PHARMACOTHERAPY HANDBOOK

TENTH EDITION

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Mc Graw Hill Education

Pharmacotherapy Handbook

Tenth Edition

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Preface

This 10th edition of the pocket companion to *Pharmacotherapy: A Pathophysiologic Approach* 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. The authors make every effort to write as clearly and succinctly as possible.

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; Nutrition Support; Oncologic Disorders; Ophthalmic Disorders; Psychiatric Disorders; Renal Disorders; Respiratory Disorders; and Urologic Disorders. Drug-induced conditions associated with drug allergy, hematologic disorders, liver disease, pulmonary disease, and kidney disease appear in five tabular appendices. Tabular information on the management of pharmacotherapy in the elderly also appears as an appendix.

Each chapter is organized in a consistent format:

- Disease state definition
- Concise review of relevant pathophysiology
- Clinical presentation
- Diagnosis
- Treatment
- Evaluation of therapeutic outcomes

The treatment section may include goals of treatment, general approach to treatment, 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,* 10th 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.

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Please provide your comments about this book, Wells et al., *Pharmacotherapy Handbook,* 10th edition, to its authors and publisher by writing to 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 10th edition of *Pharmacotherapy: A Pathophysiologic Approach* served as the basis for this book. The dedication and professionalism of these outstanding practitioners, teachers, and scientists are evident on every page of this work. These individuals are acknowledged at the end of each respective handbook chapter. We also appreciate the input of readers over the years who have helped us to make continuous improvements in this book.

CHAPTER 1

Gout and Hyperuricemia

- *Gout* involves hyperuricemia, recurrent attacks of acute arthritis with monosodium urate (MSU) crystals in synovial fluid leukocytes, deposits of MSU crystals in tissues in and around joints (tophi), interstitial renal disease, and uric acid nephrolithiasis.

PATHOPHYSIOLOGY

- Uric acid is the end product of purine degradation. An increased urate pool in individuals with gout may result from overproduction or underexcretion.
- Purines originate from dietary purine, conversion of tissue nucleic acid to purine nucleotides, and de novo synthesis of purine bases.
- Overproduction of uric acid may result from abnormalities in enzyme systems that regulate purine metabolism (eg, increased activity of phosphoribosyl pyrophosphate [PRPP] synthetase or deficiency of hypoxanthine-guanine phosphoribosyl transferase [HGPRT]).
- Uric acid may be overproduced because of increased breakdown of tissue nucleic acids, as with myeloproliferative and lymphoproliferative disorders. Cytotoxic drugs can result in overproduction of uric acid due to lysis and the breakdown of cellular matter.
- Dietary purines are insignificant in generation of hyperuricemia without some derangement in purine metabolism or elimination.
- Two thirds of uric acid produced daily is excreted in urine. The remainder is eliminated through gastrointestinal (GI) tract after degradation by colonic bacteria. Decline in urinary excretion to a level below rate of production leads to hyperuricemia and increased pool of sodium urate.
- Drugs that decrease renal uric acid clearance include diuretics, nicotinic acid, salicylates (<2 g/day), ethanol, pyrazinamide, levodopa, ethambutol, cyclosporine, and cytotoxic drugs.
- Deposition of urate crystals in synovial fluid results in inflammation, 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 discharge of proteolytic enzymes into cytoplasm. The ensuing inflammatory reaction causes 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 because of blockage of urine flow from massive precipitation of uric acid crystals in collecting ducts and ureters. Chronic urate nephropathy is caused by long-term deposition of urate crystals in the renal parenchyma.
- Tophi (urate deposits) are uncommon and are a late complication of hyperuricemia. Most common sites are the base of the fingers, olecranon bursae, ulnar aspect of forearm, Achilles tendon, knees, wrists, and hands.

CLINICAL PRESENTATION

- Acute gout attacks are characterized by rapid onset of excruciating pain, swelling, and inflammation. The attack is typically monoarticular, 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 with excruciating pain. Affected joints are erythematous, warm, and swollen. Fever and leukocytosis are common. Untreated attacks last from 3 to 14 days before spontaneous recovery.
- Acute attacks may occur without provocation or be precipitated by stress, trauma, alcohol ingestion, infection, surgery, rapid lowering of serum uric acid by uric acid–lowering agents, and ingestion of drugs known to elevate serum uric acid concentrations.

DIAGNOSIS

- Definitive diagnosis requires aspiration of synovial fluid from the affected joint and identification of intracellular crystals of MSU monohydrate in synovial fluid leukocytes.
- When joint aspiration is not feasible, a presumptive diagnosis is based on presence of characteristic signs and symptoms as well as the response to treatment.

TREATMENT

- Goals of Treatment: Terminate the acute attack, prevent recurrent attacks, and prevent complications associated with chronic deposition of urate crystals in tissues.

ACUTE GOUTY ARTHRITIS (FIG. 1–1)

Nonpharmacologic Therapy

- Local ice application is the most effective adjunctive treatment. Dietary supplements (eg, flaxseed and celery root) are not recommended.

Pharmacologic Therapy

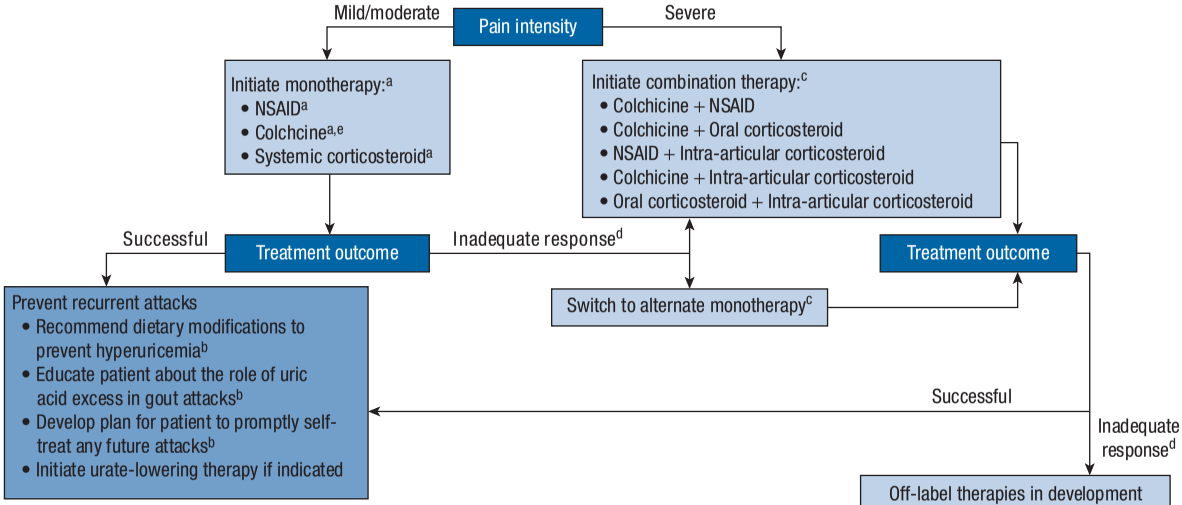
- Most patients may be treated successfully with nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or colchicine.

NSAIDS

- NSAIDs have excellent efficacy and minimal toxicity with short-term use. Indomethacin, naproxen, and sulindac have Food and Drug Administration (FDA) approval for gout, but others are likely to be effective (**Table 1–1**).
- Start therapy within 24 hours of attack onset and continue until complete resolution (usually 5–8 days). Tapering may be considered after resolution, especially if comorbidities such as hepatic or renal insufficiency make prolonged therapy undesirable.
- The most common adverse effects involve the GI tract (gastritis, bleeding, and perforation), kidneys (renal papillary necrosis and reduced creatinine clearance [CL_{cr}]), cardiovascular system (increased blood pressure, sodium and fluid retention), and central nervous system (impaired cognitive function, headache, and dizziness).
- Selective cyclooxygenase-2 inhibitors (eg, celecoxib) may be an option for patients unable to take nonselective NSAIDs, but the risk-to-benefit ratio in acute gout is unclear, and cardiovascular risk must be considered.

CORTICOSTEROIDS

- Corticosteroid efficacy is equivalent to NSAIDs; they can be used systemically or by intra-articular (IA) injection. Systemic therapy is necessary if an attack is polyarticular.



[a]Evidence Grade Level A: Supported by multiple randomized clinical trials or meta-analyses
[b]Evidence Grade Level B: Derived from a single randomized trial, or nonrandomized studies
[c]Evidence Grade Level C: Consensus opinion of experts, case studies, or standard-of-care
[d]"Inadequate Response" is defined as <20% improvement in pain score within 24 hours or <50% at ≥24 hours
[e]Colchicine is recommended only if started within 36 hours of symptom onset

FIGURE 1–1. Algorithm for management of an acute gout attack.

TABLE 1–1 Dosage Regimens of Oral Nonsteroidal Anti-Inflammatory Drugs for Treatment of Acute Gout

Generic Name	Initial Dose	Usual Range
Etodolac	300 mg twice daily	300–500 mg twice daily
Fenoprofen	400 mg three times daily	400–600 mg three to four times daily
Ibuprofen	400 mg three times daily	400–800 mg three to four times daily
Indomethacin	50 mg three times daily	50 mg three times daily initially until pain is tolerable then rapidly reduce to complete cessation
Ketoprofen	75 mg three times daily or 50 mg four times daily	50–75 mg three to four times daily
Naproxen	750 mg followed by 250 mg every 8 hours until the attack has subsided	—
Piroxicam	20 mg once daily or 10 mg twice daily	—
Sulindac	200 mg twice daily	150–200 mg twice daily for 7–10 days
Celecoxib	800 mg followed by 400 mg on day one, then 400 mg twice daily for 1 week	—

- **Prednisone** or **prednisolone** oral dosing strategies: (1) 0.5 mg/kg daily for 5 to 10 days followed by abrupt discontinuation; or (2) 0.5 mg/kg daily for 2 to 5 days followed by tapering for 7 to 10 days. Tapering is often used to reduce the hypothetical risk of a rebound attack upon steroid withdrawal.
- **Methylprednisolone dose pack** is a 6-day regimen starting with 24 mg on day 1 and decreasing by 4 mg each day.
- **Triamcinolone acetonide** 20 to 40 mg given by IA injection may be used if gout is limited to one or two joints. IA corticosteroids should generally be used with oral NSAID, colchicine, or corticosteroid therapy.
- **Methylprednisolone** (a long-acting corticosteroid) given by a single intramuscular (IM) injection followed by oral corticosteroid therapy is another reasonable approach. Alternatively, IM corticosteroid monotherapy may be considered in patients with multiple affected joints who cannot take oral therapy.
- Short-term corticosteroid use is generally well tolerated. Use with caution in patients with diabetes, GI problems, bleeding disorders, cardiovascular disease, and psychiatric disorders. Avoid long-term use because of risk for osteoporosis, hypothalamic–pituitary–adrenal axis suppression, cataracts, and muscle deconditioning.
- **Adrenocorticotropic hormone (ACTH)** gel 40 to 80 USP units may be given IM every 6 to 8 hours for 2 or 3 days and then discontinued. Limit use for patients with contraindications to first-line therapies (eg, heart failure, chronic renal failure, and history of GI bleeding) or patients unable to take oral medications.

COLCHICINE

- **Colchicine** is highly effective in relieving acute gout attacks; when it is started within the first 24 hours of onset, about two thirds of patients respond within hours. Use only within 36 hours of attack onset because the likelihood of success decreases substantially if treatment is delayed.

- Colchicine causes dose-dependent GI adverse effects (nausea, vomiting, and diarrhea). Non-GI effects include neutropenia and axonal neuromyopathy, which may be worsened in patients taking other myopathic drugs (eg, statins) or in renal insufficiency. Do not use concurrently with P-glycoprotein or strong CYP450 3A4 inhibitors (eg, clarithromycin) because reduced biliary excretion may lead to increased plasma colchicine levels and toxicity. Use with caution in renal or hepatic insufficiency.
- **Colcrys** is an FDA-approved colchicine product available in 0.6 mg oral tablets. The recommended dose is 1.2 mg (two tablets) initially, followed by 0.6 mg (one tablet) 1 hour later. Although not an FDA-approved regimen, the American College of Rheumatology (ACR) gout treatment guidelines suggest that colchicine 0.6 mg once or twice daily can be started 12 hours after the initial 1.2-mg dose and continued until the attack resolves.

HYPERURICEMIA IN GOUT

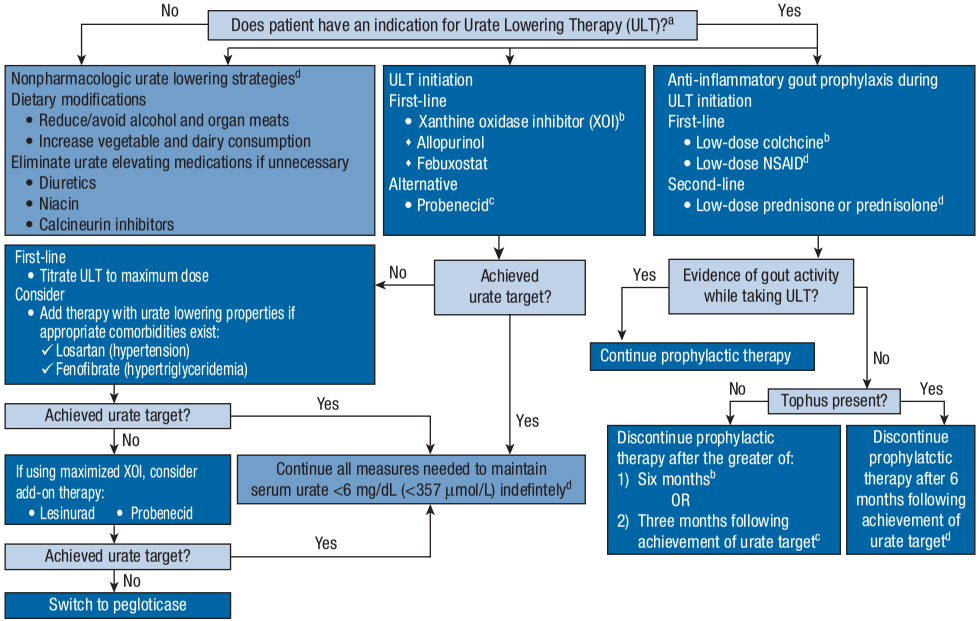
- Recurrent gout attacks can be prevented by maintaining low uric acid levels, but adherence with nonpharmacologic and pharmacologic therapies is poor.

