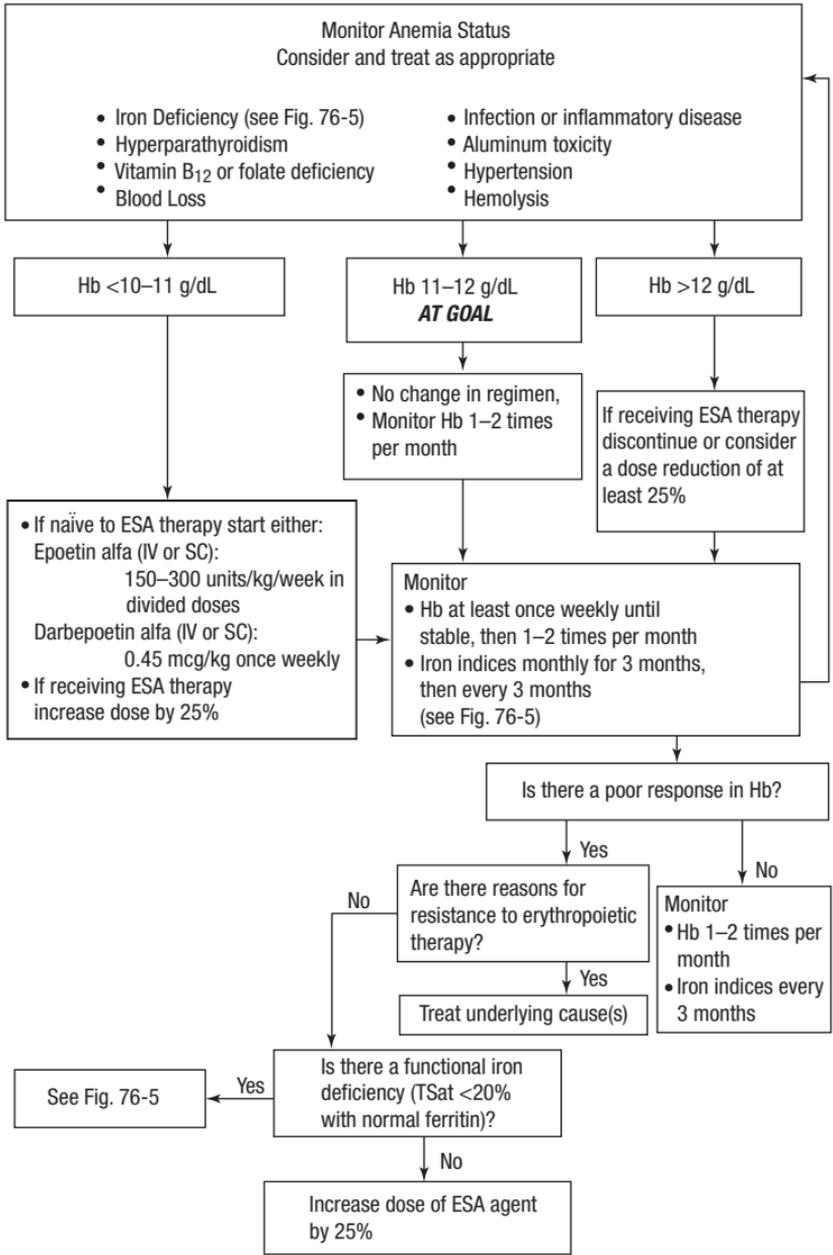


<sup>a</sup> Or Chr <29 pg/cell in hemodialysis patients

<sup>b</sup> Clinical judgment should be used to determine if iron supplementation should be continued when ferritin >500 ng/mL

<sup>c</sup> IV iron regimen may be divided over 8–10 HD sessions (depending on product used) or given in larger doses over a prolonged administration time (e.g., up to 400 mg iron sucrose over 2.5 hours) for patients on PD

**FIGURE 76-5.** Guidelines for iron therapy in the management of the anemia of chronic kidney disease (CKD). (Chr, content of hemoglobin in the reticulocytes; ESA, erythropoietic-stimulating agent; Hb, hemoglobin; HD, hemodialysis; PD, peritoneal dialysis; TSat; transferrin saturation.)



**FIGURE 76-6.** Guidelines for erythropoietic therapy in the management of the anemia of chronic kidney disease. (ESA, erythropoietic-stimulating agent; Hb, hemoglobin; TSat; transferrin saturation.)

making premature dosing changes, clinicians should evaluate response over several weeks (see Fig. 76-6).

- Patients should be monitored for potential complications, such as hypertension, which should be treated before starting an erythropoietic agent.
- For more information on anemia, see Chap. 33.

## SECONDARY HYPERPARATHYROIDISM AND RENAL OSTEODYSTROPHY

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### Pathophysiology and Clinical Presentation

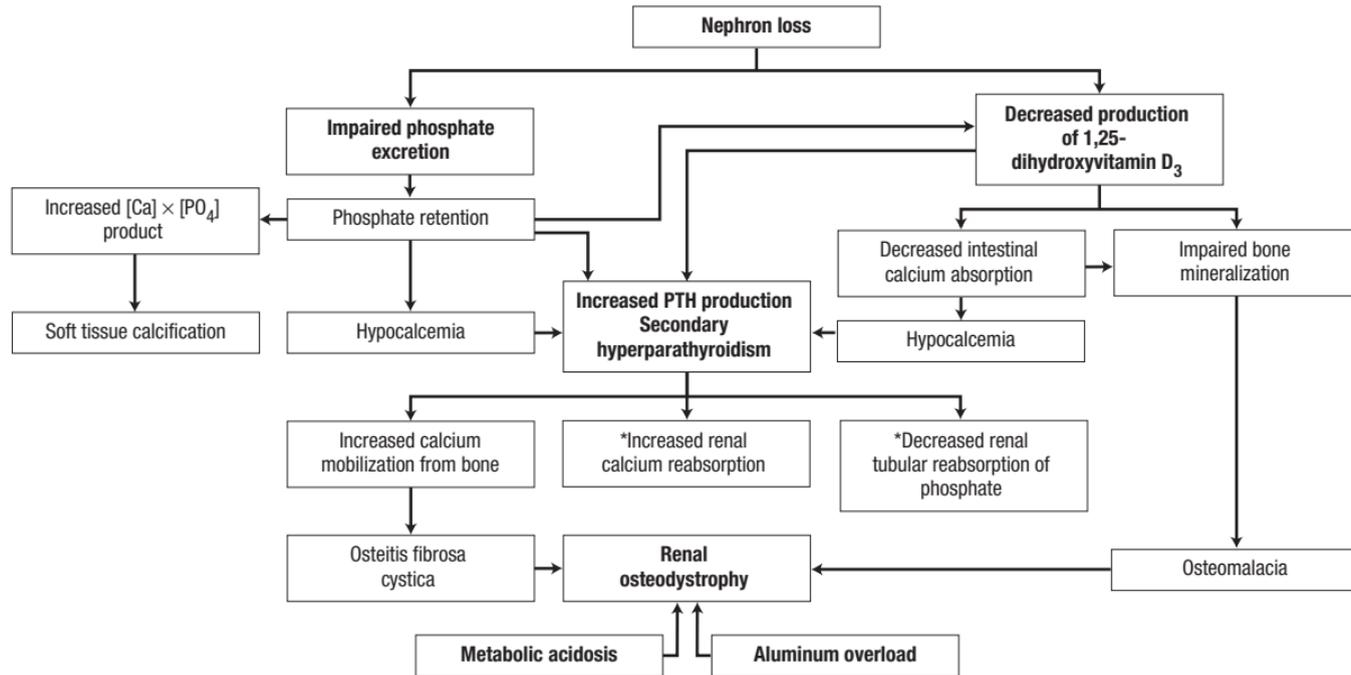
- Calcium–phosphorus balance is mediated through a complex interplay of hormones and their effects on bone, GI tract, kidney, and parathyroid gland. As kidney disease progresses, renal activation of vitamin D is impaired, which reduces gut absorption of calcium. Low blood calcium concentration stimulates secretion of parathyroid hormone (PTH). As renal function declines, serum calcium balance can be maintained only at the expense of increased bone resorption, ultimately resulting in renal osteodystrophy (ROD) (Fig. 76-7).
- Secondary hyperparathyroidism can cause altered lipid metabolism, altered insulin secretin, resistance to erythropoietic therapy, impaired neurologic and immune functions, and increased mortality.
- ROD progresses insidiously for several years before the onset of symptoms such as bone pain and fractures. Skeletal complications include osteitis fibrosa cystica (high bone turnover), osteomalacia (low bone turnover) and adynamic bone disease. When ROD symptoms appear, the disease is not easily amenable to treatment.

### Treatment

- Preventive measures should be initiated in patients in early stages of CKD to improve outcomes by the time they reach stage 5 CKD or ESRD.
- The K/DOQI guidelines provide desired ranges of calcium, phosphorus, calcium–phosphorus product, and intact PTH based on the stage of CKD (Table 76-2). Measurements should be repeated every 12 months for stage 3, every 3 months for stage 4, and more frequently for stage 5.
- Dietary phosphorus restriction (800 to 1,000 mg/day) should be first-line intervention for stage 3 or higher CKD.
- By the time ESRD develops, most patients require a combination of phosphate-binding agents, vitamin D, and calcimimetic therapy to achieve K/DOQI goals.

#### *Phosphate-Binding Agents*

- Phosphate-binding agents decrease phosphorus absorption from the gut and are first-line agents for controlling both serum phosphorus and calcium concentrations (Table 76-3).
- K/DOQI guidelines recommend that elemental calcium from calcium-containing binders should not exceed 1,500 mg/day and the total daily intake from all sources should not exceed 2,000 mg. This may necessitate combination of calcium- and noncalcium-containing products (e.g., **sevelamer HCL**, **lanthanum carbonate**).



**FIGURE 76-7.** Pathogenesis of secondary hyperparathyroidism and renal osteodystrophy in patients with chronic kidney disease. \*These adaptations are lost as renal failure progresses. (Ca, calcium; PO<sub>4</sub>, phosphate; PTH, parathyroid hormone.)

**TABLE 76-2** Kidney Disease/Dialysis Outcomes Quality Initiative (K/DOQI) Guidelines for Calcium (C), Phosphorus (P), Calcium Phosphorus Product, and Intact Parathyroid Hormone

Parameter	Chronic Kidney Disease		
	Stage 3	Stage 4	Stage 5
Corrected calcium (mg/dL)	"Normal"	"Normal"	8.4–9.5
Phosphorus (mg/dL)	2.7–4.6	2.7–4.6	3.5–5.5
Ca × P (mg <sup>2</sup> /dL <sup>2</sup> )	<55	<55	<55
Intact parathyroid hormone (pg/mL)	35–70	70–110	150–300

From Eknoyan G, Levin A, Levin NW. Bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis* 2003;42:1–201.

- Adverse effects of calcium-containing phosphate binders, as well as sevelamer and lanthanum, include constipation, diarrhea, nausea, vomiting, and abdominal pain. The risk of hypercalcemia is also a concern. To avoid potential drug interactions, phosphate binders should be administered 1 hour before or 3 hours after other oral medications.

#### Vitamin D Therapy

- Calcium (less than 9.5 mg/dL) and phosphorus (less than 4.6 mg/dL) must be controlled before vitamin D therapy is initiated.
- **Calcitriol**, 1,25-dihydroxyvitamin D<sub>3</sub>, directly suppresses PTH synthesis and secretion and upregulates vitamin D receptors, which ultimately may reduce parathyroid hyperplasia. The dose depends on the stage of CKD and type of dialysis (Table 76-4).
- The newer vitamin D analogs **paricalcitol** and **doxercalciferol** may be associated with less hypercalcemia and, for paricalcitol, hyperphosphatemia. Vitamin D therapy, regardless of agent, is associated with decreased mortality.

#### Calcimimetics

- **Cinacalcet** reduces PTH secretion by increasing the sensitivity of the calcium-sensing receptor. The most common adverse events are nausea and vomiting.
- The most effective way to use cinacalcet with other therapies has not been decided. The starting dose is 30 mg daily, which can be titrated to the desired PTH and calcium concentrations every 3 to 4 weeks and to a maximum of 180 mg daily.

## METABOLIC ACIDOSIS

- A clinically significant metabolic acidosis is commonly seen when the GFR drops below 20 to 30 mL/min (stage 4 CKD). The goals of therapy in CKD are to normalize the blood pH (7.35 to 7.45) and serum bicarbonate (22 to 26 mEq/L).
- Consequences of metabolic acidosis include renal bone disease, reduced cardiac contractility, predisposition to arrhythmias, and protein catabolism.
- Oral alkalinizing salts (e.g., **sodium bicarbonate**, **Shohl solution**, and **Bicitra**) can be used in patients with stage 4 or 5 CKD. **Polycitra**, which

**TABLE 76-3** Phosphate-Binding Agents Used in the Treatment of Hyperphosphatemia in Chronic Kidney Disease Patients

Compound	Trade Name	Compound Content (mg)	Dose Titration <sup>b</sup>	Starting Doses	Comments
Calcium carbonate <sup>d</sup> (40% elemental calcium)	Tums	500, 750, 1,000, 1,250	Increase or decrease by 500 mg per meal (200 mg elemental calcium)	0.5–1 g (elemental calcium) three times a day with meals	First-line agent; dissolution characteristics and phosphate binding affect may vary from product to product; try to limit daily intake of elemental calcium to 1,500 mg/day  Approximately 39 mg phosphorus bound per 1 g calcium carbonate
	Oscal-500	1,250			
	Caltrate 600	1,500			
	Nephro-Calci	1,500			
	LiquiCal	1,200			
Calcium acetate (25% elemental calcium)	PhosLo	667	Increase or decrease by 667 mg per meal (168 mg elemental calcium)	0.5–1 g (elemental calcium) three times a day with meals	First-line agent; comparable efficacy to calcium carbonate with half the dose of elemental calcium; do not exceed 1.5 g of elemental calcium per day  Approximately 45 mg phosphorus bound per 1 g calcium acetate By prescription only
Sevelamer hydrochloride	Renagel	400, 800	Increase or decrease by 800 mg per meal	800–1,600 mg three times a day with meals	First-line agent; lowers low-density lipoprotein cholesterol More expensive than calcium products; preferred in patients at risk for extraskeletal calcification
Sevelamer carbonate	Renvela	800	Same as HCl salt	Same as HCl salt	Same as HCl; associated with a lower risk of GI adverse events than Renagel.
Lanthanum carbonate	Fosrenol	250, 500, 750, 1,000	Increase or decrease by 250–500 mg per meal	250–500 mg three times a day with meals	First-line agent Available as chewable tablets

*(continued)*

**TABLE 76-3** Phosphate-Binding Agents Used in the Treatment of Hyperphosphatemia in Chronic Kidney Disease Patients (Continued)

Compound	Trade Name	Compound Content (mg)	Dose Titration <sup>b</sup>	Starting Doses	Comments
Aluminum hydroxide	Alterna GEL	600 mg/5 mL	—	300–600 mg three times a day with meals	Third-line agents; do not use concurrently with citrate-containing products
	Amphojel	300, 600 (tablet); 320 mg/5 mL (suspension)	—		
Aluminum carbonate	Alu-Cap	400	—	450–500 mg three times a day with meals	Reserve for short-term use (4 weeks) in patients with hyperphosphatemia not responding to other binders
	Basaljel	500 (tablet, capsule); 400 mg/5 mL (suspension)			
Magnesium carbonate	Mag-Carb	70 (capsule)	—	70 mg three times a day with meals	Third-line agent; diarrhea common; monitor serum magnesium
Magnesium hydroxide	Milk of magnesia	300, 600 (tablet); 400 mg/5 mL, 800 mg/5 mL (suspension)	—	300–400 mg three times a day with meals	Same as for magnesium carbonate
Magnesium carbonate/calcium carbonate	MagneBind 200	200	—	200 mg three times a day with meals (based on magnesium content)	Same as for calcium carbonate and magnesium carbonate

HCl, hydrochloride.

<sup>a</sup>Multiple preparations available that are not listed.

<sup>b</sup>Based on phosphorus levels, titrate every 2 to 3 weeks until phosphorus goal reached.

**TABLE 76-4** Dosing Recommendations for Vitamin D in Patients with Stage 5 Chronic Kidney Disease and Those on Hemodialysis<sup>a</sup>

PTH (pg/mL)	IV and Oral Calcitriol Dose per HD	IV Paricalcitol Dose per HD	Oral and IV Doxercalciferol Dose per HD
300–600 <sup>b</sup>	0.5–1.5 mcg oral or IV	2.5–5 mcg	5 mcg oral, 2 mcg IV
600–1,000 <sup>b</sup>	1–4 mcg oral 1–3 mcg IV	6–10 mcg	5–10 mcg oral, 2–4 mcg IV
>1,000 <sup>c</sup>	3–7 mcg oral 3–5 mcg IV	10–15 mcg	10–20 mcg oral, 4–8 mcg IV

HD, hemodialysis; PTH, parathyroid hormone.

<sup>a</sup>Peritoneal dialysis patients may be treated with oral doses of calcitriol (0.5–1 mcg) or doxercalciferol (2.5–5 mcg) two or three times weekly. May also use oral calcitriol at 0.25 mcg daily.

<sup>b</sup>If serum calcium <9.5 mg/dL, phosphorus <5.5 mg/dL, and  $\text{Ca} \times \text{P} < 55 \text{ mg}^2/\text{dL}^2$ .

<sup>c</sup>If serum calcium <10 mg/dL, phosphorus <5.5 mg/dL, and  $\text{Ca} \times \text{P} < 55 \text{ mg}^2/\text{dL}^2$ .

From Eknoyan G, Levin A, Levin NW. Bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis* 2003;42:1–201.

contains potassium citrate, should not be used in patients with severe CKD because hyperkalemia may result.

- The replacement alkali dose can be approximated by multiplying bicarbonate's volume of distribution (0.5 L/kg) by the patient's weight (in kg) and by their deficit (24 mEq/L minus patient's serum bicarbonate value). The dose should be administered over several days. The daily maintenance dose is usually 12 to 20 mEq/mL and should be titrated as needed.
- Metabolic acidosis in patients undergoing dialysis can often be managed by using higher concentrations of bicarbonate or acetate in the dialysate.
- For more information on acid–base disorders, see Chap. 74.

## HYPERTENSION

- The pathogenesis of hypertension in patients with CKD is multifactorial and includes fluid retention, increased sympathetic activity, an endogenous digitalis-like substance, elevated levels of endothelin-1, erythropoietin use, hyperparathyroidism, and structural arterial changes.
- In early stage CKD, the target blood pressure for cardiovascular risk reduction is 130/80 mm Hg. The K/DOQI guidelines propose a predialysis blood pressure of less than 140/90 mm Hg and a postdialysis blood pressure of less than 130/80 mm Hg.
- Salt (2 to 3 g/day) and fluid intake should be restricted.
- Most patients with ESRD require three or more antihypertensive agents to achieve target blood pressure. As with less advanced CKD (see Fig. 76-4), ACEIs, ARBs, and dihydropyridine calcium channel blockers are the preferred agents.
- Blood pressure should be monitored at each visit, and at home when feasible.
- For more information on hypertension, see Chap. 10.

## HYPERLIPIDEMIA

- The prevalence of hyperlipidemia increases as renal function declines.

- Hyperlipidemia should be managed aggressively in patients with ESRD to a low-density lipoprotein cholesterol goal of less than 100 mg/dL. Statins are the drugs of first choice. Although well tolerated by otherwise healthy patients, statins have the potential to cause myotoxic effects when administered in patients with hepatic disease or with interacting drugs such as azole antibiotics, cyclosporine, gemfibrozil, and niacin.
- In patients with ESRD, lipid profile should be reassessed at least annually and 2 to 3 months after changing treatment.
- For more information on hyperlipidemia, see Table 76-1 and Chap. 9.

## OTHER SECONDARY COMPLICATIONS

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### Pruritus

- Pruritus is a common problem in patients with ESRD. The pathogenesis is poorly understood but has been attributed to inadequate dialysis, skin dryness, secondary hyperparathyroidism, increased concentrations of vitamin A and histamine, and increased sensitivity to histamine.
- For more information on pruritus, see Chap. 48, Hemodialysis and Peritoneal Dialysis, authored by Edward F. Foote and Harold J. Manley, in *Pharmacotherapy: A Pathophysiologic Approach*, seventh edition.

### Nutritional Status

- Protein-energy malnutrition is common in patients with stage 4 or 5 CKD. Food intake is often inadequate because of anorexia, altered taste sensation, intercurrent illness, and unpalatability of prescribed diets.
- Daily protein intake should be 1.2 g/kg for patients undergoing hemodialysis and 1.2 to 1.3 g/kg for those undergoing peritoneal dialysis.
- Daily energy intake should be 35 kcal/kg for patients undergoing any type of dialysis. The intake should be lowered to 30 to 35 kcal/kg for patients older than 60 years.
- Vitamins A and E are elevated in ESRD whereas water-soluble vitamins should be supplemented to replace dialysis-induced loss.
- For more information on nutrition requirements, see Chap. 57.

### Uremic Bleeding

- The pathophysiology of uremic bleeding is multifactorial. The primary mechanisms are platelet biochemical abnormalities and alterations in platelet-vessel wall interactions.
- Nondialytic therapies that may temporarily shorten increased bleeding time include **cryoprecipitate**, **desmopressin** (1-deamino-8-D-arginine vasopressin), and estrogens.

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See Chap. 46, *Chronic Kidney Disease: Progression-Modifying Therapies*, authored by Melanie S. Joy, Abhijit Kshirsagar, and Nora Franceschini, and Chap. 47, *Chronic Kidney Disease: Management of Complications*, authored by Joanna Q. Hudson, for a more detailed discussion of this topic.

## GENERAL PRINCIPLES

- The pathophysiology, clinical manifestations, diagnosis, and treatment of acute renal failure and chronic kidney disease (CKD) or end-stage renal disease are discussed in Chaps. 75 and 76, respectively.
- Drug therapy individualization for patients with renal insufficiency sometimes requires only a simple proportional dose adjustment based on creatinine clearance ( $CL_{cr}$ ). Alternatively, complex adjustments are required for drugs that are extensively metabolized or undergo dramatic changes in protein binding and distribution volume.
- Patients may respond differently to a given drug because of the physiologic and biochemical changes associated with CKD.

## EFFECT ON DRUG ABSORPTION

- There is little quantitative information regarding influence of impaired renal function on drug absorption and bioavailability.
- Factors that theoretically affect bioavailability include alterations in GI transit time, gastric pH, edema of the GI tract, vomiting and diarrhea, and concomitant drug therapy, especially antacid or  $H_2$ -antagonist administration.

## EFFECT ON DRUG DISTRIBUTION

- The volume of distribution of many drugs is significantly increased or decreased in patients with CKD. Changes result from altered protein or tissue binding, or pathophysiologic alterations in body composition (e.g., fractional contribution of total body water to total body weight).
- Generally, plasma protein binding of acidic drugs (e.g., **warfarin**, **phenytoin**) is decreased in CKD, whereas binding of basic drugs (e.g., **quinidine**, **lidocaine**) is usually normal or slightly decreased or increased.
- Ideally, unbound (versus total) drug concentrations should be monitored, especially for drugs that have a narrow therapeutic range, are highly protein bound (free fraction less than 20%), and have marked variability in the free fraction (e.g., **phenytoin**, **disopyramide**).
- Methods for calculating volume of distribution ( $V_D$ ) can be influenced by renal disease. Of the commonly used terms (i.e., volumes of central compartment, terminal phase, and distribution at steady state [ $V_{SS}$ ]),  $V_{SS}$  is the most appropriate for comparing patients with renal insufficiency versus those with normal renal function because  $V_{SS}$  is independent of drug elimination.

## EFFECT ON METABOLISM

- CKD may alter nonrenal clearance of drugs as the result of changes in cytochrome P450-mediated metabolism in the liver and other organs. The clinical reductions in nonrenal clearance in CKD are generally proportional to the reductions in glomerular filtration rate (Table 77-1).

**TABLE 77-1** Effect of End-Stage Renal Disease on Nonrenal Clearance of Selected Drugs

<b>Decreased</b>			
Acyclovir	Aztreonam	Bufuralol	Captopril
Cefmenoxime	Cefmetazole	Cefonicid	Cefotaxime
Cefotiam	Cefsulodin	Ceftizoxime	Cilastatin
Cimetidine	Ciprofloxacin	Cortisol	Encainide
Erythromycin	Imipenem	Isoniazid	Methylprednisolone
Metoclopramide	Moxalactam	Nicardipine	Nimodipine
Nitrendipine	Procainamide	Quinapril	Repaglinide
Verapamil	Zidovudine		
<b>Unchanged</b>			
Acetaminophen	Chloramphenicol	Clonidine	Codeine
Diflunisal	Indomethacin	Insulin	Isradipine
Lidocaine	Morphine	Metoprolol	Nisoldipine
Nortriptyline	Pentobarbital	Propafenone	Quinidine
Theophylline	Tocainide	Tolbutamide	
<b>Increased</b>			
Bumetanide	Cefpiramide	Fosinopril	Nifedipine
Phenytoin	Rosiglitazone	Sulfadimidine	

- Patients with severe renal insufficiency can experience accumulation of metabolite(s), which can contribute to pharmacologic activity or toxicity.

## EFFECT ON RENAL EXCRETION

- Altered renal filtration, secretion, and/or absorption can have dramatic effects on the pharmacokinetics of a drug. The impact depends on the fraction of drug normally eliminated unchanged by the kidney and on the degree of renal insufficiency.
- Quantitative investigation of renal handling of drugs is needed to elucidate the relative contribution of tubular function to renal drug clearance. In the absence of clinically useful techniques to quantitate tubular function, clinical measurement or estimation of  $CL_{cr}$  remains the guiding factor for calculating drug-dosage regimen design.

## DRUG-DOSAGE REGIMEN DESIGNS

- The optimal dosage regimen for patients with renal insufficiency requires an individualized assessment (Table 77-2). The optimal regimen depends on an accurate characterization of the relationship between the drug's pharmacokinetic parameters and renal function and on an accurate assessment of the patient's residual renal function.
- If the relationship between  $CL_{cr}$  and the kinetic parameters of a drug (i.e., total body clearance [CL] and elimination rate constant [k]) is known, these data should be used to individualize drug therapy (Table 77-3).
- If the relationship between  $CL_{cr}$  and the kinetic parameters is unknown, then the patient's kinetic parameters can be based on the fraction of drug eliminated renally unchanged ( $f_e$ ) in subjects with normal renal function.

**TABLE 77-2** A Stepwise Approach to Adjust Drug Dosages for Patients with Renal Insufficiency

Step 1	Obtain history and relevant demographic/clinical information	Record demographic information; obtain past medical history, including history of renal disease; and record current laboratory information (e.g., serum creatinine)
Step 2	Estimate creatinine clearance	Use Cockcroft-Gault equation to estimate creatinine clearance or calculate creatinine clearance from timed urine collection
Step 3	Review current medications	Identify drugs for which individualization of the treatment regimen will be necessary
Step 4	Calculate individualized treatment regimen	Determine treatment goals; calculate dosage regimen based on pharmacokinetic characteristics of the drug and the patient's renal function
Step 5	Monitor	Monitor parameters of drug response and toxicity; monitor drug levels if available/applicable
Step 6	Revise regimen	Adjust regimen based on drug response or change in patient status (including renal function) as warranted

This approach assumes that  $f_e$  is known, the change in CL and  $k$  are proportional to  $CL_{Cr}$ , renal disease does not alter drug metabolism, any metabolites are inactive and nontoxic, the drug obeys first-order (linear) kinetic principles, and the drug is adequately described by a one-compartment model. The kinetic parameter/dosage adjustment factor ( $Q$ ) can be calculated as:

$$Q = 1 - [f_e(1 - KF)]$$

where  $KF$  is the ratio of the patient's  $CL_{Cr}$  to the assumed normal value of 120 mL/min per 1.73 m<sup>2</sup>. The estimated total body clearance of the patient ( $CL_{PT}$ ) can then be calculated as:

$$CL_{PT} = CL_{norm} \times Q$$

**TABLE 77-3** Relationship between Creatinine Clearance and Total-Body Clearance and Terminal Elimination Rate Constant of Selected Drugs

Drug	Elimination Rate Constant	Total Body Clearance
Acyclovir		$CL = 3.37 (CL_{Cr}) + 0.41$
Amikacin	$k = (0.0024 \times CL_{Cr}) + 0.01$	$CL = 0.6 (CL_{Cr}) + 9.6$
Ceftazidime	$k = (0.004 \times CL_{Cr}) + 0.004$	$CL = 1.15 (CL_{Cr}) + 10.6$
Ciprofloxacin		$CL = 2.83 (CL_{Cr}) + 363$
Digoxin		$CL = 0.88 (CL_{Cr}) + 23$
Gentamicin	$k = (0.0029 \times CL_{Cr}) + 0.015$	$CL = 0.983 (CL_{Cr})$
Lithium		$CL = 0.20 (CL_{Cr})$
Ofloxacin		$CL = 1.04 (CL_{Cr}) + 38.7$
Piperacillin	$k = (0.0049 \times CL_{Cr}) + 0.21$	$CL = 1.36 (CL_{Cr}) + 1.50$
Tobramycin	$k = (0.0029 \times CL_{Cr}) + 0.01$	$CL = 0.801 (CL_{Cr})$
Vancomycin	$k = (0.00083 \times CL_{Cr}) + 0.0044$	$CL = 0.69 (CL_{Cr}) + 3.7$

CL, total-body clearance;  $CL_{Cr}$ , creatinine clearance;  $k$ , elimination rate constant.

where  $CL_{\text{norm}}$  is the mean total body clearance in patients with normal renal function.

- The best method for adjusting the dosage regimen depends on whether the goal is maintaining a similar peak, trough, or average steady-state drug concentration. The principal choices are to decrease the dose, prolong the dosing interval, or both. Prolonging the interval is generally preferred because it saves costs by reducing nursing and pharmacy time as well as associated supplies.
- Drug disposition parameters can be estimated if the relationship between the pharmacokinetic parameters of the drug and renal function are known.
- The ratio ( $Q$ ) of the estimated elimination rate constant or total body clearance relative to normal renal function is used to determine the dose or dosing interval alterations needed ( $CL_{\text{fail}}$  is the clearance with impaired renal function).

$$Q = CL_{\text{fail}}/CL_{\text{norm}}$$

- The prolonged dosing interval ( $\tau_f$ ) or reduced maintenance dose ( $D_f$ ) is calculated from the following relationships, where  $\tau_n$  is the normal dosing interval and  $D_n$  is the normal dose:

$$\tau_f = \tau_n/Q$$

$$D_f = D_n \times Q \times \tau_f/\tau_p$$

- If  $V_D$  is significantly altered or a specific concentration is desired, estimation of a dosage regimen becomes more complex. The dosing interval ( $\tau_f$ ) is calculated as:

$$\tau_f = \{(-1/k_f)[\ln(C_{\text{min}}/C_{\text{max}})]\} + t_{\text{peak}}$$

where  $C_{\text{min}}$  and  $C_{\text{max}}$  are minimum and maximum concentrations, respectively, and  $t_{\text{peak}}$  is time of peak concentration. The dose is calculated as:

$$D = [FC_p^t V_D(k_a - k)]/\{k_a [e^{-kt}/(1 - e^{-kt})][e^{-kat}/(1 - e^{kat})]\}$$

where  $F$  equals the bioavailability,  $C_p^t$  equals the desired plasma concentration at time  $t$ , and  $k_a$  is the absorption rate constant. If the drug is absorbed extremely rapidly,  $\tau_f$  is calculated as:

$$\tau_f = (-1/k_f)[\ln(C_{\text{min}}/C_{\text{max}})]$$

and dose as:

$$D = V_D(C_{\text{max}} - C_{\text{min}})$$

## PATIENTS RECEIVING CONTINUOUS RENAL REPLACEMENT THERAPY

- Continuous renal replacement therapy is used for the management of fluid overload and removal of uremic toxins in patients with acute renal failure and other conditions. Drug therapy individualization for patients receiving continuous renal replacement therapy is discussed in Chap. 75.

