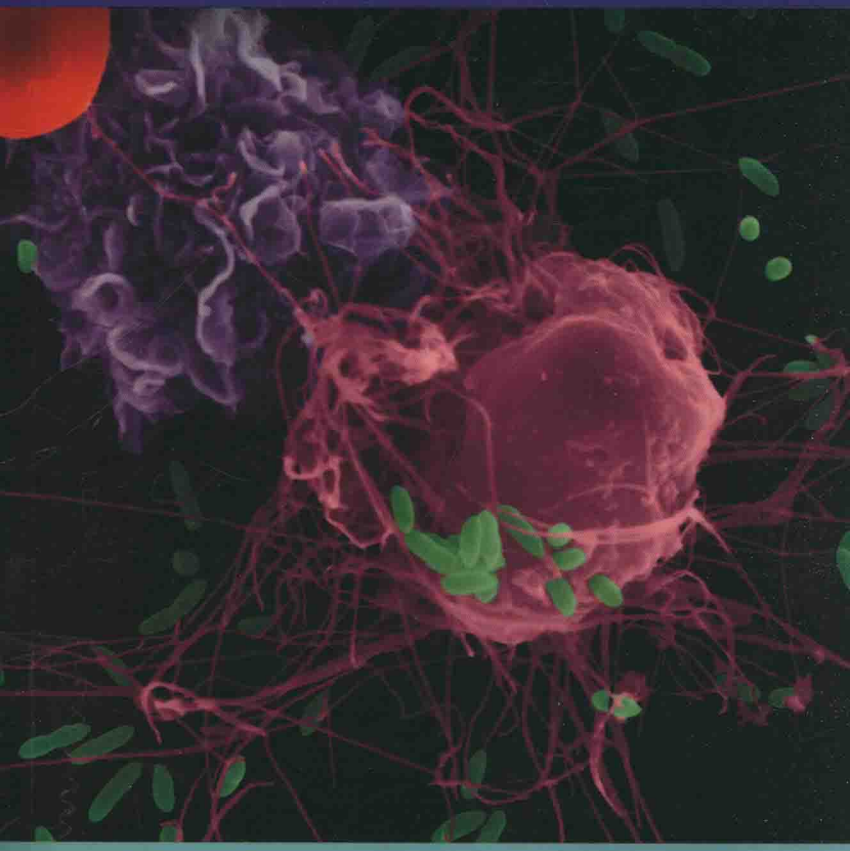
PHARMACOTHERAPY HANDBOOK

NINTH EDITION



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Mc Graw Hill Education

Pharmacotherapy Handbook

Ninth Edition

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Preface

The pocket companion to *Pharmacotherapy: A Pathophysiologic Approach*, 9th edition, is designed to provide practitioners and students with critical information that can be easily used to guide drug therapy decision making in the clinical setting. To ensure brevity and portability, the bulleted format provides the user with essential textual information, key tables and figures, and treatment algorithms. In order to reduce the number of pages and thus allow it to fit more easily in a pocket, the publisher undertook a slight redesign to save space, and the authors made 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, Nutritional Disorders, Oncologic Disorders, Ophthalmic Disorders, Psychiatric Disorders, Renal Disorders, Respiratory Disorders, and Urologic Disorders. Drug-induced conditions associated with allergic and pseudoallergic reactions, hematologic disorders, liver diseases, pulmonary disorders, and kidney disease appear in five tabular appendices. Information on the management of pharmacotherapy in the elderly is also included as an appendix.

Each chapter is organized in a consistent format:

- Disease state definition
- 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*, 9th edition.

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

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

Please provide your comments about this book—Wells et al, *Pharmacotherapy Handbook*, 9th 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 9th edition of *Pharmacotherapy: A Pathophysiologic Approach* served as the basis for this book. The dedication and professionalism of these outstanding practitioners, teachers, and clinical scientists are evident on every page of this work. The authors of the chapters from the 9th edition are acknowledged at the end of each respective handbook chapter.

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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, celery root) are not recommended.