Nonpharmacologic Therapy

- Patient education should address the recurrent nature of gout and the objective of each lifestyle/dietary modification and medication.
- Promote weight loss through caloric restriction and exercise in all patients to enhance renal urate excretion.
- Alcohol restriction is important because consumption correlates with gout attacks. ACR guidelines recommend limiting alcohol use in all gout patients and avoidance of any alcohol during periods of frequent gout attacks and in patients with advanced gout under poor control.
- Dietary recommendations include limiting consumption of high-fructose corn syrup and purine-rich foods (organ meats and some seafood) and encouraging consumption of vegetables and low-fat dairy products.
- Evaluate the medication list for potentially unnecessary drugs that may elevate uric acid levels. Gout is not necessarily a contraindication to use of thiazide diuretics in hypertensive patients. Low-dose aspirin for cardiovascular prevention should be continued in patients with gout because aspirin has a negligible effect on elevating serum uric acid.

Pharmacologic Therapy (Fig. 1–2)

- After the first attack of acute gout, prophylactic pharmacotherapy is recommended if patients have two or more attacks per year, even if serum uric acid is normal or only minimally elevated. Other indications include presence of tophi, chronic kidney disease, or history of urolithiasis.
- Urate-lowering therapy can be started during an acute attack if anti-inflammatory prophylaxis has been initiated.
- The goal of urate-lowering therapy is to achieve and maintain serum uric acid less than 6 mg/dL (357 μmol/L), and preferably less than 5 mg/dL (297 μmol/L) if signs and symptoms of gout persist.
- Urate lowering should be prescribed for long-term use. Serum urate can be reduced by decreasing synthesis of uric acid (xanthine oxidase inhibitors) or by increasing renal excretion of uric acid (uricosurics).
- Apply a step-wise approach to hyperuricemia (see Fig. 1–2). Xanthine oxidase inhibitors are recommended first-line therapy; the uricosuric agent probenecid is recommended as alternative therapy in patients with a contraindication or intolerance to xanthine oxidase inhibitors. In refractory cases, combination therapy with a xanthine oxidase inhibitor plus a drug with uricosuric properties (probenecid, losartan, or fenofibrate) is suggested. Pegloticase may be used in severe cases in which the patient cannot tolerate or is not responding to other therapies.



[a]Indications for ULT include: (1) presence of tophus, (2) ≥2 gout attacks per year, (3) CKD stage 2 or worse, and (4) past urolithiasis
[b]Evidence Grade Level A: Supported by multiple randomized clinical trials or meta-analyses
[c]Evidence Grade Level B: Derived from a single randomized trial, or nonrandomized studies
[d]Evidence Grade Level C: Consensus opinion of experts, case studies, or standard-of-care

FIGURE 1–2. Algorithm for management of hyperuricemia in gout.

XANTHINE OXIDASE INHIBITORS

- Xanthine oxidase inhibitors reduce uric acid by impairing conversion of hypoxanthine to xanthine and xanthine to uric acid. Because they are effective in both overproducers and underexcretors of uric acid, they are the most widely prescribed agents for long-term prevention of recurrent gout attacks.
- **Allopurinol** lowers uric acid levels in a dose-dependent manner. ACR guidelines recommend a starting dose no greater than 100 mg daily in patients with normal renal function and no more than 50 mg/day in patients with chronic kidney disease (stage 4 or worse) to avoid allopurinol hypersensitivity syndrome and prevent acute gout attacks common during initiation of urate-lowering therapy. The dose should be titrated gradually every 2 to 5 weeks up to a maximum dose of 800 mg/day until the serum urate target is achieved.
- Mild adverse effects of allopurinol include skin rash, leukopenia, GI problems, headache, and urticaria. More severe adverse reactions include severe rash (toxic epidermal necrolysis, erythema multiforme, or exfoliative dermatitis) and allopurinol hypersensitivity syndrome characterized by fever, eosinophilia, dermatitis, vasculitis, and renal and hepatic dysfunction that occurs rarely but is associated with a 20% mortality rate.
- **Febuxostat** (Uloric) also lowers serum uric acid in a dose-dependent manner. The recommended starting dose is 40 mg once daily. Increase the dose to 80 mg once daily for patients who do not achieve target serum uric acid concentrations after 2 weeks of therapy. Febuxostat is well tolerated, with adverse events of nausea, arthralgias, and minor hepatic transaminase elevations. Febuxostat does not require dose adjustment in mild to moderate hepatic or renal dysfunction. Due to rapid mobilization of urate deposits during initiation, give concomitant therapy with colchicine or an NSAID for at least the first 8 weeks of therapy to prevent acute gout flares.

URICOSURICS

- **Probenecid** increases renal clearance of uric acid by inhibiting the postsecretory renal proximal tubular reabsorption of uric acid. Patients with a history of urolithiasis should not receive uricosurics. Start therapy with uricosurics at a low dose to avoid marked uricosuria and possible stone formation. Maintaining adequate urine flow and alkalinization of the urine during the first several days of therapy may also decrease likelihood of uric acid stone formation.
- Initial probenecid dose is 250 mg twice daily for 1 to 2 weeks, then 500 mg twice daily for 2 weeks. Increase the daily dose thereafter by 500-mg increments every 1 to 2 weeks until satisfactory control is achieved or a maximum dose of 2 g/day is reached.
- Major side effects of probenecid include GI irritation, rash and hypersensitivity, precipitation of acute gouty arthritis, and stone formation. Contraindications include impaired renal function (CL_{cr} <50 mL/min or <0.84 mL/s) and overproduction of uric acid.
- **Lesinurad** (Zurampic) is a selective uric acid reabsorption inhibitor that inhibits urate transporter 1, a transporter in proximal renal tubules, thereby increasing uric acid excretion. It is approved as combination therapy with a xanthine oxidase inhibitor for treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels with xanthine oxidase inhibitor monotherapy.
- The only approved dose of lesinurad dose is 200 mg once daily in the morning with food and water in combination with a xanthine oxidase inhibitor. The drug should not be used in patients with creatinine clearance below 45 mL/min.
- Adverse effects of lesinurad include urticaria and elevated levels of serum creatinine, lipase, and creatine kinase. It carries a black box warning about increased risk of acute renal failure when used in the absence of xanthine oxidase inhibitor therapy.

PEGLOTICASE

- **Pegloticase** (Krystexxa) is a pegylated recombinant uricase that reduces serum uric acid by converting uric acid to allantoin, which is water soluble. Pegloticase is indicated for antihyperuricemic therapy in adults refractory to conventional therapy.

- The dose is 8 mg by IV infusion over at least 2 hours every 2 weeks. Because of potential infusion-related allergic reactions, patients must be pretreated with antihistamines and corticosteroids. Pegloticase is substantially more expensive than first-line urate-lowering therapies.
- The ideal duration of pegloticase therapy is unknown. Development of pegloticase antibodies resulting in loss of efficacy may limit the duration of effective therapy.
- Because of its limitations, reserve pegloticase for patients with refractory gout who are unable to take or have failed all other urate-lowering therapies.

ANTI-INFLAMMATORY PROPHYLAXIS DURING INITIATION OF URATE-LOWERING THERAPY

- Initiation of urate-lowering therapy can precipitate an acute gout attack due to remodeling of urate crystal deposits in joints after rapid lowering of urate concentrations. Prophylactic anti-inflammatory therapy is often used to prevent such gout attacks.
- The ACR guidelines recommend low-dose oral colchicine (0.6 mg twice daily) and low-dose NSAIDs (eg, naproxen 250 mg twice daily) as first-line prophylactic therapies, with stronger evidence supporting use of colchicine. For patients on long-term NSAID prophylaxis, a proton pump inhibitor or other acid-suppressing therapy is indicated to protect from NSAID-induced gastric problems.
- Low-dose corticosteroid therapy (eg, prednisone ≤10 mg/day) is an alternative for patients with intolerance, contraindication, or lack of response to first-line therapy. The potential severe adverse effects of prolonged corticosteroid therapy preclude their use as first-line therapy.
- Continue prophylaxis for at least 6 months or 3 months after achieving target serum uric acid, whichever is longer. For patients with one or more tophi, continue prophylactic therapy for 6 months after achieving the serum urate target (see Fig. 1–2).

EVALUATION OF THERAPEUTIC OUTCOMES

- Check the serum uric acid level 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 prophylaxis. However, acute gout can occur with normal serum uric acid concentrations.
- Monitor patients with acute gout for symptomatic relief of joint pain as well as potential adverse effects and drug interactions related to drug therapy. Acute pain of an initial gout attack 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.
- For patients receiving urate-lowering therapy, obtain baseline assessment of renal function, hepatic enzymes, complete blood count, and electrolytes. Recheck the tests every 6 to 12 months in patients receiving long-term treatment.
- During titration of urate-lowering therapy, monitor serum uric acid every 2 to 5 weeks; after the urate target is achieved, monitor uric acid every 6 months.
- Because of the high rates of comorbidities associated with gout (diabetes, chronic kidney disease, hypertension, obesity, myocardial infarction, heart failure, and stroke), elevated 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 (eg, medications, obesity, malignancy, and alcohol abuse).

See Chapter 93, Gout and Hyperuricemia, authored by Michelle A. Fravel and Michael E. Ernst, for a more detailed discussion of this topic.

CHAPTER 2

Osteoarthritis

- *Osteoarthritis* (OA) is a common, progressive disorder affecting primarily weight-bearing diarthrodial joints, characterized by progressive destruction of articular cartilage, osteophyte formation, pain, limitation of motion, deformity, and disability.

PATHOPHYSIOLOGY

- *Primary* (*idiopathic*) *OA*, the most common type, has no known cause.
- *Secondary OA* is associated with a known cause, such as trauma, metabolic or endocrine disorders, and congenital factors.
- OA usually begins with damage to articular cartilage through injury, excessive joint loading from obesity or other reasons, or joint instability or injury. Damage to cartilage increases activity of chondrocytes in attempt to repair damage, leading to increased synthesis of matrix constituents with cartilage swelling. Normal balance between cartilage breakdown and resynthesis is lost, with increasing destruction and cartilage loss.
- Subchondral bone adjacent to articular cartilage undergoes pathologic changes and releases vasoactive peptides and matrix metalloproteinases. Neovascularization and increased permeability of adjacent cartilage occur, which contribute to cartilage loss and chondrocyte apoptosis.
- Cartilage loss causes joint space narrowing and painful, deformed joints. Remaining cartilage softens and develops fibrillations, followed by further cartilage loss and exposure of underlying bone. New bone formations (osteophytes) at joint margins distant from cartilage destruction are thought to help stabilize affected joints.
- Inflammatory changes can occur in the joint capsule and synovium. Crystals or cartilage shards in synovial fluid may contribute to inflammation. Interleukin-1, prostaglandin E_2, tumor necrosis factor-α, and nitric oxide in synovial fluid may also play a role. Inflammatory changes result in synovial effusions and thickening.
- Pain may result from distention of the synovial capsule by increased joint fluid; microfracture; periosteal irritation; or damage to ligaments, synovium, or the meniscus.

CLINICAL PRESENTATION

- Risk factors include increasing age, obesity, sex, certain occupations and sports activities, history of joint injury or surgery, and genetic predisposition.
- The predominant symptom is deep, aching pain in affected joints. Pain accompanies joint activity and decreases with rest.
- Joints most commonly affected are the distal interphalangeal (DIP) and proximal interphalangeal (PIP) joints of the hand, first carpometacarpal joint, knees, hips, cervical and lumbar spine, and first metatarsophalangeal (MTP) joint of the toe.
- Limitation of motion, stiffness, crepitus, and deformities may occur. Patients with lower extremity involvement may report weakness or instability.
- Upon arising, joint stiffness typically lasts less than 30 minutes and resolves with motion.
- Presence of warm, red, and tender joints suggests inflammatory synovitis.
- Physical examination of affected joints reveals tenderness, crepitus, and possibly enlargement. Heberden and Bouchard nodes are bony enlargements (osteophytes) of the DIP and PIP joints, respectively.

DIAGNOSIS

- Diagnosis is made through patient history, physician examination, radiologic findings, and laboratory testing.

- American College of Rheumatology criteria for classification of OA of the hips, knees, and hands include presence of pain, bony changes on examination, normal erythrocyte sedimentation rate (ESR), and radiographs showing osteophytes or joint space narrowing.
- For hip OA, patient must have hip pain and two of the following: (1) ESR less than 20 mm/h (<5.6 μm/s), (2) radiographic femoral or acetabular osteophytes, and/or (3) radiographic joint space narrowing.
- For knee OA, patient must have knee pain and radiographic osteophytes in addition to one or more of the following: (1) age more than 50 years, (2) morning stiffness lasting 30 minutes or less, (3) crepitus on motion, (4) bony enlargement, (6) bony tenderness, and/or (7) palpable joint warmth.
- ESR may be slightly elevated if inflammation is present. Rheumatoid factor is negative. Analysis of synovial fluid reveals high viscosity and mild leukocytosis (<2000 white blood cells/mm^3 [$<2 \times 10^9$/L]) with predominantly mononuclear cells.

TREATMENT

- Goals of Treatment: (1) educate the patient, family members, and caregivers; (2) relieve pain and stiffness; (3) maintain or improve joint mobility; (4) limit functional impairment; and (5) maintain or improve quality of life.

NONPHARMACOLOGIC THERAPY

- Educate the patient about the disease process and extent, prognosis, and treatment options. Promote dietary counseling, exercise, and weight loss program for overweight patients.
- Physical therapy—with heat or cold treatments and an exercise program—helps maintain range of motion and reduce pain and need for analgesics.
- Assistive and orthotic devices (canes, walkers, braces, heel cups, and insoles) can be used during exercise or daily activities.
- Surgical procedures (eg, osteotomy, arthroplasty, and joint fusion) are indicated for functional disability and/or severe pain unresponsive to conservative therapy.

PHARMACOLOGIC THERAPY (TABLE 2–1)

General Approach

- Drug therapy is targeted at relief of pain. A conservative approach is warranted because OA often occurs in older individuals with other medical conditions.
- Apply an individualized approach (**Figs. 2–1** and **2–2**). Continue appropriate nondrug therapies when initiating drug therapy.

Knee and Hip OA

- **Acetaminophen** is a preferred first-line treatment; it may be less effective than oral nonsteroidal anti-inflammatory drugs (NSAIDs) but has less risk of serious gastrointestinal (GI) and cardiovascular events. Acetaminophen is usually well tolerated, but potentially fatal hepatotoxicity with overdose is well documented. It should be avoided in chronic alcohol users or patients with liver disease.
- **Nonselective NSAIDs** or **cyclooxygenase-2 (COX-2) selective inhibitors** (eg, **celecoxib**) are recommended if a patient fails acetaminophen. Nonselective NSAIDs cause minor GI complaints such as nausea, dyspepsia, anorexia, abdominal pain, flatulence, and diarrhea in 10% to 60% of patients. They may 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, and GI bleeding) include longer duration of NSAID use, higher dosage, age older than 60, past history of peptic ulcer disease of any cause, history of alcohol use, and concomitant use of glucocorticoids or anticoagulants. Options for reducing the GI risk of nonselective NSAIDs include using (1) the lowest dose possible and only when needed, (2) misoprostol four times daily with the NSAID, (3) a PPI or full-dose H_2-receptor antagonist daily with the NSAID.