## PATIENTS RECEIVING CHRONIC AMBULATORY PERITONEAL DIALYSIS

- Peritoneal dialysis has the potential to affect drug disposition; however, drug therapy individualization is often less complicated because of the continuous nature of chronic ambulatory peritoneal dialysis.
- Factors that influence drug dialyzability in chronic ambulatory peritoneal dialysis include drug-specific characteristics (e.g., molecular weight, solubility, degree of ionization, protein binding, and  $V_D$ ) and intrinsic properties of the peritoneal membrane (e.g., blood flow, pore size, and peritoneal membrane surface area).
- In general, peritoneal dialysis is less effective in removing drugs than hemodialysis and, in fact, does not contribute substantially to total body clearance.

## PATIENTS RECEIVING CHRONIC HEMODIALYSIS

- The impact of hemodialysis on drug therapy depends on drug characteristics (e.g., molecular weight, protein binding, and  $V_D$ ), dialysis prescription (e.g., dialysis membrane composition, filter surface area, blood and dialysate flow rates, and reuse of the dialysis filter), and clinical indication for dialysis.
- High-flux dialysis allows free passage of most solutes with molecular weights up to 20,000. Therefore, high-flux dialysis is more likely to remove high-molecular-weight drugs (e.g., **vancomycin**), and drugs with low- to mid-molecular weights (i.e., 100 to 1,000), than conventional dialysis (Table 77-4).
- The dialysate recovery clearance approach has become the benchmark for determining dialyzer clearance. It can be calculated as:

$$CL^r_D = R/AUC_{0-t}$$

**TABLE 77-4** Drug Disposition during Dialysis Depends on Dialyzer Characteristics

Drug	Hemodialysis Clearance (mL/min)		Half-Life during Dialysis (hour)	
	Conventional	High Flux	Conventional	High Flux
Ceftazidime	55–60	155 <sup>a</sup>	3.3	1.2 <sup>a</sup>
Cefuroxime	NR	103 <sup>b</sup>	3.8	1.6 <sup>b</sup>
Foscarnet	183	253 <sup>b</sup>	NR	NR
Gentamicin	58.2	116 <sup>b</sup>	3.0	4.3 <sup>b</sup>
Netilmicin	46	87–109	5.0–5.2	2.9–3.4
Ranitidine	43.1	67.2 <sup>b</sup>	5.1	2.9 <sup>b</sup>
Vancomycin	9–21	31–60 <sup>c</sup> 40–150 <sup>b</sup> 72–116 <sup>d</sup>	35–38	12.0 <sup>c</sup> 4.5–11.8 <sup>b</sup> NR <sup>d</sup>

NR, not reported.

<sup>a</sup>Polyamide filter.

<sup>b</sup>Polysulfone filter.

<sup>c</sup>Polycrylonitrile filter.

<sup>d</sup>Polymethylmethacrylate.

Data from Matzke GR, *J Pharmacy Practice*, Vol. 15, pp. 405–418, Copyright 2002 by Sage Publications, Inc.

where  $R$  is the total amount of drug recovered unchanged in dialysate and  $AUC_{0-t}$  is the area under the predialyzer plasma concentration-time curve during the time when the dialysate was collected. To determine  $AUC_{0-t}$ , at least two and preferably three to four plasma concentrations should be obtained during dialysis.

- Total clearance during dialysis can be calculated as the sum of the patient's residual clearance during the interdialytic period ( $CL_{RES}$ ) and dialyzer clearance ( $CL_D$ ):

$$CL_T = CL_{RES} + CL_D$$

- Half-life between hemodialysis (HD) treatments and during dialysis can then be calculated from the following relationships using a published estimate of the drug's  $V_D$ :

$$t_{1/2, \text{ off HD}} = 0.693[V_D/CL_{RES}]$$

and

$$t_{1/2, \text{ on HD}} = 0.693[V_D/(CL_{RES} + CL_D)]$$

- Once key pharmacokinetic parameters are estimated (based on population data) or calculated, they can be used to simulate the plasma concentration-time profile of the drug for the patient and to ascertain how much drug to administer and when.
- Plasma concentrations of the drug over the interdialytic interval of 24 to 48 hours can be predicted. The concentration at the end of a 30-minute infusion ( $C_{max}$ ) would be:

$$C_{max}[(D/t')(1 - e^{-kt'})]/CL_{RES}$$

- Plasma concentration before the next dialysis session ( $C_{bD}$ ) can be calculated as:

$$C_{bD} = C_{max} \times e^{-(CL_{RES}/VD) \times t}$$

- Hemodialysis clearance of most drugs is dialysis-filter dependent, and a value can be extrapolated from the literature. The concentration after dialysis can be calculated as:

$$C_{aD} = C_{bD} \times e^{-[(CL_{RES} + CL_D)/VD] \times t}$$

- Postdialysis dose can be calculated as follows if the elimination half-life is prolonged relative to the infusion time and thus minimal drug is eliminated during the infusion period:

$$D = V_D \times (C_{max} - C_{min})$$

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See Chap. 51, *Drug Therapy Individualization for Patients with Renal Insufficiency*, authored by Gary R. Matzke and Reginald F. Frye, for a more detailed discussion of this topic.

**DEFINITION**

- Fluid and electrolyte homeostasis is maintained by feedback mechanisms, hormones, and many organ systems and is necessary for the body's normal physiologic functions. Disorders of sodium and water, calcium, phosphorus, potassium, and magnesium homeostasis are addressed separately in this chapter.

**DISORDERS OF SODIUM AND WATER HOMEOSTASIS**

- Sixty percent of total body water is distributed intracellularly, and 40% is contained in the extracellular space.
- Adding an isotonic solution to the extracellular fluid (ECF) does not change intracellular volume. Adding a hypertonic solution to the ECF decreases cell volume, whereas adding a hypotonic solution increases it (Table 78-1).
- Hyponatremia and hyponatremia can be associated with conditions of high, low, or normal ECF sodium and volume. Both conditions are most commonly the result of abnormalities of water metabolism.

**HYPONATREMIA (SERUM SODIUM LESS THAN 135 MEQ/L)****Pathophysiology**

- Hyponatremia predominantly results from an excess of extracellular water relative to sodium because of impaired water excretion.
- Causes of nonosmotic release of arginine vasopressin, commonly known as *antidiuretic hormone*, include hypovolemia; decreased effective circulating volume as seen in patients with congestive heart failure; nephrosis; cirrhosis; and syndrome of inappropriate antidiuretic hormone (SIADH) release.
- Depending on serum osmolality, hyponatremia is classified as isotonic, hypertonic, or hypotonic (Fig. 78-1).
- Hypotonic hyponatremia, the most common form of hyponatremia, can be further classified as hypovolemic, euvolemic, or hypervolemic hyponatremia.
- Hypovolemic hyponatremia is associated with a loss of ECF volume and sodium, with the loss of more sodium than water.
- Euvolemic hyponatremia is associated with a normal or slightly decreased ECF sodium content and increased total body water and ECF volume.
- Hypervolemic hyponatremia is associated with an elevated total body sodium content and an expanded ECF volume.

**Clinical Presentation**

- Most patients with hyponatremia are asymptomatic.
- Presence and severity of symptoms are related to the magnitude and rapidity of onset of hyponatremia. Symptoms progress from nausea and malaise to headache and lethargy and, eventually, to seizures, coma, and death if hyponatremia is severe or develops rapidly.

**TABLE 78-1** Composition of IV Replacement Solutions

Solution	Tonicity	Distribution		
		%ECF	%ICF	Free Water/L
D <sub>5</sub> W	Hypotonic	40	60	1,000 mL
0.45% sodium chloride	Hypotonic	73	37	500 mL
0.9% sodium chloride	Isotonic	100	0	0 mL
3% sodium chloride <sup>a</sup>	Hypertonic	100 <sup>a</sup>	0	-2,331 mL

D<sub>5</sub>W, 5% dextrose in water; ECF, extracellular fluid; ICF, intracellular fluid.

<sup>a</sup>This solution will result in osmotic removal of water from the intracellular space.

- Patients with hypovolemic hyponatremia present with decreased skin turgor, orthostatic hypotension, tachycardia, and dry mucous membranes.

### Treatment

- Treatment of hyponatremia is associated with a risk of osmotic demyelination syndrome, a severe neurologic complication that can develop if the rate of serum sodium correction exceeds 8 to 12 mEq/L within 24 hours.

### Acute Symptomatic Hypotonic Hyponatremia

- Symptomatic patients, regardless of fluid status, should initially be treated with either a 0.9% or 3% concentrated saline solution. Resolution of severe symptoms may require only a 5% increase in serum sodium or an initial target serum sodium of 120 mEq/L.
- Patients with SIADH should be treated with 3% saline plus, if the urine osmolality exceeds 300 mOsm/kg, a loop diuretic (**furosemide**, 40 mg IV every 6 hours).
- Patients with hypovolemic hypotonic hyponatremia should be treated with 0.9% saline, initially at infusion rates of 200 to 400 mL/hour until symptoms moderate.
- Patients with hypervolemic hypotonic hyponatremia should be treated with 3% saline and prompt initiation of fluid restriction. Loop diuretic therapy will also likely be required to facilitate urinary excretion of free water.

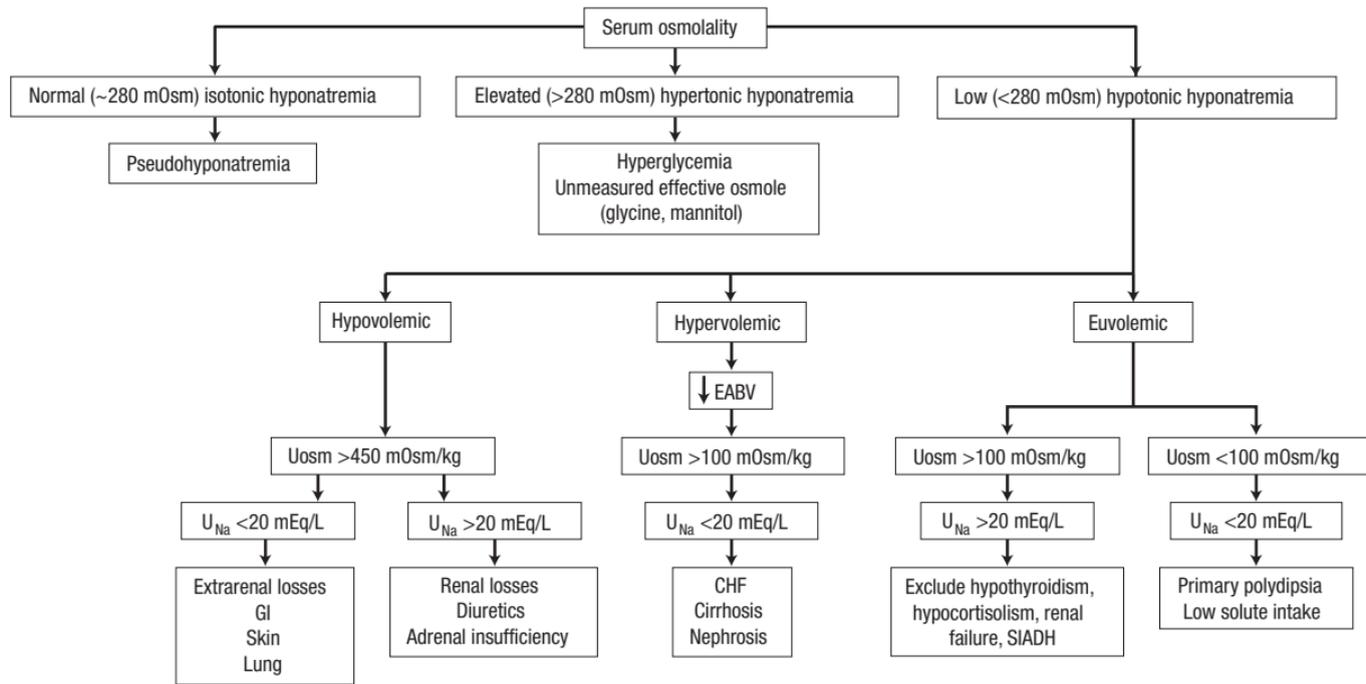
### Asymptomatic Hypotonic Hyponatremia

- Treatment of SIADH involves water restriction and correction of the underlying cause. Water should be restricted to approximately 1,000 to 1,200 mL/day. In some cases, administration of either sodium chloride or urea and a loop diuretic or of **demeclocycline** can be required.
- Treatment of asymptomatic hypervolemic hypotonic hyponatremia involves correction of the underlying cause and restriction of water intake to less than 1,000 to 1,200 mL/day. Dietary intake of sodium chloride should be restricted to 1,000 to 2,000 mg/day.

## HYPERNATREMIA (SERUM SODIUM MORE THAN 145 MEQ/L)

### Pathophysiology and Clinical Presentation

- Hyponatremia can result from water loss (e.g., diabetes insipidus [DI]); hypotonic fluid loss; or, less commonly, hypertonic fluid administration or sodium ingestion.



**FIGURE 78-1.** Diagnostic algorithm for the evaluation of hyponatremia. (CHF, congestive heart failure; EABV, effective arterial blood volume; SIADH, syndrome of inappropriate antidiuretic hormone;  $U_{Na}$ , urine sodium concentration;  $U_{osm}$ , urine osmolality.)

- Symptoms of hypernatremia are primarily caused by decreased neuronal cell volume and can include weakness, restlessness, confusion, and coma.

### Treatment

- Treatment of hypovolemic hypernatremia should begin with 0.9% saline. After hemodynamic stability is restored and intravascular volume is replaced, free-water deficit can be replaced with 5% dextrose or 0.45% saline solution.
- The correction rate should be approximately 1 mEq/L/hour for hypernatremia that developed over a few hours and 0.5 mEq/L/hour for hypernatremia that developed more slowly.
- Patients with central DI are usually treated with intranasal **desmopressin**, beginning with 10 mcg/day and titrating as needed, usually to 10 mcg twice daily.
- Patients with nephrogenic DI should decrease their ECF volume with a thiazide diuretic and dietary sodium restriction (2,000 mg/day), which often decreases urine volume by as much as 50%. Other treatment options include drugs with antidiuretic properties (Table 78-2).
- Patients with sodium overload should be treated with loop diuretics (**furosemide**, 20 to 40 mg IV every 6 hours) and 5% dextrose at a rate that decreases serum sodium by approximately 0.5 mEq/L/hour or, if hypernatremia developed rapidly, 1 mEq/L/hour.

## EDEMA

### Pathophysiology and Clinical Presentation

- Edema develops when excess sodium is retained either as a primary defect in renal sodium excretion or as a response to a decrease in the effective circulating volume despite an already expanded or normal ECF volume.
- Edema can occur in patients with decreased myocardial contractility, nephrotic syndrome, or cirrhosis.
- Edema is usually first detected in the feet or pretibial area in ambulatory patients and in the presacral area in bed-bound individuals. Edema is defined as “pitting” when the depression caused by briefly exerting pressure over a bony prominence does not rapidly refill.

**TABLE 78-2** Drugs Used to Manage Central and Nephrogenic Diabetes Insipidus (DI)

Drug	Indication	Dose
Desmopressin acetate	Central and nephrogenic DI	5–20 mcg intranasally every 12–24 hours
Chlorpropamide	Central DI	125–250 mg orally daily
Carbamazepine	Central DI	100–300 mg orally twice a day
Clofibrate	Central DI	500 mg orally four times a day
Hydrochlorothiazide	Central and nephrogenic DI	25 mg orally every 12–24 hours
Amiloride	Lithium-related nephrogenic DI	5–10 mg orally daily
Indomethacin	Central and nephrogenic DI	50 mg orally every 8–12 hours

## Treatment

- Diuretics are the primary pharmacologic therapy for edema. Loop diuretics are the most potent, followed by thiazide diuretics and then potassium-sparing diuretics.
- Pulmonary edema requires immediate pharmacologic treatment. Other forms of edema can be treated gradually with, in addition to diuretic therapy, sodium restriction and correction of underlying disease state.

## DISORDERS OF CALCIUM HOMEOSTASIS

- ECF calcium is moderately bound to plasma proteins (46%), primarily albumin. Unbound or ionized calcium is the physiologically active form.
- Each 1 g/dL drop in serum albumin concentration below 4 g/dL decreases total serum calcium concentration by 0.8 mg/dL.

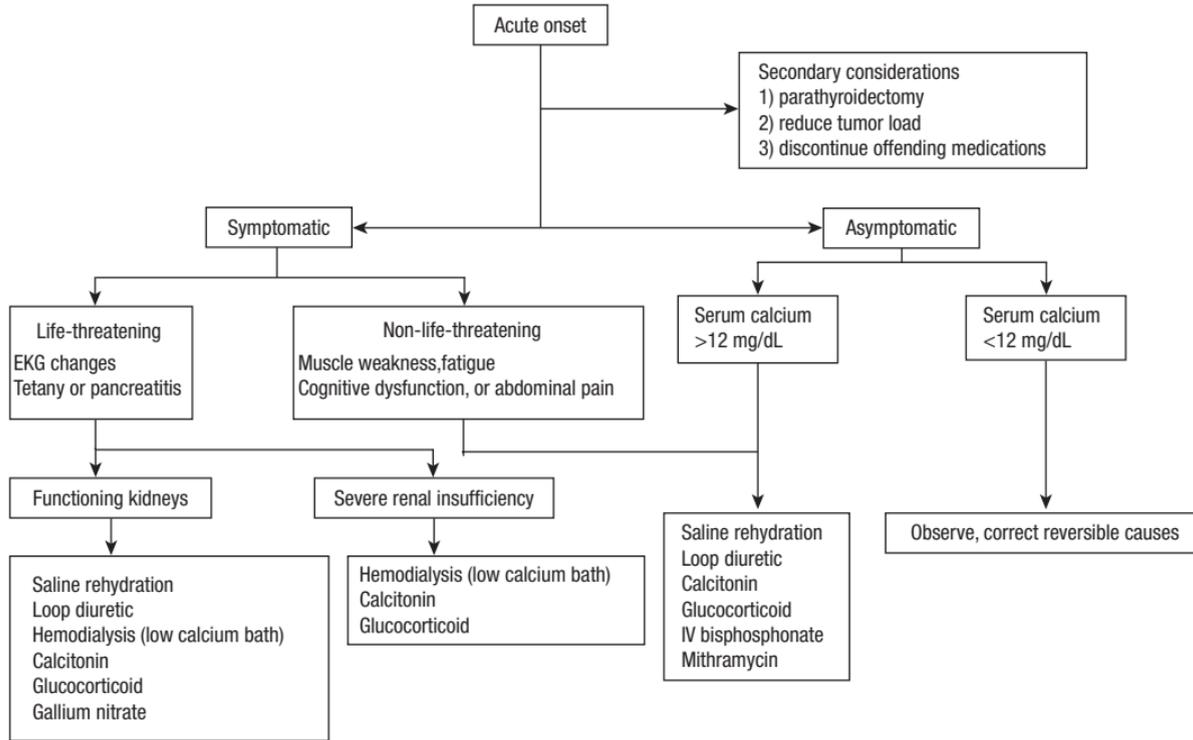
### HYPERCALCEMIA (TOTAL SERUM CALCIUM MORE THAN 10.5 MG/DL)

#### Pathophysiology and Clinical Presentation

- Cancer and hyperparathyroidism are the most common causes of hypercalcemia. The primary mechanisms are increased bone resorption, increased GI absorption, and decreased renal elimination.
- Clinical presentation depends on the degree of hypercalcemia and rate of onset. Mild to moderate hypercalcemia (less than 13 mg/dL) can be asymptomatic.
- Hypercalcemia of malignancy develops quickly and is associated with anorexia, nausea and vomiting, constipation, polyuria, polydipsia, and nocturia. Hypercalcemic crisis is characterized by acute elevation of serum calcium to greater than 15 mg/dL, acute renal failure, and obtundation. Untreated hypercalcemic crisis can progress to oliguric renal failure, coma, and life-threatening ventricular arrhythmias.
- Chronic hypercalcemia (i.e., hyperparathyroidism) is associated with metastatic calcification, nephrolithiasis, and chronic renal insufficiency.
- Electrocardiogram (ECG) changes include shortening of the QT interval and coving of the ST-T wave.

#### Treatment

- The approach to hypercalcemia depends on the degree of hypercalcemia, acuity of onset, and presence of symptoms (Fig. 78-2).
- Management of patients with asymptomatic, mild to moderate hypercalcemia begins with attention to the underlying condition and correction of fluid and electrolyte abnormalities.
- Hypercalcemic crisis and symptomatic hypercalcemia are medical emergencies requiring immediate treatment. Rehydration with normal saline followed by loop diuretics can be used in patients with normal to moderately impaired renal function. Initiate treatment with **calcitonin** in patients in whom saline hydration is contraindicated (Table 78-3).



**FIGURE 78-2.** Pharmacotherapeutic options for the acutely hypercalcemic patient. (EKG, electrocardiogram.)

**TABLE 78-3** Drug Therapy Used to Treat Acute Hypercalcemia

<b>Drug</b>	<b>Starting Dosage</b>	<b>Time Frame to Initial Response</b>	<b>Contraindications</b>	<b>Adverse Effects</b>
0.9% saline ± electrolytes	200–300 mL/hour	24–48 hours	Renal insufficiency; congestive heart failure	Electrolyte abnormalities; fluid overload
Loop diuretics	40–80 mg IV every 1–4 hours	N/A	Allergy to sulfas (use ethacrynic acid)	Electrolyte abnormalities
Calcitonin	4 units/kg every 12 hours SC/IM; 10–12 units/hour IV	1–2 hours	Allergy to calcitonin	Facial flushing, nausea/vomiting, allergic reaction
Pamidronate	30–90 mg IV over 2–24 hours	2 days	Renal insufficiency	Fever
Etidronate	7.5 mg/kg per day IV over 2 hours	2 days	Renal insufficiency	Fever
Zoledronate	4–8 mg IV over 15 minutes	1–2 days	Renal insufficiency	Fever, fatigue, skeletal pain
Ibandronate	2–6 mg IV bolus	2 days	Renal insufficiency	Fever, musculoskeletal pain
Gallium nitrate	200 mg/m <sup>2</sup> per day	?	Severe renal insufficiency	Nephrotoxicity; hypophosphatemia; nausea/vomiting/diarrhea; metallic taste
Mithramycin	25 mcg/kg IV over 4–6 hours	12 hours	Decreased liver function; renal insufficiency; thrombocytopenia	Nausea/vomiting; stomatitis; thrombocytopenia; nephrotoxicity; hepatotoxicity
Glucocorticoids	40–60 mg oral prednisone equivalents	?	Serious infections; hypersensitivity	Diabetes; osteoporosis; infection

N/A, not available.

- Rehydration with saline and **furosemide** administration can decrease total serum calcium by 2 to 3 mg/dL within 24 to 48 hours.
- Bisphosphonates are indicated for hypercalcemia of malignancy. Total serum calcium decline begins within 2 days and nadirs in 7 days.

## HYPOCALCEMIA (TOTAL SERUM CALCIUM LESS THAN 8.5 MG/DL)

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### Pathophysiology

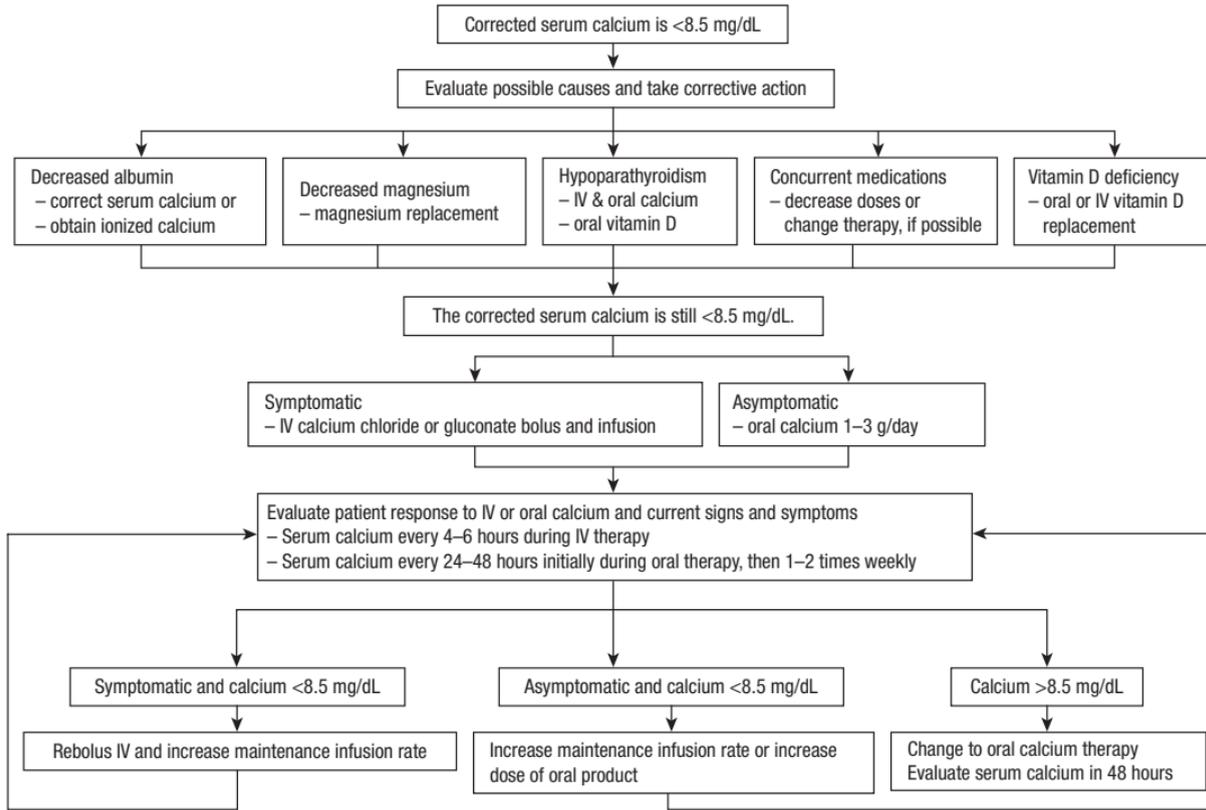
- Hypocalcemia results from altered effects of parathyroid hormone and vitamin D on the bone, gut, and kidney. The primary causes are postoperative hypoparathyroidism and vitamin D deficiency.
- Symptomatic hypocalcemia commonly occurs because of parathyroid gland dysfunction secondary to surgical procedures involving the thyroid, parathyroid, and neck.
- Hypomagnesemia can be associated with severe symptomatic hypocalcemia that is unresponsive to calcium replacement therapy.

### Clinical Presentation

- Clinical manifestations are variable and depend on the onset of hypocalcemia.
- Tetany is the hallmark sign of acute hypocalcemia, which manifests as paresthesias around the mouth and in the extremities; muscle spasms and cramps; carpopedal spasms; and, rarely, laryngospasm and bronchospasm.
- Cardiovascular manifestations result in ECG changes characterized by a prolonged QT interval and symptoms of decreased myocardial contractility often associated with heart failure.

### Treatment

- Hypocalcemia associated with hypoalbuminemia requires no treatment because ionized plasma calcium concentrations are normal.
- Acute, symptomatic hypocalcemia requires IV administration of soluble calcium salts (Fig. 78-3).
- Initially, 100 to 300 mg of elemental calcium (e.g., 1 g **calcium chloride**, 2 to 3 g **calcium gluconate**) should be given IV over 5 to 10 minutes (60 mg or less of elemental calcium per minute).
- The initial bolus is effective for only 1 to 2 hours and should be followed by a continuous infusion of elemental calcium (0.5 to 2 mg/kg/hour) usually for 2 to 4 hours and then by a maintenance dose (0.3 to 0.5 mg/kg/hour).
- **Calcium gluconate** is preferred over **calcium chloride** for peripheral administration because the latter is more irritating to veins.
- After acute hypocalcemia is corrected, the underlying cause and other electrolyte problems should be corrected.
- Magnesium supplementation is indicated for hypomagnesemia.
- Oral calcium supplementation (e.g., 1 to 3 g/day of elemental calcium) is indicated for chronic hypocalcemia due to hypoparathyroidism and vitamin D deficiency. If serum calcium does not normalize, a vitamin D preparation should be added.



**FIGURE 78-3.** Hypocalcemia diagnostic and treatment algorithm.

## DISORDERS OF PHOSPHORUS HOMEOSTASIS

### HYPERPHOSPHATEMIA (SERUM PHOSPHORUS MORE THAN 4.5 MG/DL)

#### Pathophysiology

- The most common cause of hyperphosphatemia is decreased phosphorus excretion, secondary to decreased glomerular filtration rate.
- Large amounts of phosphorus can be released from intracellular stores in patients who have rhabdomyolysis and in patients who receive chemotherapy for acute leukemia and lymphoma.

#### Clinical Presentation

- Some signs and symptoms of hyperphosphatemia are a result of the low solubility of the calcium-phosphate complexation product. Calcium-phosphate crystals are likely to form when the product of the serum calcium and phosphate concentrations exceeds 50 to 60  $\text{mg}^2/\text{dL}^2$ .
- The major effect of hyperphosphatemia is related to the development of hypocalcemia and damage resulting from calcium phosphate deposits.
- For more information on hyperphosphatemia and renal failure, see Chap. 75.

#### Treatment

- The most effective way to treat hyperphosphatemia is to decrease phosphate absorption from the GI tract with phosphate binders (see Chap. 76, Table 76-3).
- Severe symptomatic hyperphosphatemia manifesting as hypocalcemia and tetany is treated by the IV administration of calcium salts.

### HYPOPHOSPHATEMIA (SERUM PHOSPHORUS LESS THAN 2 MG/DL)

#### Pathophysiology

- Hypophosphatemia can be the result of decreased GI absorption, increased urinary excretion, or extracellular to intracellular redistribution.
- Hypophosphatemia is associated with chronic alcoholism, parenteral nutrition with inadequate phosphate supplementation, chronic ingestion of antacids, diabetic ketoacidosis, and prolonged hyperventilation.

#### Clinical Presentation

- Severe hypophosphatemia (serum phosphorus  $<1$  mg/dL) has diverse clinical manifestations that affect many organ systems.
- Neurologic manifestations of severe hypophosphatemia include a progressive syndrome of irritability, apprehension, weakness, numbness, paresthesias, dysarthria, confusion, obtundation, seizures, and coma.
- Skeletal muscle dysfunction can cause myalgia, bone pain, weakness, and potentially fatal rhabdomyolysis. Respiratory muscle weakness and diaphragmatic contractile dysfunction can cause acute respiratory failure.
- Congestive cardiomyopathy, arrhythmias, hemolysis, and increased risk of infection can also occur.

- Chronic hypophosphatemia can cause osteopenia and osteomalacia because of enhanced osteoclastic resorption of bone.

### Treatment

- Severe (less than 1 mg/dL) or symptomatic hypophosphatemia should be treated with IV phosphorus replacement. The infusion of 15 mmol of phosphorus in 250 mL of IV fluid over 3 hours is a safe and effective treatment but the recommended dosage of IV phosphorus (5 to 45 mmol or 0.08 to 0.64 mmol/kg) and infusion recommendations (over 4 to 12 hours) are highly variable.
- Asymptomatic patients or those who exhibit mild to moderate hypophosphatemia can be treated with oral phosphorus supplementation with the goal of correcting serum phosphorus concentration in 7 to 10 days (Table 78-4).
- Patients should be closely monitored with frequent serum phosphorus and calcium determinations, especially if phosphorus is given IV or if renal dysfunction is present.
- Phosphorus, 12 to 15 mmol/L, should be routinely added to hyperalimentation solutions to prevent hypophosphatemia.

