Chapter 113: Gout and Hyperuricemia

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CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 1, Gout and Hyperuricemia.

KEY CONCEPTS

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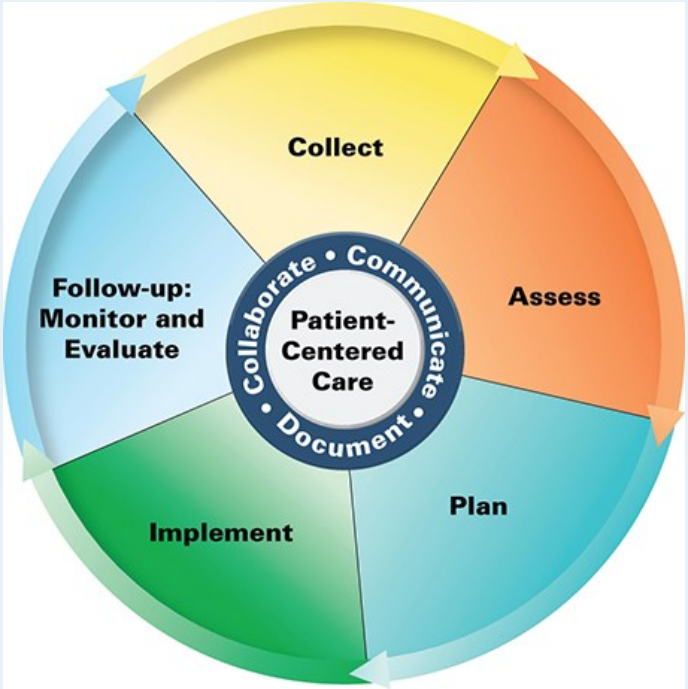
1. Treatment of hyperuricemia in the absence of a history of gout (ie, asymptomatic hyperuricemia) is not recommended.
2. An acute gout flare can be treated effectively with short courses of nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or low-dose colchicine.
3. Initiation of a xanthine oxidase inhibitor may be considered in patients with one of the following indications for urate-lowering therapy (ULT): (a) one or more subcutaneous tophi, (b) evidence of joint damage by radiography, (c) two or more gout flares per year, (d) more than one previous gout flare but infrequent flares (less than two per year), (e) first gout flare in the presence of CKD stage 3 or greater, serum uric acid >9 mg/dL (535 µmol/L), or urolithiasis.
4. The goal serum urate concentration when using ULT is less than 6 mg/dL [357 µmol/L].
5. Allopurinol is the preferred ULT given its preferable safety and efficacy profile.
6. Uricosuric drugs have limited efficacy in patients with impaired kidney function [CKD stage 3 or greater].
7. Pegloticase should be reserved for patients in whom treatment with a xanthine oxidase inhibitor, uricosuric, and other interventions have failed to achieve the serum uric acid target, and who continue to have frequent gout flares (two or more per year) or non-resolving subcutaneous tophi.
8. Low-dose colchicine, NSAID, or oral corticosteroid therapy should be administered to minimize the risk of acute gout attacks during the first 3 to 6 months of initiating ULT; therapy can be extended beyond this time period if gout flares persist.
9. Uric acid nephrolithiasis should be treated with adequate hydration (2 L/day) and 30 to 80 mEq/day (mmol/day) of potassium bicarbonate or potassium citrate.
10. Patients with hyperuricemia or a history of gouty arthritis should be evaluated for commonly associated comorbidities (eg, hypertension, diabetes, CKD, cardiovascular disease), and implement lifestyle modifications and aggressive management of risk factors (eg, weight loss, reduction of alcohol intake, control of blood pressure, glucose, and lipids).

PATIENT CARE PROCESS

Patient Care Process for Gout



Collect

- Patient characteristics (eg, age, sex, ethnicity)
- Patient medical history (see Table 113-1)
- Dietary habits that may lead to increased uric acid concentrations, including alcohol consumption, intake of high purine foods, and products containing high-fructose corn syrup
- Current medications that may contribute to hyperuricemia (see Table 113-2)
- Subjective report of acute gout symptoms
- Objective data
  - Blood pressure (BP), height, weight
  - Labs including uric acid, serum creatinine (SCr)
  - Synovial fluid aspirate

Assess

- Presence of acute gout (see Tables 113-3 and 113-5)
- Presence of hyperuricemia (>6.8 mg/dL [404 µmol/L])
- Indication for urate-lowering therapy (see Table 113-6)
- Optimal therapy given the patient-specific characteristics (see Table 113-9)
- Presence of other cardiovascular risk factors (eg, hypertension, diabetes)

Plan*

- Drug therapy regimen, including a specific agent for the treatment of acute gout: dose, route, frequency, and duration (see Table 113-6)
- Monitoring parameters for efficacy (eg, resolution of pain) and safety (eg, signs and symptoms of adverse effects associated with selected therapy), frequency and timing of follow-up
- Drug therapy regimen including specific agent for treatment of hyperuricemia if indicated: dose, route, frequency, and duration (see Table 113-6)
- Patient education (eg, the purpose of treatment vs prevention, dietary and lifestyle modification, drug-specific information, medication counseling; see Table 113-6)
- Self-monitoring for resolution of gout symptoms and occurrence of medication side effects
- Referrals to other providers when appropriate (eg, rheumatologist, dietitian)

Implement*

- Provide patient education regarding all elements of the treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up (eg, assessment of uric acid, SCr, adherence)

Follow-up: Monitor and Evaluate

- Resolution of gout symptoms (eg, pain)
- Presence of adverse effects (eg, diarrhea [colchicine], agitation [corticosteroids], rash or allopurinol hypersensitivity syndrome [allopurinol])
- Uric acid concentrations [allopurinol, febuxostat] (adjust dose as needed to achieve uric acid <6.0 mg/dL [357 µmol/L])
- Patient adherence to treatment plan using multiple sources of information

**** Collaborate with patients, caregivers, and other healthcare professionals.***

BEYOND THE BOOK

BEYOND THE BOOK

Watch the video entitled “Gout and pseudogout” from Khan Academy (Available at: https://www.youtube.com/watch?app=desktop&v=1O3F-b8FfDY&list=PL5JaZVPnPe4YY4F2P50R14mjAy3gr2giX&index=11). This 10-minute video provides a brief overview of the pathophysiology of gout versus pseudogout. The video is useful to enhance student’s understanding of differences in pathophysiology and how they impact the treatment approach for each disorder, as well as the COLLECT and ASSESS steps in the patient care process.

INTRODUCTION

The term gout describes an inflammatory response to precipitation of monosodium urate (MSU) crystals in both articular and non-articular tissues.[1] The underlying metabolic disorder of gout is an elevated serum uric acid level (hyperuricemia), which is defined physiochemically as a serum that is supersaturated with monosodium urate and begins to exceed the limit of solubility (concentrations above 6.8 mg/dL [404 µmol/L]). Although

hyperuricemia is fundamental to the development of gout, the mere presence of hyperuricemia itself is often an asymptomatic condition.[2,3]

EPIDEMIOLOGY

The prevalence of gout varies widely across the world, with many factors potentially contributing to the variance, including genetics, dietary habits, and socioeconomic factors.[4] Although the prevalence of gout continues to be highest in high-income countries, the overall global burden of gout has increased over the past 50 years, likely due to the aging population and increasing rates of obesity.[4,5] According to the National Health and Nutrition Examination Survey (NHANES), NHANES 2007-2016, the prevalence of gout among adults in the United States is 3.9%, corresponding to an estimated 9.2 million people.[5] Although this represents a 1.2% increase in prevalence compared with NHANES survey data from 1988 to 1994, the rate has remained stable between 2007 and 2016.[6]

Elevated serum urate concentrations are the single most important risk factor for the development of gout, and the relationship between the risk of an attack of acute gouty arthritis and serum urate concentration is linearly correlated. The 5-year cumulative risk of gout for patients with serum urate concentrations less than 7 mg/dL (416 µmol/L) is 0.6%, compared with a risk of 30.5% in those with urate concentrations exceeding 10 mg/dL (595 µmol/L).[2] Sustained elevation of serum urate is virtually essential for the development of gout; however, hyperuricemia does not always lead to gout, and many patients with hyperuricemia remain asymptomatic. For example, even in patients with severe hyperuricemia (>10 mg/dL [595 µmol/L]), fewer than 50% develop gout over a 15-year period.[3]

Gout and hyperuricemia are more common in older adults, with the highest prevalence (8.7%) observed in those 80 years of age and older, compared with just 0.7% in those between the ages of 20 and 39 years.[5] Obesity is associated with a twofold increased risk for gout.[7] Dietary and lifestyle factors linked to obesity have also been independently associated with gout. These include consumption of alcohol, sugary beverages, and red meat, along with a sedentary lifestyle.[8]

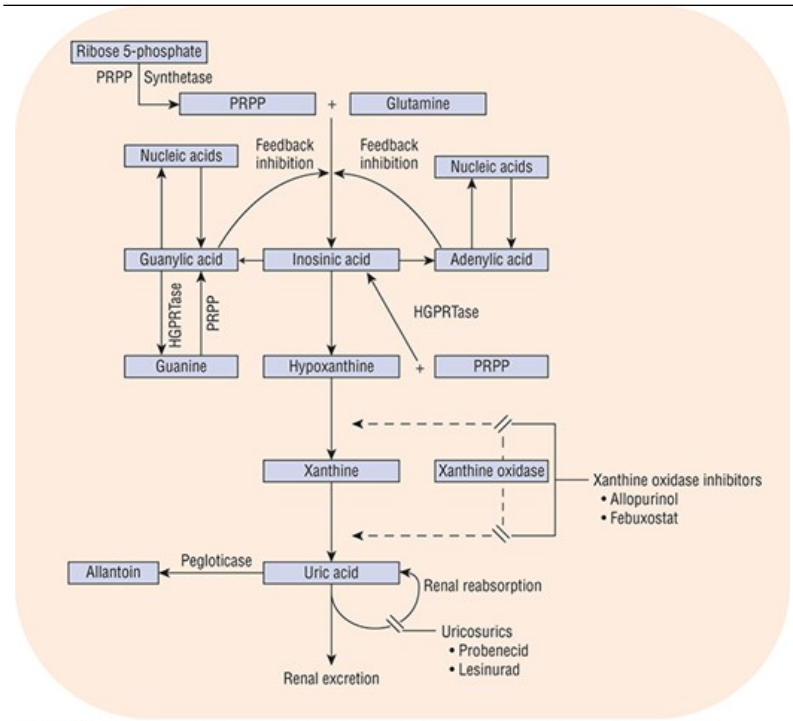
Gout affects men about 2 to 3 times more often than women in the United States; however, the impact of sex on the risk of gout and hyperuricemia varies among different ethnicities, with a risk ratio as high as 8:1 for men compared to women in Korea.[5,9] Serum uric acid concentrations in women approach those of men once menopause has occurred due to loss of estrogen-influenced uricosuria; thus, in older age groups the gap between male and female patients narrows, and approximately half of newly diagnosed cases of gout are observed in women.[10,11] Gout in men younger than 30 years of age, or in premenopausal women, may indicate an inherited enzyme defect or the presence of kidney disease.