TABLE 2–1 Medications for the Treatment of Osteoarthritis

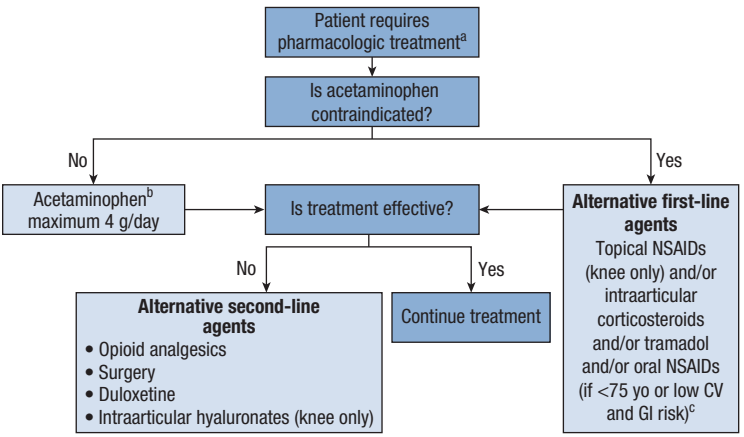
Drug	Starting Dose	Usual Range
Oral analgesics		
Acetaminophen	325–500 mg three times a day	325–650 mg every 4–6 h or 1 g three to four times/day
Tramadol	25 mg in the morning	Titrate dose in 25-mg increments to reach a maintenance dose of 50–100 mg three times a day
Tramadol ER	100 mg daily	Titrate to 200–300 mg daily
Hydrocodone/ acetaminophen	5 mg/325 mg three times daily	2.5–10 mg/325–650 mg three to five times daily
Oxycodone/ acetaminophen	5 mg/325 mg three times daily	2.5–10 mg/325–650 mg three to five times daily
Topical analgesics		
Capsaicin 0.025% or 0.075%		Apply to affected joint three to four times per day
Diclofenac 1% gel		Apply 2 or 4 g per site as prescribed, four times daily
Diclofenac 1.3% patch		Apply one patch twice daily to the site to be treated, as directed
Diclofenac 1.5% solution		Apply 40 drops to the affected knee, applying and rubbing in 10 drops at a time. Repeat for a total of four times daily.
Intra-articular corticosteroids		
Triamcinolone	5–15 mg per joint	10–40 mg per large joint (knee, hip, shoulder)
Methylprednisolone acetate	10–20 mg per joint	20–80 mg per large joint (knee, hip, shoulder)
NSAIDs		
Aspirin (plain, buffered, or enteric-coated)	325 mg three times a day	325–650 mg four times a day
Celecoxib	100 mg daily	100 mg twice daily or 200 mg daily
Diclofenac IR	50 mg twice a day	50–75 mg twice a day
Diclofenac XR	100 mg daily	100–200 mg daily
Diflunisal	250 mg twice a day	500–750 mg twice a day
Etodolac	300 mg twice a day	400–500 mg twice a day
Fenoprofen	400 mg three times a day	400–600 mg three to four times a day
Flurbiprofen	100 mg twice a day	200–300 mg/day in two to four divided doses
Ibuprofen	200 mg three times a day	1200–3200 mg/day in three to four divided doses

(*continued*)

TABLE 2–1 Medications for the Treatment of Osteoarthritis *(Continued)*

Drug	Starting Dose	Usual Range
Indomethacin	25 mg twice a day	Titrate dose by 25–50 mg/day until pain controlled or maximum dose of 50 mg three times a day
Indomethacin SR	75 mg SR once daily	Can titrate to 75 mg SR twice daily if needed
Ketoprofen	50 mg three times a day	50–75 mg three to four times a day
Meclofenamate	50 mg three times a day	50–100 mg three to four times a day
Mefenamic acid	250 mg three times a day	250 mg four times a day
Meloxicam	7.5 mg daily	15 mg daily
Nabumetone	500 mg daily	500–1000 mg one to two times a day
Naproxen	250 mg twice a day	500 mg twice a day
Naproxen sodium	220 mg twice a day	220–550 mg twice a day
Naproxen sodium CR	750–1000 mg once daily	500–1500 mg once daily
Oxaprozin	600 mg daily	600–1200 mg daily
Piroxicam	10 mg daily	20 mg daily
Salsalate	500 mg twice a day	500–1000 mg two to three times a day

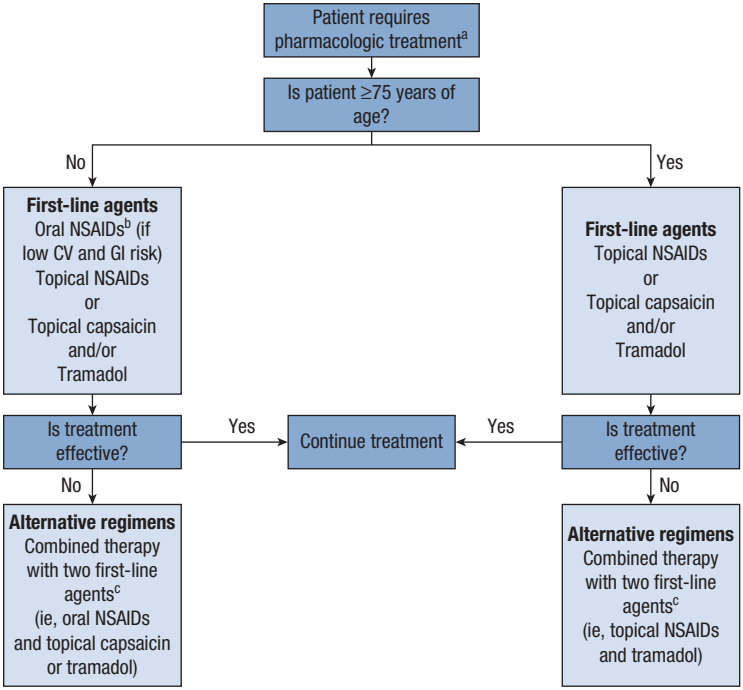
(CR, controlled-release; ER, extended-release; IR, immediate-release; SR, sustained-release; XR, extended-release.)



[a]Selection of a medication should consider patient-specific characteristics.
[b]The patient must be counseled regarding all acetaminophen-containing products.
[c]When used for chronic management of OA, consider addition of a proton-pump inhibitor.

(CV, cardiovascular; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug.)

FIGURE 2–1. Treatment recommendations for hip and knee osteoarthritis.



[a]Selection of a medication should consider patient-specific characteristics.
[b]When used for chronic management of OA, consider addition of a proton-pump inhibitor.
[c]Should not combine topical NSAIDs and oral NSAIDs.

(CV, cardiovascular; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug.)

FIGURE 2–2. Treatment recommendations for hand osteoarthritis.

- COX-2 inhibitors pose less risk for adverse GI events than nonselective NSAIDs, but this advantage may not be sustained beyond 6 months and is substantially reduced for patients taking aspirin. Both nonselective and selective NSAIDs are associated with an increased risk for cardiovascular events (hypertension, stroke, myocardial infarction, and death).
- 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. Avoid NSAIDs in late pregnancy because of risk of premature closure of the ductus arteriosus. The most potentially serious drug interactions include use of NSAIDs with lithium, warfarin, oral hypoglycemics, methotrexate, antihypertensives, angiotensin-converting enzyme inhibitors, β-blockers, and diuretics.
- **Topical NSAIDs** are recommended for knee OA if acetaminophen fails, and they are preferred over oral NSAIDs in patients older than 75 years. Topical NSAIDs provide similar pain relief with fewer adverse GI events than oral NSAIDs but may be associated with adverse events at the application site (eg, dry skin, pruritus, and rash). Patients using topical products should avoid oral NSAIDs to minimize the potential for additive side effects.

- **Intra-articular (IA) corticosteroid injections** are recommended for both hip and knee OA when analgesia with acetaminophen or NSAIDs is suboptimal. They can provide excellent pain relief, particularly when joint effusion is present. Injections can be given with concomitant oral analgesics for additional pain control. After aseptic aspiration of the effusion and corticosteroid injection, initial pain relief may occur within 24 to 72 hours, with peak relief occurring after 7 to 10 days and lasting for 4 to 8 weeks. Local adverse effects can include infection, osteonecrosis, tendon rupture, and skin atrophy at the injection site. Do not administer injections more frequently than once every 3 months to minimize systemic adverse effects. Systemic corticosteroid therapy is not recommended in OA, given lack of proven benefit and well-known adverse effects with long-term use.
- **Tramadol** is recommended for hip and knee OA in patients who have failed scheduled full-dose acetaminophen and topical NSAIDs, who are not appropriate candidates for oral NSAIDs, and who are not able to receive IA corticosteroids. Tramadol can be added to partially effective acetaminophen or oral NSAID therapy. Tramadol is associated with opioid-like adverse effects such as nausea, vomiting, dizziness, constipation, headache, and somnolence. However, tramadol is not associated with life-threatening GI bleeding, cardiovascular events, or renal failure. The most serious adverse event is seizures. Tramadol is classified as a Schedule IV controlled substance due to its potential for dependence, addiction, and diversion. There is increased risk of serotonin syndrome when tramadol is used with other serotonergic medications, including duloxetine.
- **Opioids** should be considered in patients not responding adequately to nonpharmacologic and first-line pharmacologic therapies. Patients who are at high surgical risk and cannot undergo joint arthroplasty are also candidates for opioid therapy. Opioid analgesics should be used in the lowest effective dose and the smallest quantity needed. Combinations of opioids and sedating medications should be avoided whenever possible. Patients should be informed on how to use, store, and dispose of opioid medications. Sustained-release compounds usually offer better pain control throughout the day. Common adverse effects include nausea, somnolence, constipation, dry mouth, and dizziness. Opioid dependence, addiction, tolerance, hyperalgesia, and issues surrounding drug diversion may be associated with long-term treatment.
- **Duloxetine** can be used as adjunctive treatment in patients with partial response to first-line analgesics (acetaminophen, oral NSAIDs). It may be a preferred second-line medication in patients with both neuropathic and musculoskeletal OA pain. Pain reduction occurs after about 4 weeks of therapy. Duloxetine may cause nausea, dry mouth, constipation, anorexia, fatigue, somnolence, and dizziness. Serious rare events include Stevens-Johnson syndrome and liver failure. Concomitant use with other medications that increase serotonin concentration (including tramadol) increases risk of serotonin syndrome.
- **IA hyaluronic acid** (sodium hyaluronate) is not routinely recommended because injections have shown limited benefit for knee OA and have not been shown to benefit hip OA. Injections are usually well tolerated, but acute joint swelling, effusion, stiffness, and local skin reactions (eg, rash, ecchymoses, or pruritus) have been reported. Intra-articular preparations and regimens for OA knee pain include:

  ✓ **Cross-linked hyaluronate 30 mg/3 mL** (Gel-One) single injection
  ✓ **Hyaluronan 30 mg/2 mL** (Orthovisc) once weekly for three injections
  ✓ **Hyaluronan 88 mg/4 mL** (Monovisc) single injection
  ✓ **Hylan polymers 16 mg/2 mL** (Synvisc) once weekly for three injections
  ✓ **Hylan polymers 48 mg/6 mL** (Synvisc-One) single injection
  ✓ **Sodium hyaluronate 20 mg/2 mL** (Hyalgan) once weekly for five injections
  ✓ **Sodium hyaluronate 20 mg/2 mL** (Euflexxa) once weekly for three injections
  ✓ **Sodium hyaluronate 25 mg/2.5 mL** (Supartz FX) once weekly for five injections
  ✓ **Sodium hyaluronate 25 mg/2.5 mL** (GenVisc 850) once weekly for five injections

- **Glucosamine and/or chondroitin** and **topical rubefacients** (eg, **methyl salicylate, trolamine salicylate)** lack uniform efficacy for hip and knee pain and are not preferred treatment options. Glucosamine adverse effects are mild and include flatulence, bloating, and abdominal cramps; do not use in patients with shellfish allergies. The most common adverse effect of chondroitin is nausea.

Hand OA

- **Topical NSAIDs** are a first-line option for hand OA. Diclofenac has efficacy similar to oral ibuprofen and oral diclofenac with fewer adverse GI events, albeit with some local application site events.
- **Oral NSAIDs** are an alternative first-line treatment for patients who cannot tolerate the local skin reactions or who received inadequate relief from topical NSAIDs.
- **Capsaicin cream** is an alternative first-line treatment and demonstrates modest improvement in pain scores. It is a reasonable option for patients unable to take oral NSAIDs. Capsaicin must be used regularly to be effective, and it may require up to 2 weeks to take effect. Adverse effects are primarily local with one third of patients experiencing burning, stinging, and/or erythema that usually subsides with repeated application. Warn patients not to get cream in their eyes or mouth and to wash hands after application. Application of the cream, gel, or lotion is recommended four times daily, but twice-daily application may enhance long-term adherence with adequate pain relief.
- **Tramadol** is an alternative first-line treatment and is a reasonable choice for patients who do not respond to topical therapy and are not candidates for oral NSAIDs because of high GI, cardiovascular, or renal risks. Tramadol may also be used in combination with partially effective acetaminophen, topical therapy, or oral NSAIDs.

EVALUATION OF THERAPEUTIC OUTCOMES

- To monitor efficacy, assess baseline pain with a visual analog scale, and assess range of motion for affected joints with flexion, extension, abduction, or adduction.
- Depending on the joint(s) affected, measurement of grip strength and 50-ft walking time can help assess hand and hip/knee OA, respectively.
- Baseline radiographs can document extent of joint involvement and follow disease progression with therapy.
- Other measures include the clinician's global assessment based on 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.
- Ask patients about adverse effects from medications. Monitor for signs of drug-related effects, such as skin rash, headaches, drowsiness, weight gain, or hypertension from NSAIDs.
- Obtain baseline serum creatinine, hematology profile, and serum transaminases with repeat levels at 6- to 12-month intervals to identify specific toxicities to the kidney, liver, GI tract, or bone marrow.

See Chapter 90, Osteoarthritis, authored by Lucinda M. Buys and Sara A. Wiedenfeld, for a more detailed discussion of this topic.

Osteoporosis

CHAPTER 3

- *Osteoporosis* is a bone disorder characterized by low bone density, impaired bone architecture, and compromised bone strength predisposing to fracture.