## DISORDERS OF POTASSIUM HOMEOSTASIS

### HYPOKALEMIA (SERUM POTASSIUM LESS THAN 3.5 MEQ/L)

#### Pathophysiology

- Hypokalemia results from a total body potassium deficit or shifting of serum potassium into the intracellular compartment.

**TABLE 78-4** Phosphorus Replacement Therapy

Product (Salt)	Phosphate Content	Initial Dosing Based on Serum K
<b>Oral therapy (potassium phosphate + sodium phosphate)</b>		
Neutra-Phos (7 mEq/packet each of Na and K)	250 mg (8 mmol)/packet	1 packet three times daily <sup>a</sup>
Neutra-Phos-K (14.25 mEq/packet of K)	250 mg (8 mmol)/packet	Serum K >5.5 mEq/L Not recommended
K-Phos Neutral (13 mEq/tablet Na and 1.1 mEq/tablet K)	250 mg (8 mmol)/tablet	Serum K >5.5 mEq/L one tablet three times daily
Uro-KP-Neutral (10.9 mEq/tablet Na and 1.27 mEq/tablet K)	250 mg (8 mmol)/tablet	Serum K >5.5 mEq/L one tablet three times daily
Fleet Phospho-soda (sodium phosphate solution)	4 mmol/mL	Serum K >5.5 mEq/L 2 mL three times daily
<b>IV therapy</b>		
Sodium PO <sub>4</sub> (4 mEq/mL Na)	3 mmol/mL	Serum K >3.5 mEq/L 15–30 mmol IVPB
Potassium PO <sub>4</sub> (4.4 mEq/mL K)	3 mmol/mL	Serum K < 3.5 mEq/L 15–30 mmol IVPB

IVPB, intravenous piggyback; K, potassium; Na, sodium; PO<sub>4</sub>, phosphate.

<sup>a</sup>Monitor serum K closely.

**TABLE 78-5** Mechanism of Drug-Induced Hypokalemia

Transcellular Shift	Enhanced Renal Excretion	Enhanced Fecal Elimination
<b><math>\beta_2</math>-Receptor agonists</b>	<b>Diuretics</b>	<b>Sodium polystyrene sulfonate</b>
Epinephrine	Acetazolamide	<b>Phenolphthalein</b>
Albuterol	Thiazides	<b>Sorbitol</b>
Terbutaline	Indapamide	
Pirbuterol	Metolazone	
Salmeterol	Furosemide	
Isoproterenol	Torsemide	
Ephedrine	Bumetanide	
Pseudoephedrine	Ethacrynic acid	
<b>Tocolytic agents</b>	<b>High-dose penicillins</b>	
Ritodrine	Nafcillin	
Nylidrin	Ampicillin	
<b>Theophylline</b>	Penicillin	
<b>Caffeine</b>	<b>Mineralocorticoids</b>	
<b>Insulin overdose</b>	<b>Miscellaneous</b>	
	Aminoglycosides	
	Amphotericin B	
	Cisplatin	

- Many drugs can cause hypokalemia (Table 78-5) and it is most commonly seen with use of loop and thiazide diuretics. Other causes of hypokalemia include diarrhea, vomiting, and hypomagnesemia.

### Clinical Presentation

- Signs and symptoms are nonspecific and variable and depend on the degree of hypokalemia and rapidity of onset. Mild hypokalemia is often asymptomatic.
- Cardiovascular manifestations include hypertension and cardiac arrhythmias (e.g., heart block, atrial flutter, paroxysmal atrial tachycardia, ventricular fibrillation, and digitalis-induced arrhythmias). In severe hypokalemia (serum concentration  $<2.5$  mEq/L), ECG effects include ST-segment depression or flattening, T-wave inversion, and U-wave elevation.
- Neuromuscular symptoms include muscle weakness, cramping, malaise, and myalgias.

### Treatment

- In general, every 1-mEq/L fall of potassium below 3.5 mEq/L corresponds with a total body deficit of 100 to 400 mEq. To correct mild deficits, patients receiving chronic loop or thiazide diuretics generally need 40 to 100 mEq of potassium.
- Whenever possible, potassium supplementation should be administered by mouth. Of the available salts, potassium chloride is most commonly used because it is the most effective for common causes of potassium depletion.
- IV use should be limited to patients who have severe hypokalemia, signs and symptoms of hypokalemia, or inability to tolerate oral therapy. Potassium should be administered in saline because dextrose can stimulate

insulin secretion and worsen intracellular shifting of potassium. Generally, 10 to 20 mEq of potassium is diluted in 100 mL of 0.9% saline and administered through a peripheral vein over 1 hour. If infusion rates exceed 10 mEq/hour, ECG should be monitored.

## **HYPERKALEMIA (SERUM POTASSIUM MORE THAN 5.5 MEQ/L)**

### **Pathophysiology**

- Hyperkalemia develops when potassium intake exceeds excretion or when the transcellular distribution of potassium is disturbed.
- Primary causes of true hyperkalemia are increased potassium intake, decreased potassium excretion, tubular unresponsiveness to aldosterone, and redistribution of potassium to the extracellular space.

### **Clinical Presentation**

- Hyperkalemia is frequently asymptomatic. Patients might complain of heart palpitations or skipped heartbeats.
- The earliest ECG change (serum potassium 5.5 to 6 mEq/L) is peaked T waves. The sequence of changes with further increases is widening of the PR interval, loss of the P wave, widening of the QRS complex, and merging of the QRS complex with the T wave resulting in a sine-wave pattern.

### **Treatment**

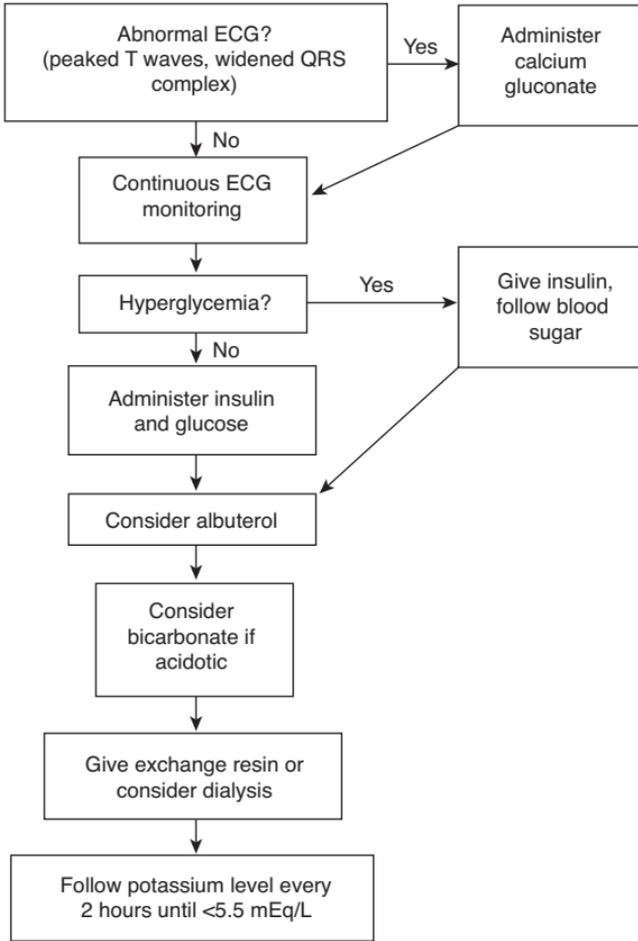
- Treatment of hyperkalemia depends on the desired rapidity and degree of lowering (Fig. 78-4, Table 78-6). Dialysis is the most rapid way to lower serum potassium concentration.
- Calcium administration rapidly reverses ECG manifestations and arrhythmias, but it does not lower serum potassium concentrations. Calcium is short acting and therefore must be repeated if signs or symptoms recur.
- Rapid correction of hyperkalemia requires administration of drugs that shift potassium intracellularly (e.g., insulin and dextrose, sodium bicarbonate, or albuterol).
- Sodium polystyrene sulfonate is a cation-exchange resin suitable for asymptomatic patients with mild to moderate hyperkalemia. Each gram of resin exchanges 1 mEq of sodium for 1 mEq of potassium. The sorbitol component promotes excretion of exchanged potassium by inducing diarrhea. The oral route is better tolerated and more effective than the rectal route.

## **DISORDERS OF MAGNESIUM HOMEOSTASIS**

### **HYPOMAGNESEMIA (SERUM MAGNESIUM LESS THAN 1.4 MEQ/L)**

#### **Pathophysiology**

- Hypomagnesemia is usually associated with disorders of the intestinal tract or kidneys. Drugs (e.g., **aminoglycosides**, **amphotericin B**, **cyclosporine**, diuretics, **digitalis**, **cisplatin**) or conditions that interfere with intestinal absorption or increase renal excretion of magnesium can cause hypomagnesemia.
- Hypomagnesemia is commonly associated with alcoholism.



**FIGURE 78-4.** Treatment algorithm for hyperkalemia. (ECG, electrocardiogram.)

**TABLE 78-6** Therapeutic Alternatives for the Management of Hyperkalemia

Medication	Dose	Route of Administration	Onset/Duration of Action
Calcium	1 g (1 ampule)	IV over 5–10 minutes	1–2 min/10–30 min
Furosemide	20–40 mg	IV	5–15 min/4–6 hours
Regular insulin	5–10 units	IV or SC	30 min/2–6 hours
Dextrose 10%	1,000 mL (100 g)	IV over 1–2 hours	30 min/2–6 hours
Dextrose 50%	50 mL (25 g)	IV over 5 minutes	30 min/2–6 hours
Sodium bicarbonate	50–100 mEq	IV over 2–5 minutes	30 min/2–6 hours
Albuterol	10–20 mg	Nebulized over 10 minutes	30 min/1–2 hours
Hemodialysis	4 hours	Not applicable	Immediate/variable
Sodium polystyrene sulfonate	15–60 g	Oral or rectal	1 hour/variable

## Clinical Presentation

- Although typically asymptomatic, the dominant organ systems involved are the neuromuscular and cardiovascular systems. Symptoms include heart palpitations, tetany, twitching, and generalized convulsions.
- Ventricular arrhythmias are the most important and potentially life-threatening cardiovascular effect.
- ECG changes include widened QRS complexes and peaked T waves in mild deficiency. Prolonged PR intervals, progressive widening of the QRS complexes, and flattening of T waves occur in moderate to severe deficiency.
- Many electrolyte disturbances occur with hypomagnesemia including hypokalemia and hypocalcemia.

## Treatment

- The severity of magnesium depletion and presence of symptoms dictate the route of magnesium supplementation (Table 78-7). Intramuscular magnesium is painful and should be reserved for patients with severe hypomagnesemia and limited venous access. IV bolus injection is associated with flushing, sweating, and a sensation of warmth.
- Magnesium should be replaced over 3 to 5 days because 50% of the dose is excreted in the urine.

## HYPERMAGNESEMIA (SERUM MAGNESIUM MORE THAN 2 MEQ/L)

### Pathophysiology

- Hypermagnesemia most commonly occurs in renal insufficiency when glomerular filtration is less than 30 mL/min.

**TABLE 78-7** Guidelines for Treatment of Magnesium Deficiency in Adults

**1. Serum magnesium <1 mEq/L (1.2 mg/dL) with life-threatening symptoms (seizure, arrhythmia)**

*Day 1*

2 g MgSO<sub>4</sub> (1 g MgSO<sub>4</sub> = 8.1 mEq Mg<sup>2+</sup>) mixed with 6 mL 0.9% NaCl in 10-mL syringe and administer IV push over 1 minute

Follow with 1 mEq Mg<sup>2+</sup>/kg lean body weight IV infusion over 24 hours

*Days 2-5*

0.5 mEq Mg<sup>2+</sup>/kg lean body weight per day divided in maintenance IV fluids

**2. Serum magnesium <1 mEq/L (1.2 mg/dL) without life-threatening symptoms**

*Day 1*

Total of 1 mEq Mg<sup>2+</sup>/kg lean body weight per day as continuous IV infusion, or divided and given IM every 4 hours for five doses

*Days 2-5*

Total of 0.5 mEq Mg<sup>2+</sup>/kg lean body weight IV infusion per day as continuous IV infusion or divided and given IM every 6-8 hours

**3. Serum magnesium >1 mEq/L (1.2 mg/dL) and <1.5 mEq/L (1.8 mg/dL) without symptoms**

As in no. 2 above, *or*

Milk of Magnesia 5 mL four times daily as tolerated, *or*

Magnesium-containing antacid 15 mL three times daily as tolerated, *or*

Magnesium oxide tablets 400 mg four times daily, increase to two tablets four times daily as tolerated

MgSO<sub>4</sub>, magnesium sulfate.

- Other causes include magnesium-containing antacids in patients with renal insufficiency, enteral or parenteral nutrition in patients with multi-organ system failure, magnesium for treatment of eclampsia, lithium therapy, hypothyroidism, and Addison's disease.

### Clinical Presentation

- Symptoms are rare when the serum magnesium concentration is less than 4 mEq/L.
- The sequence of neuromuscular signs as serum magnesium increases from 5 mEq/L to 12 mEq/L is sedation, hypotonia, hyporeflexia, somnolence, coma, muscular paralysis, and, ultimately, respiratory depression.
- The sequence of cardiovascular signs as serum magnesium increases from 3 mEq/L to 15 mEq/L is hypotension, cutaneous vasodilation, QT-interval prolongation, bradycardia, primary heart block, nodal rhythms, bundle branch block, QRS- and then PR-interval prolongation, complete heart block, and asystole.

### Treatment

- IV calcium (100 to 200 mg of elemental calcium) is indicated to antagonize the neuromuscular and cardiovascular effects of magnesium. Doses should be repeated as often as hourly in life-threatening situations.
- Hemodialysis is the treatment of choice for patients with renal dysfunction. Forced diuresis with saline and loop diuretics is the treatment of choice for patients with adequate renal function.

## EVALUATION OF THERAPEUTIC OUTCOMES

- The primary endpoint for monitoring treatment of fluid and electrolyte disorders is the correction of the abnormal serum electrolyte. The frequency depends on the presence of symptoms and degree of abnormality. In general, monitoring is initially performed at frequent intervals and, as homeostasis is restored, subsequently performed at less frequent intervals.
- All electrolytes should be monitored since individual electrolyte abnormalities typically coexist with another abnormality (e.g., hypomagnesemia with hypokalemia and hypocalcemia, or hyperphosphatemia with hypocalcemia).
- Patients should be monitored for resolution of clinical manifestations of electrolyte disturbances and for treatment-related complications.

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*See Chap. 52, Disorders of Sodium and Water Homeostasis, authored by James D. Coyle and Melanie S. Joy; Chap. 53, Disorders of Calcium and Phosphorus Homeostasis, authored by Amy Barton Pai, Mark Rohrscheib, and Melanie S. Joy; and Chap. 54, Disorders of Potassium and Magnesium Homeostasis, authored by Donald F. Brophy and Todd W. B. Gehr, for a more detailed discussion of this topic.*

## DEFINITION

- Allergic rhinitis is inflammation of the nasal mucous membrane caused by exposure to inhaled allergenic materials that elicit a specific immunologic response mediated by immunoglobulin E (IgE). There are two types:
  - ✓ *Seasonal (hay fever)*: occurs in response to specific allergens (pollen from trees, grasses, and weeds) present at predictable times of the year (spring and/or fall blooming seasons) and typically causes more acute symptoms.
  - ✓ *Perennial (intermittent or persistent)*: occurs year round in response to nonseasonal allergens (e.g., dust mites, animal dander, molds) and usually causes more subtle, chronic symptoms.
- Many patients have a combination of both types, with symptoms year-round and seasonal exacerbations.

## PATHOPHYSIOLOGY

- The initial reaction occurs when airborne allergens enter the nose during inhalation and are processed by lymphocytes, which produce antigen-specific IgE, thereby sensitizing genetically predisposed hosts to those agents. On nasal reexposure, IgE bound to mast cells interacts with airborne allergens, triggering release of inflammatory mediators.
- An immediate reaction occurs within seconds to minutes, resulting in the rapid release of preformed mediators and newly generated mediators from the arachidonic acid cascade. Mediators of immediate hypersensitivity include histamine, leukotrienes, prostaglandin, tryptase, and kinins. These mediators cause vasodilation, increased vascular permeability, and production of nasal secretions. Histamine produces rhinorrhea, itching, sneezing, and nasal obstruction.
- From 4 to 8 hours after the initial exposure to an allergen, a late-phase reaction may occur, which is thought to be due to cytokines released primarily by mast cells and thymus-derived helper lymphocytes. This inflammatory response likely is responsible for persistent, chronic symptoms including nasal congestion.

## CLINICAL PRESENTATION

- Symptoms include clear rhinorrhea, sneezing, nasal congestion, postnasal drip, allergic conjunctivitis, and pruritic eyes, ears, or nose.

- Patients may complain of loss of smell or taste, with sinusitis or polyps the underlying cause in many cases. Postnasal drip with cough or hoarseness can also be bothersome.
- Untreated rhinitis symptoms may lead to insomnia, malaise, fatigue, and poor work or school efficiency.
- Allergic rhinitis is a risk factor for asthma; up to 78% of asthma patients have nasal symptoms, and about 38% of allergic rhinitis patients have asthma.
- Recurrent and chronic sinusitis and epistaxis are complications of allergic rhinitis.

## DIAGNOSIS

- In children, physical examination may reveal dark circles under the eyes (allergic shiners), a transverse nasal crease caused by repeated rubbing of the nose, adenoidal breathing, edematous nasal turbinates coated with clear secretions, tearing, conjunctival injection and edema, and periorbital swelling. Physical findings are generally less obvious in adults.
- Microscopic examination of nasal scrapings typically reveals numerous eosinophils. The peripheral blood eosinophil count may be elevated, but it is nonspecific and has limited usefulness.
- Allergy testing can help determine whether rhinitis is caused by an immune response to allergens. Immediate-type hypersensitivity skin tests are commonly used. Percutaneous testing is safer and more generally accepted than intradermal testing, which is usually reserved for patients requiring confirmation. The radioallergosorbent test (RAST) can be used to detect IgE antibodies in the blood that are specific for a given antigen, but it is less sensitive than percutaneous tests.

## DESIRED OUTCOME

- The goal of treatment is to minimize or prevent symptoms with minimal or no side effects and reasonable medication expense.
- Patients should be able to maintain a normal lifestyle, including participation in outdoor activities and playing with pets as desired.

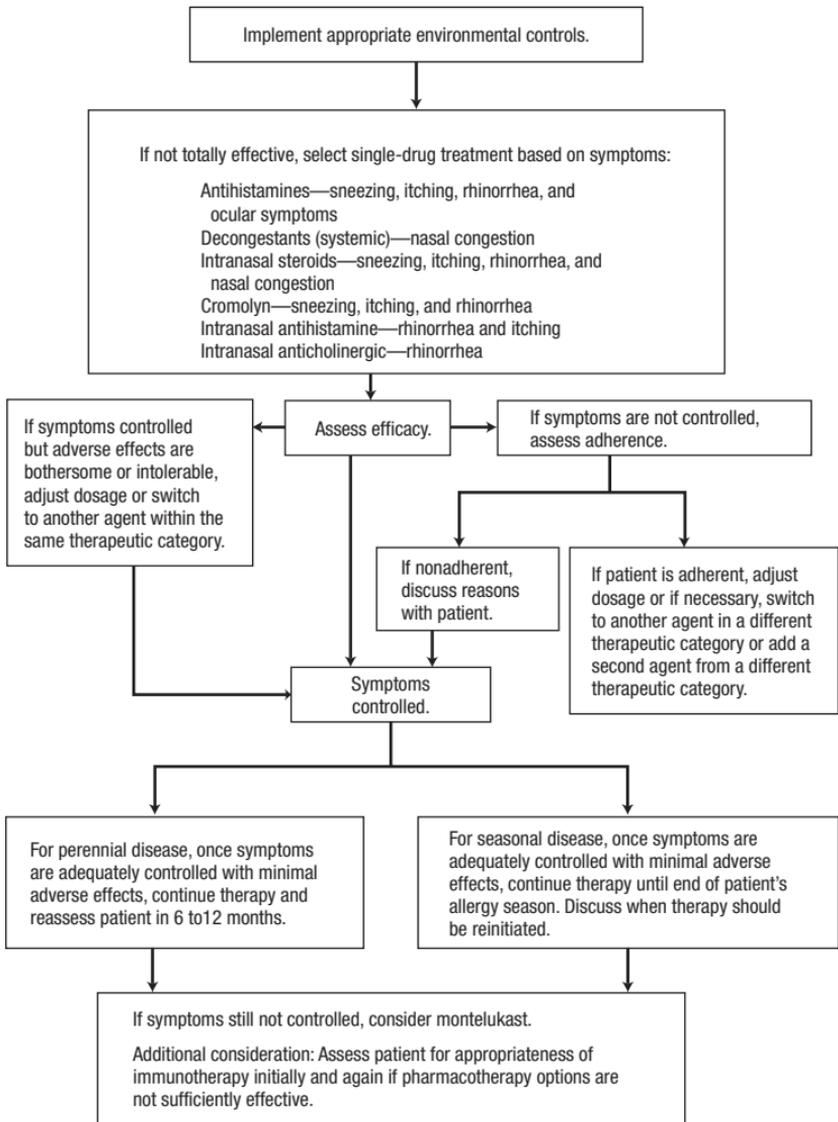
## TREATMENT

(Fig. 79-1)

### ALLERGEN AVOIDANCE

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- Avoidance of offending allergens is difficult. Mold growth can be reduced by keeping household humidity below 50% and removing obvious growth with bleach or disinfectant.
- Patients sensitive to animals benefit most by removing pets from the home, if feasible. Exposure to dust mites can be reduced by encasing



**FIGURE 79-1.** Treatment algorithm for allergic rhinitis.

mattresses and pillows with impermeable covers and washing bed linens in hot water. Washable area rugs are preferable to wall-to-wall carpeting.

- High-efficiency particulate air filters can remove lightweight particles such as pollens, mold spores, and cat allergen, thereby reducing allergic respiratory symptoms.
- Patients with seasonal allergic rhinitis should keep windows closed and minimize time spent outdoors during pollen seasons. Filter masks can be worn while gardening or mowing the lawn.

## PHARMACOLOGIC THERAPY

**Antihistamines**

- Histamine H<sub>1</sub>-receptor antagonists bind to H<sub>1</sub> receptors without activating them, preventing histamine binding and action. They are more effective in preventing the histamine response than in reversing it.
- Oral antihistamines can be divided into two major categories: nonselective (first-generation or sedating antihistamines) and peripherally selective (second-generation or nonsedating antihistamines). However, individual agents should be judged on their specific sedating effects because variation exists among agents within these broad categories (Table 79-1). The central sedating effect may depend on the ability to cross the blood–brain barrier. Most older antihistamines are lipid soluble and cross this barrier easily. The peripherally selective agents have little or no central or autonomic nervous system effects.
- Symptom relief is caused in part by anticholinergic properties, which are responsible for the drying effect that reduces nasal, salivary, and lacrimal gland hypersecretion. Antihistamines antagonize increased capillary permeability, wheal-and-flare formation, and itching.
- Drowsiness is the most frequent side effect, and it can interfere with driving ability or adequate functioning at the workplace. Sedative effects

**TABLE 79-1** Relative Adverse-Effect Profiles of Antihistamines

Medication	Relative Sedative Effect	Relative Anticholinergic Effect
<b>Alkylamine class, nonselective</b>		
Brompheniramine maleate	Low	Moderate
Chlorpheniramine maleate	Low	Moderate
Dexchlorpheniramine maleate	Low	Moderate
<b>Ethanolamine class, nonselective</b>		
Carbinoxamine maleate	High	High
Clemastine fumarate	Moderate	High
Diphenhydramine hydrochloride	High	High
<b>Ethylenediamine class, nonselective</b>		
Pyrilamine maleate	Low	Low to none
Tripelennamine hydrochloride	Moderate	Low to none
<b>Phenothiazine class, nonselective</b>		
Promethazine hydrochloride	High	High
<b>Piperidine class, nonselective</b>		
Cyproheptadine hydrochloride	Low	Moderate
Phenindamine tartrate	Low to none	Moderate
<b>Phthalazinone class, peripherally selective</b>		
Azelastine (nasal only)	Low to none	Low to none
<b>Piperazine class, peripherally selective</b>		
Cetirizine	Low to moderate	Low to none
Levocetirizine	Low to moderate	Low to none
<b>Piperidine class, peripherally selective</b>		
Desloratadine	Low to none	Low to none
Fexofenadine	Low to none	Low to none
Loratadine	Low to none	Low to none

can be beneficial in patients who have difficulty sleeping because of rhinitis symptoms.

- Although anticholinergic (drying) effects contribute to efficacy, adverse effects such as dry mouth, difficulty in voiding urine, constipation, and potential cardiovascular effects may occur (see Table 79-1). Antihistamines should be used with caution in patients predisposed to urinary retention and in those with increased intraocular pressure, hyperthyroidism, and cardiovascular disease.
- Other side effects include loss of appetite, nausea, vomiting, and epigastric distress. Taking medication with meals or a full glass of water may prevent GI side effects.
- Antihistamines are more effective when taken approximately 1 to 2 hours before anticipated exposure to the offending allergen.
- Table 79-2 lists recommended doses of commonly used oral agents.
- **Azelastine** (Astelin) is an intranasal antihistamine that rapidly relieves symptoms of seasonal allergic rhinitis. However, patients should be cau-

**TABLE 79-2** Oral Dosages of Commonly Used Antihistamines and Decongestants

Medication	Dosage and Interval <sup>a</sup>	
	Adults	Children
<b>Nonselective (first-generation) antihistamines</b>		
Chlorpheniramine maleate, plain <sup>b</sup>	4 mg q 6 h	6–12 years: 2 mg q 6 h 2–5 years: 1 mg q 6 h
Chlorpheniramine maleate, sustained-release	8–12 mg daily at bedtime or 8–12 mg q 8 h	6–12 years: 8 mg at bedtime <6 years: Not recommended
Clemastine fumarate <sup>b</sup>	1.34 mg q 8 h	6–12 years: 0.67 mg q 12 h
Diphenhydramine hydrochloride <sup>b</sup>	25–50 mg q 8 h	5 mg/kg/day divided q 8 h (up to 25 mg per dose)
<b>Peripherally selective (second-generation) antihistamines</b>		
Loratadine <sup>b</sup>	10 mg once daily	6–12 years: 10 mg once daily 2–5 years: 5 mg once daily
Fexofenadine	60 mg twice daily or 180 mg once daily	6–11 years: 30 mg twice daily
Cetirizine <sup>b</sup>	5–10 mg once daily	>6 years: 5 mg once daily
Levocetirizine	5 mg in evening	6–11 years: 2.5 mg in evening
<b>Oral decongestants</b>		
Pseudoephedrine, plain	60 mg q 4–6 h	6–12 years: 30 mg q 4–6 h 2–5 years: 15 mg q 4–6 h
Pseudoephedrine, sustained-release <sup>c</sup>	120 mg q 12 h	Not recommended
Phenylephrine	10–20 mg q 4 h	6–12 years: 10 mg q 4 h 2–6 years: 0.25% drops, 1 mL q 4 h

Note: Fexofenadine and levocetirizine are available by prescription only.

<sup>a</sup>Dosage adjustment may be needed in renal/hepatic dysfunction. Refer to manufacturers' prescribing information.

<sup>b</sup>Available in liquid form.

<sup>c</sup>Controlled-release product available: 240 mg once daily (60-mg immediate-release with 180-mg controlled-release).

tioned about its potential for drowsiness because systemic availability is approximately 40%. Patients may also experience drying effects, headache, and diminished effectiveness over time.

- **Levocabastine** (Livostin) and **olopatadine** (Patanol) are ophthalmic antihistamines that can be used for allergic conjunctivitis that is often associated with allergic rhinitis. However, systemic antihistamines are usually effective for allergic conjunctivitis, making an ocular product unnecessary. They may be a logical addition to nasal glucocorticoids when ocular symptoms occur.

### Decongestants

- Topical and systemic decongestants are sympathomimetic agents that act on adrenergic receptors in the nasal mucosa to produce vasoconstriction, shrink swollen mucosa, and improve ventilation. Decongestants work well in combination with antihistamines when nasal congestion is part of the clinical picture.
- Topical decongestants are applied directly to swollen nasal mucosa via drops or sprays (Table 79-3). They result in little or no systemic absorption.
- Prolonged use of topical agents (more than 3 to 5 days) can result in rhinitis medicamentosa, which is rebound vasodilation with congestion. Patients with this condition use more spray more often with less response. Abrupt cessation is an effective treatment, but rebound congestion may last for several days or weeks. Nasal steroids have been used successfully, but they take several days to work. Weaning the patient off the topical decongestant can be accomplished by decreasing the dosing frequency or concentration over several weeks. Combining the weaning process with nasal steroids may be helpful.
- Other adverse effects of topical decongestants include burning, stinging, sneezing, and dryness of the nasal mucosa.
- These products should be used only when absolutely necessary (e.g., at bedtime) and in doses that are as small and infrequent as possible. Duration of therapy should always be limited to 3 to 5 days.
- **Pseudoephedrine** (see Table 79-2) is an oral decongestant that has a slower onset of action than topical agents but may last longer and cause less local irritation. Also, rhinitis medicamentosa does not occur with oral decongestants. Doses up to 180 mg produce no measurable change in blood pressure

**TABLE 79-3** Duration of Action of Topical Decongestants

Medication	Duration (hours)
<b>Short-acting</b>	
Phenylephrine hydrochloride	Up to 4
<b>Intermediate-acting</b>	
Naphazoline hydrochloride	4–6
Tetrahydrozoline hydrochloride	4–6
<b>Long-acting</b>	
Oxymetazoline hydrochloride	Up to 12
Xylometazoline hydrochloride	Up to 12

or heart rate. However, higher doses (210 to 240 mg) may raise both blood pressure and heart rate. Systemic decongestants should be avoided in hypertensive patients unless absolutely necessary. Severe hypertensive reactions can occur when pseudoephedrine is given concomitantly with monoamine oxidase inhibitors. Pseudoephedrine can cause mild CNS stimulation, even at therapeutic doses. Because of misuse as a component in the illegal manufacture of methamphetamine, legal requirements now restrict pseudoephedrine to behind-the-counter sale with a limit on monthly purchases.

- **Phenylephrine** has replaced pseudoephedrine in many nonprescription antihistamine–decongestant combination products because of the legal restriction on pseudoephedrine sales. Consumers should be advised to read product labels carefully.
- Use of combination oral products containing a decongestant and antihistamine is rational because of the different mechanisms of action.

### Nasal Corticosteroids

- Intranasal corticosteroids effectively relieve sneezing, rhinorrhea, pruritus, and nasal congestion with minimal side effects (Table 79-4). They reduce inflammation by blocking mediator release, suppressing neutrophil chemotaxis, causing mild vasoconstriction, and inhibiting mast cell–mediated, late-phase reactions.
- These agents are an excellent choice for perennial rhinitis and can be useful in seasonal rhinitis, especially if begun in advance of symptoms. Some authorities recommend nasal steroids as initial therapy over antihistamines because of their high degree of efficacy when used properly along with allergen avoidance.
- Side effects include sneezing, stinging, headache, epistaxis, and rare infections with *Candida albicans*.
- Some patients improve within a few days, but peak response may require 2 to 3 weeks. The dosage may be reduced once a response is achieved.
- Blocked nasal passages should be cleared with a decongestant or saline irrigation before administration to ensure adequate penetration of the spray.