Pharmacologic Therapy

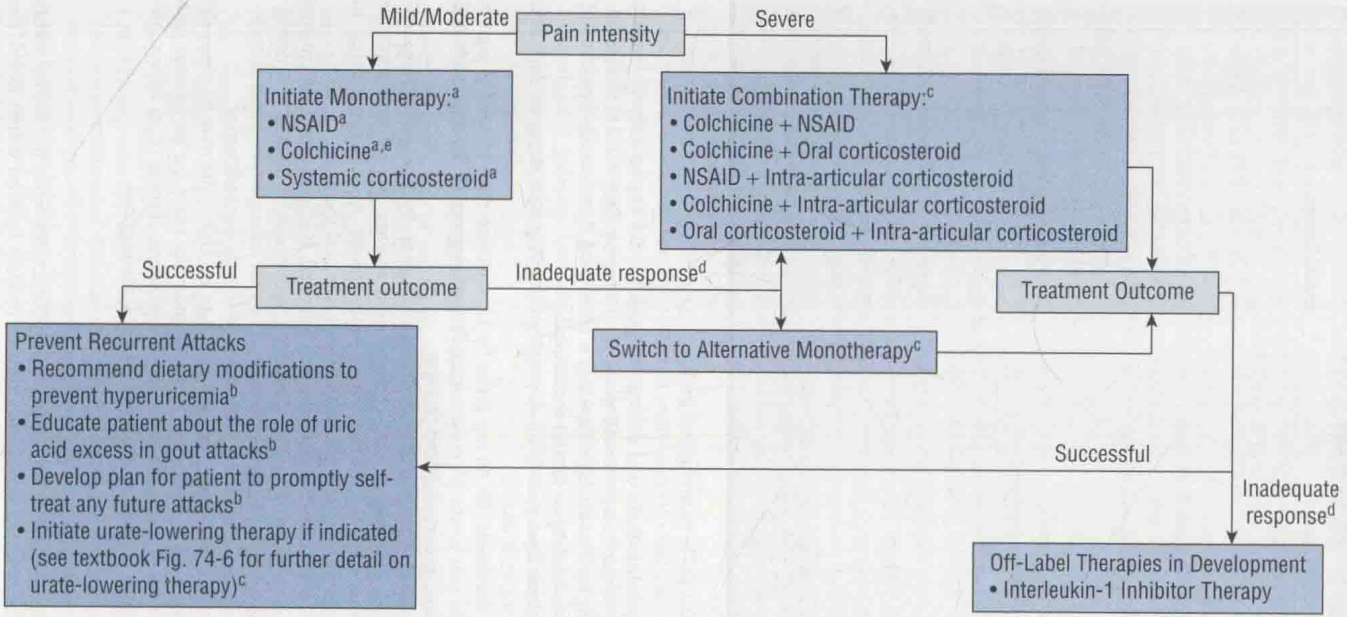
- Most patients may be treated successfully with nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or colchicine.

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, perforation), kidneys (renal papillary necrosis, reduced creatinine clearance [CL_{cr}]), cardiovascular system (increased blood pressure, sodium and fluid retention), and central nervous system (CNS) (impaired cognitive function, headache, dizziness).
- Selective cyclooxygenase-2 (COX-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 h until the attack has subsided	—
Piroxicam	20 mg once daily or 10 mg twice daily	—
Sulindac	150 mg twice daily	150–200 mg twice daily for 7–10 days
Celecoxib	800 mg followed by 400 mg on day 1, 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** 20–40 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, 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

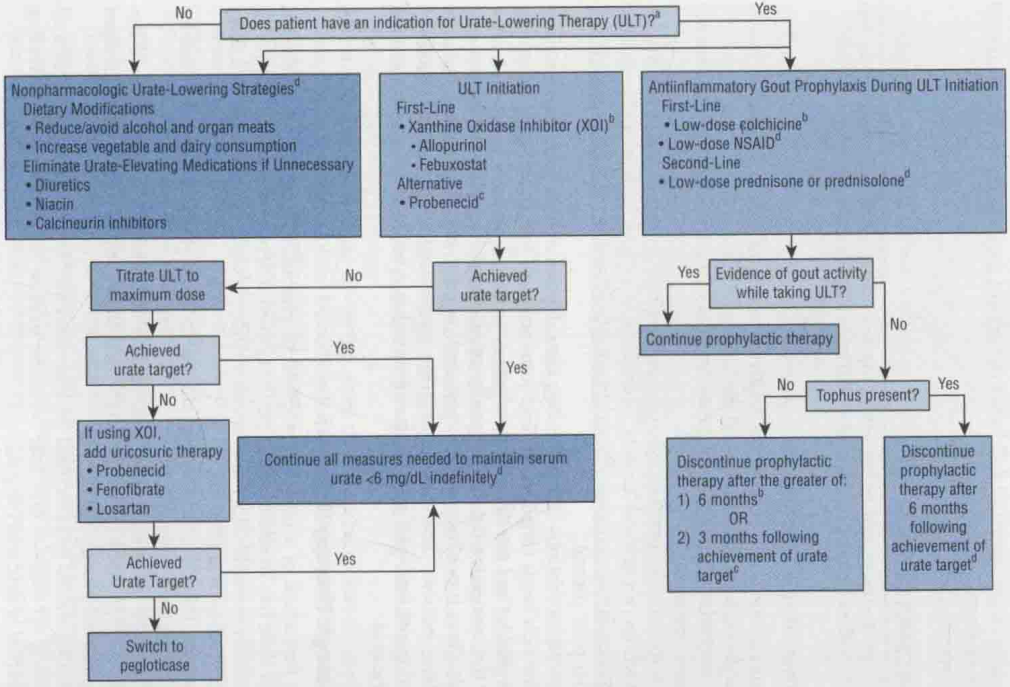
- Recurrent gout attacks can be prevented by maintaining low uric acid levels, but adherence with nonpharmacologic and pharmacologic therapies is poor.

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, or (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 and then gradually titrating every 2 to 5 weeks up to a maximum dose of 800 mg/day until the serum urate target is achieved. Patients with chronic kidney disease (stage 4 or worse) should start at a dose no greater than 50 mg per day. Conservative dosing is intended to avoid allopurinol hypersensitivity syndrome and prevent acute gout attacks common during initiation of urate-lowering therapy.
- 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.

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.

ANTIIFLAMMATORY 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 antiinflammatory therapy should be 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, 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, alcohol abuse).

See Chapter 74, Gout and Hyperuricemia, authored by Michelle A. Fravel, Michael E. Ernst, and Elizabeth C. Clark, for a more detailed discussion of this topic.