PATHOPHYSIOLOGY

- Bone loss occurs when resorption exceeds formation, usually from high bone turnover when the number or depth of bone resorption sites greatly exceeds the ability of osteoblasts to form new bone. Accelerated bone turnover can increase the amount of immature bone that is not adequately mineralized.
- Men and women begin to lose bone mass starting in the third or fourth decade because of reduced bone formation. Estrogen deficiency during menopause increases osteoclast activity, increasing bone resorption more than formation. Men are at a lower risk for developing osteoporosis and osteoporotic fractures because of larger bone size, greater peak bone mass, increase in bone width with aging, fewer falls, and shorter life expectancy. Male osteoporosis results from aging or secondary causes.
- Age-related osteoporosis results from hormone, calcium, and vitamin D deficiencies leading to accelerated bone turnover and reduced osteoblast formation.
- Drug-induced osteoporosis may result from systemic corticosteroids, thyroid hormone replacement, antiepileptic drugs (eg, phenytoin and 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 fractures involve vertebrae, proximal femur, and distal radius (wrist or Colles fracture). Vertebral fractures may be asymptomatic or present with moderate to severe back pain that radiates down a leg. Pain usually subsides after 2 to 4 weeks, but residual back pain may persist. Multiple vertebral fractures decrease height and sometimes curve the spine (kyphosis or lordosis).
- Patients with a nonvertebral fracture frequently present with severe pain, swelling, and reduced function and mobility at the fracture site.

DIAGNOSIS

- The World Health Organization (WHO) created the FRAX tool, which uses these risk factors to predict the percent probability of fracture in the next 10 years: age, race/ethnicity, sex, previous fragility fracture, parent history of hip fracture, body mass index, glucocorticoid use, current smoking, alcohol (three or more drinks per day), rheumatoid arthritis, and select secondary causes with femoral neck or total hip bone mineral density (BMD) data optional.
- The Garvan calculator uses four risk factors (age, sex, low-trauma fracture, and falls) with the option to also use BMD. It calculates 5- and 10-year risk estimates of any major osteoporotic and hip fracture. This tool corrects some disadvantages of FRAX because it includes falls and number of previous fractures, but it does not use as many other risk factors.
- Physical examination findings: bone pain, postural changes (ie, kyphosis), and loss of height (>1.5 in [3.8 cm]).
- Laboratory testing: complete blood count, creatinine, blood urea nitrogen, calcium, phosphorus, electrolytes, alkaline phosphatase, albumin, thyroid-stimulating hormone, total testosterone (for men), 25-hydroxyvitamin D, and 24-hour urine concentrations of calcium and phosphorus.

- Measurement of central (hip and spine) BMD with dual-energy x-ray absorptiometry (DXA) is the diagnostic standard. Measurement at peripheral sites (forearm, heel, and finger) with DXA or quantitative ultrasonography is used only for screening and for determining need for further testing.
- A T-score compares the patient's 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.
- Diagnosis of osteoporosis is based on low-trauma fracture or femoral neck, total hip, and/or spine DXA using WHO T-score thresholds. Normal bone mass is T-score above −1, low bone mass (osteopenia) is T-score between −1 and −2.4, and osteoporosis is T-score at or below −2.5.

TREATMENT

- Goals of Treatment: The primary goal of osteoporosis care is prevention. Optimizing peak bone mass when young reduces the future incidence of osteoporosis. After low bone mass or osteoporosis develops, the objective is to stabilize or improve bone mass and strength and prevent fractures. Goals in patients with osteoporotic fractures include reducing pain and deformity, improving function, reducing falls and fractures, and improving quality of life.
- **Figure 3–1** provides an osteoporosis management algorithm for postmenopausal women and men ages 50 and older.

NONPHARMACOLOGIC THERAPY

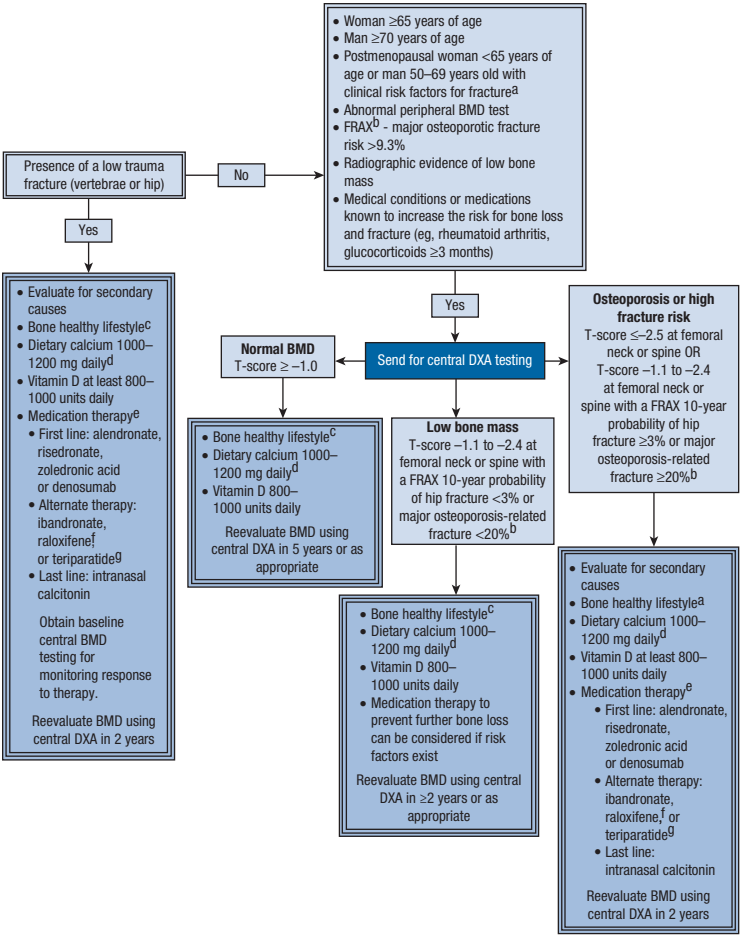
- All individuals should have a balanced diet with adequate intake of **calcium** and **vitamin D** (**Table 3–1**). Achieving daily calcium requirements from calcium-containing foods is preferred.
  - ✓ Consumers can calculate the amount of calcium in a food serving by adding a zero to the percentage of the daily value on food labels. One serving of milk (8 oz or 240 mL) has 30% of the daily value of calcium; this converts to 300 mg of calcium per serving.
  - ✓ To calculate the amount of vitamin D in a food serving, multiply the percent daily value of vitamin D listed on the food label by 4. For example, 20% vitamin D = 80 units.
- Alcohol consumption should not exceed 1 to 2 drinks per day for women and 2 to 3 drinks per day for men.
- Ideally, caffeine intake should be limited to two or fewer servings per day.
- Smoking cessation helps optimize peak bone mass, minimize bone loss, and ultimately reduce fracture risk.
- Weight-bearing aerobic and strengthening exercises can decrease risk of falls and fractures by improving muscle strength, coordination, balance, and mobility.
- Fall prevention programs that are multifactorial can decrease falls, fractures, other injuries, and nursing home and hospital admissions.
- Vertebroplasty and kyphoplasty involve injection of cement into fractured vertebra(e) for patients with debilitating pain from compression fractures. The procedures may reduce pain for some patients but may also be associated with complications.

PHARMACOLOGIC THERAPY

ANTIRESORPTIVE THERAPY

Calcium Supplementation

- **Calcium** generally maintains or increases BMD, but its effects are less than those of other therapies. Fracture prevention is only documented with concomitant vitamin D therapy. Because the fraction of calcium absorbed decreases with increasing dose, maximum single doses of 600 mg or less of elemental calcium are recommended.



[a]Major clinical risk factors for fracture: current smoker, low body weight or body mass index, history of osteoporosis/low trauma fracture in a first-degree relative, personal history of fracture as an adult (after age 50 years), excessive alcohol intake.
[b]FRAX = World Health Organization fracture risk assessment tool.
[c]Bone-healthy lifestyle includes smoking cessation, limited alcohol intake, well-balanced diet with adequate calcium and vitamin D intakes, weight-bearing/resistance exercises, and fall prevention.
[d]Dietary calcium preferred. If diet is inadequate, supplement as necessary.
[e]Sometimes men with hypogonadism also receive testosterone replacement; sometimes women with menopausal symptoms receive low dose hormone therapy for a short time.
[f]Raloxifene can be a good option in women at high risk for breast cancer.
[g]Teriparatide can be considered a first-line option in patients with a very high risk of fracture (eg, T-score <–3.5 or multiple low trauma fractures) or intolerant to other medications

(BMD, bone mineral density; DXA, dual-energy x-ray absorptiometry.)

FIGURE 3–1. Algorithm for management of osteoporosis in postmenopausal women and men aged 50 and older.

TABLE 3–1 Calcium and Vitamin D Recommended Dietary Allowances and Upper Limits

Group and Ages	Elemental Calcium (mg)	Calcium Upper Limit (mg)	Vitamin D (Units)[a]	Vitamin D Upper Limit (Units)
Infants				
Birth to 6 months	200	1000	400	1000
6–12 months	260	1500	400	1500
Children				
1–3 years	700	2500	600	2500
4–8 years	1000	2500	600	3000
9–18 years	1300	3000	600	4000
Adults				
19–50 years	1000	2500	600[b]	4000
51–70 years (men)	1000	2000	600[b]	4000
51–70 years (women)	1200	2000	600[b]	4000
>70 years	1200	2000	800[b]	4000

[a]Other guidelines recommend intake to achieve a 25(OH) vitamin D concentration of more than 30 ng/mL (mcg/L; > 75 nmol/L), which is higher than the Institute of Medicine goal of more than 20 ng/mL (mcg/L; > 50 nmol/L).
[b]2014 National Osteoporosis Foundation Guidelines recommend 400 to 800 units for adults under 50 years old and 800 to 1000 units for adults 50 years and older.

- **Calcium carbonate** is the salt of choice because it contains the highest concentration of elemental calcium (40%) and is least expensive. It should be ingested with meals to enhance absorption in an acidic environment.
- **Calcium citrate** (21% calcium) has acid-independent absorption and need not be taken with meals. It may have fewer GI side effects (eg, flatulence) than calcium carbonate.
- **Tricalcium phosphate** contains 38% calcium, but calcium-phosphate complexes could limit overall calcium absorption. It might be helpful in patients with hypophosphatemia that cannot be resolved with increased dietary intake.
- Constipation is the most common adverse reaction; treat with increased water intake, dietary fiber (given separately from calcium), and exercise. Calcium carbonate can sometimes cause flatulence or upset stomach. Calcium causes kidney stones rarely.
- Calcium can decrease the oral absorption of some drugs including iron, tetracyclines, quinolones, bisphosphonates, and thyroid supplements.

Vitamin D Supplementation

- **Vitamin D** supplementation maximizes intestinal calcium absorption and BMD; it may also reduce fractures and falls.
- Supplementation is usually provided with daily nonprescription cholecalciferol (vitamin D_3) products. Higher-dose prescription ergocalciferol (vitamin D_2) regimens given weekly, monthly, or quarterly may be used for replacement and maintenance therapy.
- The recommended dietary allowances in **Table 3–1** should be achieved through food and supplementation with a goal to achieve a 25 (OH) vitamin D concentration of 20 to 30 ng/mL (50–75 nmol/L).
- Because the half-life of vitamin D is about 1 month, recheck the vitamin D concentration after about 3 months of therapy.

Bisphosphonates

- Bisphosphonates (**Table 3–2**) inhibit bone resorption and become incorporated into the bones, giving them long biologic half-lives of up to 10 years.
- Of the antiresorptive agents available, bisphosphonates provide some of the higher BMD increases and fracture risk reductions.

TABLE 3–2 Medications Used to Prevent and Treat Osteoporosis

Drug	Brand Name	Dose	Comments
Antiresorptive Medications—Nutritional Supplements			
Calcium	Various	*Adequate daily intake:* IOM: 200–1200 mg/day, varies per age); Supplement dose is difference between required adequate intake and dietary intake. Immediate-release doses should be <500–600 mg.	Recommend food first to achieve goal intake. Available in different salts including carbonate and citrate, absorption of other salts not fully quantified. Different formulations including chewable, liquid, gummy, softgel, drink, and wafer; different combination products. Review package to determine number of units to create a serving size and desired amount of elemental calcium. Give calcium carbonate with meals to improve absorption.
Vitamin D D3 (cholecalciferol) D_2 (ergocalciferol)	Over the counter, Tablets, 400, 1000, and 2000 units Capsule, 400, 1000, 2000, 5000, and 10,000 units Gummies, 300, 500, 1000 units Drops 300, 400, 1000 and 2000 units/mL or drop Solution, 400 and 5000 units/mL Spray 1000 and 5000 units/spray Creams and lotions 500 and 1000 units per ¼ teaspoonful. Prescription, Capsule, 50,000 units Solution, 8000 units/mL	Adequate daily intake: IOM: 400–800 units/day to achieve adequate intake; NOF: 800–1000 units orally daily; If low 25(OH) vitamin D concentrations, malabsorption, or altered metabolism higher doses (>2000 units daily) might be required. *Vitamin D deficiency:* 50,000 units orally once to twice weekly for 8–12 weeks; repeat as needed until therapeutic concentrations.	Vegetarians and vegans need to read label to determine if a plant-based product. Slight advantage of D3 over D2 for increasing serum 25(OH) vitamin D concentrations. For drops, make sure measurement is correct for desired dose. Ability of sprays, lotions, and creams to resolve deficiencies or maintain adequate intakes is unknown.

Antiresorptive Prescription Medications			
Bisphosphonates			
Alendronate	Fosamax Fosamax Plus D Binosto (effervescent tab)	Treatment: 10 mg orally daily or 70 mg orally weekly Prevention: 5 mg orally daily or 35 mg orally weekly	Generic available for weekly tablet product. 70 mg dose is available as a tablet, effervescent tablet, oral liquid or combination tablet with 2800 or 5600 units of vitamin D3. Administered in the morning on an empty stomach with 6–8 ounces of plain water. Do not eat and remain upright for at least 30 minutes following administration. Do not coadminister with any other medication or supplements, including calcium and vitamin D.
Ibandronate	Boniva	Treatment: 150 mg orally monthly, 3 mg intravenous quarterly Prevention: 150 mg orally monthly	Generic available for oral product. Administration instructions same as for alendronate, except must delay eating and remain upright for at least 60 minutes.
Risedronate	Actonel Atelvia (delayed-release)	Treatment and Prevention: 5 mg orally daily, 35 mg orally weekly, 150 mg orally monthly	Generic available for immediate-release product. 35 mg dose is also available as a delayed-release product. Administration instructions same as for alendronate, except delayed-release product is taken immediately following breakfast.
Zoledronic acid	Reclast	Treatment: 5 mg intravenous infusion yearly Prevention: 5 mg intravenous infusion every 2 years	Can premedicate with acetaminophen to decrease infusion reactions. Contraindicated if CrCl <35 mL/min Also marketed under the brand name Zometa (4 mg) for treatment of hypercalcemia and prevention of skeletal-related events from bone metastases from solid tumors with different dosing.