**TABLE 79-4** Dosage of Nasal Corticosteroids

Medication	Dosage and Interval
Beclomethasone dipropionate, monohydrate	>12 years: 1–2 inhalations per nostril (42–84 mcg) twice daily 6–12 years: One inhalation per nostril twice daily to start
Budesonide	>6 years: Two sprays (64 mcg) per nostril in AM and PM or four sprays per nostril in AM (maximum, 256 mcg)
Flunisolide	Adults: Two sprays (50 mcg) per nostril twice daily (maximum, 400 mcg) Children: One spray per nostril three times a day
Fluticasone	Adults: Two sprays (100 mcg) per nostril once daily Children >4 years and adolescents: One spray per nostril once daily (maximum, 200 mcg/day)
Mometasone furoate	>12 years: Two sprays (100 mcg) per nostril once daily
Triamcinolone acetonide	>12 years: Two sprays (110 mcg) per nostril once daily (maximum, 440 mcg/day)

### Cromolyn Sodium

- **Cromolyn sodium** (Nasal crom), a mast cell stabilizer, is available as a nonprescription nasal spray for symptomatic prevention and treatment of allergic rhinitis.
- It prevents antigen-triggered mast cell degranulation and release of mediators, including histamine.
- The most common side effect is local irritation (sneezing and nasal stinging).
- The dosage for individuals at least 2 years of age is one spray in each nostril three to four times daily at regular intervals. Nasal passages should be cleared before administration, and inhaling through the nose during administration enhances distribution to the entire nasal lining.
- For seasonal rhinitis, treatment should be initiated just before the start of the offending allergen's season and continue throughout the season.
- In perennial rhinitis, the effects may not be seen for 2 to 4 weeks; antihistamines or decongestants may be needed during this initial phase of therapy.

### Ipratropium Bromide

- **Ipratropium bromide** (Atrovent) nasal spray is an anticholinergic agent useful in perennial allergic rhinitis.
- It exhibits antisecretory properties when applied locally and provides symptomatic relief of rhinorrhea associated with allergic and other forms of chronic rhinitis.
- The 0.03% solution is given as two sprays (42 mcg) two to three times daily. Adverse effects are mild and include headache, epistaxis, and nasal dryness.

### Montelukast

- **Montelukast** (Singulair) is a leukotriene receptor antagonist approved for treatment of seasonal allergic rhinitis. It is effective alone or in combination with an antihistamine.
- The dosage for adults and adolescents older than 15 years is one 10-mg tablet daily. Children aged 6 to 14 years may receive one 5-mg chewable tablet daily. Children aged 2 to 5 years may be given one 4-mg chewable tablet or oral granule packet daily. The timing of administration can be individualized. The dose should be given in the evening if the patient has combined asthma and seasonal allergic rhinitis.
- Although leukotriene antagonists represent a new therapeutic alternative, published studies to date have shown them to be no more effective than peripherally selective antihistamines and less effective than intranasal corticosteroids. However, combined use with antihistamines is more effective than antihistamine treatment alone.

## IMMUNOTHERAPY

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- Immunotherapy is the slow, gradual process of injecting increasing doses of antigens responsible for eliciting allergic symptoms in a patient with the intent of increasing tolerance to the allergen when natural exposure occurs.
- The effectiveness of immunotherapy may result from diminished IgE production, increased IgG production, changes in T lymphocytes, reduced

inflammatory mediator release from sensitized cells, and diminished tissue responsiveness.

- Because immunotherapy is expensive, has potential risks, and requires a major time commitment from patients, it should only be considered in select patients. Good candidates include patients who have a strong history of severe symptoms unsuccessfully controlled by avoidance and pharmacotherapy and patients who have been unable to tolerate the adverse effects of drug therapy. Poor candidates include patients with medical conditions that would compromise the ability to tolerate an anaphylactic-type reaction, patients with impaired immune systems, and patients with a history of nonadherence to therapy.
- In general, very dilute solutions are given initially once or twice per week. The concentration is increased until the maximum tolerated dose is achieved. This maintenance dose is continued every 2 to 6 weeks, depending on clinical response. Better results are obtained with year-round rather than seasonal injections.
- Common mild local adverse reactions include induration and swelling at the injection site. More severe reactions (generalized urticaria, bronchospasm, laryngospasm, vascular collapse, and death from anaphylaxis) occur rarely. Severe reactions are treated with epinephrine, antihistamines, and systemic corticosteroids.

## EVALUATION OF THERAPEUTIC OUTCOMES

- Patients should be monitored regularly for reduction in severity of identified target symptoms and the presence of side effects.
- Patients should be questioned about their satisfaction with the management of their allergic rhinitis. Management should result in minimal disruption to their life.
- The Medical Outcomes Study 36-Item Short Form Health Survey and the Rhinoconjunctivitis Quality of Life Questionnaire measure not only improvement in symptoms but also parameters such as sleep quality, nonallergic symptoms (e.g., fatigue, poor concentration), emotions, and participation in a variety of activities.

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*See Chap. 98, Allergic Rhinitis, authored by J. Russell May and Philip H. Smith, for a more detailed discussion of this topic.*

## DEFINITION

- The National Asthma Education and Prevention Program (NAEPP) defines asthma as a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. In susceptible individuals, inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing. These episodes are usually associated with airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an increase in bronchial hyperresponsiveness (BHR) to a variety of stimuli.

## PATHOPHYSIOLOGY

- The major characteristics of asthma include a variable degree of airflow obstruction (related to bronchospasm, edema, and hypersecretion), BHR, and airway inflammation.
- Inhaled allergens cause an early-phase allergic reaction characterized by activation of cells bearing allergen-specific immunoglobulin E (IgE) antibodies. There is rapid activation of airway mast cells and macrophages, which release proinflammatory mediators such as histamine and eicosanoids that induce contraction of airway smooth muscle, mucus secretion, vasodilation, and exudation of plasma in the airways. Plasma protein leakage induces a thickened, engorged, edematous airway wall and a narrowing of the airway lumen with reduced mucus clearance.
- The late-phase inflammatory reaction occurs 6 to 9 hours after allergen provocation and involves recruitment and activation of eosinophils, T lymphocytes, basophils, neutrophils, and macrophages.
- Eosinophils migrate to the airways and release inflammatory mediators (leukotrienes and granule proteins), cytotoxic mediators, and cytokines.
- T-lymphocyte activation leads to release of cytokines from type 2 T-helper (TH<sub>2</sub>) cells that mediate allergic inflammation (interleukin [IL]-4, IL-5, and IL-13). Conversely, type 1 T-helper (TH<sub>1</sub>) cells produce IL-2 and interferon- $\gamma$  that are essential for cellular defense mechanisms. Allergic asthmatic inflammation may result from an imbalance between TH<sub>1</sub> and TH<sub>2</sub> cells.
- Mast cell degranulation in response to allergens results in release of mediators such as histamine; eosinophil, and neutrophil chemotactic factors; leukotrienes C<sub>4</sub>, D<sub>4</sub>, and E<sub>4</sub>; prostaglandins; and platelet-activating factor (PAF). Histamine is capable of inducing smooth muscle constriction and bronchospasm and may play a role in mucosal edema and mucus secretion.
- Alveolar macrophages release a number of inflammatory mediators, including PAF and leukotrienes B<sub>4</sub>, C<sub>4</sub>, and D<sub>4</sub>. Production of neutrophil chemotactic factor and eosinophil chemotactic factor furthers the inflammatory process.
- Neutrophils are also a source of mediators (PAFs, prostaglandins, thromboxanes, and leukotrienes) that contribute to BHR and airway inflammation.

- The 5-lipoxygenase pathway of arachidonic acid metabolism is responsible for production of cysteinyl leukotrienes. Leukotrienes  $C_4$ ,  $D_4$ , and  $E_4$  are released during inflammatory processes in the lung and produce bronchospasm, mucus secretion, microvascular permeability, and airway edema.
- Bronchial epithelial cells participate in inflammation by releasing eicosanoids, peptidases, matrix proteins, cytokines, and nitric oxide. Epithelial shedding results in heightened airway responsiveness, altered permeability of the airway mucosa, depletion of epithelial-derived relaxant factors, and loss of enzymes responsible for degrading inflammatory neuropeptides.
- The exudative inflammatory process and sloughing of epithelial cells into the airway lumen impair mucociliary transport. The bronchial glands are increased in size, and the goblet cells are increased in size and number. Expecterated mucus from patients with asthma tends to have high viscosity.
- The airway is innervated by parasympathetic, sympathetic, and nonadrenergic inhibitory nerves. The normal resting tone of airway smooth muscle is maintained by vagal efferent activity, and bronchoconstriction can be mediated by vagal stimulation in the small bronchi. Airway smooth muscle contains noninnervated  $\beta_2$ -adrenergic receptors that produce bronchodilation. The nonadrenergic, noncholinergic nervous system in the trachea and bronchi may amplify inflammation in asthma by releasing nitric oxide.

## CLINICAL PRESENTATION

### CHRONIC ASTHMA

- Classic asthma is characterized by episodic dyspnea associated with wheezing, but the clinical presentation of asthma is diverse. Patients may also complain of episodes of dyspnea, chest tightness, coughing (particularly at night), wheezing, or a whistling sound when breathing. These often occur with exercise but may occur spontaneously or in association with known allergens.
- Signs include expiratory wheezing on auscultation, dry hacking cough, or signs of atopy (e.g., allergic rhinitis or eczema).
- Asthma can vary from chronic daily symptoms to only intermittent symptoms. The intervals between symptoms may be days, weeks, months, or years.
- The severity is determined by lung function, symptoms, nighttime awakenings, and interference with normal activity prior to therapy. Patients can present with mild intermittent symptoms that require no medications or only occasional use of short-acting inhaled  $\beta_2$ -agonists to severe chronic asthma symptoms despite receiving multiple medications.

### SEVERE ACUTE ASTHMA

- Uncontrolled asthma can progress to an acute state where inflammation, airway edema, excessive mucus accumulation, and severe bronchospasm result in profound airway narrowing that is poorly responsive to usual bronchodilator therapy.
- Patients may be anxious in acute distress and complain of severe dyspnea, shortness of breath, chest tightness, or burning. They may be able to say

only a few words with each breath. Symptoms are unresponsive to usual measures.

- Signs include expiratory and inspiratory wheezing on auscultation, dry hacking cough, tachypnea, tachycardia, pallor or cyanosis, and hyperinflated chest with intercostal and supraclavicular retractions. Breath sounds may be diminished with very severe obstruction.

## DIAGNOSIS

### CHRONIC ASTHMA

- The diagnosis of asthma is made primarily by a history of recurrent episodes of coughing, wheezing, chest tightness, or shortness of breath and confirmatory spirometry.
- The patient may have a family history of allergy or asthma or have symptoms of allergic rhinitis. A history of exercise or cold air precipitating dyspnea or increased symptoms during specific allergen seasons also suggests asthma.
- Spirometry demonstrates obstruction (forced expiratory volume in 1 second [ $FEV_1$ ]/forced vital capacity less than 80%) with reversibility after inhaled  $\beta_2$ -agonist administration (at least a 12% improvement in  $FEV_1$ ). Failure of pulmonary function to improve acutely does not necessarily rule out asthma. If baseline spirometry is normal, challenge testing with exercise, histamine, or methacholine can be used to elicit BHR.

### ACUTE SEVERE ASTHMA

- Peak expiratory flow (PEF) and  $FEV_1$  are less than 50% of normal predicted values. Pulse oximetry reveals decreased arterial oxygen and  $O_2$  saturations. The best predictor of outcome is early response to treatment as measured by improvement in  $FEV_1$  at 30 minutes after inhaled  $\beta_2$ -agonists.
- Arterial blood gases may reveal metabolic acidosis and a low  $PaO_2$ .
- The history and physical examination should be obtained while initial therapy is being provided. A history of previous asthma exacerbations (e.g., hospitalizations, intubations) and complicating illnesses (e.g., cardiac disease, diabetes) should be obtained. The patient should be examined to assess hydration status; use of accessory muscles of respiration; and the presence of cyanosis, pneumonia, pneumothorax, pneumomediastinum, and upper airway obstruction. A complete blood count may be appropriate for patients with fever or purulent sputum.

## DESIRED OUTCOME

### CHRONIC ASTHMA

- The NAEPP provides the following goals for chronic asthma management:
  - ✓ Reducing impairment: (1) prevent chronic and troublesome symptoms (e.g., coughing or breathlessness in the daytime, at night, or after exertion); (2) require infrequent use ( $\leq 2$  days/wk) of inhaled short-acting  $\beta_2$ -agonist for quick relief of symptoms (not including prevention of exercise-induced

bronchospasm [EIB]); (3) maintain (near-) normal pulmonary function; (4) maintain normal activity levels (including exercise and attendance at work or school); (5) Meet patients' and families' expectation of and satisfaction with care.

- ✓ Reducing risk: (1) prevent recurrent exacerbations and minimize the need for visits or hospitalizations; (2) prevent loss of lung function; for children, prevent reduced lung growth; (3) minimal or no adverse effects of therapy.

## ACUTE SEVERE ASTHMA

- The goals of treatment include: (1) correction of significant hypoxemia; (2) rapid reversal of airway obstruction (within minutes); (3) reduction of the likelihood of recurrence of severe airflow obstruction; and (4) development of a written action plan in case of a future exacerbation.

## TREATMENT

- Fig. 80-1 depicts the NAEPP stepwise approach for managing chronic asthma. Fig. 80-2 illustrates the recommended therapies for home treatment of acute asthma exacerbations.

## NONPHARMACOLOGIC THERAPY

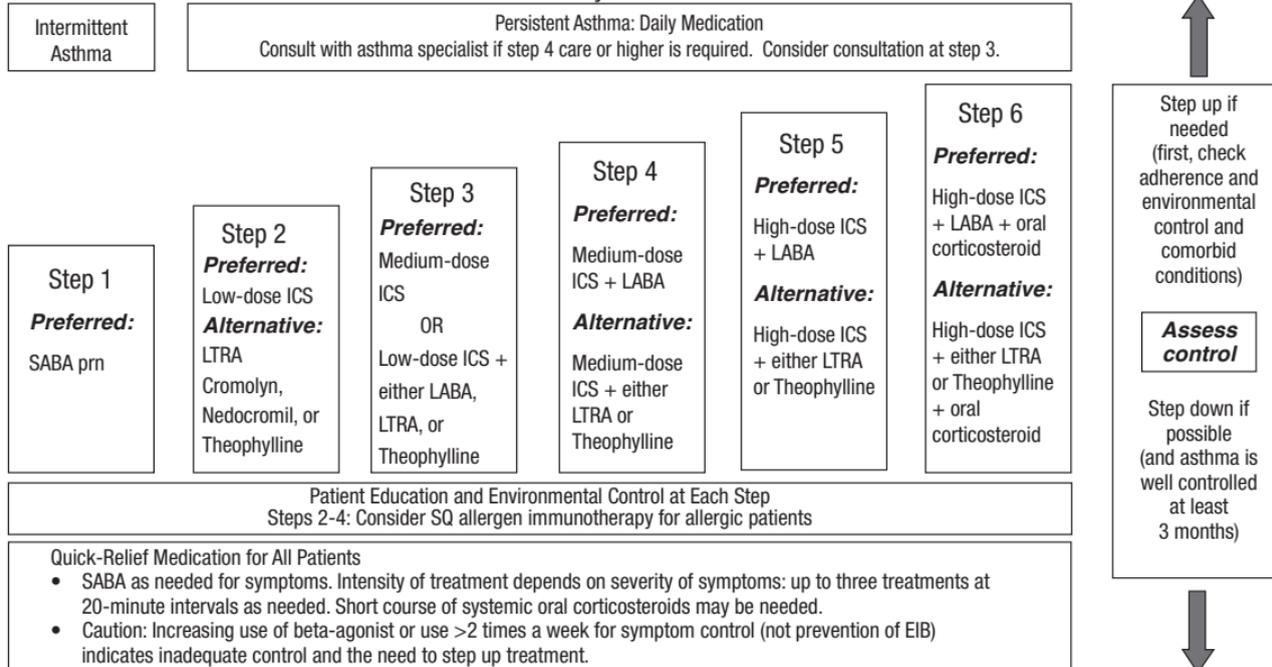
- Patient education and the teaching of self-management skills should be the cornerstone of the treatment program. Self-management programs improve adherence to medication regimens, self-management skills, and use of healthcare services.
- Objective measurements of airflow obstruction with a home peak flow meter may not necessarily improve patient outcomes. The NAEPP advocates use of PEF monitoring only for patients with severe persistent asthma who have difficulty perceiving airway obstruction.
- Avoidance of known allergenic triggers can improve symptoms, reduce medication use, and decrease BHR. Environmental triggers (e.g., animals) should be avoided in sensitive patients, and those who smoke should be encouraged to stop.
- Patients with acute severe asthma should receive supplemental oxygen therapy to maintain arterial oxygen saturation above 90% (above 95% in pregnant women and patients with heart disease). Significant dehydration should be corrected; urine specific gravity may help guide therapy in young children, in whom assessment of hydration status may be difficult.

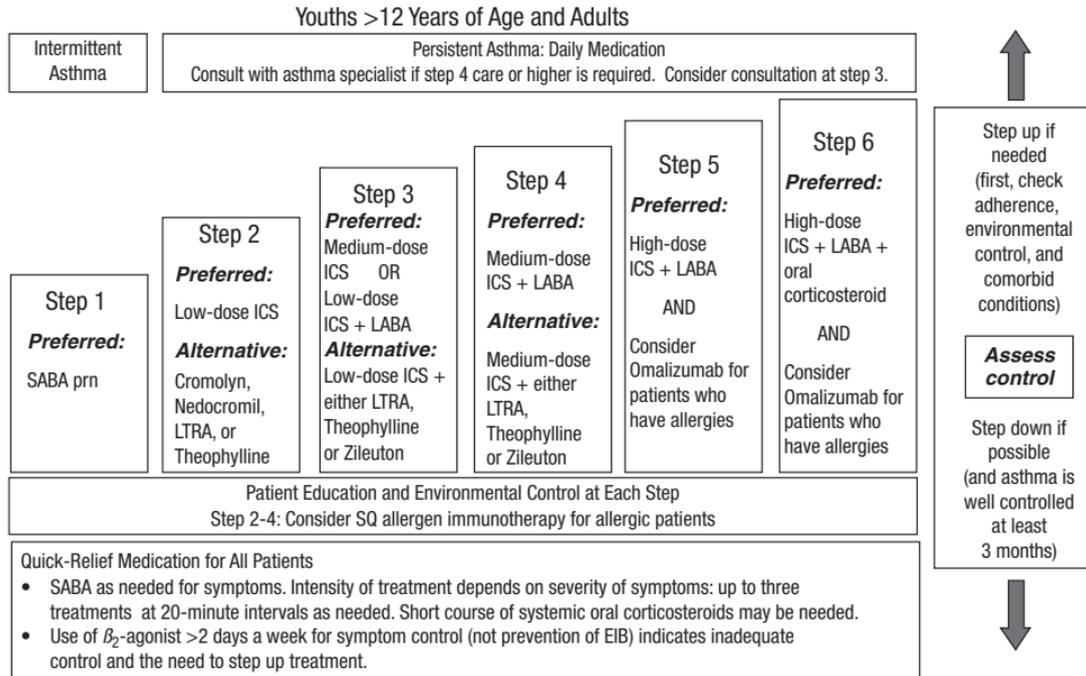
## PHARMACOTHERAPY

### $\beta_2$ -Agonists

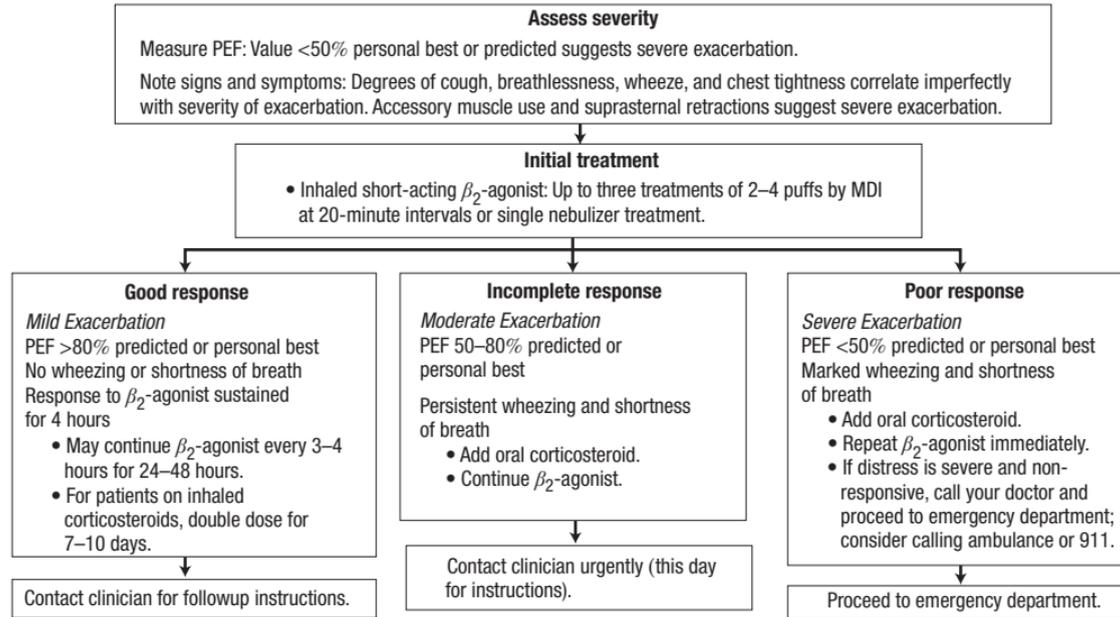
- The short-acting  $\beta_2$ -agonists (Table 80-1) are the most effective bronchodilators available.  $\beta_2$ -Adrenergic receptor stimulation activates adenylyl cyclase, which produces an increase in intracellular cyclic adenosine monophosphate. This results in smooth muscle relaxation, mast cell membrane stabilization, and skeletal muscle stimulation.

## 5–11 year olds





**FIGURE 80-1.** Stepwise approach for managing asthma in adults and children age 5 years and older. (EIB, exercise-induced bronchospasm; ICS, inhaled corticosteroid; LABA, long-acting  $\beta$ -agonist; LTRA, leukotriene receptor antagonist; SABA, short-acting  $\beta$ -agonist.) (Adapted from National Institutes of Health, National Heart, Lung, and Blood Institute. National Asthma Education and Prevention Program. Full Report of the Expert Panel: Guidelines for the diagnosis and management of asthma [EPR-3] 2007. 2007, <http://www.nhlbi.nih.gov/guidelines/asthma>.)



**FIGURE 80-2.** Home management of acute asthma exacerbation. Patients at risk of asthma-related death should receive immediate clinical attention after initial treatment. Additional therapy may be required. (MDI, metered-dose inhaler; PEF, peak expiratory flow.) (Adapted from NHLBI, National Asthma Education and Prevention Program, Expert Panel Report 2. Guidelines for the Diagnosis and Management of Asthma. NIH Publication No. 97–4051. Bethesda, MD: U.S. Department of Health and Human Services, 1997.)

**TABLE 80-1** Relative Selectivity, Potency, and Duration of Action of the  $\beta$ -Adrenergic Agonists

Agent	Selectivity		Potency, $\beta_2^a$	Duration of Action <sup>b</sup>		
	$\beta_1$	$\beta_2$		Bronchodilation (hours)	Protection (hours) <sup>c</sup>	Oral activity
Isoproterenol	++++	++++	1	0.5–2	0.5–1	No
Metaproterenol	+++	+++	15	3–4	1–2	Yes
Albuterol	+	++++	2	4–8	2–4	Yes
Pirbuterol	+	++++	5	4–8	2–4	Yes
Terbutaline	+	++++	4	4–8	2–4	Yes
Formoterol	+	++++	0.12	≥12	6–12	Yes
Salmeterol	+	++++	0.5	≥12	6–12	No

<sup>a</sup>Relative molar potency to isoproterenol: 15 = lowest potency.

<sup>b</sup>Median durations with the highest value after a single dose and lowest after chronic administration.

<sup>c</sup>Protection refers to the prevention of bronchoconstriction induced by exercise or nonspecific bronchial challenges.

- Aerosol administration enhances bronchoselectivity and provides a more rapid response and greater protection against provocations that induce bronchospasm (e.g., exercise, allergen challenges) than does systemic administration.
- **Albuterol** and other inhaled short-acting selective  $\beta_2$ -agonists are indicated for treatment of intermittent episodes of bronchospasm and are the first treatment of choice for acute severe asthma and EIB. Regular treatment (four times daily) does not improve symptom control over as-needed use.
- **Formoterol** and **salmeterol** are inhaled long-acting  $\beta_2$ -agonists indicated as adjunctive long-term control for patients with symptoms who are already on low to medium doses of inhaled corticosteroids prior to advancing to medium- or high-dose inhaled corticosteroids. Short-acting  $\beta_2$ -agonists should be continued for acute exacerbations. Long-acting agents are ineffective for acute severe asthma because it can take up to 20 minutes for onset and 1 to 4 hours for maximum bronchodilation after inhalation.
- In acute severe asthma, continuous nebulization of short-acting  $\beta_2$ -agonists (e.g., albuterol) is recommended for patients having an unsatisfactory response after three doses (every 20 minutes) of aerosolized  $\beta_2$ -agonists and potentially for patients presenting initially with PEF or FEV<sub>1</sub> values <30% of predicted normal. Dosing guidelines are presented in Table 80-2.
- Inhaled  $\beta_2$ -agonists agents are the treatment of choice for EIB. Short-acting agents provide complete protection for at least 2 hours after inhalation; long-acting agents provide significant protection for 8 to 12 hours initially, but the duration decreases with chronic regular use.
- In nocturnal asthma, long-acting inhaled  $\beta_2$ -agonists are preferred over oral sustained-release  $\beta_2$ -agonists or sustained-release theophylline. However, nocturnal asthma may be an indicator of inadequate antiinflammatory treatment.

### Corticosteroids

- Corticosteroids increase the number of  $\beta_2$ -adrenergic receptors and improve receptor responsiveness to  $\beta_2$ -adrenergic stimulation, thereby reducing

**TABLE 80-2** Dosages of Drugs for Acute Severe Exacerbations of Asthma in the Emergency Department or Hospital

Medications	Dosages		Comments
	>6 Years Old	≤6 Years Old	
<b>Inhaled <math>\beta</math>-agonists</b>			
Albuterol nebulizer solution (5 mg/mL)	2.5–5 mg every 20 minutes for 3 doses, then 2.5–10 mg q 1–4 h as needed, or 10–15 mg/h continuously	0.15 mg/kg (minimum dose 2.5 mg) every 20 minutes for three doses, then 0.15–0.3 mg/kg up to 10 mg q 1–4 h as needed, or 0.5 mg/kg/h by continuous nebulization	Only selective $\beta_2$ -agonists are recommended; for optimal delivery, dilute aerosols to minimum of 4 mL at gas flow of 6–8 L/min
Albuterol MDI (90 mcg/puff)	4–8 puffs every 30 minutes up to 4 hours, then q 1–4 h as needed	4–8 puffs every 20 minutes for three doses, then q 1–4 h as needed	In patients in severe distress, nebulization is preferred; use holding-chamber-type spacer
Levalbuterol nebulizer solution	Give at one-half the mg dose of albuterol above	Give at one-half the mg dose of albuterol above	The single isomer of albuterol is likely to be twice as potent on a mg basis
Levalbuterol MDI (45 mcg/puff)	Give at one-half the mg dose of albuterol above	Give at one-half the mg dose of albuterol above	
Pirbuterol MDI (200 mcg/puff)	See albuterol dose	See albuterol dose; one-half as potent as albuterol on a mcg basis	Has not been studied in acute severe asthma
<b>Systemic <math>\beta</math>-agonists</b>			
Epinephrine 1:1,000 (1 mg/mL)	0.3–0.5 mg every 20 minutes for three doses subcutaneously	0.01 mg/kg up to 0.5 mg every 20 minutes for three doses subcutaneously	No proven advantage of systemic therapy over aerosol
Terbutaline (1 mg/mL)	0.25 mg every 20 minutes for three doses subcutaneously	0.01 mg/kg every 20 minutes for three doses, then q 2–6 h as needed subcutaneously	Not recommended
<b>Anticholinergics</b>			
Ipratropium bromide nebulizer solution (0.25 mg/mL)	500 mcg every 30 minutes for three doses, then q 2–4 h as needed	250 mcg every 20 minutes for three doses, then 250 mcg q 2–4 h	May mix in same nebulizer with albuterol; do not use as first-line therapy; only add to $\beta_2$ -agonist therapy
Ipratropium bromide MDI (17 mcg/puff)	4–8 puffs as needed q 2–4 h	4–8 puffs as needed q 2–4 h	Not recommended because dose in inhaler is low and has not been studied in acute asthma
<b>Corticosteroids</b>			
Prednisone, methylprednisolone, prednisolone	60–80 mg in 3–4 divided doses for 48 hours, then 30–40 mg/day until PEF reaches 70% of personal best	1 mg/kg every 6 hours for 48 hours, then 1–2 mg/kg/day in two divided doses until PEF is 70% of normal predicted	For outpatient “burst” use 1–2 mg/kg/day, maximum 60 mg, for 3–7 days; it is unnecessary to taper course

FEV<sub>1</sub>, forced expiratory volume in the first second of expiration; MDI, metered-dose inhaler; PEF, peak expiratory flow.

Note: No advantage has been found for very-high-dose corticosteroids in acute severe asthma, nor is there any advantage for IV administration over oral therapy. The usual regimen is to continue the frequent multiple daily dosing until the patient achieves an FEV<sub>1</sub> or PEF of 50% of personal best or normal predicted value and then lower the dose to twice-daily dosing. This usually occurs within 48 hours. The final duration of therapy following a hospitalization or emergency department visit may be from 7 to 14 days. If patient is then started on inhaled corticosteroids, studies indicate there is no need to taper the systemic steroid dose. If the follow-up therapy is to be given once daily, studies indicate there may be an advantage to giving the single daily dose in the afternoon at around 3 PM.

mucus production and hypersecretion, reducing BHR, and reducing airway edema and exudation.

- Inhaled corticosteroids are the preferred long-term control therapy for persistent asthma in all patients because of their potency and consistent effectiveness; they are also the only therapy shown to reduce the risk of death from asthma. Comparative doses are included in Table 80-3. Most patients with moderate disease can be controlled with twice-daily dosing; some products have once-daily dosing indications. Patients with more severe disease require multiple daily dosing. Because the inflammatory response of asthma inhibits steroid receptor binding, patients should be started on higher and more frequent doses and then tapered down once control has been achieved. The response to inhaled corticosteroids is delayed; symptoms improve in most patients within the first 1 to 2 weeks and reach maximum improvement in 4 to 8 weeks. Maximum improvement in FEV<sub>1</sub> and PEF rates may require 3 to 6 weeks.