ETIOLOGY AND PATHOPHYSIOLOGY

In humans, the production of uric acid is the terminal step in the degradation of purines (Fig. 113-1). Uric acid serves no known physiologic purpose and is a waste product. Normal uric acid concentrations are near the limits of urate solubility, because of the delicate balance that exists between the amount of urate produced and excreted.[1] Humans have higher uric acid concentrations than other mammals because they do not express the enzyme uricase, which converts uric acid into the more soluble allantoin.[1]

FIGURE 113-1

Uric acid pathway and targets of drug action. (HGPRT, hypoxanthine-guanine phosphoribosyltransferase; PRPP, phosphoribosyl pyrophosphate.)



Gout occurs exclusively in humans in whom a miscible pool of uric acid exists. Under normal conditions, the amount of accumulated uric acid is about 1,200 mg in men and about 600 mg in women. The size of the urate pool is increased severalfold in individuals with gout. This excess accumulation may result from either overproduction or underexcretion of uric acid. Several conditions are associated with either decreased kidney clearance or an overproduction of uric acid, leading to hyperuricemia. Table 113-1 lists some of these conditions.

TABLE 113-1

Conditions Associated with Hyperuricemia

Primary gout	Obesity
Diabetic ketoacidosis	Sarcoidosis
Myeloproliferative disorders	Congestive heart failure
Lactic acidosis	Impaired kidney function
Lymphoproliferative disorders	Down syndrome
Starvation	Lead toxicity
Chronic hemolytic anemia	Hyperparathyroidism
Toxemia of pregnancy	Acute alcoholism
Pernicious anemia	Hypoparathyroidism
Glycogen storage disease type 1	Acromegaly
Psoriasis	Hypothyroidism
Hypoxanthine-guanine phosphoribosyltransferase deficiency	Phosphoribosylpyrophosphate synthetase overactivity
Polycythemia vera	Berylliosis
Kidney transplantation	

Overproduction of Uric Acid

The purines from which uric acid is produced originate from three sources: dietary purine, conversion of tissue nucleic acid into purine nucleotides, and de novo synthesis of purine bases. The purines derived from these three sources enter a common metabolic pathway leading to the production of either nucleic acid or uric acid. Under normal circumstances, uric acid may accumulate excessively if production exceeds excretion. The average human produces about 600 to 800 mg of uric acid each day. Dietary purines play an unimportant role in the generation of hyperuricemia in the absence of some derangement in purine metabolism or elimination. However, diet modifications are an important first step for patients who develop symptomatic hyperuricemia.

Several enzyme systems regulate purine metabolism. Abnormalities in these regulatory systems can result in overproduction of uric acid. Uric acid may also be overproduced as a consequence of increased breakdown of tissue nucleic acids and excessive rates of cell turnover, as observed with myeloproliferative and lymphoproliferative disorders, polycythemia vera, psoriasis, and some types of anemias. Cytotoxic medications used to treat these disorders can result in overproduction of uric acid secondary to lysis and breakdown of cellular matter.

Two enzyme abnormalities resulting in an overproduction of uric acid have been well described (Fig. 113-1). The first is an increase in the activity of phosphoribosyl pyrophosphate (PRPP) synthetase, which leads to an increased concentration of PRPP. PRPP is a key determinant of purine synthesis and uric acid production. The second is a deficiency of hypoxanthine-guanine phosphoribosyltransferase (HGPRT). HGPRT is responsible for the conversion of guanine to guanylic acid and hypoxanthine to inosinic acid. These two conversions require PRPP as the co-substrate and are important

reactions involved in the synthesis of nucleic acids. A deficiency in the HGPRT enzyme leads to increased metabolism of guanine and hypoxanthine to uric acid and to more PRPP to interact with glutamine in the first step of the purine pathway.[1] Complete absence of HGPRT results in the childhood Lesch–Nyhan syndrome, characterized by choreoathetosis, spasticity, intellectual disability, and markedly excessive production of uric acid. A partial deficiency of the enzyme may be responsible for marked hyperuricemia in otherwise normal, healthy individuals.

Underexcretion of Uric Acid

Normally, uric acid does not accumulate as long as production is balanced with elimination. About two-thirds of the daily uric acid production is excreted in the urine and the remainder is eliminated through the gastrointestinal (GI) tract after enzymatic degradation by colonic bacteria.

A decline in the urinary excretion of uric acid to a concentration below the rate of production leads to hyperuricemia and an increased miscible pool of sodium urate. Almost all the urate in plasma is freely filtered across the glomerulus. The concentration of uric acid appearing in the urine is determined by multiple renal tubular transport processes in addition to the filtered load. Evidence favors a four-component model including glomerular filtration, tubular reabsorption, tubular secretion, and post-secretory reabsorption.

Approximately 90% of filtered uric acid is reabsorbed in the proximal tubule, probably by both active and passive transport mechanisms. There is a close linkage between proximal tubular sodium reabsorption and uric acid reabsorption, so conditions that enhance sodium reabsorption (eg, dehydration) also lead to increased uric acid reabsorption. The exact site of tubular secretion of uric acid has not been determined; this too involves an active transport process. Post-secretory reabsorption occurs somewhere distal to the secretory site. Table 113-2 lists the drugs that decrease renal clearance of uric acid through modification of filtered load or one of the tubular transport processes.[12] By enhancing renal urate reabsorption, insulin resistance is also associated with gout.

TABLE 113-2

Drugs Capable of Inducing Hyperuricemia and Gout

Diuretics	Ethanol	Ethambutol
Nicotinic acid	Pyrazinamide	Cytotoxic drugs
Salicylates (<2 g/day)	Testosterone	Cyclosporine

CLINICAL PRESENTATION

CLINICAL PRESENTATION: Acute Gouty Arthritis

General

- Gout classically presents as an acute inflammatory monoarthritis. The first metatarsophalangeal joint is often involved ("podagra"), but any joint of the lower extremity can be affected and occasionally gout will present as a monoarthritis of the wrist or finger. The spectrum of gout also includes nephrolithiasis, gouty nephropathy, and aggregated deposits of sodium urate (tophi) in cartilage, tendons, synovial membranes, and elsewhere.

Signs and Symptoms

- Fever, intense pain, erythema, warmth, swelling, and inflammation of involved joints.

Laboratory Tests

- Elevated serum uric acid concentrations; leukocytosis.

Other Diagnostic Tests

- Observation of MSU crystals in synovial fluid or a tophus.
- For patients with long-standing gout, radiographs may show asymmetric swelling within a joint on or subcortical cysts without erosions.

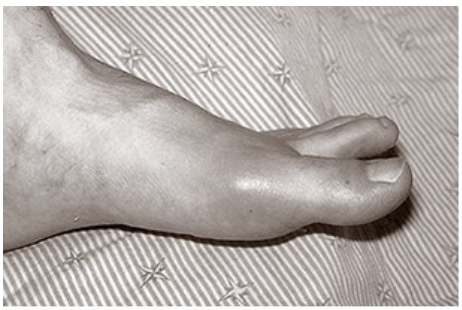
1 Gout is diagnosed clinically by the presence of symptoms, rather than laboratory tests of uric acid. In fact, asymptomatic hyperuricemia discovered incidentally generally requires no therapy because many individuals with hyperuricemia will never experience an attack of gout.[2,3] These patients should still be encouraged to implement lifestyle measures to reduce serum urate concentrations.

Acute Gouty Arthritis

A classic acute attack of gouty arthritis is characterized by rapid and localized onset of excruciating pain, swelling, and inflammation. The attack is typically monoarticular at first, most often affecting the first metatarsophalangeal joint (great toe) and then, in order of frequency, the insteps, ankles, heels, knees, wrists, fingers, and elbows. In one-half of initial attacks, the first metatarsophalangeal joint is affected, a condition commonly referred to as podagra (Fig. 113-2). Up to 90% of patients with gout will experience podagra at some point in the course of their disease.[2]

FIGURE 113-2

Acute gout attack of the first metatarsophalangeal joint. *(Reproduced with permission from Imboden J, Hellmann DB, Stone JH. Current Rheumatology Diagnosis &Treatment. 2nd ed. New York: McGraw Hill, 2004:316.)*



Atypical presentations of gout also occur. For older adults, gout can present as a chronic polyarticular arthritis that can be confused with rheumatoid arthritis or osteoarthritis. Table 113-3 summarizes the different clinical manifestations of gout.

TABLE 113-3

Clinical Manifestations of Gout

Acute gout	Monoarticular arthritis Frequently attacks the first metatarsophalangeal joint ("podagra"), although other joints of the lower extremities are also frequently involved Affected joint is swollen, erythematous, and tender
Interval gout	Asymptomatic period between attacks
Tophaceous gout	Deposits of monosodium urate crystals in soft tissues Complications include soft tissue damage, deformity, joint destruction, and nerve compression syndromes such as carpal tunnel syndrome
Atypical gout	Polyarthritis affecting any joint, upper or lower extremity May be confused with rheumatoid arthritis or osteoarthritis
Gouty nephropathy	Nephrolithiasis Acute and chronic kidney disease

The predilection of acute gout for peripheral joints of the lower extremity is probably related to the low temperature of these joints combined with high intra-articular urate concentration. Synovial effusions are likely to occur transiently in weight-bearing joints during the course of a day with routine activity. At night, water is reabsorbed from the joint space, leaving behind a supersaturated solution of monosodium urate (MSU), which can precipitate attacks of acute arthritis. Attacks generally begin at night with the patient awakened from sleep by excruciating pain.

The development of crystal-induced inflammation involves several chemical mediators causing vasodilation, increased vascular permeability, complement activation, and chemotactic activity for polymorphonuclear leukocytes.[1] Phagocytosis of urate crystals by the leukocytes results in rapid lysis of cells and a discharge of lysosomal and proteolytic enzymes into the cytoplasm. The ensuing inflammatory reaction is associated with intense joint pain, erythema, warmth, and swelling. Fever is common, as is leukocytosis. Untreated attacks may last from 3 to 14 days before spontaneous recovery.