(*continued*)

TABLE 3–2 Medications Used to Prevent and Treat Osteoporosis (*Continued*)

Drug	Brand Name	Dose	Comments
RANK Ligand Inhibitor			
Denosumab	Prolia	Treatment: 60 mg subcutaneously every 6 months	Administered by a healthcare practitioner. Correct hypocalcemia before administration. Also marketed under the brand name Xgeva (70 mg/mL) for treatment of hypercalcemia and prevention of skeletal-related events from bone metastases from solid tumors with different dosing.
Estrogen Agonist/Antagonist and Tissue Selective Estrogen Complex			
Raloxifene	Evista	60 mg daily	Generic available
Bazedoxifene with conjugated equine estrogens (CEE)	Duavee	20 mg plus 0.45 mg CEE daily	For postmenopausal women with an uterus; no progestogen needed. Bazedoxifene monotherapy available in some countries.
Calcitonin			
Calcitonin (salmon)	Fortical	200 units (1 spray) intranasally daily, alternating nares every other day. 100 units subcutaneously daily	Generic available. Refrigerate nasal spray until opened for daily use, then room temperature. Prime with first use.
Formation Medications			
Recombinant human parathyroid hormone (PTH 1–34 units)			
Teriparatide	Forteo	20 mcg subcutaneously daily for up to 2 years	First dose at night. Refrigerate before and after each use. Use new needle with each dose. Inject thigh or stomach. Discard after 28 days or if cloudy.

(IOM, Institute of Medicine; NOF, National Osteoporosis Foundation; NSAID, nonsteroidal anti-inflammatory drug.)

- BMD increases are dose dependent and greatest in the first 12 months of therapy. After discontinuation, the increased BMD is sustained for a prolonged period that varies per bisphosphonate.
- **Alendronate**, **risedronate**, and **IV zoledronic acid** are Food and Drug Administration (FDA) indicated for postmenopausal, male, and glucocorticoid-induced osteoporosis. **IV and oral ibandronate** are indicated only for postmenopausal osteoporosis. Weekly alendronate, weekly and monthly risedronate, and monthly oral and quarterly IV ibandronate therapy produce equivalent BMD changes to their respective daily regimens.
- Bisphosphonates must be administered carefully to optimize clinical benefit and minimize adverse GI effects. Each oral tablet should be taken in the morning with at least 6 oz (180 mL) of plain water (not coffee, juice, mineral water, or milk) at least 30 minutes (60 minutes for oral ibandronate) before consuming any food, supplements, or medications. An exception is delayed-release risedronate, which is administered immediately after breakfast with at least 4 oz (120 mL) of plain water. 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.
- 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.
- The most common bisphosphonate adverse effects include nausea, abdominal pain, and dyspepsia. Esophageal, gastric, or duodenal irritation, perforation, ulceration, or bleeding may occur. The most common adverse effects of IV bisphosphonates include fever, flu-like symptoms, and local injection-site reactions.
- Rare adverse effects include osteonecrosis of the jaw (ONJ) and subtrochanteric femoral (atypical) fractures. ONJ occurs more commonly in patients with cancer receiving higher-dose IV bisphosphonate therapy and other risk factors including glucocorticoid therapy and diabetes mellitus.

Denosumab

- **Denosumab** (Prolia) is a RANK ligand inhibitor that inhibits osteoclast formation and increases osteoclast apoptosis. It is indicated for treatment of osteoporosis in women and men at high risk for fracture. It is also approved to increase bone mass in men receiving androgen-deprivation therapy for nonmetastatic prostate cancer and in women receiving adjuvant aromatase inhibitor therapy for breast cancer who are at high risk for fracture.
- Denosumab is administered as a 60-mg subcutaneous injection in the upper arm, upper thigh, or abdomen once every 6 months.
- Adverse reactions not associated with the injection site include back pain, arthralgia, eczema, cellulitis, and infection. Osteonecrosis of the jaw and atypical femoral shaft fracture occur rarely. Denosumab is contraindicated in patients with hypocalcemia until the condition is corrected.

Mixed Estrogen Agonists/Antagonists and Tissue-Selective Estrogen Complexes

- **Raloxifene** (Evista) is an estrogen agonist on bone receptors but an antagonist at breast receptors, with minimal effects on the uterus. It is approved for prevention and treatment of postmenopausal osteoporosis.
- **Bazedoxifene** is an estrogen agonist/antagonist that is combined with **conjugated equine estrogens** (CEE), making it a tissue-selective estrogen complex (proprietary product DUAVEE). It is approved for prevention of postmenopausal osteoporosis and vasomotor menstrual symptoms.
- Raloxifene and bazedoxifene decrease vertebral but not hip fractures. The drugs increase spine and hip BMD, but to a lesser extent than bisphosphonates. The fracture-prevention effects of bazedoxifene combined with CEE are unknown. After raloxifene discontinuation, the beneficial effect is lost, and bone loss returns to age- or disease-related rates.

- Hot flushes are common with raloxifene but decreased with bazedoxifene/CEE. Raloxifene rarely causes endometrial thickening and bleeding; bazedoxifene decreases these events making progestogen therapy unnecessary when combined with CEE. Leg cramps and muscle spasms are common with these agents. Thromboembolic events are uncommon but can be fatal. Bazedoxifene with CEE has all the contraindications and precautions for estrogens as a class.

Calcitonin

- **Calcitonin** is an endogenous hormone 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 indicated for osteoporosis treatment for women at least 5 years past menopause. An FDA Advisory Committee Panel voted against use for postmenopausal osteoporosis, but it can be used if alternative therapies are not appropriate.
- Only vertebral fractures have been documented to decrease with intranasal calcitonin therapy. Calcitonin does not consistently affect hip BMD. No data exist for men. Intranasal calcitonin may provide some pain relief in patients with acute vertebral fractures. If used for this purpose, calcitonin should be prescribed for short-term (4 weeks) treatment and should not be used in place of other more effective and less expensive analgesics nor should it preclude use of more appropriate osteoporosis therapy.

Hormone Therapies

- Hormone therapies are not recommended solely for osteoporosis but have positive bone effects when used for other indications. Estrogens are FDA-indicated for prevention of osteoporosis in women at significant risk and for whom other osteoporosis medications cannot be used. Estrogens are an option for women in early menopause when positive bone effects are needed in addition to vasomotor symptom reduction.
- Estrogen with or without a progestogen significantly decreases fracture risk and bone loss in women. Oral and transdermal estrogens at equivalent doses and continuous or cyclic regimens have similar BMD effects. Effect on BMD is dose dependent, with some benefit seen with lower estrogen doses. When estrogen therapy is discontinued, bone loss accelerates and fracture protection is lost.

Testosterone

- Testosterone is not FDA indicated for osteoporosis. No fracture data are available, but some data support minor bone loss prevention for testosterone use in men and women.

ANABOLIC THERAPIES

Teriparatide

- **Teriparatide** (Forteo) is a recombinant human product representing the first 34 amino acids in human parathyroid hormone. Teriparatide increases bone formation, bone remodeling rate, and osteoblast number and activity.
- Teriparatide is indicated for postmenopausal women at high risk for fracture, men with idiopathic or hypogonadal osteoporosis at high fracture risk, men or women intolerant to other osteoporosis medications, and patients with glucocorticoid-induced osteoporosis.
- Two years of teriparatide therapy reduces fracture risk in postmenopausal women, but no fracture data are available in men or patients taking corticosteroids. Lumbar spine BMD increases are higher than with other osteoporosis medications. Although wrist BMD is decreased, wrist fractures are not increased. Discontinuation of therapy results in decreased BMD, which can be alleviated with subsequent antiresorptive therapy.
- Transient hypercalcemia rarely occurs. Teriparatide is contraindicated in patients at increased risk for osteosarcoma and should not be used in patients with hypercalcemia, metabolic bone diseases other than osteoporosis, metastatic or skeletal cancers, premenopausal women of childbearing potential, or men who received previous radiation therapy.

GLUCOCORTICOID-INDUCED OSTEOPOROSIS

- Glucocorticoids decrease bone formation through decreased proliferation and differentiation as well as enhanced apoptosis of osteoblasts. They also increase bone resorption, decrease calcium absorption, and increase renal calcium excretion.
- Bone losses are rapid, with up to 12% to 15% loss over the first year, the greatest decrease occurs in the first 6 months of therapy. Bone loss is about 2% to 3% per year after the first year.
- Measure baseline BMD using central DXA for all patients starting on prednisone 5 mg or more daily (or equivalent) for at least 6 months. Consider BMD testing at baseline in patients being started on shorter durations of systemic glucocorticoids if they are at high risk for low bone mass and fractures. Because bone loss can occur rapidly, central DXA can be repeated yearly or more often if needed.
- All patients starting or receiving systemic glucocorticoid therapy (any dose or duration) should practice a bone-healthy lifestyle and ingest 1200 to 1500 mg elemental calcium and 800 to 1200 units of vitamin D daily to achieve therapeutic 25(OH) vitamin D concentrations. Use the lowest possible corticosteroid dose and duration.
- Treatment guidelines divide recommendations for prescription medication use by fracture risk, age, menopause and childbearing status, glucocorticoid dose and duration, and fragility fracture. Alendronate, risedronate, zoledronic acid, and teriparatide are FDA approved for glucocorticoid-induced osteoporosis. Standard osteoporosis therapy doses are used. Raloxifene and denosumab do not have FDA indications but have some clinical data documenting decreased bone loss.

EVALUATION OF THERAPEUTIC OUTCOMES

- To evaluate efficacy, obtain a central DXA BMD measurement 2 years after initiating medication therapy. Central DXAs are repeated every 2 years until BMD is stable, at which time the reassessment interval can be expanded. More frequent monitoring may be warranted in patients with conditions associated with high rates of bone loss (eg, glucocorticoid use).
- Assess medication adherence and tolerance at each visit.
- Ask patients about possible fracture symptoms (eg, bone pain or disability) at each visit. Assessment of fracture, back pain, and height loss can help identify worsening osteoporosis.

See Chapter 92, Osteoporosis and Osteomalacia, authored by Mary Beth O'Connell and Jill S. Borchert, for a more detailed discussion of this topic.

Rheumatoid Arthritis

CHAPTER 4

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

PATHOPHYSIOLOGY

- RA results from dysregulation of humoral and cell-mediated immunity. Most patients produce antibodies called *rheumatoid factors*; these seropositive patients tend to have a more aggressive course than seronegative patients.
- Immunoglobulins (Ig) 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. 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-α (TNF-α), interleukin-1 (IL-1), and IL-6 are proinflammatory cytokines important in initiation and continuance of inflammation.
- Activated T cells produce cytotoxins and cytokines, which stimulate further activation of inflammatory processes and attract cells to areas of inflammation. Macrophages are stimulated to release prostaglandins and cytotoxins. T-cell activation requires both stimulation by proinflammatory cytokines as well as interaction between cell surface receptors, called *costimulation*. One such costimulation interaction is between CD28 and CD80/86.
- Activated B cells produce plasma cells, which form antibodies that, in combination with the complement system, result in accumulation of polymorphonuclear leukocytes. These leukocytes release cytotoxins, oxygen-free radicals, and hydroxyl radicals that promote damage to synovium and bone.
- Signaling molecules are important for activating and maintaining inflammation. Janus kinase (JAK) is a tyrosine kinase responsible for regulating leukocyte maturation and activation. JAK also has effects on production of cytokines and immunoglobulins.
- Vasoactive substances (histamine, kinins, and prostaglandins) are released at sites of inflammation, increasing blood flow and vascular permeability. This causes edema, warmth, erythema, and pain, and facilitates granulocyte passage from blood vessels to sites of inflammation.
- Chronic inflammation of 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. End results may be loss of joint space and joint motion, bony fusion (ankylosis), joint subluxation, tendon contractures, and chronic deformity.

CLINICAL PRESENTATION

- Nonspecific prodromal symptoms developing over weeks to months include fatigue, weakness, low-grade fever, anorexia, and joint pain. Stiffness and myalgias may precede development of synovitis.
- Joint involvement tends to be symmetric and affect small joints of the hands, wrists, and feet; 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 apparent only by palpation. Tissue is soft, spongy, warm, and may be erythematous. Joint deformities may involve subluxations of wrists, metacarpophalangeal joints, and proximal interphalangeal joints (swan neck deformity, boutonnière deformity, and 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 College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) revised criteria for diagnosis of RA in 2010. These criteria are intended for patients early in their disease and emphasize early manifestations. Late manifestations (bone erosions, subcutaneous nodules) are no longer in the diagnostic criteria. Patients with synovitis of at least one joint and no other explanation for the finding are candidates for assessment. The criteria use a scoring system with a combined score of 6 or more out of 10 indicating that the patient has definite RA.
- Laboratory abnormalities include normocytic, normochromic anemia; thrombocytosis or thrombocytopenia; leukopenia; elevated erythrocyte sedimentation rate and C-reactive protein; positive rheumatoid factor (60%–70% of patients); positive anticitrullinated protein antibody (ACPA) (50%–85% of patients); and positive antinuclear antibodies (25% of patients).
- Aspirated synovial fluid may reveal turbidity, leukocytosis, reduced viscosity, and normal or low glucose relative to serum concentrations.
- Early radiologic findings include soft tissue swelling and osteoporosis near the joint (periarticular osteoporosis). Erosions 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.

TREATMENT

- Goals of Treatment: The ultimate goal is to induce complete remission or low disease activity (referred to as "treat to target"). Additional goals are to control disease activity and joint pain, maintain ability to function in daily activities, slow destructive joint changes, and delay disability.