**TABLE 80-3** Available Inhaled Corticosteroid Products, Lung Delivery, and Comparative Daily Dosages

Inhaled Corticosteroids	Product	Lung Delivery <sup>a</sup>
Beclothemason dipropionate (BDP)	40 and 80 mcg/actuation HFA MDI, 120 actuations	55–60%
Budesonide (BUD)	200 mcg/dose DPI, Turbuhaler, 200 doses 200- and 500-mcg ampules, 2 mL each	32% (16–59%) 6%
Flunisolide (FLU)	250 mcg/actuation CFC MDI, 100 actuations 80 mcg/actuation HFA MDI, 120 actuations	20% 68%
Fluticasone propionate (FP)	44, 110, and 220 mcg/actuation HFA MDI, 120 actuations	20–25%
Mometasone furoate (MF)	50 mcg/dose DPI, Diskus, 60 doses 200 and 400 mcg/dose DPI, Twisthaler, 14, 30, 60, and 120 doses	15% 11%
Triamcinolone acetonide (TAA)	75 mcg/actuation CFC MDI, 240 actuations with spacer	22%

	Comparative Daily Dosages (mcg) of Inhaled Corticosteroids		
	Low Daily Dose Child <sup>b</sup> /Adult	Medium Daily Dose Child <sup>b</sup> /Adult	High Daily Dose Child <sup>b</sup> /Adult
BDP			
HFA MDI	80–160/80–240	>160–320/>240–480	>320/>480
BUD			
DPI	200–400/200–600	>400–800/>600–1,200	>800/>1,200
Nebules	500/UK	1,000/UK	2,000/UK
FLU			
CFC MDI	500–750/500–1,000	1,000–1,250/1,000–2,000	>1,250/>2,000
HFA MDI	160/320	320/320–640	≥640/>640
FP			
HFA MDI	88–176/88–264	176–352/264–440	>352/>440
DPIs	100–200/100–300	200–400/300–500	>400/>500
MF, DPI	UK/200	UK/400	UK/>400
TAA, CFC MDI	300–600/300–750	600–900/750–1,500	>900/>1,500

CFC, chlorofluorocarbon; DPI, dry-powder inhaler; HFA, hydrofluoroalkane; MDI, metered-dose inhaler; UK, unknown.

<sup>a</sup>Lung delivery from in vivo radiolabel scintigraphy or pharmacokinetic studies.

<sup>b</sup>5–11 years of age.

**TABLE 80-4** Comparison of the Systemic Corticosteroids

Systemic	Anti-inflammatory Potency	Mineralocorticoid Potency	Duration of Biologic Activity (hours)	Elimination Half-Life (hours)
Hydrocortisone	1	1	8–12	1.5–2
Prednisone	4	0.8	12–36	2.5–3.5
Methylprednisolone	5	0.5	12–36	3.3
Dexamethasone	25	0	36–54	3.4–4

- Systemic toxicity of inhaled corticosteroids is minimal with low to moderate inhaled doses, but the risk of systemic effects increases with high doses. Local adverse effects include dose-dependent oropharyngeal candidiasis and dysphonia, which can be reduced by the use of a spacer device. The ability of spacer devices to enhance lung delivery is inconsistent and should not be relied on.
- Systemic corticosteroids (Table 80-4) are indicated in all patients with acute severe asthma not responding completely to initial inhaled  $\beta_2$ -agonist administration (every 20 minutes for three to four doses). Prednisone, 1 to 2 mg/kg/day (up to 40 to 60 mg/day), is administered orally in two divided doses for 3 to 10 days. Because short-term (1 to 2 weeks), high-dose systemic steroids do not produce serious toxicities, the ideal method is to use a short burst and then maintain the patient on appropriate long-term control therapy with inhaled corticosteroids.
- In patients who require chronic systemic corticosteroids for asthma control, the lowest possible dose should be used. Toxicities may be decreased by alternate-day therapy or high-dose inhaled corticosteroids.

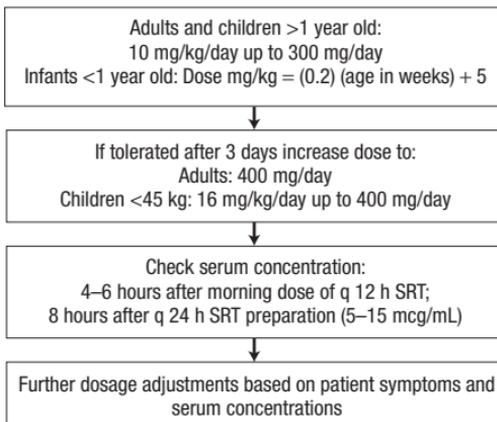
### Methylxanthines

- **Theophylline** appears to produce bronchodilation by inhibiting phosphodiesterases, which may also result in antiinflammatory and other nonbronchodilator activity through decreased mast cell mediator release, decreased eosinophil basic protein release, decreased T-lymphocyte proliferation, decreased T-cell cytokine release, and decreased plasma exudation.
- Methylxanthines are ineffective by aerosol and must be taken systemically (orally or IV). Sustained-release theophylline is the preferred oral preparation, whereas its complex with ethylenediamine (**aminophylline**) is the preferred parenteral product due to increased solubility. IV theophylline is also available.
- Theophylline is eliminated primarily by metabolism via hepatic cytochrome P450 mixed-function oxidase microsomal enzymes (primarily CYP1A2 and CYP3A4) with 10% or less excreted unchanged in the kidney. The hepatic cytochrome P450 enzymes are susceptible to induction and inhibition by various environmental factors and drugs. Clinically significant reductions in clearance can result from cotherapy with cimetidine, erythromycin, clarithromycin, allopurinol, propranolol, ciprofloxacin, interferon, ticlopidine, zileuton, and other drugs. Some substances that enhance clearance include rifampin, carbamazepine, phenobarbital, phenytoin, charcoal-broiled meat, and cigarette smoking.

- Because of large interpatient variability in theophylline clearance, routine monitoring of serum theophylline concentrations is essential for safe and effective use. A steady-state range of 5 to 15 mcg/mL is effective and safe for most patients.
- Fig. 80-3 gives recommended dosages, monitoring schedules, and dosage adjustments for theophylline.
- Sustained-release oral preparations are favored for outpatient therapy, but each product has different release characteristics and some products are susceptible to altered absorption from food or gastric pH changes. Preparations unaffected by food that can be administered a minimum of every 12 hours in most patients are preferable.
- Adverse effects include nausea, vomiting, tachycardia, jitteriness, and difficulty sleeping; more severe toxicities include cardiac tachyarrhythmias and seizures.
- Sustained-release theophylline is less effective than inhaled corticosteroids and no more effective than oral sustained-release  $\beta_2$ -agonists, cromolyn, or leukotriene antagonists.
- The addition of theophylline to optimal inhaled corticosteroids is similar to doubling the dose of the inhaled corticosteroid and is less effective overall than the long-acting  $\beta_2$ -agonists as adjunctive therapy.

### Anticholinergics

- **Ipratropium bromide** and **tiotropium bromide** are competitive inhibitors of muscarinic receptors; they produce bronchodilation only in cholinergic-mediated bronchoconstriction. Anticholinergics are effective bronchodilators but are not as potent as  $\beta_2$ -agonists. They attenuate, but do not block, allergen- or exercise-induced asthma in a dose-dependent fashion.



**FIGURE 80-3.** Algorithm for slow titration of theophylline dosage and guide for final dosage adjustment based on serum theophylline concentration measurement. For infants younger than 1 year of age, the initial daily dosage can be calculated by the following regression equation:

$$\text{Dose (mg/kg)} = (0.2) (\text{age in weeks}) + 5.$$

Whenever side effects occur, dosage should be reduced to a previously tolerated lower dose. (SRT, sustained-release theophylline.)

- The time to reach maximum bronchodilation from aerosolized ipratropium is longer than from aerosolized short-acting  $\beta_2$ -agonists (30 to 60 minutes vs. 5 to 10 minutes). This is of little clinical consequence because some bronchodilation is seen within 30 seconds and 50% of maximum response occurs within 3 minutes. Ipratropium bromide has a duration of action of 4 to 8 hours; tiotropium bromide has a duration of 24 hours.
- Inhaled ipratropium bromide is only indicated as adjunctive therapy in severe acute asthma not completely responsive to  $\beta_2$ -agonists alone because it does not improve outcomes in chronic asthma. Tiotropium bromide has not been studied in asthma.

### Mast Cell Stabilizers

- **Cromolyn sodium** and **nedocromil sodium** have beneficial effects that are believed to result from stabilization of mast cell membranes. They inhibit the response to allergen challenge as well as EIB but do not cause bronchodilation.
- These agents are effective only by inhalation and are available as metered-dose inhalers; cromolyn also comes as a nebulizer solution.
- Both drugs are remarkably nontoxic. Cough and wheezing have been reported after inhalation of each agent, and bad taste and headache after nedocromil.
- Cromolyn and nedocromil are indicated for the prophylaxis of mild persistent asthma in children and adults regardless of etiology. Their effectiveness is comparable to theophylline or leukotriene antagonists for persistent asthma. Neither agent is as effective as inhaled corticosteroids for controlling persistent asthma. Neither is as effective as the inhaled  $\beta_2$ -agonists for preventing EIB, but they can be used in conjunction for patients not responding completely to inhaled  $\beta_2$ -agonists.
- Most patients experience improvement in 1 to 2 weeks, but it may take longer to achieve maximum benefit. Patients should initially receive cromolyn or nedocromil four times daily; after stabilization of symptoms the frequency may be reduced to two times daily for nedocromil and three times daily for cromolyn.

### Leukotriene Modifiers

- **Zafirlukast** (Accolate) and **montelukast** (Singulair) are oral leukotriene receptor antagonists that reduce the proinflammatory (increased microvascular permeability and airway edema) and bronchoconstriction effects of leukotriene  $D_4$ . In adults and children with persistent asthma, they improve pulmonary function tests, decrease nocturnal awakenings and  $\beta_2$ -agonist use, and improve asthma symptoms. However, they are less effective in asthma than low-dose inhaled corticosteroids. They are not used to treat acute exacerbations and must be taken on a regular basis, even during symptom-free periods. The adult dose of zafirlukast is 20 mg twice daily, taken at least 1 hour before or 2 hours after meals; the dose for children aged 5 through 11 years is 10 mg twice daily. For montelukast, the adult dose is 10 mg once daily, taken in the evening without regard to food; the dose for children aged 6 to 14 years is one 5-mg chewable tablet daily in the evening.

- Zafirlukast and montelukast are generally well tolerated. Rare elevations in serum aminotransferase concentrations and clinical hepatitis have been reported. An idiosyncratic syndrome similar to the Churg-Strauss syndrome, with marked circulating eosinophilia, heart failure, and associated eosinophilic vasculitis, has been reported in a small number of patients; a direct causal association has not been established.
- **Zileuton** (Zyflo) is an inhibitor of leukotriene synthesis. The dose of zileuton tablets is 600 mg four times daily with meals and at bedtime. The recommended dose of zileuton extended-release tablets is two 600-mg tablets twice daily, within 1 hour after morning and evening meals (total daily dose 2,400 mg).
- Use of zileuton is limited due to the potential for elevated hepatic enzymes (especially in the first 3 months of therapy), and inhibition of the metabolism of some drugs metabolized by CYP3A4 (e.g., theophylline, warfarin). Serum alanine aminotransferase should be monitored before treatment and then periodically thereafter.

### Combination Controller Therapy

- The addition of a second long-term control medication to inhaled corticosteroid therapy is one recommended treatment option in moderate to severe persistent asthma.
- Single-inhaler combination products containing fluticasone propionate and salmeterol (Advair) or budesonide and formoterol (Symbicort) are currently available. The inhalers contain varied doses of the inhaled corticosteroid with a fixed dose of the long-acting  $\beta_2$ -agonist. The addition of a long-acting  $\beta_2$ -agonist allows a 50% reduction in inhaled corticosteroid dosage in most patients with persistent asthma. Combination therapy is more effective than higher-dose inhaled corticosteroids alone in reducing asthma exacerbations in patients with persistent asthma.
- Leukotriene receptor antagonists also are successful as additive therapy in patients inadequately controlled on inhaled corticosteroids alone and as corticosteroid-sparing therapy. However, the magnitude of these benefits is less than that reported with the addition of long-acting  $\beta_2$ -agonists.

### Omalizumab

- **Omalizumab** (Xolair) is an anti-IgE antibody approved for the treatment of allergic asthma not well controlled by oral or inhaled corticosteroids. The dosage is determined by the patient's baseline total serum IgE (international units/mL) and body weight (kg). Doses range from 150 to 375 mg given subcutaneously at either 2- or 4-week intervals.
- Because of its high cost, it is only indicated as step 5 or 6 care for patients who have allergies and severe persistent asthma that is inadequately controlled with the combination of high-dose inhaled corticosteroids and long-acting  $\beta_2$ -agonists.
- Because it is associated with a 0.1% incidence of anaphylaxis, patients should remain in the physician's office for a reasonable period after the injection because 70% of reactions occur within 2 hours. Some reactions have occurred up to 24 hours after injection.

## EVALUATION OF THERAPEUTIC OUTCOMES

### CHRONIC ASTHMA

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- Control of asthma is defined as reducing both impairment and risk domains. Regular follow-up is essential (at 1- to 6-month intervals, depending on control).
- Components of the assessment of control include symptoms, nighttime awakenings, interference with normal activities, pulmonary function, quality of life, exacerbations, adherence, treatment-related adverse effects, and satisfaction with care. The categories of well controlled, not well controlled, and very poorly controlled are recommended. Validated questionnaires can be administered regularly, such as the Asthma Therapy Assessment Questionnaire, Asthma Control Questionnaire, and Asthma Control Test.
- Spirometric tests are recommended at initial assessment, after treatment is initiated, and then every 1 to 2 years. Peak flow monitoring is recommended in moderate to severe persistent asthma.
- Patients should also be asked about exercise tolerance.
- All patients on inhaled drugs should have their inhalation technique evaluated monthly initially and then every 3 to 6 months.
- After initiation of antiinflammatory therapy or an increase in dosage, most patients should begin experiencing a decrease in symptoms within 1 to 2 weeks and achieve maximum symptomatic improvement within 4 to 8 weeks. Improvement in baseline FEV<sub>1</sub> or PEF should follow a similar time frame, but a decrease in BHR as measured by morning PEF, PEF variability, and exercise tolerance may take longer and improve over 1 to 3 months.

### ACUTE SEVERE ASTHMA

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- Patients at risk for acute severe exacerbations should monitor morning peak flows at home.
- Lung function, either spirometry or peak flows, should be monitored 5 to 10 minutes after each treatment.
- Oxygen saturations can be easily monitored continuously with pulse oximetry. For young children and adults, pulse oximetry, lung auscultation, and observation for supraclavicular retractions is useful.
- Most patients respond with the first hour of initial inhaled  $\beta$ -agonists. Patients not achieving an initial response should be monitored every 0.5 to 1 hour.

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*See Chap. 28, Asthma, authored by H. William Kelly and Christine A. Sorkness, for a more detailed discussion of this topic.*

## DEFINITION

- Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases. The most common conditions comprising COPD are chronic bronchitis and emphysema.
- Chronic bronchitis is associated with chronic or recurrent excess mucus secretion into the bronchial tree with cough that occurs on most days for at least 3 months of the year for at least 2 consecutive years when other causes of cough have been excluded.
- Emphysema is defined as abnormal, permanent enlargement of the air-spaces distal to the terminal bronchioles, accompanied by destruction of their walls, but without obvious fibrosis.

## PATHOPHYSIOLOGY

- The most common etiology is exposure to environmental tobacco smoke, but other chronic inhalational exposures can also lead to COPD. Inhalation of noxious particles and gases stimulates the activation of neutrophils, macrophages, and CD8<sup>+</sup> lymphocytes, which release a variety of chemical mediators, including tumor necrosis factor- $\alpha$ , interleukin-8, and leukotriene B<sub>4</sub>. These inflammatory cells and mediators lead to widespread destructive changes in the airways, pulmonary vasculature, and lung parenchyma.
- Other pathophysiologic processes may include oxidative stress and an imbalance between aggressive and protective defense systems in the lungs (proteases and antiproteases). Increased oxidants generated by cigarette smoke react with and damage various proteins and lipids, leading to cell and tissue damage. Oxidants also promote inflammation directly and exacerbate the protease-antiprotease imbalance by inhibiting antiprotease activity.
- The protective antiprotease  $\alpha_1$ -antitrypsin (AAT) inhibits several protease enzymes, including neutrophil elastase. In the presence of unopposed AAT activity, elastase attacks elastin, which is a major component of alveolar walls. A hereditary deficiency of AAT results in an increased risk for premature development of emphysema. In the inherited disease, there is an absolute deficiency of AAT. In emphysema resulting from cigarette-smoking, the imbalance is associated with increased protease activity or reduced activity of antiproteases. Activated inflammatory cells release several other proteases, including cathepsins and metalloproteinases. In addition, oxidative stress reduces antiprotease (or protective) activity.
- An inflammatory exudate is often present in the airways that leads to an increased number and size of goblet cells and mucus glands. Mucus

secretion increases, and ciliary motility is impaired. There is thickening of the smooth muscle and connective tissue in the airways. Chronic inflammation leads to scarring and fibrosis. Diffuse airway narrowing occurs and is more prominent in small peripheral airways.

- Parenchymal changes affect the gas-exchanging units of the lungs (alveoli and pulmonary capillaries). Smoking-related disease most commonly results in centrilobular emphysema that primarily affects respiratory bronchioles. Panlobular emphysema is seen in AAT deficiency and extends to the alveolar ducts and sacs.
- Vascular changes include thickening of pulmonary vessels that may lead to endothelial dysfunction of the pulmonary arteries. Later, structural changes increase pulmonary pressures, especially during exercise. In severe COPD, secondary pulmonary hypertension leads to right-sided heart failure (cor pulmonale).

## CLINICAL PRESENTATION

- Initial symptoms of COPD include chronic cough and sputum production; patients may have these symptoms for several years before dyspnea develops.
- The physical examination is normal in most patients who present in the milder stages of COPD. When airflow limitation becomes severe, patients may have cyanosis of mucosal membranes, development of a “barrel chest” due to hyperinflation of the lungs, an increased resting respiratory rate, shallow breathing, pursing of the lips during expiration, and use of accessory respiratory muscles.
- Patients experiencing a COPD exacerbation may have worsening dyspnea, increase in sputum volume, or increase in sputum purulence. Other common features of an exacerbation include chest tightness, increased need for bronchodilators, malaise, fatigue, and decreased exercise tolerance.

## DIAGNOSIS

- The diagnosis of COPD is based in part on the patient’s symptoms and a history of exposure to risk factors such as tobacco smoke and occupational exposures.

## PULMONARY FUNCTION TESTS

- Assessment of airflow limitation through spirometry is the standard for diagnosing and monitoring COPD. The forced expiratory volume after 1 second ( $FEV_1$ ) is generally reduced except in very mild disease. The forced vital capacity (FVC) may also be decreased. The hallmark of COPD is a reduced  $FEV_1:FVC$  ratio to less than 70%. A postbronchodilator  $FEV_1$  that is less than 80% of predicted confirms the presence of airflow limitation that is not fully reversible.
- An improvement in  $FEV_1$  of less than 12% after inhalation of a rapid-acting bronchodilator is considered to be evidence of irreversible airflow obstruction.

- Peak expiratory flow measurements are not adequate for diagnosis of COPD because of low specificity and a high degree of effort dependence. However, a low peak expiratory flow is consistent with COPD.

## ARTERIAL BLOOD GASES

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- Significant changes in arterial blood gases are not usually present until the FEV<sub>1</sub> is less than 1 L. At this stage, hypoxemia and hypercapnia may become chronic problems. Hypoxemia usually occurs initially with exercise but develops at rest as the disease progresses.
- Patients with severe COPD can have a low arterial oxygen tension (PaO<sub>2</sub> 45 to 60 mm Hg) and an elevated arterial carbon dioxide tension (PaCO<sub>2</sub> 50 to 60 mm Hg). Hypoxemia results from hypoventilation (V) of lung tissue relative to perfusion (Q) of the area. The low V:Q ratio progresses over several years, resulting in a consistent decline in the PaO<sub>2</sub>.
- Some patients lose the ability to increase the rate or depth of respiration in response to persistent hypoxemia. This decreased ventilatory drive may be due to abnormal peripheral or central respiratory receptor responses. This relative hypoventilation leads to hypercapnia; in this situation the central respiratory response to a chronically increased PaCO<sub>2</sub> can be blunted. Because these changes in PaO<sub>2</sub> and PaCO<sub>2</sub> are subtle and progress over many years, the pH is usually near normal because the kidneys compensate by retaining bicarbonate.
- If acute respiratory distress develops (e.g., due to pneumonia or a COPD exacerbation) the PaCO<sub>2</sub> may rise sharply resulting in an uncompensated respiratory acidosis.

## DIAGNOSIS OF ACUTE RESPIRATORY FAILURE IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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- The diagnosis of acute respiratory failure in COPD is made on the basis of an acute drop in PaO<sub>2</sub> of 10 to 15 mm Hg or any acute increase in PaCO<sub>2</sub> that decreases the serum pH to 7.3 or less.
- Additional acute clinical manifestations include restlessness, confusion, tachycardia, diaphoresis, cyanosis, hypotension, irregular breathing, miosis, and unconsciousness.
- The most common cause of acute respiratory failure in COPD is acute exacerbation of bronchitis with an increase in sputum volume and viscosity. This serves to worsen obstruction and further impair alveolar ventilation, resulting in worsening hypoxemia and hypercapnia. Additional causes are pneumonia, pulmonary embolism, left ventricular failure, pneumothorax, and CNS depressants.

## DESIRED OUTCOME

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- The goals of therapy are to prevent disease progression, relieve symptoms, improve exercise tolerance, improve overall health status, prevent and treat exacerbations, prevent and treat complications, and reduce morbidity and mortality.

## TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

### NONPHARMACOLOGIC THERAPY

- Smoking cessation is the most effective strategy to reduce the risk of developing COPD and the only intervention proven to affect the long-term decline in FEV<sub>1</sub> and slow the progression of COPD.
- Pulmonary rehabilitation programs include exercise training along with smoking cessation, breathing exercises, optimal medical treatment, psychosocial support, and health education. Supplemental oxygen, nutritional support, and psychoeducational care (e.g., relaxation) are important adjuncts in a pulmonary rehabilitation program.
- Annual vaccination with the inactivated intramuscular influenza vaccine is recommended.
- One dose of the polyvalent pneumococcal vaccine is indicated for patients at any age with COPD; revaccination is recommended for patients older than 65 years if the first vaccination was more than 5 years earlier and the patient was younger than 65 years.

### PHARMACOLOGIC THERAPY

- A stepwise approach to managing stable COPD based on disease severity is shown in Fig. 81-1. Bronchodilators are used to control symptoms; no single pharmacologic class has been proven to provide superior benefit over others, although inhaled therapy is generally preferred. Medication selection is based on likely patient adherence, individual response, and side effects. Medications can be used as needed or on a scheduled basis, and additional therapies should be added in a stepwise manner depending on response and disease severity. Clinical benefits of bronchodilators include increased exercise capacity, decreased air trapping, and relief of symptoms such as dyspnea. However, significant improvements in pulmonary function measurements such as FEV<sub>1</sub> may not be observed.

#### Sympathomimetics

- $\beta_2$ -Selective sympathomimetics cause relaxation of bronchial smooth muscle and bronchodilation by stimulating the enzyme adenylyl cyclase to increase the formation of cyclic adenosine monophosphate. They may also improve mucociliary clearance.
- Administration via metered-dose inhaler (MDI) or dry-powder inhaler is at least as effective as nebulization therapy and is usually favored for reasons of cost and convenience. Refer to Table 80-1 in Chap. 80 for a comparison of the available agents.
- **Albuterol, levalbuterol, bitolterol, pirbuterol, and terbutaline** are the preferred short-acting agents because they have greater  $\beta_2$  selectivity and longer durations of action than other short-acting agents (isoproterenol, metaproterenol, and isoetharine). The inhalation route is preferred to the oral and parenteral routes in terms of both efficacy and adverse effects.

	<b>0: At risk</b>	<b>I: Mild</b>	<b>II: Moderate</b>	<b>III: Severe</b>	<b>IV: Very severe</b>
Characteristics	<ul style="list-style-type: none"> <li>• Chronic symptoms</li> <li>• Exposure to risk factors</li> <li>• Normal spirometry</li> </ul>	<ul style="list-style-type: none"> <li>• FEV<sub>1</sub>:FVC &lt;70%</li> <li>• FEV<sub>1</sub> ≥80%</li> <li>• With or without symptoms</li> </ul>	<ul style="list-style-type: none"> <li>• FEV<sub>1</sub>:FVC &lt;70%</li> <li>• 50% &gt; FEV<sub>1</sub> &lt;80%</li> <li>• With or without symptoms</li> </ul>	<ul style="list-style-type: none"> <li>• FEV<sub>1</sub>:FVC &lt;70%</li> <li>• 30% &gt; FEV<sub>1</sub> &lt;50%</li> <li>• With or without symptoms</li> </ul>	<ul style="list-style-type: none"> <li>• FEV<sub>1</sub>:FVC &lt;70%</li> <li>• FEV<sub>1</sub> &lt;30% or presence of chronic respiratory failure or right heart failure</li> </ul>
	Avoidance of risk factor(s); influenza vaccination pneumococcal vaccine				
	Add short-acting bronchodilator when needed				
	Add regular treatment with one or more long-acting bronchodilators Add rehabilitation				
			Add inhaled glucocorticosteroids if repeated exacerbations		
					Add long-term oxygen if chronic respiratory failure Consider surgical treatments

**FIGURE 81-1.** Recommended therapy of stable chronic obstructive pulmonary disease. (FEV<sub>1</sub>, forced expiratory volume in the first second of expiration; FVC, forced vital capacity.) (From Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease. NHLBI/WHO workshop report. Bethesda, MD: National Heart, Lung and Blood Institute, April 2001; Updated November 2006. Available at <http://www.goldcopd.com>.)

Short-acting agents can be used for acute relief of symptoms or on a scheduled basis to prevent or reduce symptoms. The duration of action of short-acting  $\beta_2$ -agonists is 4 to 6 hours.

- **Formoterol** and **salmeterol** are long-acting inhaled  $\beta_2$ -agonists that are dosed every 12 hours on a scheduled basis and provide bronchodilation throughout the dosing interval. In 2007, formoterol and **arformoterol** became available in the United States as nebulized solutions. Long-acting inhaled  $\beta_2$ -agonists should be considered when patients demonstrate a frequent need for short-acting agents. They are also useful to decrease nocturnal symptoms and improve quality of life. They are not indicated for acute relief of symptoms.

### Anticholinergics

- When given by inhalation, anticholinergic agents produce bronchodilation by competitively inhibiting cholinergic receptors in bronchial smooth muscle. This activity blocks acetylcholine, with the net effect being a reduction in cyclic guanosine monophosphate, which normally acts to constrict bronchial smooth muscle.
- **Ipratropium bromide** has a slower onset of action than short-acting  $\beta_2$ -agonists (15 to 20 minutes vs. 5 minutes for albuterol). For this reason, it may be less suitable for as-needed use, but it is often prescribed in this manner. Ipratropium has a more prolonged bronchodilator effect than short-acting  $\beta_2$ -agonists. Its peak effect occurs in 1.5 to 2 hours and its duration is 4 to 6 hours. The recommended dose via MDI is two puffs four times a day with upward titration often to 24 puffs/day. It is also available as a solution for nebulization. The most frequent patient complaints are dry mouth, nausea, and, occasionally, metallic taste. Because it is poorly absorbed systemically, anticholinergic side effects are uncommon (e.g., blurred vision, urinary retention, nausea, and tachycardia).
- **Tiotropium bromide** is a long-acting agent that protects against cholinergic bronchoconstriction for more than 24 hours. Its onset of effect is within 30 minutes with a peak effect in 3 hours. It is delivered via the HandiHaler, a single-load, dry-powder, breath-actuated device. The recommended dose is inhalation of the contents of one capsule once daily using the HandiHaler inhalation device. Because it acts locally, tiotropium is well tolerated; the most common complaint is dry mouth. Other anticholinergic effects have also been reported.

### Combination Anticholinergics and Sympathomimetics

- The combination of an inhaled anticholinergic and  $\beta_2$ -agonist is often used, especially as the disease progresses and symptoms worsen over time. Combining bronchodilators with different mechanisms of action allows the lowest effective doses to be used and reduces adverse effects from individual agents. Combination of both short- and long-acting  $\beta_2$ -agonists with ipratropium has been shown to provide added symptomatic relief and improvements in pulmonary function.
- A combination product containing **albuterol** and **ipratropium** (**Combivent**) is available as an MDI for chronic maintenance therapy of COPD. Other similar combination products may become available in the future.

## Methylxanthines

- **Theophylline** and **aminophylline** may produce bronchodilation by inhibition of phosphodiesterase (thereby increasing cyclic adenosine monophosphate levels), inhibition of calcium ion influx into smooth muscle, prostaglandin antagonism, stimulation of endogenous catecholamines, adenosine receptor antagonism, and inhibition of release of mediators from mast cells and leukocytes.
- Chronic theophylline use in COPD has been shown to produce improvements in lung function, including vital capacity and FEV<sub>1</sub>. Subjectively, theophylline has been shown to reduce dyspnea, increase exercise tolerance, and improve respiratory drive. Nonpulmonary effects that may contribute to better functional capacity include improved cardiac function and decreased pulmonary artery pressure.
- Methylxanthines are no longer considered first-line therapy for COPD. Inhaled bronchodilator therapy is preferred over theophylline for COPD because of theophylline's risk for drug interactions and the interpatient variability in dosage requirements. Theophylline may be considered in patients who are intolerant or unable to use an inhaled bronchodilator. A methylxanthine may also be added to the regimen of patients who have not achieved an optimal clinical response to an inhaled anticholinergic and  $\beta_2$ -agonist.
- As with other bronchodilators in COPD, parameters other than objective measurements such as FEV<sub>1</sub> should be monitored to assess efficacy. Subjective parameters, such as perceived improvements in dyspnea and exercise tolerance, are important in assessing the acceptability of methylxanthines for COPD patients.
- Sustained-release theophylline preparations improve patient compliance and achieve more consistent serum concentrations than rapid-release theophylline and aminophylline preparations. Caution should be used in switching from one sustained-release preparation to another because there are considerable variations in sustained-release characteristics.
- The role of theophylline in COPD is as maintenance therapy in non-acutely ill patients. Therapy can be initiated at 200 mg twice daily and titrated upward every 3 to 5 days to the target dose; most patients require daily doses of 400 to 900 mg.
- Dose adjustments should generally be made based on trough serum concentration results. A conservative therapeutic range of 8 to 15 mcg/mL is often targeted, especially in elderly patients, to minimize the likelihood of toxicity. Once a dose is established, concentrations should be monitored once or twice a year unless the disease worsens, medications that interfere with theophylline metabolism are added, or toxicity is suspected.
- The most common side effects of theophylline include dyspepsia, nausea, vomiting, diarrhea, headache, dizziness, and tachycardia. Arrhythmias and seizures may occur, especially at toxic concentrations.
- Factors that may decrease theophylline clearance and lead to reduced dosage requirements include advanced age, bacterial or viral pneumonia, heart failure, liver dysfunction, hypoxemia from acute decompensation, and use of drugs such as cimetidine, macrolides, and fluoroquinolone antibiotics.

- Factors that may enhance theophylline clearance and result in the need for higher doses include tobacco and marijuana smoking, hyperthyroidism, and use of drugs such as phenytoin, phenobarbital, and rifampin.