Although acute attacks of gouty arthritis may occur without apparent provocation, several conditions may precipitate an attack. These include stress, trauma, alcohol ingestion, infection, surgery, rapid lowering of serum uric acid by ingestion of uric acid-lowering agents, and ingestion of certain drugs known to elevate serum uric acid concentrations (Table 113-2). The natural course of an acute flare, if left untreated, varies among patients and may resolve after several hours or may take up to 2 weeks. Furthermore, acute flares of gouty arthritis may initially occur infrequently. Over time the duration of untreated attacks may become longer and the interval between attacks may shorten if appropriate measures to correct hyperuricemia are not undertaken. Later in the disease, tophaceous deposits of MSU in the skin or subcutaneous tissues may be found. These tophi are often found on the hands, wrists, elbows, or knees. It takes 10 or more years for tophi to develop.

Diagnostic Evaluation

Table 113-4 lists the differential diagnosis of gout.[10] A definitive diagnosis of gout requires aspiration of synovial fluid from the affected joint and identification of intracellular crystals of monosodium urate monohydrate in synovial fluid leukocytes.[1] Identification of MSU crystals are highly dependent on the experience of the observer. Crystals are needle-shaped, and when examined under polarizing light microscopy, they are strongly negatively birefringent (Fig. 113-3). Crystals can be observed in synovial fluid during asymptomatic periods.[13] If an affected joint is tapped, the resulting

synovial fluid may have white cells and appear purulent. Such findings should always raise the question of infection. If any clinical features of infection are present, such as high fever, elevated white blood cell count, multiple joints affected, or an identified source of infection, proper diagnosis and treatment are critical. Patients with gout can have septic arthritis. Diabetes, alcohol abuse, and advanced age increase the likelihood of septic arthritis.

FIGURE 113-3

Urate crystal ingested by a polymorphonuclear leukocyte in synovial fluid. *(Reproduced with permission from Imboden J, Hellmann DB, Stone JH. Current Rheumatology Diagnosis &Treatment. 2nd ed. New York: McGraw Hill, 2004:317.)*

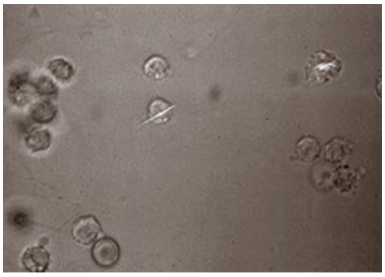


TABLE 113-4

Differential Diagnosis of Gout

1. Pseudogout (calcium pyrophosphate crystal-related arthritis)
2. Rheumatoid disease
3. Psoriatic arthritis
4. Osteoarthritis
5. Septic arthritis/bursitis
6. Cellulitis
7. Osteomyelitis
8. Unrelated hyperuricemia (as in psoriasis, hypertension) when joint pain is not caused by gout

In lieu of obtaining a synovial fluid sample from an affected joint to inspect for urate crystals, a clinical diagnosis may be supported by the following characteristics: monoarticular involvement of a foot or ankle joint, previous similar episode, rapid onset of severe pain and swelling (peak pain intensity in <24 hours), erythema, male sex, presence of cardiovascular disease, and hyperuricemia. However, this approach has limitations, including a failure to recognize atypical gout presentations and the fact that serum uric acid concentrations can be normal or even low during an acute gout attack.[10,14] Radiographs may show evidence of MSU crystal deposits; however, ultrasound may be more helpful in the identification of tophi or a double contour sign at cartilage surfaces, which is specific for articular urate deposits.[15] The presence of chondrocalcinosis on radiographs may indicate pseudogout (see additional discussion on pseudogout below). Table 113-5 summarizes the European League Against Rheumatism (EULAR) evidence-based diagnostic principles for gout.[15]

TABLE 113-5

EULAR Recommendations for Diagnosis of Gout

Recommendations	Level of Evidence	Grade of Evidence
1. Searching for crystals in synovial fluid or tophus aspirates is recommended in every person with suspected gout, because demonstration of MSU crystals allows a definitive diagnosis of gout.	2b	B
2. Gout should be considered in the diagnosis of any acute arthritis in an adult. When synovial fluid analysis is not feasible, a clinical diagnosis of gout is supported by the following suggestive features: monoarticular involvement of a foot (especially the first MTP) or ankle joint; previous similar acute arthritis episodes; rapid onset of severe pain and swelling (at its worst in <24 hours); erythema; male gender; and associated cardiovascular diseases and hyperuricemia. These features are highly suggestive, but not specific, for gout.	2b	B
3. Synovial fluid aspiration and examination for crystals in any patient with undiagnosed inflammatory arthritis is recommended.	3	C
4. The diagnosis of gout should not be made on the presence of hyperuricemia alone.	2a	B
5. When a clinical diagnosis of gout is uncertain and crystal identification is not possible, patients should be investigated with imaging (see #6 below) to search for MSU crystal deposition and features of any alternative diagnosis.	1b	A
6. Plain radiographs are indicated to search for imaging evidence of MSU crystal deposition but have limited value for the diagnosis of gout flare. Ultrasound scanning can be more helpful in establishing a diagnosis in patients with suspected gout flare or chronic gouty arthritis by detection of tophi not evident on clinical examination, or a double contour sign at cartilage surfaces, which is highly specific for urate deposits in joints.	1b	A
7. Risk factors for chronic hyperuricemia should be searched for in every person with gout; these include chronic kidney disease; obesity, medications (including diuretics, low-dose aspirin, cyclosporine, tacrolimus); excess consumption of alcohol (particularly beer and spirits), non-diet sodas, red meat, and shellfish.	1a	A
8. Systematic assessment for the presence of associated comorbidities in people with gout is recommended, including obesity, kidney disease, hypertension, ischemic heart disease, heart failure, diabetes, and dyslipidemia.	1a	A

EULAR, The European League Against Rheumatism; MSU, monosodium urate.

Data from Reference 20.

Level of Evidence: 1A = meta-analysis of cohort studies, 1B = meta-analysis of case-control studies, 2A = cohort studies, 2B = case-control studies, 3 = non-comparative descriptive studies, 4 = expert option.

Grade of Evidence: A = category 1 evidence, B = category 2 evidence or extrapolated recommendations from category 1 evidence, C = category 3 evidence or extrapolated recommendations from category 2 evidence, D = category 4 evidence or extrapolated recommendations from category 3 evidence.

The American College of Rheumatology (ACR) and EULAR have also jointly developed recommendations for the classification of gout to assist in identifying subjects potentially eligible for enrollment into clinical trials of gout treatments.[16] Although it is specifically stated that the recommendations should not be used clinically to diagnose gout, the classification system may be a useful reference when evaluating a patient presenting with symptoms suggestive of gout. The recommendations utilize a point-based system that incorporates clinical, laboratory, and imaging information, which can be used when a patient presents with at least one episode of swelling, pain, or tenderness in a peripheral joint or bursa but has

no evidence of MSU crystals. An online calculator is available at http://goutclassificationcalculator.auckland.ac.nz/.

Other crystal-induced arthropathies that may resemble gout on clinical presentation are caused by calcium hydroxyapatite crystals and calcium pyrophosphate dihydrate crystals (calcium pyrophosphate deposition disease [CPDD] or "pseudogout"), which are associated with calcific periarthritis, tendinitis, and arthritis.[17-19] Pseudogout is relatively common, occurring in up to 7% of all adults in Europe and the United States. Furthermore, its prevalence increases with age, doubling with every decade over 60 years.[17] Identification of calcium pyrophosphate crystals in the synovial fluid of an affected joint in combination with positive radiology findings (eg, chondrocalcinosis, hook-like osteophytes, and axial skeletal involvement) are key methods used for diagnosis of pseudogout. Importantly, calcium pyrophosphate crystals differ from uric acid crystals in that they are positively birefringent when exposed to light microscopy. Furthermore, the clinical picture may provide clues as pseudogout rarely presents with podagra and more commonly affects the knee or wrist. Although initial management of an acute flare of pseudogout is similar to the approach used for treatment of gout, management of chronic pseudogout may require use of hydroxychloroquine, methotrexate, and, ultimately, joint replacement. Recommended therapies used to prevent gout by lowering uric acid will not impact the progression of pseudogout. For these reasons, differentiating between pseudogout and gout, although challenging, is important to insure successful clinical outcomes.

Uric Acid Nephrolithiasis

Clinicians should be suspicious of hyperuricemic states in patients who present with kidney stones, as nephrolithiasis occurs in approximately 14% of patients with gout.[20] The frequency of urolithiasis depends on serum uric acid concentrations, acidity of the urine, and urinary uric acid concentration. Typically, patients with uric acid nephrolithiasis have a urinary pH of less than 6 and frequently less than 5.5. When acidic urine is saturated with uric acid, spontaneous precipitation of stones may occur.

Other factors that predispose individuals to uric acid nephrolithiasis include excessive urinary excretion of uric acid and highly concentrated urine. In addition to pure uric acid stones, hyperuricosuric individuals are at increased risk for mixed uric acid–calcium oxalate stones and pure calcium oxalate stones.

Gouty Nephropathy

There are two types of gouty nephropathy: acute uric acid nephropathy and chronic urate nephropathy.[21] In acute uric acid nephropathy, acute kidney injury occurs as a result of blockage of urine flow secondary to massive precipitation of uric acid crystals in the collecting ducts and ureters. This syndrome is a known complication for patients with myeloproliferative or lymphoproliferative disorders and is a result of massive malignant cell turnover, particularly after initiation of chemotherapy.

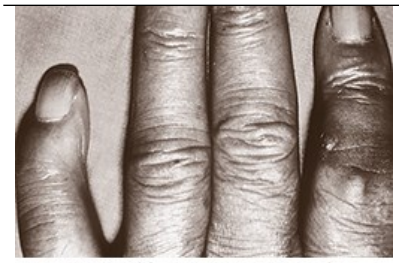
Chronic urate nephropathy is caused by the long-term deposition of urate crystals in the renal parenchyma. Microtophi may form, with a surrounding giant-cell inflammatory reaction. A decrease in the kidneys' ability to concentrate urine and the presence of proteinuria may be the earliest pathophysiologic disturbances. Hypertension and nephrosclerosis are common associated findings. Although kidney failure occurs in a higher percentage of gouty patients than expected, it is not clear if hyperuricemia per se has a harmful effect on the kidneys. The chronic kidney disease seen in individuals with gout may result largely from the coexistence of hypertension, diabetes mellitus, and atherosclerosis.

Tophaceous Gout

Tophi (urate deposits) are uncommon in the general population of patients with gout, but are a late complication of untreated hyperuricemia. The most common sites of tophaceous deposits for patients with recurrent acute gouty arthritis are the base of the fingers, olecranon bursae, ulnar aspect of the forearm, Achilles tendon, knees, wrists, and hands (Fig. 113-4).[21] Eventually, even the hips, shoulders, and spine may be affected. In addition to causing obvious deformities, tophi may damage surrounding soft tissue, cause joint destruction and pain, and can even lead to nerve compression syndromes including carpal tunnel syndrome.