NONPHARMACOLOGIC THERAPY

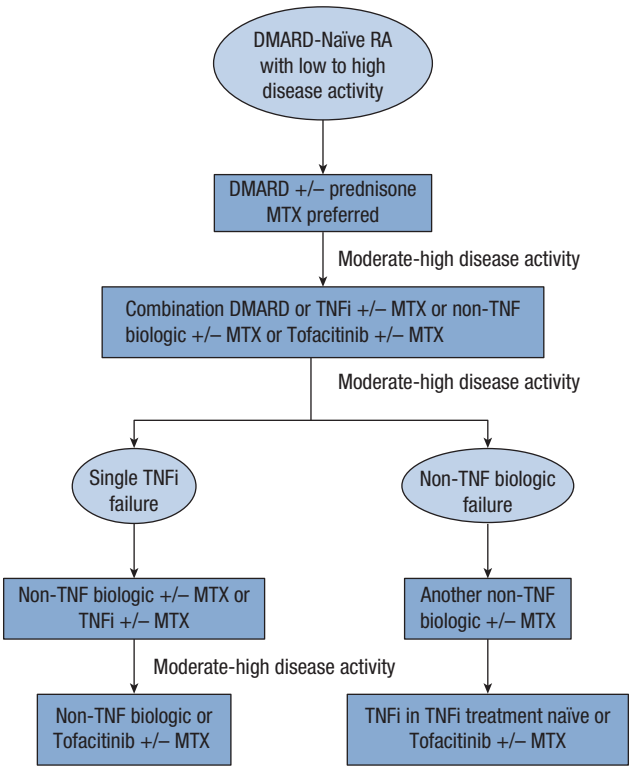
- Adequate rest, weight reduction if obese, occupational therapy, physical therapy, and use of assistive devices may improve symptoms and help maintain joint function.
- Patients with severe disease may benefit from surgical procedures such as tenosynovectomy, tendon repair, and joint replacements.
-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

PHARMACOLOGIC THERAPY

General Approach

- Pharmacologic agents that reduce RA symptoms and impede radiographic joint damage are categorized as either conventional synthetic disease-modifying antirheumatic drugs (referred to simply as *DMARDs*) or biologic disease-modifying drugs (referred to as *biologics*). The 2015 American College of Rheumatology (ACR) guideline considers **tofacitinib** (a synthetic small molecule) separately.
- Common DMARDs include **methotrexate (MTX)**, **leflunomide**, **hydroxychloroquine**, and **sulfasalazine**.
- Biologics include the anti-TNF agents **etanercept**, **infliximab**, **adalimumab**, **certolizumab**, and **golimumab**; the costimulation modulator **abatacept**; the IL-6 receptor antagonist **tocilizumab**; and **rituximab**, which depletes peripheral B cells. Biologics have proven effective for patients failing treatment with DMARDs.

- Agents used infrequently because of less efficacy and/or greater toxicity include **anakinra** (IL-1 receptor antagonist), **azathioprine**, **penicillamine**, **gold** (including **auranofin**), **minocycline**, **cyclosporine**, and **cyclophosphamide**.
- DMARDs should be started as soon as possible after disease onset because they slow disease progression, and early treatment results in more favorable outcomes, including lower mortality rates.
- Treatment guidelines recommend initial therapy with a DMARD, preferably methotrexate (MTX), for most patients regardless of clinical disease activity (**Fig. 4–1**). Patients with moderate-to-severe disease activity despite initial treatment should be switched to another DMARD, a biologic agent, or combination DMARD therapy. Recommended DMARD combinations include (1) MTX plus hydroxychloroquine, (2) MTX plus leflunomide, (3) MTX plus sulfasalazine, and (4) MTX plus hydroxychloroquine plus sulfasalazine.
- The ACR guideline endorses use of anti-TNF biologics as monotherapy or in combination with DMARDs in patients with moderate-to-high disease activity after treatment with DMARD therapy. Use of biologics in combination with MTX is more effective than biologic monotherapy. Dual biologic use is not recommended due to the risk of infection associated with immunosuppression.



(DMARD, disease-modifying antirheumatic drug; MTX, methotrexate; TNFi, tumor necrosis factor inhibitor.)

FIGURE 4–1. Algorithm for treatment of rheumatoid arthritis (RA) in early (<6 months) or established (≥ 6 months) RA with low to high disease activity.

- Nonsteroidal anti-inflammatory 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 to take effect. However, NSAIDs have no impact on disease progression, and corticosteroids have potential for long-term complications.
- Because DMARDs, biologics, and some corticosteroid regimens result in immunosuppression, vaccination status should be assessed and updated before therapy is started to protect against vaccine-preventable infections. Some biologics are contraindicated in the setting of hepatitis C or malignancies because of immunosuppression.
- Patients who achieve remission can be considered for tapering but not discontinuation of all RA therapies. Patients who achieve low disease activity should continue RA treatment.
- See **Tables 4–1** and **4–2** for usual dosages and monitoring parameters for DMARDs, biologics, and NSAIDs used in RA.

Nonsteroidal Anti-inflammatory Drugs

- NSAIDs inhibit prostaglandin synthesis, which is only a small portion of the inflammatory cascade. They possess both analgesic and anti-inflammatory properties and reduce stiffness, but they do not slow disease progression or prevent bony erosions or joint deformity. Common NSAID dosage regimens are shown in **Table 4–3**.

Corticosteroids

- Corticosteroids have anti-inflammatory and immunosuppressive properties but should not be used as monotherapy. They interfere with antigen presentation to T lymphocytes, inhibit prostaglandin and leukotriene synthesis, and inhibit neutrophil and monocyte superoxide radical generation.
- Oral corticosteroids (eg, **prednisone**, **methylprednisolone**) can be used to control pain and synovitis while DMARDs are taking effect ("bridging therapy").
- 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 long-term adverse effects. Use the lowest dose that controls symptoms. Alternate-day dosing of low-dose oral corticosteroids is usually ineffective in RA.
- High-dose oral or IV bursts may be used for several days to suppress disease flares. After symptoms are controlled, taper the drug to the lowest effective dose.
- The intramuscular route is preferable in nonadherent patients. Depot forms (**triamcinolone acetonide**, **triamcinolone hexacetonide**, and **methylprednisolone acetate**) provide 2 to 6 weeks of symptomatic control. Onset of effect may be delayed for several days. The depot effect provides a physiologic taper, avoiding hypothalamic-pituitary axis suppression.
- Intra-articular injections of depot forms may be useful when only a few joints are involved. If effective, injections may be repeated every 3 months. Do not inject any one joint more than two or three times per year.
- Adverse effects of systemic glucocorticoids limit long-term use. Consider dosage tapering and eventual discontinuation at some point during chronic therapy.

DMARDs

Methotrexate

- **Methotrexate (MTX)** inhibits cytokine production and purine biosynthesis, and may stimulate adenosine release, all of which may lead to anti-inflammatory properties. Onset is as early as 2 to 3 weeks, and 45% to 67% of patients remained on it in studies ranging from 5 to 7 years.
- Concomitant folic acid may reduce some adverse effects without loss of efficacy. Monitor liver injury tests 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.

TABLE 4–1 Usual Doses and Monitoring Parameters for Antirheumatic Drugs

Drug	Usual Dose	Initial Monitoring Tests	Maintenance Monitoring Tests
NSAIDs	See **Table 4–3**	S_{cr} or BUN, CBC every 2–4 weeks after starting therapy for 1–2 months; salicylates: serum salicylate levels if therapeutic dose and no response	Same as initial plus stool guaiac every 6–12 months
Corticosteroids	Oral, IV, IM, IA, and soft-tissue injections: variable	Glucose; blood pressure every 3–6 months	Same as initial
Methotrexate	Oral or IM: 7.5–15 mg/week	Baseline: AST, ALT, ALK-P, albumin, total bilirubin, hepatitis B and C studies, CBC with platelets, S_{cr}	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, 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	Baseline: CBC with platelets, then every week for 1 month	Same as initial every 1–2 months
Minocycline	Oral: 100–200 mg daily	None	None
Etanercept	50 mg SC once weekly or 25 mg twice weekly	Tuberculin skin test	None
Infliximab	3 mg/kg IV at 0, 2, 6 weeks, then every 8 weeks	Tuberculin skin test	None
Adalimumab	40 mg SC every 2 weeks	Tuberculin skin test	None
Certolizumab	400 mg (2 doses of 200 mg) SC at weeks 0, 2, 4, then 200 mg every 2 weeks	Tuberculin skin test	None
Golimumab	50 mg SC once monthly	Tuberculin skin test	None
Rituximab	1000-mg IV infusion given twice, 2 weeks apart	Tuberculin skin test	None

Abatacept	IV infusion: 30-min weight-based infusion: <60 kg = 500 mg; 60–100 kg = 750 mg; >100 kg = 1000 mg SC injection: 125 mg SC within 24 h after a single IV infusion loading dose of ~10 mg/kg; then 125 mg SC every 7 days	Tuberculin skin test	None
Tocilizumab	4–8 mg/kg IV every 4 weeks	Tuberculin skin test, AST/ALT, CBC with platelets, lipids	AST/ALT, CBC with platelets, lipids every 4–8 weeks
Anakinra	100 mg SC daily	Tuberculin skin test, neutrophil count	Neutrophil count monthly for 3 months, then quarterly for up to 1 year
Tofacitinib	Oral: 5 mg twice daily Oral XR: 11 mg once daily	Tuberculin skin test, CBC with differential; hepatic enzymes, lipids	CBC with differential after 4–8 weeks and every 3 months thereafter
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
Cyclosporine	Oral: 2.5 mg/kg/day divided twice daily	S_{cr}, blood pressure every month	Same as initial

(ALK-P, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CBC, complete blood cell count; IA, intra-articular; IM, intramuscular; IV, intravenous; NSAIDs, nonsteroidal anti-inflammatory drugs; SC, subcutaneous; Scr, serum creatinine; UA, urinalysis.)

TABLE 4–2 Clinical Monitoring of Drug Therapy in Rheumatoid Arthritis

Drug	Toxicities Requiring Monitoring	Symptoms to Inquire About[a]
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[b]	Blood pressure, polyuria, polydipsia, edema, shortness of breath, visual changes, weight gain, headaches, broken bones or bone pain
Methotrexate	GI (stomatitis, nausea/vomiting, diarrhea), myelosuppression (thrombocytopenia, leukopenia), hepatic (elevated enzymes, rarely cirrhosis), pulmonary (fibrosis, pneumonitis), rash	Symptoms of myelosuppression, shortness of breath, nausea/vomiting, lymph node swelling, coughing, mouth sores, diarrhea, jaundice
Leflunomide	Hepatotoxicity, myelosuppression, GI distress, alopecia	Nausea/vomiting, gastritis, diarrhea, hair loss, jaundice
Hydroxychloroquine	GI (nausea/vomiting, diarrhea), ocular (benign corneal deposits, blurred vision, scotomas, night blindness, preretinopathy), dermatologic (rash, alopecia, pigmentation), neurologic (headache, vertigo, insomnia)	Visual changes, including a decrease in night or peripheral vision, rash, diarrhea
Sulfasalazine	GI (anorexia, nausea/vomiting, diarrhea), dermatologic (rash, urticaria), myelosuppression (leukopenia, rarely agranulocytosis), elevated hepatic enzymes	Symptoms of myelosuppression, photosensitivity, rash, nausea/vomiting
Etanercept, adalimumab, certolizumab, golimumab, tocilizumab, anakinra	Local injection site reactions, infection	Symptoms of infection
Infliximab, rituximab, abatacept	Immune reactions, infection	Postinfusion reactions, symptoms of infection
Tofacitinib	Infection, malignancy, GI perforation, upper respiratory tract infection, headache, diarrhea, nasopharyngitis, elevated hepatic enzymes and lipids	Symptoms of infection or myelosuppression, shortness of breath, blood in stool, black stool, dyspepsia
Gold (intramuscular or oral)	Myelosuppression, proteinuria, rash, stomatitis	Symptoms of myelosuppression, edema, rash, oral ulcers, diarrhea
Azathioprine	Myelosuppression, hepatotoxicity, lymphoproliferative disorders	Symptoms of myelosuppression (extreme fatigue, easy bleeding or bruising, infection), jaundice

(*continued*)

TABLE 4–2 Clinical Monitoring of Drug Therapy in Rheumatoid Arthritis (*Continued*)

Drug	Toxicities Requiring Monitoring	Symptoms to Inquire About[a]
Penicillamine	Myelosuppression, proteinuria, stomatitis, rash, dysgeusia	Symptoms of myelosuppression, edema, rash, diarrhea, altered taste perception, oral ulcers
Cyclophosphamide	Alopecia, infertility, GI distress, hemorrhagic cystitis, myelosuppression, nephrotoxicity, cardiotoxicity	Nausea/vomiting, gastritis, diarrhea, hair loss, urination difficulties, chest pain, rash, respiratory difficulties
Cyclosporine	Hepatotoxicity, nephrotoxicity, hypertension, headache, malignancy, infections, GI distress	Nausea/vomiting, diarrhea, symptoms of infection, symptoms of elevated blood pressure

(GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs.)
[a]Altered immune function increases infection, which should be considered particularly in patients taking azathioprine, methotrexate, corticosteroids, or other drugs that may produce myelosuppression.
[b]Osteoporosis is not likely to manifest early in treatment, but all patients should be taking appropriate steps to prevent bone loss.

- MTX is contraindicated in pregnant and nursing women, chronic liver disease, immunodeficiency, pleural or peritoneal effusions, leukopenia, thrombocytopenia, preexisting blood disorders, and creatinine clearance of less than 40 mL/min (0.67 mL/s).

Leflunomide

- **Leflunomide** (Arava) inhibits pyrimidine synthesis, which reduces lymphocyte proliferation and modulation of inflammation. Efficacy for RA is similar to that of MTX.
- A loading dose of 100 mg/day for 3 days may result in 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, alopecia, or other dose-related toxicity.
- Leflunomide is contraindicated in patients with preexisting liver disease. It is teratogenic and must be avoided during pregnancy.

Hydroxychloroquine

- **Hydroxychloroquine** is often used in mild RA or as an adjuvant in combination DMARD therapy. It lacks the myelosuppressive, hepatic, and renal toxicities seen with some other DMARDs, which simplifies monitoring. 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.
- 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 within 2 months.
- GI symptoms may be minimized by starting with low doses, dividing the dose evenly throughout the day, and taking it with food.

Minocycline

- Minocycline may inhibit metalloproteinases active in damaging articular cartilage. It may be an alternative for patients with mild disease and without features of poor prognosis.

TABLE 4–3 Dosage Regimens for Nonsteroidal Anti-inflammatory Drugs

Drug	Recommended Total Daily Anti-inflammatory Dosage		
	Adult	***Children***	**Dosing Schedule**
Aspirin	2.6–5.2 g	60–100 mg/kg	4 times daily
Celecoxib	200–400 mg	–	Once or twice daily
Diclofenac	150–200 mg	–	3 or 4 times daily; extended release: twice daily
Diflunisal	0.5–1.5 g	–	Twice daily
Etodolac	0.2–1.2 g (max 20 mg/kg)	–	2–4 times daily
Fenoprofen	0.9–3 g	–	4 times daily
Flurbiprofen	200–300 mg	–	2–4 times daily
Ibuprofen	1.2–3.2 g	20–40 mg/kg	3 or 4 times daily
Indomethacin	50–200 mg	2–4 mg/kg (max 200 mg)	2–4 times daily; extended release: once daily
Meclofenamate	200–400 mg	–	3–4 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	–	2–6 times daily
Oxaprozin	0.6–1.8 g (max 26 mg/kg)	–	1–3 times daily
Piroxicam	10–20 mg	–	Once daily
Sulindac	300–400 mg	–	Twice daily
Tolmetin	0.6–1.8 g	15–30 mg/kg	2–4 times daily

Tofacitinib

- **Tofacitinib** (Xeljanz) is a nonbiologic JAK inhibitor indicated for patients with moderate to severe RA who have failed or have intolerance to MTX.
- The recommended dose is 5 mg twice daily (or extended-release 11 mg once daily) as monotherapy or in combination with other DMARDs. It should not be given with biologic agents.
- Labeling includes black-box warnings about serious infections, lymphomas, and other malignancies. Live vaccinations should not be given during treatment. Patients should be tested and treated for latent tuberculosis before starting therapy. Elevated liver enzymes and lipids and gastrointestinal perforations have been reported.