### **Corticosteroids**

- The antiinflammatory mechanisms whereby corticosteroids exert their beneficial effect in COPD include reduction in capillary permeability to decrease mucus, inhibition of release of proteolytic enzymes from leukocytes, and inhibition of prostaglandins.
- The clinical benefits of systemic corticosteroid therapy in the chronic management of COPD are often not evident, and there is a high risk of toxicity. Consequently, chronic, systemic corticosteroids should be avoided if possible.
- Appropriate situations to consider corticosteroids in COPD include (1) short-term systemic use for acute exacerbations; and (2) inhalation therapy for chronic stable COPD.
- The role of inhaled corticosteroids in COPD is controversial. Major clinical trials have failed to demonstrate any benefit from chronic treatment in modifying long-term decline in lung function. However, other important benefits have been observed in some patients, including a decrease in exacerbation frequency and improvements in overall health status.
- Consensus guidelines indicate that inhaled corticosteroid therapy should be considered for symptomatic patients with stage III or IV disease (FEV<sub>1</sub> less than 50%) who experience repeated exacerbations despite bronchodilator therapy.
- Side effects of inhaled corticosteroids are relatively mild and include hoarseness, sore throat, oral candidiasis, and skin bruising. Severe side effects such as adrenal suppression, osteoporosis, and cataract formation are reported less frequently than with systemic corticosteroids, but clinicians should monitor patients receiving high-dose chronic inhaled therapy.
- Several studies have shown an additive effect with the combination of inhaled corticosteroids and long-acting bronchodilators. Combination therapy with salmeterol plus fluticasone or formoterol plus budesonide is associated with greater improvements in FEV<sub>1</sub>, health status, and exacerbation frequency than either agent alone. The availability of combination inhalers makes administration of both drugs convenient and decreases the total number of inhalations needed daily.

## **TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE EXACERBATION**

### **DESIRED OUTCOMES**

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- The goals of therapy for patients experiencing exacerbations of COPD are prevention of hospitalization or reduction in length of hospital stay, prevention of acute respiratory failure and death, resolution of symptoms, and a return to baseline clinical status and quality of life.

### **NONPHARMACOLOGIC THERAPY**

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- Oxygen therapy should be considered for any patient with hypoxemia during an exacerbation. Caution must be used because many COPD

patients rely on mild hypoxemia to trigger their drive to breathe. Overly aggressive oxygen administration to patients with chronic hypercapnia may result in respiratory depression and respiratory failure. Oxygen therapy should be used to achieve a  $\text{PaO}_2$  of greater than 60 mm Hg or oxygen saturation of greater than 90%. Arterial blood gases should be obtained after oxygen initiation to monitor carbon dioxide retention resulting from hypoventilation.

- Noninvasive positive-pressure ventilation (NPPV) provides ventilatory support with oxygen and pressurized airflow using a face or nasal mask with a tight seal but without endotracheal intubation. In patients with acute respiratory failure due to COPD exacerbations, NPPV was associated with lower mortality, lower intubation rates, shorter hospital stays, and greater improvements in serum pH in 1 hour compared with usual care. Use of NPPV reduces the complications that often arise with invasive mechanical ventilation. NPPV is not appropriate for patients with altered mental status, severe acidosis, respiratory arrest, or cardiovascular instability.
- Intubation and mechanical ventilation may be considered in patients failing a trial of NPPV or those who are poor candidates for NPPV.

## PHARMACOLOGIC THERAPY

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### Bronchodilators

- The dose and frequency of bronchodilators are increased during acute exacerbations to provide symptomatic relief. Short-acting  $\beta_2$ -agonists are preferred because of their rapid onset of action. Anticholinergic agents may be added if symptoms persist despite increased doses of  $\beta_2$ -agonists.
- Bronchodilators may be administered via MDIs or nebulization with equal efficacy. Nebulization may be considered for patients with severe dyspnea who are unable to hold their breath after actuation of an MDI.
- Clinical evidence supporting theophylline use during exacerbations is lacking, and thus theophylline should generally be avoided. It may be considered for patients not responding to other therapies.

### Corticosteroids

- Results from clinical trials suggest that patients with acute COPD exacerbations should receive a short course of IV or oral corticosteroids. Although the optimal dose and duration of treatment are unknown, it appears that a regimen of prednisone 40 mg orally daily (or equivalent) for 10 to 14 days can be effective for most patients.
- If treatment is continued for longer than 2 weeks, a tapering oral schedule should be employed to avoid hypothalamic-pituitary-adrenal axis suppression.

### Antimicrobial Therapy

- Although most exacerbations of COPD are thought to be caused by viral or bacterial infections, as many as 30% of exacerbations are caused by unknown factors.
- Antibiotics are of most benefit and should be initiated if at least two of the following three symptoms are present: (1) increased dyspnea; (2) increased sputum volume; and (3) increased sputum purulence. The utility of sputum

Gram stain and culture is questionable because some patients have chronic bacterial colonization of the bronchial tree between exacerbations.

- Selection of empiric antimicrobial therapy should be based on the most likely organisms. The most common organisms for acute exacerbation of COPD are *Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pneumoniae*, and *H. parainfluenzae*.
- Therapy should be initiated within 24 hours of symptoms to prevent unnecessary hospitalization and generally continued for at least 7 to 10 days. Five-day courses with some agents may produce comparable efficacy.
- In uncomplicated exacerbations, recommended therapy includes a **macrolide (azithromycin, clarithromycin)**, **second- or third-generation cephalosporin**, or **doxycycline**. Trimethoprim-sulfamethoxazole should not be used because of increasing pneumococcal resistance. Amoxicillin and first-generation cephalosporins are not recommended because of  $\beta$ -lactamase susceptibility. Erythromycin is not recommended because of insufficient activity against *H. influenzae*.
- In complicated exacerbations where drug-resistant pneumococci,  $\beta$ -lactamase-producing *H. influenzae* and *M. catarrhalis*, and some enteric gram-negative organisms may be present, recommended therapy includes **amoxicillin/clavulanate** or a fluoroquinolone with enhanced pneumococcal activity (**levofloxacin, gemifloxacin, moxifloxacin**).
- In complicated exacerbations with risk of *Pseudomonas aeruginosa*, recommended therapy includes a fluoroquinolone with enhanced pneumococcal and *P. aeruginosa* activity (**levofloxacin**). If IV therapy is required, a  $\beta$ -lactamase resistant penicillin with antipseudomonal activity or a third- or fourth-generation cephalosporin with antipseudomonal activity should be used.

## EVALUATION OF THERAPEUTIC OUTCOMES

- In chronic stable COPD, pulmonary function tests should be assessed with any therapy addition, change in dose, or deletion of therapy. Other outcome measures include dyspnea score, quality-of-life assessments, and exacerbation rates (including emergency department visits and hospitalizations).
- In acute exacerbations of COPD, white blood cell count, vital signs, chest x-ray, and changes in frequency of dyspnea, sputum volume, and sputum purulence should be assessed at the onset and throughout the exacerbation. In more severe exacerbations, arterial blood gases and oxygen saturation should also be monitored.
- Patient adherence to therapeutic regimens, side effects, potential drug interactions, and subjective measures of quality of life must also be evaluated.

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See Chap. 29, *Chronic Obstructive Pulmonary Disease*, authored by Dennis M. Williams and Sharya V. Bourdet, for a more detailed discussion of this topic.

## DEFINITION

- Benign prostatic hyperplasia (BPH), a nearly ubiquitous condition, is the most common benign neoplasm of American men and occurs as a result of androgen-driven prostate growth.

## PATHOPHYSIOLOGY

- The prostate gland comprises three types of tissue: epithelial or glandular, stromal or smooth muscle, and capsule. Both stromal tissue and capsule are embedded with  $\alpha_1$ -adrenergic receptors.
- The precise pathophysiologic mechanisms that cause BPH are not clear. However, both intraprostatic dihydrotestosterone (DHT) and type II 5 $\alpha$ -reductase are thought to be involved.
- BPH commonly results from both static (gradual enlargement of the prostate) and dynamic (agents or situations that increase  $\alpha$ -adrenergic tone and constrict the gland's smooth muscle) factors. Examples of drugs that can exacerbate symptoms include testosterone,  $\alpha$ -adrenergic agonists (e.g., decongestants), and anticholinergic agents (e.g., antihistamines, phenothiazines, tricyclic antidepressants, anticholinergic antispasmodics, and anticholinergics for Parkinson's disease).

## CLINICAL PRESENTATION

- Patients with BPH can present with a variety of signs and symptoms categorized as obstructive or irritative. Symptoms vary over time. Mild disease may stabilize whereas other patients experience progressive disease over time.
- Obstructive signs and symptoms result when dynamic and/or static factors reduce bladder emptying. Patients experience urinary hesitancy; urine dribbles out of the penis, and the bladder feels full even after voiding.
- Irritative signs and symptoms result from long-standing obstruction at the bladder neck. Patients experience frequency, urgency, and nocturia.
- Complications include chronic kidney disease, gross hematuria, urinary incontinence, recurrent urinary tract infection, bladder diverticula, and bladder stones.

## DIAGNOSIS

- Diagnosis of BPH requires a careful medical history, physical examination, objective measures of bladder emptying (e.g., peak and average urinary

flow rate, postvoid residual urine volume), and laboratory tests (e.g., urinalysis, blood urea nitrogen, and prostate-specific antigen [PSA]).

- Medication history should include all prescription and nonprescription medications as well as dietary supplements.
- On digital rectal examination, the prostate is usually, but not always, enlarged (more than 20 g), soft, smooth, and symmetric.

## DESIRED OUTCOME

- BPH treatment is aimed primarily at relieving manifestations of the disease that are bothersome for the patient. A secondary, but controversial, aim is to prevent serious complications in selected patients.

## TREATMENT

- Management options for BPH include watchful waiting, drug therapy, and surgical intervention. The choice depends on the severity of signs and symptoms (Table 82-1).
- Watchful waiting is appropriate for patients with mild disease and for those with moderate disease with only mildly bothersome symptoms and without complications.
- Watchful waiting involves reassessment at yearly intervals. Patients should be educated about behavior modification such as fluid restriction before bedtime, avoiding caffeine and alcohol, frequent emptying of the bladder, and avoiding drugs that exacerbate symptoms.

## PHARMACOLOGIC THERAPY

- Pharmacologic therapy is appropriate for patients with moderately severe BPH and as an interim measure for patients with severe BPH.
- Pharmacologic therapy interferes with the stimulatory effect of testosterone on prostate gland enlargement (reduces the static factor) or relaxes prostatic smooth muscle (reduces the dynamic factor) (Table 82-2).
- Initial therapy with an  $\alpha$ -adrenergic antagonist provides faster onset of symptom relief. A 5 $\alpha$ -reductase inhibitor is preferred as initial therapy in

**TABLE 82-1** Categories of BPH Disease Severity Based on Symptoms and Signs

Disease Severity	AUA Symptom Score	Typical Symptoms and Signs
Mild	≤7	Asymptomatic Peak urinary flow rate <10 mL/s Postvoid residual urine volume >25–50 mL Increased BUN and serum creatinine
Moderate	8–19	All of the above signs plus obstructive voiding symptoms and irritative voiding symptoms (signs of detrusor instability)
Severe	≥20	All of the above plus one or more complications of BPH

AUA, American Urological Association; BPH, benign prostatic hyperplasia; BUN, blood urea nitrogen.

**TABLE 82-2** Summary of Medical Treatment Options for Benign Prostatic Hyperplasia

Category	Mechanism	Drug (Brand Name)
Reduces dynamic factor	Blocks $\alpha_1$ -adrenergic receptors in prostatic stromal tissue	Prazosin (Minipress)
		Alfuzosin (Uroxatral)
Reduces static factor	Blocks $\alpha_{1A}$ -receptors in the prostate	Terazosin (Hytrin)
		Doxazosin (Cardura)
	Blocks $5\alpha$ -reductase enzyme	Tamsulosin (Flomax)
		Finasteride (Proscar)
	Blocks dihydrotestosterone at its intracellular receptor	Dutasteride (Avodart)
		Bicalutamide (Casodex)
Blocks pituitary release of luteinizing hormone	Flutamide (Eulexin)	
Blocks pituitary release of luteinizing hormone and blocks androgen receptor	Leuprolide (Lupron)	
	Nafarelin (Synarel)	
		Megestrol acetate

patients with a prostate gland >40 g. Combination therapy should be considered for symptomatic patients with a prostate gland >40 g and PSA  $\geq 1.4$  ng/mL.

- Agents that interfere with androgen stimulation of the prostate are not popular in the United States because of adverse effects. The luteinizing hormone-releasing hormone agonists **leuprolide** and **goserelin** decrease libido and can cause erectile dysfunction, gynecomastia, and hot flashes. The antiandrogens **bicalutamide** and **flutamide** cause nausea, diarrhea, and hepatotoxicity.

### $\alpha$ -Adrenergic Antagonists

- $\alpha$ -Adrenergic antagonists relax the smooth muscle in the prostate and bladder neck, thereby increasing urinary flow rates by 2 to 3 mL/sec in 60% to 70% of patients and reducing postvoid residual urine volumes. **Tamsulosin** and **doxazosin** produce durable responses for 6 and 10 years, respectively.
- $\alpha$ -Adrenergic antagonists do not decrease prostate volume or PSA levels.
- Terazosin**, **doxazosin**, and **alfuzosin** are second-generation  $\alpha$ -adrenergic antagonists. They antagonize peripheral vascular  $\alpha_1$ -adrenergic receptors in addition to those in the prostate. Therefore, their adverse effects include first-dose syncope, orthostatic hypotension, and dizziness. Alfuzosin is less likely to cause cardiovascular adverse effects than other second-generation agents.
- Patients should be slowly titrated to a maintenance dose and should take these drugs at bedtime to minimize orthostatic hypotension and first-dose syncope with terazosin and doxazosin. Sample titration schedules for terazosin include:

#### Titration Schedules

##### **Terazosin Slow**

Days 1–3: 1 mg at bedtime  
 Days 4–14: 2 mg at bedtime  
 Weeks 2–6: 5 mg at bedtime  
 Weeks 7 and on: 10 mg at bedtime

##### **Terazosin Quicker**

Days 1–3: 1 mg at bedtime  
 Days 4–14: 2 mg at bedtime  
 Weeks 2–3: 5 mg at bedtime  
 Weeks 4 and on: 10 mg at bedtime

- Tamsulosin, the only third-generation  $\alpha$ -adrenergic antagonist, is selective for prostatic  $\alpha_{1A}$ -receptors. Therefore, tamsulosin does not cause peripheral vascular smooth muscle relaxation.
- Tamsulosin is a good choice for patients who cannot tolerate hypotension; have severe coronary artery disease, volume depletion, cardiac arrhythmias, severe orthostasis, or liver failure; or are taking multiple antihypertensives. Tamsulosin is also suitable for patients who want to avoid the delay of dose titration.
- Caution is needed to avoid potential drug interactions. Tamsulosin decreases metabolism of **cimetidine** and **diltiazem**. **Carbamazepine** and **phenytoin** increase catabolism of  $\alpha$ -adrenergic antagonists.

### 5 $\alpha$ -Reductase Inhibitors (Dutasteride and Finasteride)

- 5 $\alpha$ -Reductase inhibitors interfere with the stimulatory effect of testosterone. These agents slow disease progression and decrease the risk of complications.
- Compared with  $\alpha$ -adrenergic antagonists, 5 $\alpha$ -reductase inhibitors have the disadvantages of requiring 6 months to maximally shrink an enlarged prostate, being less likely to induce objective improvement, and causing more sexual dysfunction.
- Whether the pharmacodynamic advantages of **dutasteride** confer clinical advantages over **finasteride** is unknown. Dutasteride inhibits types I and II 5 $\alpha$ -reductase, whereas finasteride inhibits only type II. Dutasteride more quickly and completely suppresses intraprostatic DHT (vs. 80% to 90% for finasteride) and decreases serum DHT by 90% (versus 70%).
- 5 $\alpha$ -Reductase inhibitors may be preferred in patients with uncontrolled arrhythmias, poorly controlled angina, use of multiple antihypertensives, or inability to tolerate hypotensive effects of  $\alpha$ -adrenergic antagonists.
- 5 $\alpha$ -Reductase inhibitors reduce serum PSA levels by 50%. PSA should be measured at baseline and repeated after 6 months. If PSA does not decrease by 50% after 6 months of therapy in a compliant patient, the patient should be evaluated for prostate cancer.
- 5 $\alpha$ -Reductase inhibitors are in FDA pregnancy category X and are therefore contraindicated in pregnant females. Pregnant and potentially pregnant women should not handle the tablets or have contact with semen from men receiving 5 $\alpha$ -reductase inhibitors.

## SURGICAL INTERVENTION

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- Prostatectomy, performed transurethraly or suprapubically, is the gold standard for treatment of patients with moderate or severe symptoms of BPH and for all patients with complications.
- Retrograde ejaculation is a complication of up to 75% of transurethral prostatectomy procedures. Other complications seen in 2% to 15% of patients include bleeding, urinary incontinence, and erectile dysfunction.

## PHYTOTHERAPY

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- Although widely used in Europe for BPH, phytotherapy with products such as saw palmetto berry (*Serenoa repens*), stinging nettle (*Urtica dioica*),

and African plum (*Pygeum africanum*) should be avoided. Studies of these herbal medicines are inconclusive, and the purity of available products is questionable.

## EVALUATION OF THERAPEUTIC OUTCOMES

- The primary therapeutic outcome of BPH therapy is restoring adequate urinary flow without causing adverse effects.
- Outcome depends on the patient's perception of effectiveness and acceptability of therapy. The American Urological Association Symptom Score is a validated standardized instrument that can be used to assess patient quality of life.
- Objective measures of bladder emptying (e.g., uroflowmeter and postvoid residual urine volumes) are also useful after 6 to 12 months of 5 $\alpha$ -reductase inhibitor therapy or 3 to 4 weeks of  $\alpha$ -adrenergic antagonist therapy.
- Laboratory tests (e.g., blood urea nitrogen, creatinine, PSA) and urinalysis should be monitored regularly. In addition, patients should have an annual digital rectal examination.

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*See Chap. 87, Management of Benign Prostatic Hyperplasia, authored by Mary Lee, for a more detailed discussion of this topic.*

## DEFINITION

- Erectile dysfunction (ED) is the failure to achieve a penile erection suitable for sexual intercourse. Patients often refer to it as impotence.

## PATHOPHYSIOLOGY

- ED can result from an abnormality in one of the four systems necessary for a normal penile erection or from a combination of abnormalities. Vascular, nervous, or hormonal etiologies of ED are referred to as organic ED. Abnormality of the fourth system (i.e., patient's psychological receptivity to sexual stimuli) is referred to as psychogenic ED.
- The penis has two corpora cavernosa, which have many interconnected sinuses that fill with blood to produce an erection. The penis also has one corpus spongiosum, which surrounds the urethra and forms the glans penis.
- Acetylcholine works with other neurotransmitters (i.e., cyclic guanylate monophosphate, cyclic adenosine monophosphate, vasoactive intestinal polypeptide) to produce penile arterial vasodilation and ultimately an erection.
- Causes of organic ED include diseases that compromise vascular flow to the corpora cavernosum (e.g., peripheral vascular disease, arteriosclerosis, essential hypertension), impair nerve conduction to the brain (e.g., spinal cord injury, stroke), and are associated with hypogonadism (e.g., prostate or testicular cancer, hypothalamic or pituitary disorders).
- Causes of psychogenic ED include malaise, reactive depression or performance anxiety, sedation, Alzheimer's disease, hypothyroidism, and mental disorders. Patients with psychogenic ED generally have a higher response rate to interventions than patients with organic ED.
- Social habits (e.g., cigarette smoking, excessive ethanol intake) and medications (Table 83-1) can also cause ED.

## CLINICAL PRESENTATION

- Signs and symptoms of ED can be difficult to detect. The patient's mate is often the first to report ED to the healthcare provider.
- Emotional manifestations include depression, performance anxiety, or embarrassment.
- Nonadherence to drugs thought to cause ED can be a sign of ED.

## DIAGNOSIS

- The diagnostic workup should be designed to identify underlying causes of ED.
- Key diagnostic assessments include ED severity, medical history, concurrent medications, physical examination, and laboratory tests (i.e., serum blood glucose, lipid profile, testosterone level).
- A standardized questionnaire can be used to assess the severity of ED.

**TABLE 83-1** Medication Classes That Can Cause Erectile Dysfunction

Drug Class	Proposed Mechanism of Erectile Dysfunction	Special Notes
Anticholinergic agents: antihistamines, antiparkinsonian agents, tricyclic antidepressants, phenothiazines	Anticholinergic activity	Second-generation nonsedating antihistamines (e.g., loratadine) are not associated with erectile dysfunction. Selective serotonin reuptake inhibitor antidepressants can be substituted for tricyclic antidepressants if erectile dysfunction is a problem. Phenothiazines with fewer anticholinergic effects can be substituted in some patients if erectile dysfunction is a problem.
Dopamine agonists (e.g., metoclopramide, phenothiazines)	Inhibit prolactin inhibitory factor, thereby increasing prolactin levels	Increased prolactin levels are associated with blocking testosterone production from the testes; depressed libido results.
Estrogens, antiandrogens (e.g., luteinizing hormone-releasing hormone superagonists, digoxin, spironolactone, ketoconazole, cimetidine)	Suppress testosterone-mediated stimulation of libido	In the face of a decreased libido, a secondary erectile dysfunction develops.
CNS depressants (e.g., barbiturates, narcotics, benzodiazepines, short-term use of large doses of alcohol)	Suppress perception of psychogenic stimuli	—
Agents that decrease penile blood flow (e.g., diuretics, $\beta$ -adrenergic antagonists, or central sympatholytics [methyldopa, domidone, guanethidine])	Reduce arteriolar flow to corpora	Any diuretic that produces a significant decrease in intravascular volume can decrease penile arteriolar flow. Safer antihypertensives include angiotensin-converting enzyme inhibitors, postsynaptic $\alpha_1$ -adrenergic antagonists (terazosin, doxazosin), calcium channel blockers, and angiotensin II antagonists.

From Thomas A, Woodard C, Rovner ES, Wein AJ. Urologic complications of nonurologic medications. *Urol Clin North Am* 2003;30:123–131; and Lee M, Sharifi R. Sexual dysfunction in males. In Tisdale JE, Miller DA, eds. *Drug-Induced Diseases: Prevention, Detection, and Management*. Bethesda, MD: ASHP, 2005:455–467.

## DESIRED OUTCOME

- The goal of treatment is to improve the quantity and quality of penile erections suitable for intercourse.

## TREATMENT

- The first step in management of ED is to identify and, if possible, reverse underlying causes. Psychotherapy can be used as monotherapy for psychogenic ED or as an adjunct to specific treatments.
- Treatment options include medical devices, drugs (Table 83-2), and surgery. Although no option is ideal, the least invasive options are chosen first.

**TABLE 83-2** Dosing Regimens for Selected Drug Treatments for Erectile Dysfunction

Route of Administration	Generic Name (Brand Name)	Dosage Form	Common Dosing Regimen
Oral	Yohimbine (Aphrodyne, Yocon, Yohimex)	5.4-mg tablet or capsule	5.4 mg three times per day
	Sildenafil (Viagra)	25-mg, 50-mg, 100-mg tablet	25–100 mg 1 hour before intercourse
	Apomorphine (Uprima) <sup>a</sup>	10-mg sublingual tablet, 25-mg tablet and capsule	10–40 mg daily
	Fluoxymesterone (Halotestin)	2-mg, 5-mg, 10-mg, 50-mg tablet	5–20 mg daily
	Trazodone (Desyrel)	100-mg, 150-mg, 300-mg tablet	50–150 mg daily
	Vardenafil (Levitra)	2.5-mg, 5-mg, 10-mg, 20-mg tablet	5–10 mg 1 hour before intercourse
	Tadalafil (Cialis)	5-mg, 10-mg, 20-mg tablet	5–20 mg before intercourse
Topical	Testosterone patch (Testoderm)	4 mg/patch, 6 mg/patch	4–6 mg/day; apply to scrotum
	Testosterone patch (Testoderm TTS)	4 mg/patch, 6 mg/patch	4–6 mg/day; apply to arm, buttock, back
	Testosterone patch (Androderm)	2.5 mg/patch	2.5–5 mg/day; apply to arm, back, abdomen, thigh
	Testosterone gel (AndroGel 1%)	5 g/pkt, 10 g/pkt	5–10 g/day; apply to shoulders, upper arms, abdomen
Intramuscular	Testosterone cypionate (Depo-Testosterone)	100 mg/mL, 200 mg/mL	200–400 mg every 2–4 weeks
	Testosterone enanthate (Delatestryl)	100 mg/mL, 200 mg/mL	200–400 mg every 2–4 weeks
Subcutaneous implant	Testosterone (Testopel)	75-mg pellet	150–450 mg every 3–4 months
Intraurethral	Alprostadil (MUSE)	125-mcg, 250-mcg, 500-mcg, 1,000-mcg pellet	125–1,000 mcg 5–10 minutes before intercourse
Intracavernosal	Alprostadil (Caverject)	5-mcg, 10-mcg, 20-mcg injection	2.5–60 mcg 5–10 minutes before intercourse
	Alprostadil (Edex)	5-mcg, 20-mcg, 40-mcg injection	2.5–60 mcg 5–10 minutes before intercourse
	Papaverine <sup>b</sup>	30 mg/mL injection	Variable, usually used in combination with alprostadil and phentolamine
	Phentolamine <sup>b</sup>	2.5 mg/mL injection	Variable, usually used in combination with alprostadil and papaverine

<sup>a</sup>Not commercially available in the United States as a sublingual formulation; only available in United States as subcutaneous injection that is FDA approved for Parkinson's disease.<sup>b</sup>Not FDA approved for this use.

## MEDICAL DEVICES

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- Vacuum erection devices (VEDs) are first-line therapy for older patients. VEDs should be limited to patients who have stable sexual relations, because the onset of action is slow (i.e., approximately 30 minutes).
- To prolong the erection, the patient can also use constriction bands or tension rings, which are placed at the base of the penis to retain arteriolar blood and reduce venous outflow from the penis.
- VEDs can be used as second-line therapy after failure of oral or injectable drugs. Adding **alprostadil** to a VED improves the response rate.
- VEDs are contraindicated in patients with sickle cell disease. VEDs should be used cautiously in patients on warfarin because, through a poorly understood and idiosyncratic mechanism, it can cause priapism.

## PHARMACOLOGIC TREATMENTS

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### Phosphodiesterase Inhibitors

- Phosphodiesterase mediates catabolism of cyclic guanylate monophosphate, a vasodilatory neurotransmitter in the corporal tissue.
- Unless otherwise stated, general information applies to the entire class of phosphodiesterase inhibitors. **Sildenafil** is highlighted because it was the first to be marketed and is the most thoroughly studied. The newer agents **tadalafil** and **varденаfil** have different pharmacokinetic profiles (Table 83-3), drug–food interactions, and adverse effects.
- Phosphodiesterase inhibitors are selective for isoenzyme type 5 in genital tissue. Inhibition of this isoenzyme in nongenital tissues (e.g., peripheral vascular tissue, tracheal smooth muscle, and platelets) can produce adverse effects.
- Phosphodiesterase inhibitors are first-line therapy for younger patients. Sildenafil, 25 to 100 mg, induces satisfactory erections in 56% to 82% of patients. Approximately half of the remaining patients can have satisfactory responses after being instructed on proper use of phosphodiesterase inhibitors.
  - ✓ For the best response, patients must engage in sexual stimulation (foreplay).
  - ✓ For the fastest response, patients should take sildenafil on an empty stomach, at least 2 hours before meals. The other two agents can be taken without regard to meals.
  - ✓ For maximal absorption, patients should avoid taking sildenafil or vardenafil with a fatty meal. A fatty meal does not affect absorption of tadalafil.
  - ✓ If the first dose is not effective, patients should continue trying for five to eight doses. Some patients benefit from titration up to 100 mg of sildenafil, 20 mg of vardenafil, or 20 mg of tadalafil.
- Sildenafil and vardenafil have similar pharmacokinetic profiles with a rapid onset of action and short duration. Tadalafil has a delayed onset of action and prolonged duration of effect. All three drugs are metabolized by cytochrome P450 enzymes, primarily 3A4. Patients should avoid exceeding prescribed doses because higher doses do not improve response. Depending on the phosphodiesterase inhibitor, the dose should be reduced if the patient is elderly, has renal or hepatic impairment, or receives an inhibitor of cytochrome P450 3A4 (see Table 83-3).

**TABLE 83-3** Pharmacodynamics and Pharmacokinetics of Phosphodiesterase Inhibitors

	<b>Sildenafil<sup>a</sup></b>	<b>Vardenafil<sup>a</sup></b>	<b>Tadalafil<sup>a</sup></b>
Trade name	Viagra	Levitra	Cialis
Inhibits PDE-5	Yes	Yes	Yes
Inhibits PDE-6	Yes	Minimally	No
Inhibits PDE-11	No	No	Yes
Time to peak plasma level (hours)	0.5–1	0.7–0.9	2
Fatty meal decreases rate of oral absorption?	Yes	Yes	No
Mean plasma half-life (hours)	3.7	4.4–4.8	18
Percentage of dose excreted in feces	80	91–95	61
Percentage of dose excreted in urine	13	2–6	36
Duration (hours)	4	4	24–36
Usual daily dose (mg)	25–100	5–20	5–20
Daily dose in patients ≥65 years (mg)	25	5	5–20
Daily dose in moderate renal impairment (mg)	25–100	5–20	5
Daily dose in severe renal impairment (mg)	25	5–20	5
Daily dose in mild hepatic impairment (mg)	25–100	5–20	10
Daily dose in moderate hepatic impairment (mg)	25–100	5–10	10
Daily dose in severe hepatic impairment (mg)	25	Not evaluated	Not recommended
Dose in patients taking cytochrome P450 3A4 inhibitors <sup>d</sup>	25 mg daily	2.5–5 mg q 24–72 h	10 mg q 72 h

PDE, phosphodiesterase.

<sup>a</sup>Sildenafil doses should be decreased when any potent cytochrome P450 3A4 inhibitor is used (e.g., cimetidine, erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir, and saquinavir). Vardenafil doses vary according to which agent is used (2.5 mg q 72 h for ritonavir, 2.5 mg q 24 h for indinavir, ketoconazole 400 mg daily, and itraconazole 400 mg daily; and 5 mg q 24 h for ketoconazole 200 mg daily, itraconazole 200 mg daily, and erythromycin). Tadalafil doses are reduced only when it is used with the most potent cytochrome P450 3A4 inhibitors (e.g., ketoconazole or ritonavir).

- In usual doses, the most common adverse effects are headache, facial flushing, dyspepsia, nasal congestion, and dizziness.
- Sildenafil and vardenafil decrease systolic/diastolic blood pressure by 8 to 10/5 to 6 mm Hg for 1 to 4 hours after a dose. Although most patients are asymptomatic, multiple antihypertensives, **nitrates**, and baseline hypotension increase the risk of developing adverse effects. Although tadalafil does not decrease blood pressure, it should be used with caution in patients with cardiovascular disease because of the inherent risk associated with sexual activity.
- Guidelines are available for stratifying patients on the basis of their cardiovascular risk (Table 83-4).
- Phosphodiesterase inhibitors should be used cautiously in patients at risk for retinitis pigmentosa and by pilots who rely on blue and green lights to land airplanes. Patients who experience sudden vision loss should be evaluated before continuing treatment.
- Tadalafil inhibits type 11 phosphodiesterase, which is thought to account for the dose-related back and muscle pain seen in 7% to 30% of patients.