FIGURE 113-4

Tophaceous gout with subcutaneous nodule almost breaking through the skin. *(Reproduced with permission from South-Paul JE, Matheny SC, Lewis EL. Current Diagnosis and Treatment in Family Medicine. New York: McGraw Hill, 2004:275.)*



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

TREATMENT

Desired Outcomes

The goals in the treatment of gout are to terminate the acute attack, prevent recurrent attacks of gouty arthritis, and prevent complications associated with chronic deposition of urate crystals in joints and tissues. These can be accomplished through a combination of pharmacologic and nonpharmacologic methods, including focused patient education efforts. Several organizations, including ACR, EULAR, and the American College of Physicians, have developed guidelines for the management of gout.

The first-ever ACR evidence- and consensus-based guidelines for the management of gout were published in 2012 and were most updated in 2020.[22-24] These guidelines provide specific recommendations for treatment of acute gout attacks, management of hyperuricemia in gout, and anti-inflammatory prophylaxis of acute gout during initiation of ULT. Tables 113-6 and 113-7 summarize dosing and monitoring information for available pharmacotherapy used in management and prevention of gout.

TABLE 113-6

Pharmacotherapy of Acute Gout, Anti-Inflammatory Prophylaxis During Initiation of Urate-Lowering Therapy and Hyperuricemia in Gout[a]

Drug	Brand Name	Initial Dose	Usual Range	Special Population Dose	Other
Acute Gout					
NSAIDs					In general, not recommended in patients with advanced kidney disease as NSAID use may decrease kidney function; use with caution in patients with mild to moderate kidney impairment Use caution in patients taking anticoagulants given increased bleeding risk when used in combination with NSAIDs Use caution in patients with heart failure as NSAIDs can contribute to fluid retention leading to increased risk of heart failure exacerbation
Etodolac	Lodine, various	300 mg twice daily	300-500 mg twice daily		
Fenoprofen	Nalfon, various	400 mg three times daily	400-600 mg three to four times daily		
Ibuprofen	Advil, various	400 mg three times daily	400-800 mg three to four times daily		
Indomethacin	Indocin	50 mg three times daily	50 mg three times daily initially until pain is tolerable then rapidly reduce to complete cessation		

Ketoprofen	Orudis, various	75 mg three times daily or 50 mg four times daily	50-75 mg three to four times daily	Severe kidney impairment (GFR <25 mL/min [0.42 mL/s]): 100 mg maximum daily dose Mildly impaired kidney function: 150 mg maximum daily dose Impaired liver function with serum albumin <3.5 g/dL (35 g/L): 100 mg maximum daily dose	
Naproxen	Naprosyn, various	750 mg followed by 250 mg every 8 hours until the attack has subsided		Not recommended in severe kidney impairment (creatinine clearance <30 mL/min [0.5 mL/s])	
Piroxicam	Feldene	20 mg once daily or divided twice daily			
Sulindac	Clinoril	200 mg twice a day	150-200 mg twice daily for 7-10 days		
Meloxicam	Mobic	5 mg daily	7.5-15 mg daily	Not recommended if creatinine clearance <15 mL/min (0.25 mL/s)	
Celecoxib	Celebrex	800 mg followed by 400 mg on day one then 400 mg twice daily for 1 week			Option for patients with GI contraindications to nonselective NSAIDs; unclear risk-to-benefit ratio now due to cardiovascular concerns
Colchicine	Colcrys	1.2 mg initially, followed		See Table 113-8	Dose adjustment

		by 0.6 mg 1 hour later, with ongoing anti-inflammatory therapy until the flare resolves			recommended when used with selected CYP3A4 and P-glycoprotein inhibitors
Corticosteroids					
Oral		0.5 mg/kg prednisone equivalent daily for 5-10 days followed by discontinuation or 0.5 mg/kg daily for 2-5 days followed by tapering for 7-10 days	30-60 mg prednisone equivalent once daily for 3-5 days, then taper in 5-mg decrements spread over 10-14 days until discontinuation		The use of an oral methylprednisolone dose pack may be considered
Intramuscular		Triamcinolone acetonide 60 mg IM once; methylprednisolone 100 mg IM once	Triamcinolone acetonide 60 mg IM once; methylprednisolone 100-150 mg IM daily for 1-2 days		Administration of intramuscular triamcinolone is to be followed by oral prednisone or prednisolone
Intra-articular	Kenalog	Triamcinolone acetonide 10 mg (large joints), 5 mg (small joints)	Triamcinolone acetonide 10-40 mg (large joints), 5-20 mg (small joints)		Intra-articular administration is acceptable when only one to two joints involved and should be used in combination with NSAIDs, colchicine, or oral corticosteroids
Corticotropin	H.P. Acthar Gel	20-40 units IM or SC	Dose may be repeated as clinically indicated; a dose of 40-80 units every 24-72 hours is used for other inflammatory conditions		Contraindicated for IV administration
Interleukin-1 inhibitors					Reserve use for refractory cases
Anakinra	Kineret	100 mg SC daily for 5 days			
Canakinumab	Ilaris	Single dose 150 mg SC			
Anti-Inflammatory Prophylaxis During Initiation of Urate-Lowering Therapy					
NSAIDs			Lowest effective		

			dosage		
Colchicine	Colcrys	0.6 mg daily	0.6 mg once or twice daily	See Table 113-8	
Prednisone or prednisolone		≤10 mg daily			
Interleukin-1 inhibitors					Reserve use for refractory cases Studied for 16-week duration
Rilonacept	Arcalyst	320 mg loading dose followed by 160 mg weekly (SC)			
Canakinumab	Ilaris	Single SC dose (50 mg-300 mg) or four times weekly SC dosing (50 mg—50 mg—25 mg—25 mg)			
Hyperuricemia in Gout					
Xanthine oxidase inhibitors					
Allopurinol	Lopurin, Zyloprim	100 mg daily	100-800 mg daily to achieve serum urate concentration <6 mg/dL (357 µmol/L)	Start at dose of 50 mg daily for patients with a glomerular filtration rate <30 mL/min/1.73 m^2 (0.29 mL/s/m^2)	
Febuxostat	Uloric	40 mg daily	40-80 mg/daily	No dosage adjustment necessary for patients with mild-moderate kidney impairment (creatinine clearance 30-89 mL/min [0.5-1.49 mL/s]) Insufficient data in patients with creatinine clearance <30 mL/min (0.5 mL/s)	

Uricosurics					
Probenecid	Probalan	250 mg twice daily for 1 week	500-2,000 mg/day (target serum urate concentration <6 mg/dL [357 mol/L])	Not recommended if creatinine clearance <50 mL/min (0.83 mL/s)	
Lesinurad	Zurampic	200 mg once daily in combination with a xanthine oxidase inhibitor		Not recommended if creatinine clearance <45 mL/min (0.75 mL/s) Not studied in patients with severe hepatic disease Contraindicated in tumor lysis syndrome and Lesch-Nyhan syndrome	Should be used in combination with a xanthine oxidase inhibitor due to increased risk of acute kidney injury with lesinurad monotherapy Use is not recommended in patients taking allopurinol doses <300 mg daily (normal kidney function) or <200 mg daily (creatinine clearance <60 mL/min [1 mL/s]) Not currently marketed in the United States
Combination Therapy					
Lesinurad/Allopurinol	Duzallo	Lesinurad 200 mg/allopurinol 300 mg: one tablet daily		Lesinurad 200 mg/allopurinol 200 mg: one tablet daily recommended if creatinine clearance is 45-60 mL/min (0.75-1 mL/s) Not recommended if creatinine clearance <45 mL/min (0.75 mL/s)	See above for lesinurad and allopurinol comments Not currently marketed in the United States
Other					
Pegloticase	Krystexxa	8 mg IV every 2 weeks			Optimal treatment duration has not been established Reserved for patients with

					refractory gout who have failed other therapies and continue to have frequent gout flares (≥2 flares/year) OR who have non-resolving subcutaneous tophi

[a]Agents available in the United States.

CYP, cytochrome P; GFR, glomerular filtration rate; IM, intramuscular; IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug; SC, subcutaneous.

TABLE 113-7

Drug Monitoring

Drug	Adverse Drug Reaction	Monitoring Parameter	Comments
NSAIDs	Impaired kidney function (acute and chronic) gastritis (worse with concurrent aspirin), fluid retention, blood pressure elevation	Therapeutic Resolution of pain Avoidance of gout attacks when used for prophylaxis Toxic Blood pressure Kidney function Edema Dark stools	Avoid in patients with peptic ulcer disease, active bleeding Use caution in heart failure, dehydration, impaired kidney function Consider coadministration with a proton-pump inhibitor when used long term for patients at risk for GI bleeding
Systemic corticosteroids	GI upset, increased appetite, nervousness/restlessness, transient glucose intolerance, fluid retention, blood pressure elevation	Therapeutic Resolution of pain Avoidance of gout attacks when used for prophylaxis Toxic Glucose levels in patients with diabetes	Limit duration of therapy in patients with diabetes
Intra-articular corticosteroids	Injection pain, rebound arthritis	Therapeutic Resolution of pain Toxic Signs of rebound arthritis (pain relief followed by reemergence of pain)	Avoid if joint sepsis cannot be ruled out
Corticotropin	Increased appetite, nervousness/restlessness, transient glucose intolerance, fluid retention, blood pressure elevation	Therapeutic Resolution of pain	Requires intact pituitary–adrenal axis Less effective for patients receiving long-term oral corticosteroid therapy

Colchicine	Dose-dependent GI adverse effects (diarrhea, nausea, vomiting), rare myelosuppression, and reversible neuromyopathy	Therapeutic Resolution of pain Avoidance of gout attacks when used for prophylaxis Toxic GI symptoms Complete blood count	
Interleukin-1 inhibitors	Injection site reaction, neutropenia, immune hypersensitivity reaction, infectious disease, malignancy	Therapeutic Resolution of pain Avoidance of gout attacks when used for prophylaxis Toxic Neutrophil count (prior to initiation, monthly for the first 3 months of therapy then after 6, 9, and 12 months of therapy) Temperature (periodically to detect infection)	Safety for use in acute gout and gout prophylaxis during initiation of urate-lowering therapy has not yet been established; not FDA-approved for use in gout
Allopurinol	Rash, potential for fatal hypersensitivity syndrome	Therapeutic Serum urate level Reduced frequency of gout attacks Toxic Rash Kidney function	Testing for the HLA–B*5801 allele prior to starting allopurinol is recommended for patients of Southeast Asian (eg, Han Chinese, Korean, Thai) and African descent
Febuxostat	Liver enzyme elevation, nausea, arthralgias, and rash	Therapeutic Serum urate level Reduced frequency of gout attacks Toxic Liver function tests Kidney function	Use not recommended in patients with cardiovascular disease
Probenecid	Urolithiasis	Therapeutic Serum urate level Reduced frequency of gout attacks Toxic	Avoid in patients with CKD (stage 3 or greater)

		Kidney function	
Pegloticase	Acute gout attack during treatment initiation, anaphylaxis, GI symptoms (constipation, nausea, vomiting), chest pain, nasopharyngitis	Therapeutic Serum urate levels Reduced frequency of gout attacks Toxic Signs/symptoms of anaphylaxis following infusion	Reserved for patients with severe gout refractory to conventional therapies
Lesinurad	Acute gout attack during treatment initiation, headache, GERD, major adverse cardiovascular events have been observed although a causal relationship has not been established	Therapeutic Serum urate levels Reduced frequency of gout attacks Toxic Kidney function	Reserved for patients with hyperuricemia associated with gout who do not achieve target serum uric acid levels with conventional therapies Can be used in both urate overproduction and urate underexcretion Must be used in combination with a xanthine oxidase inhibitor due to increased risk of acute kidney injury with monotherapy Not currently marketed in the United States

FDA, Food and Drug Administration; GERD, gastroesophageal reflux disease; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug; CKD, chronic kidney disease.