BIOLOGIC AGENTS

- Biologic may be effective when DMARDs fail to achieve adequate responses but are considerably more expensive.
- These agents have no toxicities requiring laboratory monitoring, but they do carry a small increased risk for infection, including tuberculosis. Tuberculin skin testing or interferon gamma release assay (IGRA) blood test should be performed before treatment to detect latent tuberculosis.

- Biologics should be at least temporarily discontinued in patients who develop infections while on therapy until the infection is cured. Live vaccines should not be given to patients taking biologic agents.

TNF-α Inhibitors

- Inhibitors of TNF-α are generally the first biologics used. About 30% of patients eventually discontinue use owing to inadequate efficacy or adverse effects. In such situations, addition of a DMARD may be beneficial if the patient is not already taking one. Choosing an alternative TNF inhibitor may benefit some patients; treatment with rituximab or abatacept may also be effective in patients failing TNF inhibitors.
- Congestive heart failure (HF) is a relative contraindication for anti-TNF agents due to reports of increased cardiac mortality and HF exacerbations. Patients with New York Heart Association class III or IV and an ejection fraction of 50% or less should not use anti-TNF therapy. Discontinue the drugs if HF worsens during treatment.
- Anti-TNF therapy has been reported to induce a multiple sclerosis (MS)–like illness or exacerbate MS in patients with the disease. Discontinue therapy if patients develop neurologic symptoms suggestive of MS.
- TNF inhibitors are associated with increased risk of cancer, especially lymphoproliferative cancers. The drugs contain a black-box warning about increased risk of lymphoproliferative and other cancers in children and adolescents treated with these drugs.
- See Tables 4–1 and 4–2 for dosing and monitoring information.
  - ✓ **Etanercept** (Enbrel) is a fusion protein consisting of two p75-soluble TNF receptors linked to an Fc fragment of human IgG_1. It binds to and inactivates TNF, preventing it from interacting with the cell-surface TNF receptors and thereby activating cells. Clinical trials using etanercept in patients who failed DMARDs demonstrated responses in 60% to 75% of patients. It slows erosive disease progression more than oral MTX in patients with inadequate response to MTX monotherapy.
  - ✓ **Infliximab** (Remicade) is a chimeric anti-TNF antibody fused to a human constant-region IgG_1. It binds to TNF and prevents its interaction with TNF receptors on inflammatory cells. To prevent formation of an antibody response to this foreign protein, MTX must be given orally in doses used to treat RA for as long as the patient continues infliximab. In clinical trials, the combination of infliximab and MTX halted progression of joint damage and was superior to MTX monotherapy. 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_1 antibody to TNF-α that is less antigenic than infliximab. It has response rates similar to other TNF inhibitors.
  - ✓ **Golimumab** (Simponi) is a human antibody to TNF-α with activity and precautions similar to other TNF-α inhibitors.
  - ✓ **Certolizumab** (Cimzia) is a humanized antibody specific for TNF-α with precautions and side effects similar to other TNF-α inhibitors.

Abatacept

- **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.

Rituximab

- **Rituximab** (Rituxan) is a monoclonal chimeric antibody consisting of 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 who failed MTX or TNF inhibitors. Give methylprednisolone 100 mg 30 minutes prior to rituximab to reduce 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 optimal therapeutic outcomes.

Tocilizumab

- **Tocilizumab** (Actemra) is a humanized monoclonal antibody that attaches to IL-6 receptors, preventing the cytokine from interacting with IL-6 receptors. It is approved for adults with moderately to severely active RA who have failed to respond to one or more DMARDs. It is used as either monotherapy or in combination with MTX or another DMARD.

Anakinra

- **Anakinra** (Kineret) is an IL-1 receptor antagonist; it is less effective than other biologics and is not included in the current ACR treatment recommendations. However, select patients with refractory disease may benefit. It can be used alone or in combination with any of the other DMARDs except TNF-α inhibitors.

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 assessing response to therapy but is essential for detecting and preventing adverse drug effects (see **Table 4–2**).
- Ask patients about the presence of symptoms that may be related to adverse drug effects (see **Table 4–3**).

See Chapter 91, Rheumatoid Arthritis, authored by Kimberly Wahl and Arthur A. Schuna, for a detailed discussion of this topic.

CHAPTER 5

Acute Coronary Syndromes

- *Acute coronary syndrome* (ACS) includes all syndromes compatible with acute myocardial ischemia resulting from imbalance between myocardial oxygen demand and supply.
- ACS is classified according to electrocardiographic (ECG) changes into: (1) ST-segment-elevation myocardial infarction (STEMI) or (2) non–ST-segment-elevation ACS (NSTE-ACS), which includes non–ST-segment-elevation MI (NSTEMI) and unstable angina (UA).

PATHOPHYSIOLOGY

- Endothelial dysfunction, inflammation, and formation of fatty streaks contribute to development of atherosclerotic coronary artery plaques.
- With rupture of an atherosclerotic plaque, exposure of collagen and tissue factor induces platelet adhesion and activation, promoting release of adenosine diphosphate (ADP) and thromboxane A_2 from platelets, leading to vasoconstriction and platelet activation. A change in the conformation of the glycoprotein IIb/IIIa surface receptors of platelets occurs that cross-links platelets to each other through fibrinogen bridges.
- 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 leads to formation of a fibrin clot composed of fibrin strands, cross-linked platelets, and trapped red blood cells.
- Subtypes of MI are based on etiology:
  - ✓ Type 1: Rupture, fissure, or erosion of an atherosclerotic plaque (90% of cases);
  - ✓ Type 2: Reduced myocardial oxygen supply or increased demand in the absence of a coronary artery process;
  - ✓ Type 3: MI resulting in death without the possibility of measuring biomarkers;
  - ✓ Type 4: MI associated with percutaneous coronary intervention (PCI; Type 4a) or stent thrombosis (Type 4b); and
  - ✓ Type 5: MI associated with coronary artery bypass graft (CABG) surgery.
- Ventricular remodeling after MI is characterized by left ventricular (LV) dilation and reduced pumping function, leading to heart failure (HF).
- Complications of MI include cardiogenic shock, HF, valvular dysfunction, arrhythmias, pericarditis, stroke secondary to LV thrombus embolization, venous thromboembolism, LV free-wall or septal rupture, aneurysm formation, and ventricular and atrial tachyarrhythmias.

CLINICAL PRESENTATION

- The predominant symptom is midline anterior chest pain (usually at rest), severe new-onset angina, or increasing angina that lasts at least 20 minutes. Discomfort may radiate to the shoulder, down the left arm, to the back, or to the jaw. Accompanying symptoms may include nausea, vomiting, diaphoresis, and shortness of breath.
- No specific features indicate ACS on physical examination. However, patients with ACS may present with signs of acute decompensated HF or arrhythmias.

DIAGNOSIS

- Obtain 12-lead ECG within 10 minutes of presentation. Key findings indicating myocardial ischemia or MI are STE, ST-segment depression, and T-wave inversion. Appearance of a new left bundle-branch block with 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 coronary artery disease (CAD) should be assessed.
- Diagnosis of MI is confirmed with detection of rise and/or fall of cardiac biomarkers (mainly troponin T or I) with at least one value above the 99th percentile of the upper reference limit and at least one of the following: (1) symptoms of ischemia; (2) new significant ST-segment–T-wave changes or new left bundle-branch block; (3) pathological Q waves; or (4) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. Typically, a blood sample is obtained once in the emergency department, then 3 to 6 hours after symptom onset.
- Patient symptoms, past medical history, ECG, and biomarkers are used to stratify patients into low, medium, or high risk of death, MI, or likelihood of failing pharmacotherapy and needing urgent coronary angiography and PCI.

TREATMENT

- Goals of Treatment: Short-term goals 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 death and other complications, (3) prevention of coronary artery reocclusion, (4) relief of ischemic chest discomfort, and (5) resolution of ST-segment and T-wave changes on ECG. Long-term goals include control of cardiovascular (CV) risk factors, prevention of additional CV events, and improvement in quality of life.

GENERAL APPROACH

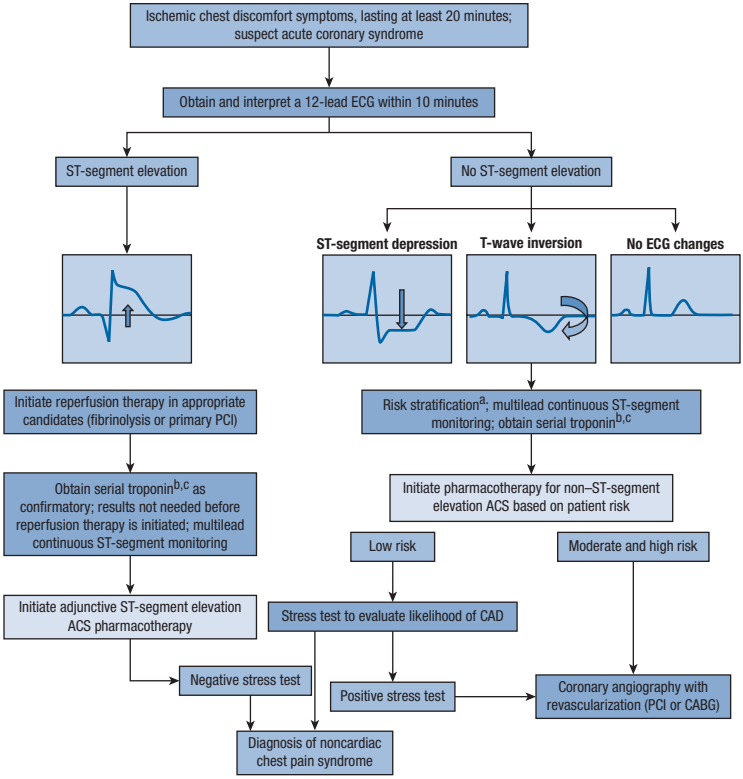
- General measures include hospital admission, oxygen if saturation is low, continuous multilead ST-segment monitoring for arrhythmias and ischemia, frequent measurement of vital signs, bed rest for 12 hours in hemodynamically stable patients, use of stool softeners to avoid Valsalva maneuver, and pain relief.
- Assess kidney function (serum creatinine, creatinine clearance) to identify patients who may need dosing adjustments and those at high risk of morbidity and mortality.
- Obtain complete blood cell count (CBC) and coagulation tests (aPTT, INR) because most patients will receive antithrombotic therapy.
- Fasting lipid panel is optional.
- Triage and treat patients according to their risk category (**Fig. 5–1**).
- Patients with STEMI are at high risk of death, so initiate immediate efforts to reestablish coronary perfusion and adjunctive pharmacotherapy.

NONPHARMACOLOGIC THERAPY

- For patients with STEMI presenting within 12 hours of symptom onset, early reperfusion with primary PCI of the infarct artery within 90 minutes of first medical contact is the reperfusion treatment of choice.
- For patients with NSTE-ACS, practice guidelines recommend an early (within 24 hours) invasive strategy with left heart catheterization, coronary angiography, and revascularization with either PCI or CABG surgery as early treatment for high-risk patients; such an approach may also be considered for patients not at high risk.

EARLY PHARMACOTHERAPY FOR STEMI (FIG. 5–2)

- In addition to reperfusion therapy, all patients with STEMI and without contraindications should receive within the first day of hospitalization and preferably in the emergency department: (1) intranasal oxygen (if oxygen saturation is low), (2) sublingual (SL) nitroglycerin (NTG), (3) aspirin, (4) a $P2Y_{12}$ platelet inhibitor, and (5) anticoagulation with bivalirudin, unfractionated heparin (UFH), enoxaparin, or fondaparinux (depending on reperfusion strategy).



[a]As described in textbook Table 17–1.
[b]"Positive": Above the myocardial infarction decision limit.
[c]"Negative": Below the myocardial infarction decision limit.

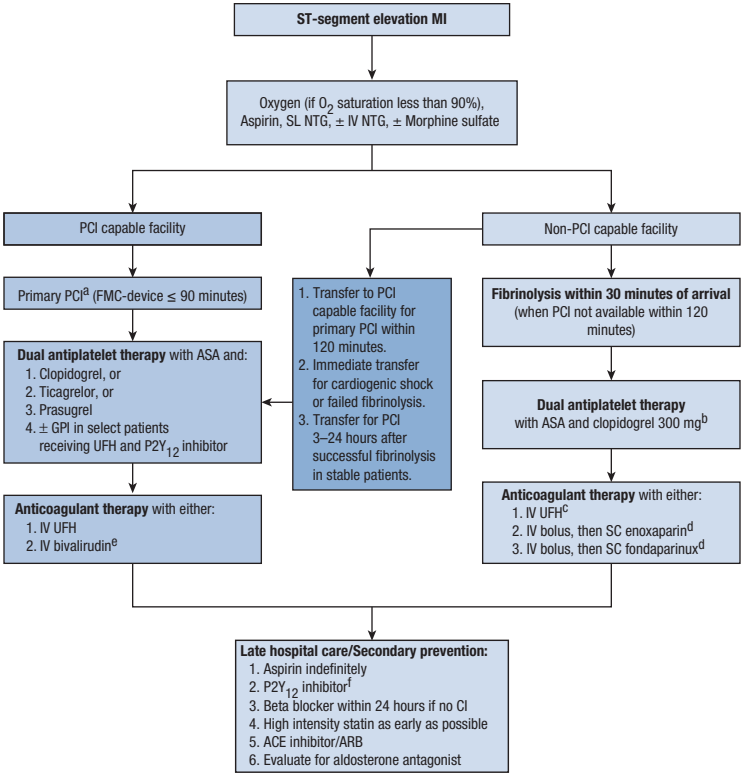
(ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CAD, coronary artery disease; ECG, electrocardiogram; PCI, percutaneous coronary intervention.)

FIGURE 5–1. Evaluation of the acute coronary syndrome patient. (Modified from Rogers KC, de Denus S, Finks SW. Acute Coronary Syndromes. In: Chisholm-Burns MA, Schwinghammer TL, Wells BG, et al, eds. *Pharmacotherapy: Principles and Practice*. 4th ed. New York: McGraw-Hill Companies; 2016:111-136.)

- A glycoprotein IIb/IIIa receptor inhibitor (GPI) may be administered with UFH to patients undergoing primary PCI.
- Intravenous NTG may be given to select patients.
- β-Blockers are reasonable at the time of presentation for patients with hypertension and ongoing ischemia but without cardiogenic shock or other contraindications.
- Morphine may be given for refractory angina as an analgesic and venodilator to lower preload, but its use should be limited.
- An angiotensin-converting enzyme (ACE) inhibitor is recommended within 24 hours in patients who have either anterior wall MI or LV ejection fraction (LVEF) of 40% or less and no contraindications.