**TABLE 83-4** Recommendations of the Second Princeton Consensus Conference for Cardiovascular Risk Stratification of Patients Being Considered for Phosphodiesterase Inhibitor Therapy

Risk Category	Description of Patient's Condition	Management Approach
Low risk	Has asymptomatic cardiovascular disease with <3 risk factors for cardiovascular disease Has well-controlled hypertension Has mild, stable angina Has mild congestive heart failure (NYHA class I) Has mild valvular heart disease Had a myocardial infarction >6 weeks ago	Patient can be started on phosphodiesterase inhibitor
Intermediate risk	Has ≥3 risk factors for cardiovascular disease Has moderate, stable angina Had a recent myocardial infarction or stroke within the past 6 weeks Has moderate congestive heart failure (NYHA class II)	Patient should undergo complete cardiovascular workup and treadmill stress test to determine tolerance to increased myocardial energy consumption associated with increased sexual activity
High risk	Has unstable or symptomatic angina, despite treatment Has uncontrolled hypertension Has severe congestive heart failure (NYHA class III or IV) Had a recent myocardial infarction or stroke within past 2 weeks Has moderate or severe valvular heart disease Has high-risk cardiac arrhythmias Has obstructive hypertrophic cardiomyopathy	Phosphodiesterase inhibitor is contraindicated; sexual intercourse should be deferred

NYHA, New York Heart Association.

From Rosen RC, Jackson G, Kostis JB. Erectile dysfunction and cardiac disease: Recommendations of the Second Princeton Conference. *Curr Urol Rep* 2006;7:490-496; and Kostis JB, Jackson G, Rosen R, et al. Sexual dysfunction and cardiac risk (the Second Princeton Consensus Conference). *Am J Cardiol* 2005;96:313-321.

- Phosphodiesterase inhibitors are contraindicated in patients taking nitrates. Phosphodiesterase inhibitors should not be administered within 4 hours of an  $\alpha$ -adrenergic antagonist.

### Testosterone-Replacement Regimens

- **Testosterone**-replacement regimens restore serum testosterone levels to the normal range (300 to 1,100 ng/dL). These regimens are indicated for symptomatic patients with hypogonadism as confirmed by low testosterone concentrations.
- Instead of directly correcting ED, testosterone-replacement regimens correct secondary ED by improving libido. Usually within days or weeks of starting therapy, they restore muscle strength and sexual drive and improve mood.
- Testosterone can be replaced orally, parenterally, or transdermally (see Table 83-2). Injectable regimens are preferred because they are effective, are inexpensive, and do not have the bioavailability problems or adverse hepatotoxic effects of oral regimens. Testosterone patches and gel are more expensive than other forms and should be reserved for patients who refuse injections.

- Before starting testosterone replacement, patients 40 years and older should be screened for benign prostatic hyperplasia and prostate cancer. To ensure an adequate treatment trial, the patient should continue treatment for 2 to 3 months.
- Testosterone replacement can cause sodium retention, which can cause weight gain or exacerbate hypertension, congestive heart failure, and edema; gynecomastia; deleterious serum lipoprotein changes; and polycythemia. Exogenous testosterone can also exacerbate benign prostatic hyperplasia and enhance prostate cancer growth.
- Oral testosterone-replacement regimens can cause hepatotoxicity, ranging from mildly elevated hepatic transaminases to serious liver diseases (e.g., peliosis hepatitis, hepatocellular and intrahepatic cholestasis, and benign or malignant tumors).

### **Alprostadil**

- **Alprostadil**, or prostaglandin E<sub>1</sub>, stimulates adenylyl cyclase to increase production of cyclic adenosine monophosphate, a neurotransmitter that ultimately enhances blood flow to and blood filling of the corpora.
- Alprostadil is approved as monotherapy for the management of ED. It is generally prescribed after failure of VEDs and phosphodiesterase inhibitors and for patients who cannot use these therapies. Of the available routes, the intracavernosal route is preferred over the intraurethral route because of better efficacy.

### ***Intracavernosal Injection***

- Intracavernosal alprostadil is effective in 70% to 90% of patients. However, a high proportion of patients discontinue its use because of perceived ineffectiveness; inconvenience of administration; unnatural, nonspontaneous erection; needle phobia; loss of interest; and cost of therapy.
- Intracavernosal alprostadil has been used successfully in combination with VEDs or vasoactive agents (e.g., papaverine, phentolamine, atropine) that act by different mechanisms. Phosphodiesterase inhibitors should not be added to intracavernosal alprostadil because the combination can cause prolonged erections and priapism.
- Intracavernosal alprostadil acts rapidly with an onset of 5 to 15 minutes. The duration of action is dose related and, within the usual dosage range, lasts less than 1 hour.
- The usual dose of intracavernosal alprostadil is 10 to 20 mcg up to a maximum of 60 mcg. Patients should start with 1.25 mcg, which should be increased by 1.25 to 2.50 mcg at 30-minute intervals to the lowest dose that produces a firm erection for 1 hour and does not produce adverse effects. In clinical practice, however, most patients start with 10 mcg and titrate quickly.
- To minimize the risk of complications, patients should use the lowest effective dose.
- Intracavernosal alprostadil should be injected 5 to 10 minutes before intercourse using a 0.5-inch, 27- or 30-gauge needle or an autoinjector. The maximum number of injections is one per day and three per week.
- Intracavernosal alprostadil is most commonly associated with local adverse effects, usually during the first year of therapy. Adverse events include

cavernosal plaques or fibrosis at the injection site (2% to 12% of patients), penile pain (10% to 44%), and priapism (1% to 15%). Penile pain is usually mild and self-limiting, but priapism (i.e., painful, drug-induced erection lasting more than 1 hour) necessitates immediate medical attention.

- Intracavernosal injection therapy should be used cautiously in patients at risk of priapism (e.g., sickle cell disease or lymphoproliferative disorders) and bleeding complications secondary to injections.

### ***Intraurethral Administration***

- Intraurethral alprostadil, 125 to 1,000 mcg, should be administered 5 to 10 minutes before intercourse. Before administration, the patient should empty his bladder and void completely. No more than two doses per day are recommended.
- Intraurethral administration is associated with pain in 24% to 32% of patients, which is usually mild and does not require discontinuation of treatment. Prolonged painful erections are rare.
- Female partners may experience vaginal burning, itching, or pain, which is probably related to transfer of alprostadil from the man's urethra to the women's vagina during intercourse.

### **Unapproved Agents**

- Many other remedies are used, which may or may not be effective.
- Examples of other agents include **trazodone** (50 to 200 mg/day), **yohimbine** (5.4 mg three times daily), **papaverine** (7.5 to 60 mg [single agent therapy] or 0.5 to 20 mg [combination therapy] intracavernosal injection), and **phentolamine** (1 mg [combination therapy] intracavernosal injection).

## **SURGERY**

- Surgical insertion of a penile prosthesis, the most invasive treatment for ED, is used after failure of less invasive treatments and for patients who are not candidates for other treatments.
- Adverse effects of prosthesis insertion include early and late onset infection, mechanical failure, and erosion of the rods through the penis.

## **EVALUATION OF THERAPEUTIC OUTCOMES**

- The primary therapeutic outcomes for ED are improving the quantity and quality of penile erections suitable for intercourse and avoiding adverse drug reactions and drug interactions.
- To assess improvement, the physician should conduct specific assessments at baseline and after a trial period of 1 to 3 weeks.
- To avoid adverse effects due to excessive use, patients with unrealistic expectations should be identified and should be counseled accordingly.

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*See Chap. 86, Erectile Dysfunction, authored by Mary Lee, for a more detailed discussion of this topic.*

## DEFINITION

- Urinary incontinence (UI) is the complaint of involuntary leakage of urine.

## PATHOPHYSIOLOGY

- The urethral sphincter, a combination of smooth and striated muscles within and external to the urethra, maintains adequate resistance to the flow of urine from the bladder until voluntary voiding is initiated. Normal bladder emptying occurs with opening of the urethra concomitant with a volitional bladder contraction.
- Acetylcholine is the neurotransmitter that mediates both volitional and involuntary contractions of the bladder. Bladder smooth muscle cholinergic receptors are mainly of the  $M_2$  variety; however,  $M_3$  receptors are responsible for both emptying contraction of normal micturition and involuntary bladder contractions, which can result in UI. Therefore, most pharmacologic antimuscarinic therapy is anti- $M_3$  based.
- UI occurs as a result of overfunctioning or underfunctioning of the urethra, bladder, or both.
- Urethral underactivity is known as stress UI (SUI) and occurs during activities such as exercise, lifting, coughing, and sneezing. The urethral sphincter no longer resists the flow of urine from the bladder during periods of physical activity.
- Bladder overactivity is known as urge UI (UUI) and is associated with increased urinary frequency and urgency, with or without urge incontinence. The detrusor muscle is overactive and contracts inappropriately during the filling phase.
- Urethral overactivity and/or bladder underactivity is known as overflow incontinence. The bladder is filled to capacity but is unable to empty, causing urine to leak from a distended bladder past a normal outlet and sphincter. Common causes of urethral overactivity include benign prostatic hyperplasia (see Chap. 82); prostate cancer (see Chap. 65); and, in women, cystocele formation or surgical overcorrection after UI surgery.
- Mixed incontinence includes the combination of bladder overactivity and urethral underactivity.
- Functional incontinence is not caused by bladder- or urethra-specific factors but rather occurs in patients with conditions such as cognitive or mobility deficits.
- Many medications can aggravate voiding dysfunction and UI (Table 84-1).

## CLINICAL PRESENTATION

- Signs and symptoms of UI depend on the underlying pathophysiology (Table 84-2). Patients with SUI generally complain of urinary leakage with

**TABLE 84-1** Medications Influencing Lower Urinary Tract Function

Medication	Effect
Diuretics, acetylcholinesterase inhibitors	Polyuria, frequency, urgency
$\alpha$ -Receptor antagonists	Urethral relaxation and SUI in women
$\alpha$ -Receptor agonists	Urethral constriction and urinary retention in men
Calcium channel blockers	Urinary retention
Narcotic analgesics	Urinary retention from impaired contractility
Sedative hypnotics	Functional incontinence caused by delirium, immobility
Antipsychotics	Anticholinergic effects and urinary retention
Anticholinergics	Urinary retention
Antidepressants, tricyclic	Anticholinergic effects, $\alpha$ -antagonist effects
Alcohol	Polyuria, frequency, urgency, sedation, delirium
ACEIs	Cough as a result of ACEI can aggravate SUI by increasing intraabdominal pressure

ACEIs, angiotensin-converting enzyme inhibitors; SUI, stress urinary incontinence.

physical activity, whereas those with UII complain of nocturia and nocturnal incontinence.

- Urethral overactivity and/or bladder underactivity is a rare, but important, cause of UI. Patients complain of lower abdominal fullness, hesitancy, straining to void, decreased force of stream, interrupted stream, and sense of incomplete bladder emptying. Patients can also have urinary frequency, urgency, and abdominal pain.

## DIAGNOSIS

- Patients should undergo a complete medical history with assessment of symptoms, physical examination (i.e., abdominal examination to exclude distended bladder, pelvic examination in women looking for evidence of prolapse or hormonal deficiency, and genital and prostate examination in men), and brief neurologic assessment of the perineum and lower extremities.

**TABLE 84-2** Differentiating Bladder Overactivity from Urethral Underactivity

Symptoms	Bladder Overactivity	Urethral Underactivity
Urgency (strong, sudden desire to void)	Yes	Sometimes
Frequency with urgency	Yes	Rarely
Leaking during physical activity (e.g., coughing, sneezing, lifting)	No	Yes
Amount of urinary leakage with each episode of incontinence	Large if present	Usually small
Ability to reach the toilet in time following an urge to void	No or just barely	Yes
Nocturnal incontinence (presence of wet pads or undergarments in bed)	Yes	Rare
Nocturia (waking to pass urine at night)	Usually	Seldom

- For SUI, the preferred diagnostic test is observation of urethral meatus while the patient coughs or strains.
- For UUI, the preferred diagnostic tests are urodynamic studies. Urinalysis and urine culture should be performed to rule out urinary tract infection.
- For urethral overactivity and/or bladder underactivity, digital rectal exam or transrectal ultrasound should be performed to rule out prostate enlargement. Renal function tests should be performed to rule out renal failure.

## DESIRED OUTCOME

- The goal of therapy is to decrease the signs and symptoms of most distress to the patient.

## TREATMENT

### NONPHARMACOLOGIC TREATMENT

- Nonpharmacologic treatment (e.g., lifestyle modifications, toilet scheduling regimens, pelvic floor muscle rehabilitation) is the chief form of UI management at the primary care level.
- Surgery rarely plays a role in the initial management of UI but can be required for secondary complications (e.g., skin breakdown or infection). Otherwise, the decision to surgically treat symptomatic UI requires that lifestyle compromise warrants an elective operation and that nonoperative therapy be proven undesirable or ineffective.

### PHARMACOLOGIC TREATMENT

- The choice of pharmacologic therapy (Table 84-3) depends on the type of UI.
- Pharmacologic therapies should be combined with nonpharmacologic therapies.

#### Urethral Underactivity: Stress Urinary Incontinence

- The goal of treatment of SUI is to improve urethral closure by stimulating  $\alpha$ -adrenergic receptors in the smooth muscle of the bladder neck and proximal urethra, enhancing supportive structures underlying the urethral epithelium, or enhancing serotonin and norepinephrine effects in the micturition reflex pathways.

#### *Estrogens*

- Historically, local and systemic **estrogens** have been the mainstays of pharmacologic management of SUI.
- In open trials, estrogens were administered orally, intramuscularly, vaginally, or transdermally. Regardless of the route, estrogens exerted variable effects on urodynamic parameters, such as maximum urethral closure pressure, functional urethral length, and pressure transmission ratio.
- Results of four placebo-controlled comparative trials have not been as favorable, finding no significant clinical or urodynamic effect for oral estrogen compared with placebo.

**TABLE 84-3** Pharmacotherapeutic Options in Patients with Urinary Incontinence

Type	Drug Class	Drug Therapy (Usual Dose)	Comments
Overactive bladder	Anticholinergic agents/antispasmodics	Oxybutynin TDS (3.9 mg/day; apply one patch twice weekly), tolterodine IR (1–2 mg twice daily), tolterodine LA (2–4 mg daily), trospium chloride (20 mg once or twice daily), solifenacin (5–10 mg daily), darifenacin (7.5–15 mg daily)	Anticholinergics are first-line drug therapy (oxybutynin or tolterodine is preferred).
	TCA	Imipramine, doxepin, nortriptyline, or desipramine (25–100 mg at bedtime)	TCA
Stress	Topical estrogen (only in women with urethritis or vaginitis)	Conjugated estrogen vaginal cream (0.5 g) three times per week for up to 8 months. Repeat course if symptom recurrence, or use estradiol vaginal insert/ring (2 mg [one ring]) and replace after 90 days if needed.	Marginally effective; few adverse effects with vaginal cream and insert.
	Duloxetine <sup>a</sup>	40–80 mg/day (one or two doses)	Even though not FDA approved, duloxetine is first-line therapy; most adverse events diminish with time, so support patient during initial period of use.
	$\alpha$ -Adrenergic agonists	Pseudoephedrine (15–60 mg three times daily) with food, water, or milk Phenylephrine (10 mg four times daily)	Pseudoephedrine and phenylephrine are alternative first-line therapies for women with no contraindication (notably hypertension); phenylpropranolamine was the preferred agent in the class until its removal from the U.S. market in 2000.
Overflow (atonic bladder)	Estrogen	See estrogens (above). Works best if urethritis or vaginitis is present.	Considered a less-effective alternative to $\alpha$ -adrenergic agonists and duloxetine. Combined $\alpha$ -adrenergic agonist and estrogen may be somewhat more effective than $\alpha$ -adrenergic agonist alone in postmenopausal women.
	Imipramine Cholinomimetics	25–100 mg at bedtime Bethanechol (25–50 mg three or four times daily) on an empty stomach	Imipramine is an optional therapy when first-line therapy is inadequate. Avoid use if patient has asthma or heart disease. Short-term use only. Never give IV or IM because of life-threatening cardiovascular and severe GI reactions.

IR, immediate-release; LA, long-acting; TCAs, tricyclic antidepressants; TDS, transdermal system; XL, extended-release.

<sup>a</sup>Investigational. Doses provided are those best supported by clinical trials to date.

***α-Adrenergic Receptor Agonists***

- Many open trials support the use of a variety of  $\alpha$ -adrenergic receptor agonists in SUI. Combining an  $\alpha$ -adrenergic receptor agonist with an estrogen yields somewhat superior clinical and urodynamic responses compared with monotherapy.
- Contraindications to these agents include hypertension, tachyarrhythmias, coronary artery disease, myocardial infarction, cor pulmonale, hyperthyroidism, renal failure, and narrow-angle glaucoma.

***Duloxetine***

- **Duloxetine**, a dual inhibitor of serotonin and norepinephrine reuptake indicated for depression and painful diabetic neuropathy, is expected to become first-line therapy for SUI. Duloxetine is thought to facilitate the bladder-to-sympathetic reflex pathway, increasing urethral and external urethral sphincter muscle tone during the storage phase.
- Six placebo-controlled studies showed that duloxetine reduces incontinent episode frequency and the number of daily micturitions, increases micturition interval, and improves quality-of-life scores. These benefits were statistically significant but clinically modest.
- To avoid drug interactions, clinicians should be careful when administering duloxetine with substrates or inhibitors of cytochrome P450 (CYP450) isoenzymes 2D6 and 1A2.
- The adverse-event profile might make adherence problematic. Adverse events include nausea, headache, insomnia, constipation, dry mouth, dizziness, fatigue, somnolence, vomiting, and diarrhea.

**Bladder Overactivity: Urge Urinary Incontinence**

- The pharmacotherapy of first choice for UUI is anticholinergic/antispasmodic drugs, which antagonize muscarinic cholinergic receptors.

***Oxybutynin***

- **Oxybutynin immediate-release (IR)** has been the drug of first choice for UUI and the “gold standard” against which other drugs are compared. Financial considerations favor generic oxybutynin IR.
- Many patients discontinue oxybutynin IR because of adverse effects due to antimuscarinic effects (e.g., dry mouth, constipation, vision impairment, confusion, cognitive dysfunction, and tachycardia),  $\alpha$ -adrenergic inhibition (e.g., orthostatic hypotension), and histamine H<sub>1</sub> inhibition (e.g., sedation, and weight gain).
- Oxybutynin IR is best tolerated when the dose is gradually escalated from less than or equal to 2.5 mg twice daily to 2.5 mg three times daily after 1 month. Oxybutynin IR can be further increased in 2.5-mg/day increments every 1 to 2 months until the desired response, maximum recommended dose of 5 mg three times daily, or maximum tolerated dose is attained.
- **Oxybutynin extended-release** is better tolerated than oxybutynin IR and is as effective in reducing the number of UI episodes, restoring continence, decreasing the number of micturitions per day, and increasing urine volume voided per micturition.

- The maximum benefit of oxybutynin extended-release is not realized for up to 4 weeks after starting therapy or dose escalation.
- **Oxybutynin transdermal system** has similar efficacy but is better tolerated than oxybutynin IR presumably because this route avoids first-pass metabolism in the liver, which generates the metabolite thought to cause adverse events, especially dry mouth.

### *Tolterodine*

- Tolterodine, a competitive muscarinic receptor antagonist, is considered first-line therapy in patients with urinary frequency, urgency, or urge incontinence.
- Controlled studies demonstrate that tolterodine is more effective than placebo and as effective as oxybutynin IR in decreasing the number of daily micturitions and increasing the volume voided per micturition. However, most studies have not shown a decrease in the number of daily UI episodes as compared with placebo.
- Tolterodine undergoes hepatic metabolism involving CYP450 2D6 and 3A4 isoenzymes. Therefore, elimination can be impaired by CYP450 3A4 inhibitors including **fluoxetine**, **sertraline**, **fluvoxamine**, macrolide antibiotics, imidazoles, and grapefruit juice.
- Tolterodine's most common adverse effects are dry mouth, dyspepsia, headache, constipation, and dry eyes. The maximum benefit of tolterodine is not realized for up to 8 weeks after starting therapy or dose escalation.

### *Other Pharmacologic Therapies for Urge Urinary Incontinence*

- **Tropium chloride**, a quaternary ammonium anticholinergic, is superior to placebo and is equivalent to oxybutynin IR and tolterodine IR. However, clinical studies are limited by their focus on cystometric rather than clinical endpoints, small absolute benefits compared with placebo, and lack of comparisons with LR formulations.
- Tropium chloride causes the expected anticholinergic adverse effects with increased frequency in patients  $\geq 75$  years old.
- **Solifenacin succinate** and **darifenacin** are antagonists of  $M_1$ ,  $M_2$ , and  $M_3$  muscarinic cholinergic receptors. These antagonists do not offer significant advances over other anticholinergics despite being "uroselective" in preclinical studies. Both behave like nonselective anticholinergic in humans, causing dry mouth and other anticholinergic effects.
- Drug interactions are possible if CYP450 inhibitors are given with solifenacin succinate (metabolized by 3A4 isoenzyme) or darifenacin (metabolized by 2D6 and 3A4 isoenzymes).
- Other agents, including tricyclic antidepressants, **propranolol**, **flavoxate**, **hyoscyamine**, and **dicyclomine hydrochloride**, are less effective, not safer, or have not been adequately studied.
- Patients with UUI and elevated postvoid residual urine volume should be treated by intermittent self-catheterization along with frequent voiding between catheterizations.

### *Overflow Incontinence*

- Overflow incontinence secondary to benign or malignant prostatic hyperplasia may be amenable to pharmacotherapy (see Chaps. 65 and 82).

## EVALUATION OF THERAPEUTIC OUTCOMES

- Total elimination of UI signs and symptoms may not be possible. Therefore, realistic goals should be established for therapy.
- In the long-term management of UI, the clinical symptoms of most distress to the individual patient need to be monitored.
- Survey instruments used in UI research along with quantitating the use of ancillary supplies (e.g., pads) can be used in clinical monitoring.
- Therapies for UI frequently have nuisance adverse effects, which need to be carefully elicited. Adverse effects can necessitate drug dosage adjustments, use of alternative strategies (e.g., chewing sugarless gum, sucking on hard sugarless candy, or use of saliva substitutes for xerostomia), or even drug discontinuation.

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*See Chap. 88, Urinary Incontinence, authored by Eric S. Rovner, Jean Wyman, Thomas Lackner, and David Guay, for a more detailed discussion of this topic.*

## Allergic and Pseudoallergic Drug Reactions

**TABLE A1-1** Classification of Allergic Drug Reactions

Type	Descriptor	Characteristics	Typical Onset	Drug Causes
I	Anaphylactic (IgE mediated)	Allergen binds to IgE on basophils or mast cells, resulting in release of inflammatory mediators.	Within 30 minutes	Penicillin immediate reaction Blood products Polypeptide hormones Vaccines Dextran
II	Cytotoxic	Cell destruction occurs because of cell-associated antigen that initiates cytolysis by antigen-specific antibody (IgG or IgM). Most often involves blood elements.	Typically 5–12 hours	Penicillin, quinidine, phenylbutazone, thiouracils, sulfonamides, methyldopa
III	Immune complex	Antigen–antibody complexes form and deposit on blood vessel walls and activate complement. Result is a serum sickness-like syndrome.	3–8 hours	May be caused by penicillins, sulfonamides, radiocontrast agents, hydantoins
IV	Cell-mediated (delayed)	Antigens cause activation of lymphocytes, which release inflammatory mediators.	24–48 hours	Tuberculin reaction

Ig, immunoglobulin.

**TABLE A1-2** Top 10 Drugs or Agents Reported to Cause Skin Reactions

	Reactions per 1,000 Recipients
Amoxicillin	51.4
Trimethoprim-sulfamethoxazole	33.8
Ampicillin	33.2
Iopodate	27.8
Blood	21.6
Cephalosporins	21.1
Erythromycin	20.4
Dihydralazine hydrochloride	19.1
Penicillin G	18.5
Cyanocobalamin	17.9

Data from Roujeau JC, Stern RS. *N Engl J Med* 1994;331:1272-1285.

**TABLE A1-3** Procedure for Performing Penicillin Skin Testing**A. Percutaneous (Prick) Skin Testing**

Materials	Volume
Pre-Pen $6 \times 10^6$ M (currently not commercially available in the United States)	1 drop
Penicillin G 10,000 units/mL	1 drop
$\beta$ -Lactam drug 3 mg/mL	1 drop
0.03% albumin-saline control	1 drop
Histamine control (1 mg/mL)	1 drop

- Place a drop of each test material on the volar surface of the forearm.
- Prick the skin with a sharp needle inserted through the drop at a  $45^\circ$  angle, gently tenting the skin in an upward motion.
- Interpret skin responses after 15 minutes.
- A wheal at least  $2 \times 2$  mm with erythema is considered positive.
- If the prick test is nonreactive, proceed to the intradermal test.
- If the histamine control is nonreactive, the test is considered uninterpretable.

**B. Intradermal Skin Testing**

Materials	Volume
Pre-Pen $6 \times 10^6$ M (currently not commercially available in the United States)	0.02 mL
Penicillin G 10,000 units/mL	0.02 mL
$\beta$ -Lactam drug 3 mg/mL	0.02 mL
0.03% albumin-saline control	0.02 mL
Histamine control (0.1 mg/mL)	0.02 mL

- Inject 0.02-0.03 mL of each test material intradermally (amount sufficient to produce a small bleb).
- Interpret skin responses after 15 minutes.
- A wheal at least  $6 \times 6$  mm with erythema and at least 3 mm greater than the negative control is considered positive.
- If the histamine control is nonreactive, the test is considered uninterpretable.

**Antihistamines may blunt the response and cause false-negative reactions.**

From Sullivan TJ. *Current Therapy in Allergy*. St. Louis: Mosby, 1985:57-61, with permission.

**TABLE A1-4** Treatment of Anaphylaxis

1. Place patient in recumbent position and elevate lower extremities.
2. Monitor vital signs frequently (every 2–5 minutes) and stay with the patient.
3. Administer epinephrine 1:1,000 into nonoccluded site (adults: 0.01 mL/kg up to a maximum of 0.2–0.5 mL every 10 to 15 minutes as needed, children: 0.01 mL/kg up to a maximum dose of 0.2–0.5 mL) subcutaneously or intramuscularly. If necessary, repeat every 15 minutes, up to 2 doses.
4. Administer oxygen, usually 8–10 L/min; however, lower concentrations may be appropriate for patients with chronic obstructive pulmonary disease. Maintain airway with oropharyngeal airway device.
5. Administer the antihistamine diphenhydramine (Benadryl, adults 25–50 mg; children 1–2 mg/kg) usually given parenterally. Apply tourniquet proximal to site of antigen injection; remove every 10–15 minutes.
6. If anaphylaxis is caused by an injection, administer aqueous epinephrine 1:1,000 into site of antigen injection; 0.15–0.3 mL into the injection site.
7. Treat hypotension with IV fluids or colloid replacement, and consider use of a vasopressor such as dopamine.
8. Treat bronchospasm with a  $\beta_2$ -agonist given intermittently or continuously, consider the use of aminophylline 5.6 mg/kg as an IV loading dose, given over 20 minutes, or to maintain a blood level of 8–15 mcg/mL.
9. Give hydrocortisone, 5 mg/kg, or approximately 250 mg IV (prednisone 20 mg orally can be given in mild cases) to reduce the risk of recurring or protracted anaphylaxis. These doses can be repeated every 6 hours as required.
10. In refractory cases not responding to epinephrine because a  $\beta$ -adrenergic blocker is complicating management, glucagon 1 mg IV as a bolus may be useful. A continuous infusion of glucagon, 1–5 mg/hour, may be given if required.

Reprinted and adapted from *J Allergy Clin Immunol* 1998;101:S465–S528.

**TABLE A1-5** Protocol for Oral Desensitization

Step <sup>a</sup>	Phenoxymethyl Penicillin			
	Concentration (units/mL)	Volume (mL)	Dose (units)	Cumulative Dose (units)
1	1,000	0.1	100	100
2	1,000	0.2	200	300
3	1,000	0.4	400	700
4	1,000	0.8	800	1,500
5	1,000	1.6	1,600	3,100
6	1,000	3.2	3,200	6,300
7	1,000	6.4	6,400	12,700
8	10,000	1.2	12,000	24,700
9	10,000	2.4	24,000	48,700
10	10,000	4.8	48,000	96,700
11	80,000	1.0	80,000	176,700
12	80,000	2.0	160,000	336,700
13	80,000	4.0	320,000	656,700
14	80,000	8.0	640,000	1,296,700
		Observe for 30 minutes		
15	500,000	0.25	125,000	
16	500,000	0.5	250,000	
17	500,000	1.0	500,000	
18	500,000	2.25	1,125,000	

<sup>a</sup>The interval between steps is 15 minutes.

Reprinted from Weiss ME, Adkinson NF. *Immunol Allerg Clin North* 1998;18:731–734.

**TABLE A1-6** Parenteral Desensitization Protocol

Injection No.	Benzylpenicillin Concentration (units)	Volume (mL)	Route
1 <sup>a,b</sup>	100	0.1	ID
2	100	0.2	SC
3	100	0.4	SC
4	100	0.8	SC
5 <sup>b</sup>	1,000	0.1	ID
6	1,000	0.3	SC
7	1,000	0.6	SC
8 <sup>b</sup>	10,000	0.1	ID
9	10,000	0.2	SC
10	10,000	0.4	SC
11	10,000	0.8	SC
12 <sup>b</sup>	100,000	0.1	ID
13	100,000	0.3	SC
14	100,000	0.6	SC
15 <sup>b</sup>	1,000,000	0.1	ID
16	1,000,000	0.2	SC
17	1,000,000	0.2	IM
18	1,000,000	0.4	IM
19	Continuous IV infusion at 1,000,000 units/hour		

<sup>a</sup>Administer doses at intervals of not less than 20 minutes.

<sup>b</sup>Observe and record skin wheal-and-flare response.

Reprinted from Weiss ME, Adkinson NF. *Immunol Allerg Clin North* 1998;18:731-734.

See Chapter 91, *Allergic and Pseudoallergic Drug Reactions*, authored by Joseph T. DiPiro, for a more detailed discussion of this topic.

**TABLE A2-1** Physiologic Changes with Aging

Organ System	Manifestation
Body composition	<ul style="list-style-type: none"> <li>↓ Total body water</li> <li>↓ Lean body mass</li> <li>↑ Body fat</li> <li>↔ or ↓ Serum albumin</li> <li>↔ or ↑ <math>\alpha_1</math>-Acid glycoprotein (↑ by several disease states)</li> </ul>
Cardiovascular	<ul style="list-style-type: none"> <li>↓ Myocardial sensitivity to <math>\beta</math>-adrenergic stimulation</li> <li>↓ Baroreceptor activity</li> <li>↓ Cardiac output</li> <li>↑ Total peripheral resistance</li> </ul>
CNS	<ul style="list-style-type: none"> <li>↓ Weight and volume of the brain</li> <li>Alterations in several aspects of cognition</li> </ul>
Endocrine	<ul style="list-style-type: none"> <li>Thyroid gland atrophies with age</li> <li>Increased incidence of diabetes mellitus, thyroid disease</li> <li>Menopause</li> </ul>
GI	<ul style="list-style-type: none"> <li>↑ Gastric pH</li> <li>↓ GI blood flow</li> <li>Delayed gastric emptying</li> <li>Slowed intestinal transit</li> </ul>
Genitourinary	<ul style="list-style-type: none"> <li>Atrophy of the vagina due to decreased estrogen</li> <li>Prostatic hypertrophy due to androgenic hormonal changes</li> <li>Age-related changes may predispose to incontinence</li> </ul>
Immune	<ul style="list-style-type: none"> <li>↓ Cell-mediated immunity</li> </ul>
Liver	<ul style="list-style-type: none"> <li>↓ Hepatic size</li> <li>↓ Hepatic blood flow</li> </ul>
Oral	<ul style="list-style-type: none"> <li>Altered dentition</li> <li>↓ Ability to taste sweetness, sourness, bitterness</li> </ul>
Pulmonary	<ul style="list-style-type: none"> <li>↓ Respiratory muscle strength</li> <li>↓ Chest wall compliance</li> <li>↓ Total alveolar surface</li> <li>↓ Vital capacity</li> <li>↓ Maximal breathing capacity</li> </ul>
Renal	<ul style="list-style-type: none"> <li>↓ Glomerular filtration rate</li> <li>↓ Renal blood flow</li> <li>↑ Filtration fraction</li> <li>↓ Tubular secretory function</li> <li>↓ Renal mass</li> </ul>
Sensory	<ul style="list-style-type: none"> <li>↓ Accommodation of the lens of the eye, causing farsightedness</li> <li>Presbycusis (loss of auditory acuity)</li> <li>↓ Conduction velocity</li> </ul>
Skeletal	<ul style="list-style-type: none"> <li>Loss of skeletal bone mass (osteopenia)</li> </ul>
Skin/hair	<ul style="list-style-type: none"> <li>Skin dryness, wrinkling, changes in pigmentation, epithelial thinning, loss of dermal thickness</li> <li>↓ Number of hair follicles</li> <li>↓ Number of melanocytes in hair bulbs</li> </ul>

↓, decreased; ↑, increased; ↔, no change.