General Approach to Treatment

Treatment of gout can be separated into three categories: (1) treatment of the pain and inflammation associated with an acute gout attack, (2) use of ULT to prevent recurrence of future gout attacks, and (3) use of anti-inflammatory prophylaxis to prevent acute gout attacks during initiation of urate-lowering therapy, which can occur paradoxically as a result of the rapid decline in serum urate after initiation of these therapies. Each of these categories will be covered in further detail throughout the remainder of the treatment section of this chapter.

Acute Gouty Arthritis

Nonpharmacologic Therapy

Nonpharmacologic therapies have an important role in modifying the underlying hyperuricemia and reducing the risk of an acute gout attack before one occurs. However, nonpharmacologic therapies for treatment of an acute gout attack are limited and are recommended strictly as adjuvants.

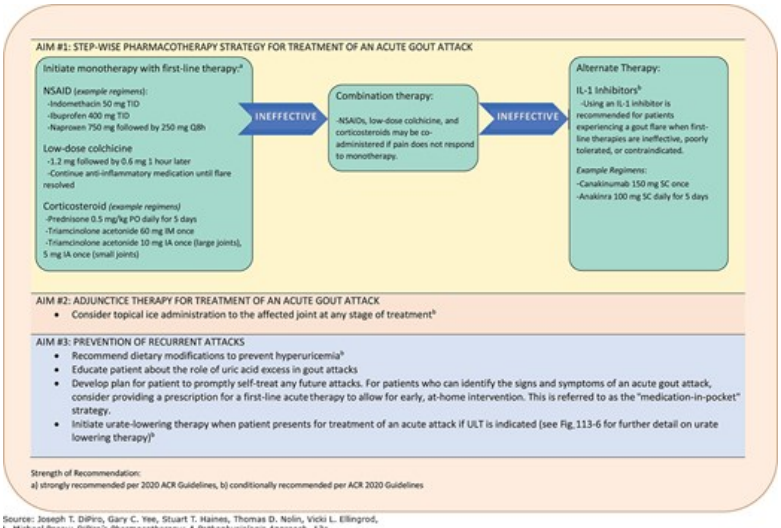
Local ice application to the affected joint is the most effective adjuvant.[24] Localized ice application results in significantly greater pain reduction in those receiving the therapy compared with those not treated with ice.[25] Complementary and alternative medicines, including vitamin C, flaxseed, cherry, and celery root, are not recommended for treatment of acute gout due to unproven benefit.[23,24]

Pharmacologic Therapy

For most patients, acute attacks of gouty arthritis may be treated successfully with NSAIDs, corticosteroids, or colchicine. The ACR guidelines recognize these three monotherapies equally as first-line treatments of acute gout.[23,24,26,27] Treatment should commence as soon as possible after the onset of an attack. In more severe cases involving inadequate response to first-line therapy, combination first-line therapy or off-label use of IL-1 inhibitor therapy may be considered (Fig. 113-5).[23,26]

FIGURE 113-5

Comprehensive management of an acute gout attack. (IM, intramuscular; IA, intra-articular; SC, subcutaneous.) *(Data from FitzGerald JD, Dalbeth N, Mikuls TB, 2020 American College of Rheumatology Guideline for the Management of Gout. Arthritis Care Res. 72:744–760.)*



Nonsteroidal Anti-Inflammatory Drugs

NSAIDs are a mainstay of therapy for acute attacks of gouty arthritis because of their excellent efficacy and minimal toxicity with short-term use. Indomethacin has been historically favored as the NSAID of choice for acute gout flares, but there is little evidence to support one NSAID as being more efficacious than another. Three agents (indomethacin, naproxen, and sulindac) have US Food and Drug Administration (FDA)-approved labeling for the treatment of gout, although several others are likely to be effective.[23] The most important determinant of therapeutic success is not which NSAID is chosen, but rather, how soon it is initiated. Early initiation of treatment is more likely to be effective than if delayed; therefore, ensuring patients have a plan to access therapy on their own when needed (referred to as the "medication-in-pocket" strategy) is an important cornerstone of an optimized gout management strategy.[24] Following resolution of the attack, tapering of NSAID therapy may be considered, especially in patients with comorbidities such as impaired hepatic or kidney function where prolonged therapy would be undesirable.[23] Resolution of an acute attack for most patients generally occurs within 5 to 8 days after initiating therapy.

All NSAIDs have the potential to cause similar adverse effects. The most common areas affected include the gastrointestinal (GI) system (gastritis, bleeding, perforation), kidneys (renal papillary necrosis, reduced glomerular filtration rate), cardiovascular system (sodium and fluid retention, increased blood pressure), and central nervous system (CNS) (impaired cognitive function, headache, dizziness). Caution should be exercised when using NSAIDs in individuals with a history of peptic ulcer disease, congestive heart failure, uncontrolled hypertension, impaired kidney function, coronary artery disease, or who are concurrently receiving anticoagulants or antiplatelets. Patients with active peptic ulcer disease, decompensated congestive heart failure, chronic kidney disease, or a history of hypersensitivity to aspirin or other NSAIDs should not be prescribed an NSAID.

Selective cyclooxygenase-2 (COX-2) inhibitors present a potentially less risky alternative to nonselective NSAIDs in patients with GI issues.[28] Specific COX-2 inhibitors, etoricoxib and lumiracoxib, have demonstrated efficacy in the treatment of acute gout; however, these agents are not available in the United States. The effectiveness of high-dose celecoxib (1,200 mg on day 1 followed by 400 mg twice daily thereafter) in the treatment of acute gout has been established, but concerns regarding the cardiovascular risk of COX-2 inhibitors must be considered when using these agents (see Chapter 110,

Osteoarthritis, for further discussion of COX-2 inhibitors).[29]

Corticosteroids

Corticosteroids have historically been reserved for treatment of acute gout flares when contraindications to other therapies exist, largely due to lack of evidence from controlled clinical trials. However, evidence indicates that corticosteroids are equivalent to NSAIDs in the treatment of acute gout flares.[30,31] They can be used either systemically or by intra-articular injection. With systemic therapy, a hypothetical risk exists for a rebound attack upon steroid withdrawal; therefore, gradual tapering is often employed when discontinuing. Examples of appropriate tapers include 0.5 mg/kg daily for 5 to 10 days followed by abrupt discontinuation, 0.5 mg/kg daily for 2 to 5 days followed by tapering for 7 to 10 days, or using a methylprednisolone dose pack—a 6-day regimen that starts with 24 mg on day 1 and decreases by 4 mg each day.[23]

Intra-articular administration of triamcinolone acetonide in a dose of 20 to 40 mg may be useful in treating acute gout limited to one or two joints. Injection should be done under an aseptic technique in a joint determined not to be infected. A single intramuscular injection of a long-acting corticosteroid, such as methylprednisolone, followed by a short course of oral corticosteroid therapy is another recognized therapeutic approach to the treatment of acute gout.[23] Alternatively, intramuscular corticosteroid monotherapy could be considered in patients with multiple affected joints who are unable to take oral therapy.

The adverse effects of corticosteroids are generally dose and duration dependent. Short-term use for treatment of acute attacks is generally well tolerated. Corticosteroids should be used with caution for patients with diabetes as they can increase blood sugar. In addition, patients with a history of GI problems, bleeding disorders, cardiovascular disease, and psychiatric disorders should be monitored closely for exacerbation of these conditions. Long-term corticosteroid use should be avoided because of the increased risk for osteoporosis, hypothalamic–pituitary axis suppression, cataracts, and muscle deconditioning.

Corticotropin, or adrenocorticotropic hormone (ACTH), which stimulates the adrenal cortex to produce cortisol and corticosterone, can be administered to treat acute gout. A dose of 25 to 40 international units given subcutaneously and repeated as needed has been recommended in the past for treatment of acute gout.[23] Studies with ACTH are limited, but it provides similar efficacy to systemic anti-inflammatory doses of corticosteroids.[32] Unfortunately, access to ACTH has been impacted following changes in the manufacturer of ACTH in 2007. This change in ownership resulted in a dramatic increase in the price of the medication such that it is no longer a viable treatment option.[33] The ACR guidelines support use of other first-line agents over ACTH primarily due to reduced cost effectiveness with ACTH.[24]

Colchicine

Colchicine is an antimitotic drug that is highly effective at relieving acute attacks of gout.[34] When begun within the first 24 hours of an acute attack, colchicine produces a response in two-thirds of patients within hours of administration.[35] Although it is highly effective, oral colchicine can cause dose-dependent GI adverse effects, including nausea, vomiting, and diarrhea. Other important non-GI adverse effects include neutropenia and axonal neuromyopathy, which may be worsened for patients taking other myopathic drugs such as β-hydroxy-β-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) or for those with impaired kidney function.