Fibrinolytic Therapy

- A fibrinolytic agent is indicated in patients with STEMI who present within 12 hours of the onset of chest discomfort to a hospital not capable of primary PCI and have at least



[a]Options after coronary angiography also include medical management alone or CABG surgery.
[b]Clopidogrel preferred $P2Y_{12}$ inhibitor when fibrinolytic therapy is utilized. No loading dose recommended if age older than 75 years.
[c]Given for up to 48 hours or until revascularization.
[d]Given for the duration of hospitalization, up to 8 days or until revascularization.
[e]If pretreated with UFH, stop UFH infusion for 30 minutes prior to administration of bivalirudin (bolus plus infusion).
[f]In patients with STEMI receiving a fibrinolytic or who do not receive reperfusion therapy, administer clopidogrel for at least 14 days and ideally up to 1 year.

(ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ASA, aspirin; CI, contraindication; FMC, first medical contact; GPI, glycoprotein IIb/IIIa inhibitor; IV, intravenous; MI, myocardial infarction; NTG, nitroglycerin; PCI, percutaneous coronary intervention; SC, subcutaneous; SL, sublingual; UFH, unfractionated heparin.)

FIGURE 5–2. Initial pharmacotherapy for ST-segment elevation myocardial infarction. (Reproduced with permission from Rogers KC, de Denus S, Finks SW. Acute Coronary Syndromes. In: Chisholm-Burns MA, et al, eds. *Pharmacotherapy: Principles and Practice*. 4th ed. New York: McGraw-Hill; 2016:111-136.)

a 1-mm STE in two or more contiguous ECG leads, have no absolute contraindications to fibrinolytic therapy and cannot be transferred and undergo primary PCI within 120 minutes of medical contact. Fibrinolytic use between 12 and 24 hours after symptom onset should be limited to patients with ongoing ischemia.

- It is not necessary to obtain the troponin result before initiating fibrinolytic therapy.
- Contraindications to fibrinolytic therapy include: any prior intracranial hemorrhage, known structural cerebrovascular lesion (eg, AV malformation), known intracranial neoplasm, ischemic stroke within 3 months, active bleeding (excluding menses), and significant closed head or facial trauma within 3 months. Primary PCI is preferred in these situations.

- A fibrin-specific agent (alteplase, reteplase, or tenecteplase) is preferred over the non–fibrin-specific agent streptokinase.
- Treat eligible patients 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 intravenous (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 less than 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
- Intracranial hemorrhage (ICH) and major bleeding are the most serious side effects of fibrinolytics. 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

- Administer **aspirin** to all patients without contraindications within 24 hours before or after hospital arrival. It provides additional mortality benefit in patients receiving fibrinolytic therapy.
- Give non–enteric-coated aspirin (which may be chewed for more rapid effect) 162 to 325 mg regardless of the reperfusion strategy being considered. Patients undergoing PCI not previously taking aspirin should receive 325-mg non–enteric-coated aspirin.
- A daily maintenance dose of 75 to 162 mg is recommended thereafter and should be continued indefinitely. Because of increased bleeding risk in patients receiving aspirin plus a $P2Y_{12}$ inhibitor, low-dose aspirin (81 mg daily) is preferred following PCI.
- Discontinue other nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 (COX-2) selective inhibitors at the time of STEMI due to increased risk of death, reinfarction, HF, and myocardial rupture.
- The most frequent side effects of aspirin include dyspepsia and nausea. Inform patients about the risk of GI bleeding.

Platelet $P2Y_{12}$ Inhibitors

- Clopidogrel, prasugrel, and ticagrelor are oral agents that block a subtype of ADP receptor (the $P2Y_{12}$ receptor) on platelets, preventing binding of ADP to the receptor and subsequent expression of platelet GP IIb/IIIa receptors, reducing platelet aggregation. Doses are as follows:
  - ✓ **Clopidogrel:** 300-mg oral loading dose followed by 75 mg orally daily in patients receiving a fibrinolytic or who do not receive reperfusion therapy. Avoid loading dose in patients aged 75 years or more. A 600-mg oral loading dose is recommended before primary PCI, except that 300 mg should be given if within 24 hours of fibrinolytic therapy.
  - ✓ **Prasugrel:** 60-mg oral loading dose followed by 10 mg orally once daily for patients weighing 60 kg (132 lb) or more. Consider 5 mg once daily for patients weighing less than 60 kg.
  - ✓ **Ticagrelor:** 180-mg oral loading dose in patients undergoing PCI, followed by 90 mg orally twice daily.
- **Cangrelor** is an IV drug indicated as an adjunct to PCI to reduce periprocedural MI, repeat revascularization, and stent thrombosis in patients not receiving oral $P2Y_{12}$ inhibitors or planned GPIs. The dose is 30 mcg/kg IV bolus prior to PCI followed by 4 mcg/kg/min infusion for duration of PCI or 2 hours, whichever is longer.

- A $P2Y_{12}$ receptor inhibitor in addition to aspirin is recommended for all patients with STEMI. For patients undergoing primary PCI, clopidogrel, prasugrel, ticagrelor, or IV cangrelor should be given in addition to aspirin to prevent subacute stent thrombosis and longer-term CV events.
- The recommended duration of $P2Y_{12}$ inhibitors for a patient undergoing PCI (either STEMI or NSTE-ACS) is at least 12 months for patients receiving either a bare metal or drug-eluting stent.
- If elective CABG surgery is planned, withhold clopidogrel and ticagrelor for 5 days prior, and prasugrel at least 7 days prior, to reduce risk of postoperative bleeding, unless the need for revascularization outweighs the bleeding risk. The hold time for urgent surgery is 24 hours.
- The most frequent side effects of clopidogrel and prasugrel are nausea, vomiting, and diarrhea, (2%–5% of patients). Clopidogrel hypersensitivity (usually a rash) develops in up to 6% of patients. Thrombotic thrombocytopenic purpura has been reported rarely with clopidogrel. Ticagrelor is associated with nausea (4%), diarrhea (3%), dyspnea (up to 19%), and, rarely, ventricular pauses, and bradyarrhythmias.
- In STEMI patients receiving fibrinolysis, early therapy with clopidogrel 75 mg once daily during hospitalization and up to 28 days reduces mortality and reinfarction without increasing risk of major bleeding. In adults younger than 75 years receiving fibrinolytics, the first dose of clopidogrel can be a 300-mg loading dose.
- For patients with STEMI who do not undergo reperfusion therapy with either primary PCI or fibrinolysis, clopidogrel (added to aspirin) is the preferred $P2Y_{12}$ inhibitor and should be continued for at least 14 days (and up to 1 year). Ticagrelor may also be an option in medically managed patients with ACS not receiving fibrinolytics.

Glycoprotein IIb/IIIa Receptor Inhibitors

- GPIs block the final common pathway of platelet aggregation, namely, cross-linking of platelets by fibrinogen bridges between the GP IIb and IIIa receptors on the platelet surface.
- Abciximab (IV or intracoronary administration), eptifibatide, or tirofiban may be administered in patients with STEMI undergoing primary PCI who are treated with UFH. Do not administer GPIs to patients with STEMI who will not be undergoing PCI.
- **Abciximab:** 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.
- **Eptifibatide:** 180-mcg/kg IV bolus, repeated in 10 minutes, followed by infusion of 2 mcg/kg/min for 18 to 24 hours after PCI.
- **Tirofiban:** 25-mcg/kg IV bolus, then 0.15 mcg/kg/min up to 18 to 24 hours after PCI.
- Routine use of a GPI is not recommended in patients who have received fibrinolytics or in those receiving bivalirudin because of increased bleeding risk.
- Bleeding is the most significant adverse effect of GPIs. Do not use GPIs in patients with a history of hemorrhagic stroke or recent ischemic stroke. Risk of bleeding is increased in patients with chronic kidney disease; reduce the dose of eptifibatide and tirofiban in renal impairment. An immune-mediated thrombocytopenia occurs in approximately 5% of patients with abciximab and fewer than 2% of patients receiving eptifibatide or tirofiban.

Anticoagulants

- Either UFH or bivalirudin is preferred for patients undergoing primary PCI, whereas for fibrinolysis, either UFH, enoxaparin, or fondaparinux may be used.
- **UFH** initial dose for primary PCI is 50 to 70 units/kg IV bolus if a GPI is planned and 70 to 100 units IV bolus if no GPI is planned; give supplemental IV bolus doses to maintain the target activated clotting time. UFH initial dose with fibrinolytics is 60 units IV bolus (maximum 4000 units), followed by constant IV infusion of 12 units/kg/h (maximum 1000 units/h). Titrate to maintain a target activated partial

thromboplastin time (aPTT) of 1.5 to 2 times control (50–70 seconds) for STE-ACS with fibrinolytics. Measure the first aPTT at 3 hours in patients with STE-ACS who are treated with fibrinolytics and at 4 to 6 hours in patients not receiving thrombolytics or undergoing primary PCI. Continue for 48 hours or until the end of PCI.

- **Enoxaparin** dose is 1 mg/kg subcutaneous (SC) every 12 hours (creatinine clearance [Cl_{cr}] ≥30 mL/min) or once every 24 hours if impaired renal function (Cl_{cr} 15–29 mL/min). For patients with STEMI receiving fibrinolytics, enoxaparin 30-mg IV bolus is followed immediately by 1 mg/kg SC every 12 hours if younger than 75 years. In patients 75 years and older, give enoxaparin 0.75 mg/kg SC every 12 hours. Continue enoxaparin throughout hospitalization or up to 8 days.
- **Bivalirudin** dose for PCI in STEMI is 0.75 mg/kg IV bolus, followed by 1.75 mg/kg/h infusion. Discontinue at the end of PCI or continue at 0.25 mg/kg/h if prolonged anticoagulation is necessary.
- **Fondaparinux** dose is 2.5 mg IV bolus followed by 2.5 mg SC once daily starting on hospital day 2.
- For patients undergoing PCI, discontinue anticoagulation immediately after the procedure. In patients receiving an anticoagulant plus a fibrinolytic, continue UFH for a minimum of 48 hours and enoxaparin and fondaparinux for the duration of hospitalization, up to 8 days. In patients who do not undergo reperfusion therapy, anticoagulant therapy may be administered for up to 48 hours for UFH or for the duration of hospitalization for enoxaparin or fondaparinux.

β-Adrenergic Blockers

- Benefits result from blockade of β_1 receptors in the myocardium, which reduces heart rate, myocardial contractility, and BP, thereby decreasing myocardial oxygen demand. Reduced heart rate increases diastolic time, thus improving ventricular filling and coronary artery perfusion.
- β-Blockers reduce risk for recurrent ischemia, infarct size, reinfarction, and ventricular arrhythmias in the hours and days after an MI.
- Because of an early risk of cardiogenic shock in susceptible patients, β-blockers (particularly when given IV) should be limited to patients who present with hypertension or signs of myocardial ischemia and do not have signs or symptoms of acute HF. Patients already taking β-blockers can continue taking them.
- Usual doses of β-blockers, with target resting heart rate of 50 to 60 beats/min:
  - ✓ **Metoprolol:** 5 mg by slow (over 1–2 minutes) IV bolus, repeated every 5 minutes for total initial dose of 15 mg, followed in 1 to 2 hours by 25 to 50 mg orally every 6 hours. If a very conservative regimen is desired, reduce initial doses to 1 to 2 mg. If appropriate, initial IV therapy may be omitted and treatment started with oral dosing.
  - ✓ **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 once daily beginning 1 to 2 hours after the IV dose. The initial IV therapy may be omitted.
- The most serious side effects early in ACS include hypotension, acute HF, bradycardia, and heart block. Initial acute administration of β-blockers is not appropriate for patients presenting with acute HF but may be attempted in most patients before discharge after treatment of acute HF.
- Continue β-blockers for at least 3 years in patients with normal LV function and indefinitely in patients with LV systolic dysfunction and LVEF of 40% or less.

Statins

- Administer a high-intensity statin (**atorvastatin** 80 mg or **rosuvastatin** 40 mg) to all patients prior to PCI (regardless of prior lipid-lowering therapy) to reduce the frequency of periprocedural MI (Type IVa MI) following PCI.

Nitrates

- 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.
- Immediately upon presentation, administer one **SL NTG** tablet (0.4 mg) every 5 minutes for up to three doses to relieve chest pain and myocardial ischemia.
- **Intravenous NTG** is indicated for patients with an ACS who do not have a contraindication and who have persistent ischemic discomfort, HF, or uncontrolled high BP. The usual dose is 5 to 10 mcg/min by continuous infusion, titrated up to 75 to 100 mcg/min until relief of symptoms or limiting side effects (eg, headache or hypotension). Discontinue IV infusion after 24 to 48 hours.
- 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.
- The most significant adverse effects of nitrates include 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.

Calcium Channel Blockers

- After STEMI, calcium channel blockers (CCBs) are used for relief of ischemic symptoms in patients who have contraindications to β-blockers. There is little clinical benefit beyond symptom relief, so avoid CCBs in acute management of ACS unless there is a clear symptomatic need or contraindication to β-blockers.
- A CCB that lowers heart rate (diltiazem or verapamil) is preferred unless the patient has LV systolic dysfunction, bradycardia, or heart block. In those cases, either amlodipine or felodipine is preferred. Avoid nifedipine because it causes reflex sympathetic activation, tachycardia, and worsened myocardial ischemia.
  - ✓ **Diltiazem:** 120 to 360 mg sustained release orally once daily
  - ✓ **Verapamil:** 180 to 480 mg sustained release orally once daily
  - ✓ **Amlodipine:** 5 to 10 mg orally once daily

EARLY PHARMACOTHERAPY FOR NSTE-ACS (FIG. 5–3)

- Early pharmacotherapy for NSTE-ACS is similar to that for STEMI.
- In absence of contraindications, treat all patients in the emergency department with intranasal oxygen (if oxygen saturation is low), SL NTG, aspirin, and an anticoagulant (UFH, enoxaparin, fondaparinux, or bivalirudin).
- High-risk patients should proceed to early angiography and may receive a GPI (optional with either UFH or enoxaparin but should be avoided with bivalirudin).
- Administer a $P2Y_{12}$ inhibitor to all patients; choice and timing depend on the interventional approach selected.
- Give IV β-blockers and IV NTG to select patients.
- Initiate oral β-blockers within the first 24 hours in patients without cardiogenic shock.
- Give morphine to patients with refractory angina, as described previously.
- Never administer fibrinolytic therapy in NSTE-ACS.

Aspirin

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

Anticoagulants

- For patients treated by an early invasive approach with early coronary angiography and PCI, administer **UFH**, **enoxaparin**, **fondaparinux**, or **bivalirudin**.