From Kane RL, Ouslander JC, Abrass IB. *Clinical implications of the aging process*. In: *Essentials of Clinical Geriatrics*, 5th ed. New York: McGraw-Hill, 2004:3–15; and Masoro EJ. *Physiology of aging*. In: Tallis R, Fillit H, eds. *Brocklehurst's Textbook of Geriatric Medicine*, 6th ed. London, Churchill-Livingstone, 2003:291–299.

**TABLE A2-2** Age-Related Changes in Drug Pharmacokinetics

Pharmacokinetic Phase	Pharmacokinetic Parameters
GI absorption	Unchanged passive diffusion and no change in bioavailability for most drugs ↓ Active transport and ↓ bioavailability for some drugs
Distribution	↓ First-pass extraction and ↑ bioavailability for some drugs ↓ Volume of distribution and ↑ plasma concentration of water-soluble drugs ↑ Volume of distribution and ↑ terminal disposition half-life ( $t_{1/2}$ ) for fat-soluble drugs ↑ or ↓ Free fraction of highly plasma protein-bound drugs
Hepatic metabolism	↓ Clearance and ↑ $t_{1/2}$ for some oxidatively metabolized drugs ↓ Clearance and ↑ $t_{1/2}$ for drugs with high hepatic extraction ratios
Renal excretion	↓ Clearance and ↑ $t_{1/2}$ for renally eliminated drugs and active metabolites

↓, decreased; ↑, increased.

From Cusack BJ. Pharmacokinetics in older persons. *Am J Geriatr Pharm* 2004;2:274–302; and Chapron DJ. Drug disposition and response. In: Delafuente JC, Stewart RB, eds. *Therapeutics in the Elderly*, 3rd ed. Cincinnati, OH: Harvey Whitney, 2000:257–288.

**TABLE A2-3** Drugs/Drug Classes Associated with Altered Cognition and/or Cognitive Disorders

Antiarrhythmic agents (e.g., disopyramide)
Antiemetic/antivertigo agents (e.g., meclizine)
Antihistamines (e.g., diphenhydramine, hydroxyzine)
Antiparkinsonian agents (e.g., benztropine, trihexyphenidyl)
Antipsychotic agents (e.g., thioridazine)
Antispasmodic agents (e.g., belladonna, flavoxate)
Benzodiazepines
CNS drugs, especially when several agents are used concomitantly (as in polypharmacy)
Digoxin
Histamine H <sub>2</sub> receptor antagonists
Nonsteroidal antiinflammatory drugs
Opioid agonists (especially meperidine, pentazocine)
Skeletal muscle relaxants (e.g., cyclobenzaprine)
Tricyclic antidepressants (e.g., amitriptyline)

Data from Kotylar M, Gray SL, Lindblad CJ, Hanlon JT. Psychiatric Manifestations of Medications in the Elderly. In Malletta G, Agronin M (editors). *Principles and Practice of Geriatric Psychiatry*, 1st ed. Philadelphia, PA: Lippincott Williams and Wilkins 2005;605–615.

**TABLE A2-4** Centers for Medicare and Medicaid Services  
Guidelines for Monitoring Medication Use

<b>Drug</b>	<b>Monitoring</b>
Acetaminophen (>4 g/day)	Hepatic function tests
Aminoglycosides	Serum creatinine, drug levels
Hypoglycemic agents	Blood sugar levels
Antiepileptic agents (older)	Drug levels
Angiotensin-converting enzyme inhibitors	Potassium levels
Antipsychotic agents	Extrapyramidal adverse effects
Appetite stimulants	Weight, appetite
Digoxin	Serum creatinine, drug levels
Diuretic	Potassium levels
Erythropoiesis stimulants	Blood pressure, iron and ferritin levels, complete blood count
Fibrates	Hepatic function test, complete blood count
Iron	Iron and ferritin levels, complete blood count
Lithium	Drug levels
Niacin	Blood sugar levels, hepatic function tests
Statins	Hepatic function tests
Theophylline	Drug levels
Thyroid replacement	Thyroid function tests
Warfarin	Prothrombin time/international normalized ratio

From Center for Medicaid and Medicare Services Unnecessary Medication Use (Tag F329) 2007, <http://www.cms.hhs.gov/transmittals/downloads/R22SOMA.pdf>.

See Chapter 8, *Geriatrics*, authored by Catherine I. Starner, Shelly L. Gray, David R. P. Guay, Emily R. Hajjar, Steven M. Handler, and Joseph T. Hanlon, for a more detailed discussion of this topic.

**TABLE A3-1** Drugs Associated with Aplastic Anemias

Observational study evidence	Case report evidence ( <i>probable or definite causality rating</i> )
Carbamazepine	Acetazolamide
Furosemide	Aspirin
Gold salts	Captopril
Mebendazole	Chloramphenicol
Methimazole	Chloroquine
Nonsteroidal antiinflammatory drugs	Chlorothiazide
Oxyphenbutazone	Chlorpromazine
Penicillamine	Dapsone
Phenobarbital	Felbamate
Phenothiazines	Interferon alfa
Phenytoin	Lisinopril
Propylthiouracil	Lithium
Sulfonamides	Nizatidine
Thiazides	Pentoxifylline
Tocainide	Quinidine
	Sulindac
	Ticlopidine

**TABLE A3-2** Drugs Associated with Agranulocytosis

Observational Study Evidence	Case Report Evidence ( <i>probable or definite causality rating</i> )	
$\beta$ -Lactam antibiotics	Acetaminophen	Levodopa
Carbamazepine	Acetazolamide	Meprobamate
Carbimazole	Ampicillin	Methazolamide
Clomipramine	Captopril	Methyldopa
Digoxin	Carbenicillin	Metronidazole
Dipyridamole	Cefotaxime	Nafcillin
Ganciclovir	Cefuroxime	Nonsteroidal antiinflammatory drugs
Glyburide	Chloramphenicol	Olanzapine
Gold salts	Chlorpromazine	Oxacillin
Imipenem-cilastatin	Chlorpropamide	Penicillamine
Indomethacin	Chlorpheniramine	Penicillin G
Macrolide antibiotics	Clindamycin	Pentazocine
Methimazole	Clozapine	Phenytoin
Mirtazapine	Colchicine	Primidone
Phenobarbital	Doxepin	Procainamide
Phenothiazines	Dapsone	Propylthiouracil
Prednisone	Desipramine	Pyrimethamine
Propranolol	Ethacrynic acid	Quinidine
Spironolactone	Ethosuximide	Quinine
Sulfonamides	Flucytosine	Rifampin
Sulfonylureas	Gentamicin	Streptomycin
Ticlopidine	Griseofulvin	Terbinafine
Valproic acid	Hydralazine	Ticarcillin
Zidovudine	Hydroxychloroquine	Tocainide
	Imipenem-cilastatin	Tolbutamide
	Imipramine	Vancomycin
	Lamotrigine	

**TABLE A3-3** Drugs Associated with Hemolytic Anemia**Observational study evidence**

Phenobarbital

Phenytoin

**Case report evidence (probable or definite causality rating)**

Acetaminophen

Angiotensin-converting enzyme inhibitors

 $\beta$ -Lactam antibiotics

Cephalosporins

Ciprofloxacin

Clavulanate

Erythromycin

Hydrochlorothiazide

Indinavir

Interferon alfa

Ketoconazole

Lansoprazole

Levodopa

Levofloxacin

Methyldopa

Minocycline

Nonsteroidal antiinflammatory drugs

Omeprazole

p-Aminosalicylic acid

Phenazopyridine

Probenecid

Procainamide

Quinidine

Rifabutin

Rifampin

Streptomycin

Sulbactam

Sulfonamides

Sulfonylureas

Tacrolimus

Tazobactam

Teicoplanin

Tolbutamide

Tolmetin

Triamterene

**TABLE A3-4** Drugs Associated with Oxidative Hemolytic Anemia**Observational study evidence**

Dapsone

**Case report evidence (probable or definite causality rating)**

Ascorbic acid

Metformin

Methylene blue

Nalidixic acid

Nitrofurantoin

Phenazopyridine

Primaquine

Sulfacetamide

Sulfamethoxazole

Sulfanilamide

**TABLE A3-5** Drugs Associated with Megaloblastic Anemia**Case report evidence (probable or definite causality rating)**

Azathioprine

Chloramphenicol

Colchicine

Cotrimoxazole

Cyclophosphamide

Cytarabine

5-Fluorodeoxyuridine

5-Fluorouracil

Hydroxyurea

6-Mercaptopurine

Methotrexate

Oral contraceptives

p-Aminosalicylate

Phenobarbital

Phenytoin

Primidone

Pyrimethamine

Sulfasalazine

Tetracycline

Vinblastine

**TABLE A3-6** Drugs Associated with Thrombocytopenia

<b>Observational study evidence</b>	Diazoxide	Nalidixic acid
Carbamazepine	Diclofenac	Naphazoline
Phenobarbital	Diethylstilbestrol	Naproxen
Phenytoin	Digoxin	Nitroglycerin
Valproic acid	Ethambutol	Octreotide
<b>Case report evidence (probable or definite causality rating)</b>	Felbamate	Oxacillin
Abciximab	Fluconazole	p-Aminosalicylic acid
Acetaminophen	Gold salts	Penicillamine
Acyclovir	Haloperidol	Pentoxifylline
Albendazole	Heparin	Piperacillin
Aminoglutethimide	Hydrochlorothiazide	Primidone
Aminosalicylic acid	Ibuprofen	Procaïnamide
Amiodarone	Inamrinone	Pyrazinamide
Amphotericin B	Indinavir	Quinidine
Ampicillin	Indomethacin	Quinine
Aspirin	Interferon alfa	Ranitidine
Atorvastatin	Isoniazid	Recombinant hepatitis B vaccine
Captopril	Isotretinoin	Rifampin
Chlorothiazide	Itraconazole	Simvastatin
Chlorpromazine	Levamisole	Sirolimus
Chlorpropamide	Linezolid	Sulfasalazine
Cimetidine	Lithium	Sulfonamides
Ciprofloxacin	Low-molecular-weight heparins	Sulindac
Clarithromycin	Measles, mumps, and rubella vaccine	Tamoxifen
Clopidogrel	Meclofenamate	Tolmetin
Danazol	Mesalamine	Trimethoprim
Deferoxamine	Methyldopa	Vancomycin
Diazepam	Minoxidil	
	Morphine	

See Chapter 107, *Drug-Induced Hematologic Disorders*, authored by Dale H. Whitby and Thomas E. Johns, for a more detailed discussion of this topic.

**TABLE A4-1** An Approach to Evaluating a Suspected Hepatotoxic Reaction Using a Clinical Diagnostic Scale

Patient Presents with Elevated Liver Enzymes	Score	Component Subscore
<i>Literature</i>		
Literature supports this drug (drug combination) and pattern of liver enzyme elevation	+2	
No literature supports this, but the drug has been on the market less than 5 years	+0	–
No literature supports this, and the drug has been on the market for 5 years or more	–3	
<i>Alternative causes</i>		
Alternative causes (e.g., viral, alcohol) are completely ruled out	+3	
Alternative causes are partially ruled out	+0	–
Alternative causes cannot be ruled out and are possible or even probable	–1	
<i>Presentation</i>		
The presentation includes 4 or more extrahepatic (fever, malaise, etc.) symptoms	+3	
The presentation includes 2–3 extrahepatic symptoms	+2	–
The presentation includes only 1 identifiable extrahepatic symptom	+1	
The presentation is essentially a laboratory abnormality, with no extrahepatic symptoms	+0	
<i>Temporality</i>		
Initiation of drug therapy to onset is 4–56 days	+3	
Initiation of drug therapy to onset is <4 or >56 days	+1	
Discontinuance of therapy to onset is 0–7 days	+3	–
Discontinuance of therapy to onset is 8–15 days	+0	
Discontinuance of therapy to onset is >15 days	–1	
<i>Rechallenge</i>		
Rechallenge was positive	+3	–
Rechallenge was negative or not attempted	+0	
<b>Total Score</b>		–

The likelihood that this presentation is an adverse reaction in the liver increases linearly with an increasing score. The maximum score is 14, and scores below 7 are associated with an ever-decreasing likelihood that the drug or drug combination in question caused the problem. This approach is not designed for the assessment of hepatic cancers or cirrhotic conditions.

Reprinted from *J Clin Epidemiol*, Vol 46, Danan G, Benichou C. Causality assessment of adverse reactions to drugs—I. A novel method based on the conclusions of international consensus meetings: Application to drug-induced liver injuries: pages 1323–1330, Copyright 1993, with permission from Elsevier.

**TABLE A4-2** Environmental Hepatotoxins and Associated Occupations at Risk for Exposure

Hepatotoxin	Associated Occupations at Risk for Exposure
Arsenic	Chemical plant, construction, agricultural workers
Carbon tetrachloride	Chemical plant workers, laboratory technicians
Copper	Plumbers, outdoor sculpture artists, copper foundry workers
Dimethylformamide	Chemical plant workers, laboratory technicians
2,4-Dichlorophenoxyacetic acid	Horticulturists
Fluorine	Chemical plant workers, laboratory technicians
Toluene	Chemical plant workers, agricultural workers, laboratory technicians
Trichloroethylene	Printers, dye workers, cleaners, laboratory technicians
Vinyl chloride	Plastics plant workers; also found as a river pollutant

**TABLE A4-3** Relative Patterns of Hepatic Enzyme Elevation versus Type of Hepatic Lesion

Enzyme	Abbreviations	Necrotic	Cholestatic	Chronic
Alkaline phosphatase	Alk Phos, AP	↑	↑↑↑	↑
5'-Nucleotidase	5-NC, 5NC	↑	↑↑↑	↑
γ-Glutamyltransferase	GGT, GGTP	↑	↑↑↑	↑↑
Aspartate aminotransferase	AST, SGOT	↑↑↑	↑	↑↑
Alanine aminotransferase	ALT, SGPT	↑↑↑	↑	↑↑
Lactate dehydrogenase	LDH	↑↑↑	↑	↑

↑, <100% of normal; ↑↑, >100% of normal; ↑↑↑, >200% of normal.

**TABLE A4-4** An Approach to Determining a Drug-Monitoring Plan to Detect Hepatotoxicity

The patient is to be started on a drug that may cause a hepatotoxic reaction



Is the patient pregnant?

Is the patient older than age 60 years?

Is the patient exposed to an environmental hepatotoxin at work or at home?

Is the patient drinking more than one alcoholic beverage per day or bingeing on weekends?

Is the patient using any injected recreational drug?

Is the patient using herbal remedies or tisanes that are associated with hepatic damage?

Is the patient's diet deficient in magnesium, vitamin E, vitamin C, or  $\alpha$ - or  $\beta$ -carotenes?

Is the patient's diet excessive in vitamin A, iron, or selenium?

Does the patient have hypertriglyceridemia or type 2 diabetes mellitus?

Does the patient have juvenile arthritis or systemic lupus erythematosus?

Is the patient HIV-positive, have AIDS, or on reverse transcriptase inhibitors?

Does the patient have chronic or chronic remitting viral hepatitis (hepatitis B or C)?



Draw a baseline set of blood samples for liver enzymes, bilirubin, albumin, and transferrin before beginning the drug



Does the patient have more than two risk factors?

Is the drug identified as one that may cause a predictable hepatotoxic reaction?<sup>a</sup>

↓Yes

Redraw liver enzymes every 60–90 days depending on the drug, for the first year

↓No

Redraw liver enzymes if other signs or symptoms manifest

If no toxicity is manifested during the first year of therapy, then redraw liver enzymes every 6–12 months; assess liver for cirrhosis every 1–2 years by ultrasound and every 4–6 years by CT or MRI scan; biopsy as directed by other findings

AIDS, acquired immune deficiency syndrome; CT, computer tomography; HIV, human immunodeficiency virus; MRI, magnetic resonance imaging.

<sup>a</sup>A drug can become a predictable risk if it is administered concurrently with another drug or food that is known to induce or inhibit its metabolism.

See Chapter 40, *Drug-Induced Liver Disease*, authored by William R. Kirchain and Rondall E. Allen, for a more detailed discussion of this topic.

**TABLE A5-1** Drugs That Induce Apnea

	Relative Frequency of Reactions
<b>CNS depression</b>	
Narcotic analgesics	F
Barbiturates	F
Benzodiazepines	F
Other sedatives and hypnotics	I
Tricyclic antidepressants	R
Phenothiazines	R
Ketamine	R
Promazine	R
Anesthetics	R
Antihistamines	R
Alcohol	I
Fenfluramine	R
L-Dopa	R
Oxygen	R
<b>Respiratory muscle dysfunction</b>	
Aminoglycoside antibiotics	I
Polymyxin antibiotics	I
Neuromuscular blockers	I
Quinine	R
Digitalis	R
<b>Myopathy</b>	
Corticosteroids	F
Diuretics	I
Aminocaproic acid	R
Clofibrate	R

F, frequent; I, infrequent; R, rare.

**TABLE A5-2** Drugs That Induce Bronchospasm

	Relative Frequency of Reactions
<b>Anaphylaxis (IgE-mediated)</b>	
Penicillins	F
Sulfonamides	F
Serum	F
Cephalosporins	F
Bromelin	R
Cimetidine	R
Papain	F
Pancreatic extract	I
Psyllium	I
Subtilase	I
Tetracyclines	I
Allergen extracts	I
L-Asparaginase	F
Pyrazolone analgesics	I

(continued)

**TABLE A5-2** Drugs That Induce Bronchospasm (Continued)

<b>Direct airway irritation</b>	
Acetate	R
Bisulfite	F
Cromolyn	R
Smoke	F
<i>N</i> -acetylcysteine	F
Inhaled steroids	I
<b>Precipitating IgG antibodies</b>	
$\beta$ -Methyl dopa	R
Carbamazepine	R
Spiramycin	R
<b>Cyclooxygenase inhibition</b>	
Aspirin/nonsteroidal antiinflammatory drugs	F
Phenylbutazone	I
Acetaminophen	R
<b>Anaphylactoid mast-cell degranulation</b>	
Narcotic analgesics	I
Ethylenediamine	R
Iodinated-radiocontrast media	F
Platinum	R
Local anesthetics	I
Steroidal anesthetics	I
Iron-dextran complex	I
Pancuronium bromide	R
Benzalkonium chloride	I
<b>Pharmacologic effects</b>	
$\alpha$ -Adrenergic receptor blockers	I-F
Cholinergic stimulants	I
Anticholinesterases	R
$\beta$ -Adrenergic agonists	R
Ethylenediamine tetraacetic acid	R
<b>Unknown mechanisms</b>	
Angiotensin-converting enzyme inhibitors	I
Anticholinergics	R
Hydrocortisone	R
Isoproterenol	R
Monosodium glutamate	I
Piperazine	R
Tartrazine	R
Sulfinpyrazone	R
Zinostatin	R
Losartan	R

F, frequent; I, infrequent; Ig, immunoglobulin; R, rare.

**TABLE A5-3** Tolerance of Antiinflammatory and Analgesic Drugs in Aspirin-Induced Asthma

<b>Cross-Reactive Drugs</b>	<b>Drugs with No Cross-Reactivity</b>
Diclofenac	Acetaminophen <sup>a</sup>
Diflunisal	Benzydamine
Fenoprofen	Chloroquine
Flufenamic acid	Choline salicylate
Flurbiprofen	Corticosteroids
Hydrocortisone hemisuccinate	Dextropropoxyphene
Ibuprofen	Phenacetin <sup>a</sup>
Indomethacin	Salicylamide
Ketoprofen	Sodium salicylate
Mefenamic acid	
Naproxen	
Noramidopyrine	
Oxyphenbutazone	
Phenylbutazone	
Piroxicam	
Sulindac	
Sulfinpyrazone	
Tartrazine	
Tolmetin	

<sup>a</sup>A very small percentage (5%) of aspirin-sensitive patients react to acetaminophen and phenacetin.

**TABLE A5-4** Drugs That Induce Pulmonary Edema

	Relative Frequency of Reactions
<b>Cardiogenic pulmonary edema</b>	
Excessive IV fluids	F
Blood and plasma transfusions	F
Corticosteroids	F
Phenylbutazone	R
Sodium diatrizoate	R
Hypertonic intrathecal saline	R
$\beta_2$ -Adrenergic agonists	I
<b>Noncardiogenic pulmonary edema</b>	
Heroin	F
Methadone	I
Morphine	I
Oxygen	I
Propoxyphene	R
Ethchlorvynol	R
Chlordiazepoxide	R
Salicylate	R
Hydrochlorothiazide	R
Triamterene + hydrochlorothiazide	R
Leukoagglutinin reactions	R
Iron-dextran complex	R
Methotrexate	R
Cytosine arabinoside	R
Nitrofurantoin	R
Dextran 40	R
Fluorescein	R
Amitriptyline	R
Colchicine	R
Nitrogen mustard	R
Epinephrine	R
Metaraminol	R
Bleomycin	R
Iodide	R
Cyclophosphamide	R
VM-26	R

F, frequent; I, infrequent; R, rare.

**TABLE A5-5** Drugs That Induce Pulmonary Infiltrates with Eosinophilia (Loeffler's Syndrome)

Drug	Relative Frequency of Reactions	Drug	Relative Frequency of Reactions
Nitrofurantoin	F	Tetracycline	R
para-Aminosalicylic acid	F	Procarbazine	R
Sulfonamides	I	Cromolyn	R
Penicillins	I	Nitridazole	R
Methotrexate	I	Gold salts	R
Imipramine	I	Chlorpromazine	R
Chlorpropamide	R	Naproxen	R
Carbamazepine	R	Sulindac	R
Phenytoin	R	Ibuprofen	R
Mephesisin	R		

F, frequent; I, infrequent; R, rare.

**TABLE A5-6** Drugs That Induce Pneumonitis and/or Fibrosis

Drug	Relative Frequency of Reactions	Drug	Relative Frequency of Reactions
Oxygen	F	Chlorambucil	R
Radiation	F	Melphalan	R
Bleomycin	F	Lomustine and semustine	R
Busulfan	F	Zinostatin	R
Carmustine	F	Procarbazine	R
Hexamethonium	F	Teniposide	R
Paraquat	F	Sulfasalazine	R
Amiodarone	F	Phenytoin	R
Mecamylamine	I	Gold salts	R
Pentolinium	I	Pindolol	R
Cyclophosphamide	I	Imipramine	R
Practolol	I	Penicillamine	R
Methotrexate	I	Phenylbutazone	R
Mitomycin	I	Chlorphentermine	R
Nitrofurantoin	I	Fenfluramine	R
Methysergide	I	Leflunomide	R
Sirolimus	I	Mefloquine	R
Azathioprine, 6-mercaptopurine	R	Pergolide	R

F, frequent; I, infrequent; R, rare.

**TABLE A5-7** Possible Causes of Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (fibrosing alveolitis)
Pneumoconiosis (asbestosis, silicosis, coal dust, talc berylliosis)
Hypersensitivity pneumonitis (molds, bacteria, animal proteins, toluene diisocyanate, epoxy resins)
Smoking
Sarcoidosis
Tuberculosis
Lipoid pneumonia
Systemic lupus erythematosus
Rheumatoid arthritis
Systemic sclerosis
Polymyositis/dermatomyositis
Sjögren's syndrome
Polyarteritis nodosa
Wegener's granuloma
Byssinosis (cotton workers)
Siderosis (arc welders' lung)
Radiation
Oxygen
Chemicals (thioureas, trialkylphosphorothioates, furans)
Drugs (see Tables A5-5, A5-6, and A5-8)

**TABLE A5-8** Drugs That May Induce Pleural Effusions and Fibrosis

	Relative Frequency of Reactions
<b>Idiopathic</b>	
Methysergide	F
Practolol	F
Pindolol	R
Methotrexate	R
Nitrofurantoin	R
<b>Drug-induced lupus syndrome</b>	
Procainamide	F
Hydralazine	F
Isoniazid	R
Phenytoin	R
Mephenytoin	R
Griseofulvin	R
Trimethadione	R
Sulfonamides	R
Phenylbutazone	R
Streptomycin	R
Ethosuximide	R
Tetracycline	R
<b>Pseudolymphoma syndrome</b>	
Cyclosporine	R
Phenytoin	R

F, frequent; I, infrequent; R, rare.

See Chapter 31, *Drug-Induced Pulmonary Diseases*, authored by Hengameh H. Raissy, Michelle Harkins, and Patricia L. Marshik, for a more detailed discussion of this topic.

**TABLE A6-1** Drug-Induced Renal Structural–Functional Alterations**Tubular epithelial cell damage**

Acute tubular necrosis

- Adefovir, cidofovir, tenofovir
- Aminoglycoside antibiotics
- Amphotericin B
- Cisplatin, carboplatin
- Cyclosporine, tacrolimus
- Foscarnet

- Pentamidine
- Radiographic contrast media
- Zoledronate

Osmotic nephrosis

- Dextran
- Intravenous immunoglobulin
- Mannitol

**Hemodynamically mediated kidney injury**

- Angiotensin-converting enzyme inhibitors
- Angiotensin II receptor blockers

- Cyclosporine, tacrolimus
- Nonsteroidal antiinflammatory drugs
- OKT3

**Obstructive nephropathy**

Intratubular obstruction

- Acyclovir
- Foscarnet
- Indinavir
- Methotrexate
- Sulfonamides

Nephrolithiasis

- Indinavir
- Sulfonamides
- Triamterene

**Glomerular disease**

- Gold
- Lithium

- Nonsteroidal antiinflammatory drugs, cyclooxygenase-2 inhibitors
- Pamidronate

**Tubulointerstitial disease**

Acute allergic interstitial nephritis

- Ciprofloxacin
- Loop diuretics
- Nonsteroidal antiinflammatory drugs, cyclooxygenase-2 inhibitors
- Penicillins
- Proton pump inhibitors

Nephrocalcinosis

- Oral sodium phosphate solution

Papillary necrosis

- Nonsteroidal antiinflammatory drugs, combined phenacetin, aspirin, and caffeine analgesics

Chronic interstitial nephritis

- Cyclosporine
- Lithium
- Aristolochic acid

**Renal vasculitis, thrombosis, and cholesterol emboli**

Vasculitis and thrombosis

- Hydralazine
- Propylthiouracil
- Allopurinol
- Penicillamine
- Gemcitabine

- Mitomycin C
- Methamphetamines
- Cyclosporine, tacrolimus

Cholesterol emboli

- Warfarin
- Thrombolytic agents

**TABLE A6-2** Potential Risk Factors for Aminoglycoside Nephrotoxicity

- A. Related to aminoglycoside dosing:
- Large total cumulative dose
  - Prolonged therapy
  - Trough concentration exceeding 2 mg/L
  - Recent previous aminoglycoside therapy
- B. Related to synergistic nephrotoxicity. Aminoglycosides in combination with:
- Amphotericin B
  - Cyclosporine
  - Diuretics
  - Vancomycin
- C. Related to predisposing conditions in the patient:
- Dehydration
  - Gram-negative bacteremia
  - Hypoalbuminemia
  - Increased age
  - Liver disease
  - Obstructive jaundice
  - Preexisting kidney disease
  - Poor nutrition
  - Potassium or magnesium deficiencies
  - Shock

**TABLE A6-3** Recommended Interventions for Prevention of Contrast Nephrotoxicity

Intervention	Recommendation	Recommendation Grade <sup>a</sup>
Contrast	• Minimize contrast volume/dose	A-1
	• Use noniodinated contrast studies	A-2
	• Use low- or isoosmolar contrast agents	A-2
Medications	• Avoid concurrent use of potentially nephrotoxic drugs (e.g., nonsteroidal antiinflammatory drugs, aminoglycosides)	A-2
Normal (0.9%) saline	• Initiate infusion at least 3 hours prior to contrast exposure and continue 8–24 hours postexposure • Infuse at 1 mL/kg/hour up to 150 mL/hour, adjusting postexposure as clinically indicated	A-1
Sodium bicarbonate 154 mEq/L	• Initiate infusion at 3 mL/kg/hour, beginning 1 hour prior to contrast exposure, then continue at 1 mL/kg/hour for 6 hours postexposure	B-2
<i>N</i> -acetylcysteine	• Administer 600 mg orally, every 12 hours × 4 doses beginning prior to contrast exposure (i.e., one dose prior to exposure and 3 doses postexposure)	B-1

<sup>a</sup>Strength of recommendations: A, B, C, good, moderate, and poor evidence to support recommendation, respectively. Quality of evidence: 1, Evidence from more than one properly randomized, controlled trial. 2, Evidence from more than one well-designed clinical trial with randomization, from cohort or case-controlled analytic studies or multiple time series; or dramatic results from uncontrolled experiments. 3, Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert communities.

Derived from data in Barrett BJ, Parfrey PS. *N Engl J Med* 2006;354:379–386; Rudnick MR, Kesselheim A, Goldfarb S. *Cleve Clin J Med* 2006;73:75–77; Bagshaw SM, McAlister FA, Manns BJ, Ghali WA. *Arch Intern Med* 2006;166:161–166; and Schweiger MJ, Chambers CE, Davidson CJ, et al. *Catheter Cardiovasc Interv* 2006;69:135–140.

**TABLE A6-4** Drugs Associated with Allergic Interstitial Nephritis**Antimicrobials**

Acyclovir	Indinavir
Aminoglycosides	Rifampin
Amphotericin B	Sulfonamides
$\beta$ -Lactams	Tetracyclines
Erythromycin	Trimethoprim-sulfamethoxazole
Ethambutol	Vancomycin

**Diuretics**

Acetazolamide	Loop diuretics
Amiloride	Triamterene
Chlorthalidone	Thiazide diuretics

**Neuropsychiatric**

Carbamazepine	Phenytoin
Lithium	Valproic acid
Phenobarbital	

**Nonsteroidal antiinflammatory drugs**

Aspirin	Ketoprofen
Cyclooxygenase-2 inhibitors	Naproxen
Diclofenac	Phenylbutazone
Diffunisal	Piroxicam
Ibuprofen	Zomepirac
Indomethacin	

**Miscellaneous**

Acetaminophen	Lansoprazole
Allopurinol	Methyldopa
Aspirin	Omeprazole
Azathioprine	p-Aminosalicylic acid
Captopril	Phenylpropanolamine
Cimetidine	Propylthiouracil
Clofibrate	Radiographic contrast media
Cyclosporine	Ranitidine
Glyburide	Sulfinpyrazone
Gold	Warfarin
Interferon-alfa	

See Chapter 49, *Drug-Induced Kidney Disease*, authored by Thomas D. Nolin and Jonathan Himmelfarb, for a more detailed discussion of this topic.

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