Colchicine was used for many years to treat acute gouty arthritis, but as an unapproved drug without having undergone formal FDA review for safety and efficacy. In 2009, the FDA-approved a 0.6-mg tablet of colchicine (under the brand name Colcrys®) for oral use, which was followed by an order for all unapproved colchicine products to stop manufacturing within 90 days. Following enforcement of market exclusivity for the branded colchicine product, use of colchicine to treat acute gouty arthritis declined immediately thereafter due to the significant cost.[36] Colchicine is now once again available generically; however, increased cost remains a potential barrier given the unique patent agreements established which may reduce competition among generic producers until 2029.[37]

One benefit of the 2009 FDA approval of Colcrys® was new information on dosing. A substantially lower dose of colchicine (1.2 mg initially, followed by a single 0.6 mg dose 1 hour later) is as effective as traditionally used higher doses (continued hourly dosing until symptoms subside or GI symptoms become intolerable).[38] In addition to the low-dose regimen, the ACR guidelines also suggest that following the low-dose colchicine regimen, anti-inflammatory medication may be continued until the flare resolves.[24] This off-label dosing recommendation is based upon pharmacokinetic data that

suggest that colchicine concentrations begin to decline 12 hours after administration.[38]

Postmarketing safety information suggests an increased risk of adverse events for patients receiving colchicine administered concurrently with P-glycoprotein or cytochrome P450 3A4 inhibitors (eg, clarithromycin or cyclosporine) (Table 113-8).[39] These interactions are thought to result in an increased colchicine concentration. Colchicine should also be used carefully for patients with impaired kidney and hepatic function. Colchicine dosing recommendations in these special situations are listed in Table 113-8.

TABLE 113-8

Colchicine Dosing in Special Situations/Colchicine Drug Interactions

	Treatment of Acute Gout Flares	Prophylaxis of Gout Flares
Impaired Kidney Function[a]		
Mild/moderate (creatinine clearance = 30-80 mL/min [0.5-1.33 mL/s])	Dose adjustment not required	Dose adjustment not required
Severe (creatinine clearance <30 mL/min [0.5 mL/s])	Dose adjustment not required; treatment course should be repeated no more than once every 2 weeks	0.3 mg daily (starting dose)
Dialysis	Single 0.6 mg dose; treatment course should not be repeated more than once every 2 weeks	0.3 mg twice weekly (starting dose)
Hepatic Impairment[b]		
Mild/moderate	Dose adjustment not required	Dose adjustment not required
Severe	Dose adjustment not required; treatment course should be repeated no more than once every 2 weeks	Dose reduction should be considered
Colchicine Drug Interactions		
Strong CYP3A4 inhibitors • Atazanavir • Clarithromycin • Darunavir/ritonavir • Indinavir • Itraconazole • Ketoconazole • Lopinavir/ritonavir • Nefazodone • Nelfinavir • Ritonavir • Saquinavir • Telithromycin • Tipranavir/ritonavir	Single 0.6 mg dose followed by 0.3 mg 1 hour later; dose to be repeated no earlier than 3 days	0.3 mg once every other day to 0.3 mg once daily
Moderate CYP3A4 inhibitors	Single 1.2 mg dose; dose to be repeated no earlier than 3 days	0.3 g-0.6 mg daily (0.6 mg dose may be

		given as 0.3 mg twice daily)
• Amprenavir • Aprepitant • Diltiazem • Erythromycin • Fluconazole • Fosamprenavir • Grapefruit juice and related citrus products • Verapamil		
P-glycoprotein inhibitors	Single 0.6 mg dose; dose to be repeated no earlier than 3 days	0.3 mg once every other day to 0.3 mg once daily
• Cyclosporine • Ranolazine		

[a]Treatment of gout flares with colchicine is not recommended in patients with impaired kidney function who are receiving colchicine for prophylaxis.

[b]Treatment of gout flares with colchicine is not recommended in patients with hepatic impairment who are receiving colchicine for prophylaxis.

Management of Hyperuricemia in Gout

Nonpharmacologic Therapy

Following treatment and resolution of an acute gout attack, the focus should shift to the prevention of future episodes. Recurrent gout attacks can be prevented by maintaining low uric acid concentrations. Although both nonpharmacologic and pharmacologic efforts to maintain low uric acid concentrations are critical in the management of gout, nonadherence with ULT is common.[40] A likely explanation for this lack in patient adherence is the silent nature of intercritical gout (the period of time between two gout attacks). Patient education, therefore, is a critical first step in the management of hyperuricemia.[24] Education should address the recurrent nature of the disease and reinforce the objective of each lifestyle/dietary modification and medication therapy recommended.

Weight loss through caloric restriction and exercise should be promoted in all patients with gout and hyperuricemia who are overweight/obese, as this may enhance renal excretion of urate.[24] Specifically, the urate-lowering effect of the DASH diet (Dietary Approaches to Stop Hypertension) has been examined. This diet includes vegetables, fruits, whole grains, reduced-fat dairy, lean meats, beans, and nuts along with avoidance of foods high in saturated fats and sweetened beverages/foods. Studies have demonstrated a reduction of ~1.0 mg/dL (~60 µmol/L) in serum uric acid levels in patients with hyperuricemia who adhere to the diet.[41,42] Restriction of alcohol intake can also aid in the management of gout, as increased alcohol consumption has been associated with an increased risk of gout attacks.[43,44] Acute ingestions of alcohol cause lactic acidemia, which reduces renal urate excretion, and long-term alcohol intake promotes production of purines as a by-product of the conversion of acetate to acetyl coenzyme A in the metabolism of alcohol.[45] The ACR guidelines conditionally recommend limiting alcohol use in all gout patients.[24] The guidelines also conditionally recommend limiting consumption of high-fructose corn syrup and purine-rich foods (organ meats and some seafood), which have also been linked to uric acid elevation.

Consumption of cherry-containing products, such as cherries and tart cherry extract, has received considerable attention and a wide variety of non-FDA-regulated supplements purporting benefits for gout are available. Uric acid lowering associated with cherry consumption has been demonstrated, although a physiologic mechanism for this effect has not been described.[46] For example, cherry intake over a 2-day period was associated with a 35% lower risk of gout attacks compared with no intake.[47] Randomized controlled trials are needed to better establish the role of cherry products before they can be recommended for management of hyperuricemia. Furthermore, the caloric and sugar content of each cherry-containing product should

be considered. Since many patients with hyperuricemia can benefit from weight loss, use of these caloric-dense products is not optimal.

Another strategy to lower uric acid before initiating urate-lowering pharmacotherapy is to evaluate the patient's medication list for potentially unnecessary drugs that may elevate uric acid concentrations. Additionally, when clinically appropriate, medications that increase serum uric acid levels may be switched to equally effective medications without this effect (Table 113-2). Although the presence of gout is not an absolute contraindication to the use of thiazide diuretics in hypertensive patients, the ACR guidelines conditionally recommend that hydrochlorothiazide, specifically, be switched to an alternative antihypertensive medication when feasible.[24] This is particularly important if the patient has had frequent gout attacks or continues to have an elevated serum uric acid concentration despite appropriate therapy for gout. Importantly, the ACR guidelines specifically highlight the importance of continuing low-dose aspirin when used for an appropriate indication in patients with gout, despite its uric acid elevating properties.[24]

Pharmacologic Therapy

After the first attack of acute gouty arthritis, a decision to institute prophylactic urate-lowering pharmacotherapy may be considered. This decision should carefully balance risk and benefit.

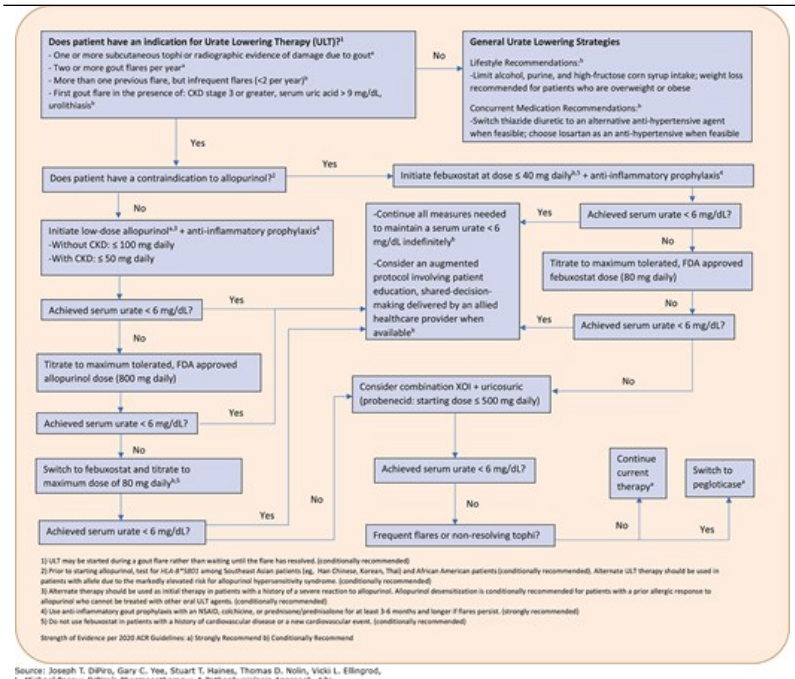
3 The ACR guidelines recognize the occurrence of frequent gout flares (two or more attacks per year) as an indication for pharmacologic ULT. Other indications include the presence of one or more tophus and radiographic evidence of damage attributable to gout. A conditional recommendation for ULT initiation exists for patients who have experienced more than one gout attack, but who have infrequent flares (fewer than two per year), as well as for patients experiencing their first flare who have CKD (stage 3 or greater), serum uric acid level greater than 9 mg/dL (535 µmol/L), or urolithiasis.[24] ACR guidelines conditionally recommend that pharmacologic ULT can be safely started during an acute gout attack, citing evidence that initiation of ULT during an acute attack did not prolong duration or worsen severity of the attack compared to delayed initiation.[24,48-50]

Reduction in serum urate concentrations can be accomplished pharmacologically by decreasing the synthesis of uric acid (xanthine oxidase inhibitors) or by increasing the renal excretion of uric acid (uricosurics).

The ACR guidelines provide a step-wise approach to the treatment of hyperuricemia in patients with gout (Fig. 113-6).[24]

FIGURE 113-6

Algorithm for management of hyperuricemia. (CKD, chronic kidney disease; XOI, xanthine-oxidase inhibitor.) Serum urate levels expressed as 6 mg/dL is equivalent to 357 µmol/L. *(Data from FitzGerald JD, Dalbeth N, Mikuls TB, 2020 American College of Rheumatology Guideline for the Management of Gout. Arthritis Care Res. 72:744–760.)*



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

A xanthine oxidase inhibitor, allopurinol, is recommended as first-line therapy, with an alternate xanthine oxidase inhibitor, febuxostat, as second-line therapy for those with a contraindication or intolerance to allopurinol or who do not achieve target serum urate. In refractory cases, combination therapy including a xanthine oxidase inhibitor plus an agent with uricosuric properties may be considered. Finally, in severe cases, in which the patient is not achieving the target serum uric acid level and is continuing to experience frequent gout flares or non-resolving tophi despite preferred treatments, pegloticase is recommended.

4 The target serum uric acid concentration identified by ACR guidelines is less than 6 mg/dL (357 µmol/L).[24]

Given that the factors associated with uric acid elevation are typically persistent throughout life, urate-lowering therapy is usually prescribed for long-term use. Furthermore, long-term ULT administration has been demonstrated to be more effective in controlling gouty attacks compared to intermittent administration.[51] For these reasons, ACR guidelines recommend indefinite ULT in patients in whom therapy is indicated.[24]

Xanthine Oxidase Inhibitors

5 Xanthine oxidase inhibitors reduce uric acid by impairing the ability of xanthine oxidase to convert hypoxanthine to xanthine and xanthine to uric acid (Fig. 113-1). Because they are efficacious for prophylaxis in both underexcreters and overproducers of uric acid, xanthine oxidase inhibitors are the most widely prescribed agents for the long-term prevention of recurrent attacks of gout. There are two commercially available xanthine oxidase inhibitors, allopurinol and febuxostat.

Allopurinol is an effective urate-lowering agent,[52] but not all patients are able to take it due to adverse effects, and long-term adherence with allopurinol is low.[40] Mild adverse effects such as skin rash, leukopenia, GI problems, headache, and urticaria can occur with allopurinol administration. A more severe adverse reaction known as "allopurinol hypersensitivity syndrome," which includes severe rash (toxic epidermal necrolysis, erythema multiforme, or exfoliative dermatitis), hepatitis, interstitial nephritis, and eosinophilia, reportedly occurs in approximately 1:1,000 patients and is associated with a 20% to 25% mortality rate.[22] The annual incidence rate of allopurinol hypersensitivity is up to 4.68 per 1,000 patients. Risk factors associated with the development of allopurinol hypersensitivity include female sex, age above 60 years, initial starting dose of allopurinol exceeding 100 mg/day, kidney disease, cardiovascular disease, and use of allopurinol for treatment of asymptomatic hyperuricemia.[53] Additionally, the presence of the *HLA-B*5801* allele is associated with increased risk for allopurinol hypersensitivity syndrome (see Pharmacotherapy Considerations later in the chapter).

As evidence has linked higher starting doses of allopurinol with an increased incidence of allopurinol hypersensitivity syndrome, conservative initial

dosing is important.[54] ACR guidelines recommend that allopurinol be started at a dose no greater than 100 mg daily in patients with normal kidney function and limited to 50 mg daily in patients with chronic kidney disease (stage 3 or worse).[22,24,26] Despite the cautious approach of initiating at lower doses in patients with CKD, titrating allopurinol to the maximum approved dose has been proven to be safe and effective in this population.[24,55,56] Ideally, the dose of allopurinol should be gradually titrated based on serial serum uric acid measurements until the serum urate target is met, up to a maximum dose of 800 mg/day.[24] During titration, patients should be educated about the signs and symptoms of a serious reaction, including pruritus and rash.

Similar to allopurinol, febuxostat lowers serum urate concentrations in a dose-dependent manner.[57] The recommended starting dose is 40 mg daily and this can be titrated to the maximum FDA-approved dose of 80 mg daily. Although febuxostat and allopurinol may have similar efficacy in serum uric acid lowering and reduction in gout flares,[58,59] an increase in all-cause mortality and cardiovascular mortality has been shown with febuxostat compared to allopurinol.[58] These findings are reflected in an FDA black box warning stating that febuxostat should be reserved for patients unable to take allopurinol.[60] Consistent with this warning, the ACR guidelines recommend febuxostat as an alternative urate-lowering therapy in patients unable to tolerate or unresponsive to allopurinol. Additionally, the guidelines suggest switching to an alternative oral urate-lowering medication in patients taking febuxostat who have a history or cardiovascular disease or a new CVD-related event.[24]

Uricosuric Drugs

6 Uricosuric drugs increase the renal clearance of uric acid by inhibiting post-secretory renal proximal tubular reabsorption of uric acid. One uricosuric, probenecid, is available for use in the United States. An alternative uricosuric, benzbromarone, is available in Europe but not in the United States. A third uricosuric, lesinurad, is FDA-approved in the United States but is not currently marketed.[10] Uricosurics offer an alternative and complementary mechanism to xanthine oxidase inhibitors to enhance serum uric acid lowering. Although this class of medications can contribute to meaningful urate lowering and is well tolerated overall, uricosuric therapy is associated with less efficacy in patients with impaired kidney function and, therefore, is not generally recommended in patients with moderate-to-severe CKD (stage 3 or greater).[24,61]

Probenecid

Probenecid is given initially at a dose of 250 mg twice daily for 1 to 2 weeks and then 500 mg twice daily for 2 weeks. Thereafter, the daily dose is increased by 500 mg increments every 1 to 2 weeks until satisfactory control is achieved or a maximum dose of 2 g is reached. Uricosuric therapies, through their action to increase the elimination of uric acid (Fig. 113-1), cause marked uricosuria and may cause stone formation. Probenecid, specifically, has been associated with a 9% to 11% risk of urolithiasis.[22] For this reason, patients with a history of urolithiasis should not use uricosuric drugs.[24,61] The maintenance of adequate fluid intake when using uricosuric therapy is important to diminish the possibility of uric acid stone formation.[61]

In addition to urolithiasis, adverse effects associated with uricosuric therapy include GI irritation, rash/hypersensitivity, and precipitation of acute gouty arthritis. A disadvantage of uricosurics is that salicylates may interfere with this mechanism and result in treatment failure; however, low doses (325 mg/day or less) of enteric-coated aspirin may be used cautiously. In addition, probenecid can inhibit the tubular secretion of other organic acids; thus, increased plasma concentrations of penicillins, cephalosporins, sulfonamides, and indomethacin can occur.

Lesinurad

Lesinurad (Zurampic®) is the first FDA-approved selective uric acid reabsorption inhibitor (SURI). It works by inhibiting urate transporter 1 (URAT1), a transporter found in the proximal renal tubule. Inhibition of URAT1 results in uric acid excretion (Fig. 113-1).

Lesinurad is approved as a combination therapy with a xanthine oxidase inhibitor (including allopurinol and febuxostat) for the treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid concentrations with xanthine oxidase inhibitor monotherapy. Because lesinurad works by increasing renal uric acid secretion, it has been associated with adverse renal events (serum creatinine elevation and kidney stones), particularly when used as monotherapy.[62,63] For these reasons, lesinurad carries a black box warning which highlights the increased risk of acute kidney injury when used in the absence of xanthine oxidase inhibitor therapy.[63] Lesinurad retains approval in the United

States, but is not currently being marketed.

Pegloticase

Pegloticase (Krystexxa®) is a pegylated recombinant uricase administered intravenously that works to reduce serum uric acid by converting uric acid to allantoin, a water-soluble and easily excreted substance (Fig. 113-1).

Biweekly pegloticase therapy demonstrates efficacy in reducing serum uric acid and resolving tophi in patients with severe gout and hyperuricemia (uric acid more than or equal to 8 mg/dL [476 µmol/L]) who fail or have a contraindication to allopurinol therapy.[64] Severe gout is defined by having at least one of the following criteria: (a) three or more gout flares within the most recent 18 months, (b) one or more tophi, or (c) joint damage due to gout. Although clearly efficacious, pegloticase has several drawbacks that limit widespread use. One is the route of administration. The biweekly IV infusions of pegloticase must be given over no less than 2 hours, a potential inconvenience to many patients. Furthermore, given potential infusion-related allergic reactions, patients must be treated with antihistamines and corticosteroids before therapy. Cost is another major consideration. Pegloticase is estimated to cost several thousand dollars per month, not including administration costs associated with an IV infusion.[65] This represents a significantly greater cost burden compared with other ULT.[65]

The ideal duration of pegloticase therapy is unknown. Other ULTs such as allopurinol or febuxostat are typically used indefinitely in patients with gout and hyperuricemia. Immunogenicity issues associated with pegloticase therapy may limit the duration with which it may be used effectively. Patients may develop pegloticase antibodies that result in a loss of efficacy after several months.[64]

7 Given these many limitations and the narrow patient population in which the drug has been studied, ACR guidelines recommend reserving use of pegloticase for patients with refractory gout for whom all other urate-lowering therapies have failed to reach target serum uric acid and who continue to have frequent gout flares (two or more per year), or who have non-resolving tophi.

Miscellaneous Urate-Lowering Agents

Fenofibrate has been demonstrated to reduce uric acid levels as an ancillary benefit by increasing the clearance of hypoxanthine and xanthine, leading to a sustained reduction in serum urate concentrations. Reductions of 20% to 30% in urate concentrations have been observed with fenofibrate use.[66,67] Despite demonstrated urate-lowering effects, ACR guidelines recommend against adding or switching cholesterol-lowering agents to fenofibrate,[24] as fenofibrate is not considered a preferred therapy in current lipid guidelines.

Losartan, an angiotensin II receptor antagonist, has also demonstrated benefit in reducing serum urate concentrations independent of its primary mechanism, angiotensin receptor antagonism.[68,69] Losartan inhibits renal tubular reabsorption of uric acid and increases urinary excretion, and this effect seems to be a unique property of losartan that is not shared with other angiotensin II receptor antagonists.[70] In addition, it alkalinizes the urine, which helps reduce the risk for stone formation. The ACR guidelines recommend choosing losartan preferentially as antihypertensive therapy in patients with gout when feasible.[24]

Anti-Inflammatory Gout Prophylaxis During Initiation of Pharmacologic Urate-Lowering Therapy

8 Initiation of ULT can prompt an acute attack of gout due to remodeling of urate crystal deposits in joints as a result of rapid lowering of urate concentrations.[23] The frequency of this phenomenon ranges from as few as 25% up to 75% of patients.[71] Given this possibility, prophylactic anti-inflammatory pharmacotherapy is recommended to prevent gout attacks and, secondarily, to assist in ensuring patient acceptance of, and adherence with, ULT. The ACR guidelines strongly recommend anti-prophylaxis with NSAIDs, colchicine or prednisone/prednisolone during the first 3 to 6 months of ULT initiation, and longer as needed if gout flares persist.[24] Examples of prophylactic doses for each medication include: colchicine 0.6 mg twice daily, naproxen 250 mg twice/day, and prednisone 10 mg daily (Table 113-6).

Given the considerable duration of therapy required for anti-inflammatory prophylaxis during initiation of ULT, the potential for adverse effects must be considered. Although the risk for gastric ulceration and bleeding is relatively small with short-term NSAID therapy normally employed when treating acute gout flares, administration of a proton-pump inhibitor or other acid-suppressing therapy should be considered to protect from NSAID-induced gastric problems for patients on long-term prophylactic therapy.[23] Prolonged corticosteroid therapy may be linked to many adverse effects not

experienced with short-term therapy used for acute treatment (ie, hyperglycemia, Cushing syndrome, fluid retention, hypertension, osteoporosis, glaucoma, depression/euphoria). Therefore, when used for longer-term anti-inflammatory prophylaxis, these risk must be considered.

Cost is another major consideration when selecting prophylactic pharmacotherapy given the need for an extended duration of therapy (3 to 6 months of therapy compared to approximately 1 week for acute gout treatment). Although generic colchicine again became commercially available in 2015, the lack of competition among manufacturers of generic colchicine may allow the cost per tablet to remain high well into the future.[37,72] The cost of colchicine, if not covered by insurance, remains a potential challenge to therapy for certain patients making NSAIDs and corticosteroids more affordable options for patients.

Investigational Drugs

Prior to the approvals of febuxostat in 2009 and pegloticase in 2010, several decades passed without the release of any new pharmacotherapeutic agents for the treatment of gout. Given the increased prevalence of gout and the presence of both treatment intolerance and treatment refractory cases, discovery of novel therapies continues to be a focus of ongoing research.[73]

Interleukin-1 Inhibitors

During acute gout attacks, urate crystals elicit an inflammatory response that triggers the production of interleukin-1 (IL-1).[10] This finding has led to the investigational use of IL-1 inhibitors in the treatment and prevention of acute gout.

Two IL-1 inhibitors, anakinra and canakinumab, have demonstrated efficacy in the treatment of acute gout.[74-76] Neither is approved for the treatment of acute gout by the FDA, and their use remains off-label. As such, the ACR guidelines suggest that use of IL-1 inhibitors should be reserved for treatment for patients experiencing an acute gout attack for whom first-line treatments are ineffective, poorly tolerated, or contraindicated.[24]

Limited evidence also suggests efficacy of IL-1 inhibitors in the prevention of acute gout during the first 16 weeks of ULT initiation (subcutaneous rilonacept 320-mg loading dose followed by 160 mg weekly and subcutaneous canakinumab single dose [50-300 mg] or four times weekly dosing [50 mg—50 mg—25 mg—25 mg]).[76-78] Given the limited evidence and lack of FDA approval for this indication, the ACR guidelines do not provide a recommendation for the use of IL-1 inhibitors for anti-inflammatory prophylaxis during initiation of ULT.

Other Investigational Agents

Several investigational agents intended to be used for the management of gout are at various stages of development. Uricosurics in development include verinurad and arhalofenate.[73] Arhalofenate also suppresses the production of IL-1β which may potentially lead to a reduction in gout flares, in addition to urate lowering.[79] Other novel mechanisms of action include purine nucleoside phosphorylase (PNP) inhibition (ulodesine) and glucose transporter 9 (GLUT9) inhibition (tranilast).[76,78] Other agents include a xanthine oxidase inhibitor, topioxostat, and a uricase, pergsiticase. Continued research will ultimately define the role of these agents in the management of gout and hyperuricemia.

Nephrolithiasis

The medical management of uric acid nephrolithiasis includes hydration sufficient to maintain a urine volume of at least 2 to 3 L/day, alkalinization of urine, avoidance of purine-rich foods, moderation of protein intake, and reduction of urinary uric acid excretion.

Maintenance of a 24-hour urine volume of at least 2 L with an adequate intake of fluids is desirable for all patients with gout, but especially for those who form stones. Alkalinizing agents should be used with the objective of making the urine less acidic. Urine pH should be maintained at 6 to 6.5.[80] In this pH range, up to 85% of uric acid will be in the form of the soluble urate ion.

Reduction of urine acidity is usually accomplished by the administration of potassium bicarbonate or potassium citrate 30 to 80 mEq/day (mmol/day).[80] Administration of alkali via sodium salts is a less desirable option for two reasons. First, the sodium-induced volume expansion will increase sodium excretion and can secondarily cause hypercalcemia because calcium passively follows the reabsorption of sodium in the proximal tubule and loop of Henle. In the presence of uric acid, the resultant hypercalcemia can lead to calcium oxalate stone formation. Second, older patients

with uric acid kidney stones may also have hypertension, heart failure, or impaired kidney function. Because of these conditions, they should not be overloaded with alkalinizing sodium salts or unlimited fluid intake, as these can worsen these conditions.[80]

Carbonic anhydrase inhibitors (eg, acetazolamide and topiramate) produce rapid and effective urinary alkalinization; however, they are not recommended because they cause metabolic acidosis and hypocitraturia which may result in increased urinary saturation of calcium salts and calcium stone formation.[80]

The mainstay of drug therapy for recurrent uric acid nephrolithiasis is xanthine oxidase inhibitors. They are effective in reducing both serum and urinary uric acid concentrations, thus preventing the formation of calculi.

Uric Acid Lowering in the Absence of Gout

Asymptomatic Hyperuricemia

Questions are often raised regarding the use of drug therapy to treat hyperuricemia in patients who have never experienced a gout attack (ie, asymptomatic hyperuricemia). The purported benefits include prevention of acute gouty arthritis, tophi formation, nephrolithiasis, and chronic urate nephropathy. Furthermore, gout is associated with many comorbidities (eg, CKD, hypertension, obesity, heart failure, diabetes, myocardial infarction, stroke) and increasing levels of hyperuricemia have been associated with increased prevalence of these comorbidities.[81] Drug treatment of asymptomatic hyperuricemia to mitigate development of these conditions is not recommended, as it has not been demonstrated that uric acid lowering therapy prevents disease in such individuals.[10,82,83] Nevertheless, an incidental finding of hyperuricemia should prompt further evaluation of other cardiovascular risk factors.

Pharmacotherapy Considerations

While the ACR guidelines provide clear recommendations regarding use of pharmacotherapy in the management of gout and hyperuricemia, application of these recommendations requires personalization to fit the needs of a specific patient. When making therapeutic choices for an individual, it is critical to evaluate the adverse effect profile of a particular pharmacotherapeutic agent while considering a patient's baseline risk for those unwanted effects. This involves an analysis of patient demographics and comorbidities.

Allopurinol hypersensitivity syndrome is perhaps the most concerning adverse effect of all potential side effects associated with gout therapies, given the high mortality rate associated with this reaction. As such, it would be ideal if patients at high risk for developing this syndrome could be screened for and, consequently, guided to alternative therapy. The *HLA-B*5801* allele has been associated with a significant increase risk for allopurinol hypersensitivity syndrome. Patients of Korean, Han Chinese, Thai, and African descent have been identified as having a high prevalence of this allele and, therefore, at increased risk for allopurinol hypersensitivity syndrome. For this reason, the ACR guidelines recommend that *HLA-B*5801* testing be pursued before allopurinol initiation in these specific populations.[24] For those found to be positive, alternative therapy should be used.[84]

Certain comorbidities may warrant dose adjustment of some gout therapies or, in certain instances, complete avoidance of certain medications. For example, patients with impaired kidney function should generally avoid NSAID therapy and should receive colchicine at reduced doses. Patients with GI disease should also avoid NSAID therapy and may not be able to tolerate colchicine therapy; in these patients, corticosteroid therapy may be a better option. Patients with uncontrolled diabetes may experience hyperglycemia with use of corticosteroids and, therefore, should avoid these agents and preferably use NSAIDs or colchicine instead. In addition to comorbidities, polypharmacy and cost considerations may affect treatment decisions in an individual patient. The comprehensive management of gout provides ample opportunity for pharmacists to apply medication expertise, and care models incorporating pharmacists in the management of gout have demonstrated improved outcomes compared to standard practice.[85] Refer to Table 113-9 for an overview of important factors to consider when personalizing pharmacotherapy for an individual patient with gout.

TABLE 113-9

Pharmacotherapy Considerations in Gout

Conditions and	Limitations to Pharmacotherapy	Alternative Therapies

Situations		
Impaired Kidney Function	NSAIDs may lead to exacerbation of kidney impairment	Consider reduced-dose colchicine or corticosteroids for short-term treatment of acute gout Consider reduced-dose colchicine for prophylaxis during initiation of urate-lowering therapy
	Uricosuric therapy is ineffective in patients with impaired kidney function	Consider allopurinol or febuxostat
	Lesiurad is not indicated in patients with impaired kidney function	Consider allopurinol or febuxostat for first-line urate-lowering therapy; consider pegloticase for refractory cases
GI disease	Colchicine may cause GI upset and diarrhea	Consider corticosteroids for treatment of acute gout If monoarticular, consider joint injection
	NSAIDs may cause GI bleeding or ulceration	Consider gastroprotection with coadministration of proton-pump inhibitor when NSAID therapy is used Consider colchicine or corticosteroids for treatment of acute gout Consider low-dose colchicine for prophylaxis during initiation of urate-lowering therapy
Congestive heart failure	NSAIDs may cause a congestive heart failure exacerbation	Consider colchicine for treatment of acute gout Consider colchicine for prophylaxis during initiation of urate-lowering therapy
	Concurrent use of diuretic may increase serum urate	If diuretic remains necessary, consider initiating urate-lowering therapy Consider losartan as a therapy for congestive heart failure given its uricosuric properties
Hypertension	Diuretics may increase uric acid	Consider losartan as alternative or additional antihypertensive therapy given its uricosuric properties Consider non-diuretic anti-hypertensive agents as alternative therapy Consider addition of urate-lowering therapy if diuretic remains necessary
	NSAIDs may worsen blood pressure control	Consider colchicine or corticosteroids for treatment of acute gout Consider colchicine for prophylaxis during initiation of urate-lowering therapy
Polypharmacy	CYP3A4 inhibitors and P-glycoprotein inhibitors interact with colchicine leading to elevated colchicine levels	Reduce the dose of colchicine used for the treatment and prophylaxis of acute gout

		Consider NSAIDs or corticosteroids for treatment of acute gout Consider NSAIDs for prophylaxis during initiation of urate-lowering therapy
	Added pharmacotherapy may be undesirable in a patient with a large medication burden	Consider losartan as urate-lowering therapy in patients with comorbid hypertension Consider fenofibrate as urate-lowering therapy in patients with hypertriglyceridemia
Financial limitations	Febuxostat and colchicine are considerably more costly compared with other gout treatments	Consider allopurinol as urate-lowering therapy Consider NSAIDs or corticosteroids for treatment of acute gout Consider NSAIDs for prophylaxis of gout during initiation of urate-lowering therapy

CYP, cytochrome P450; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug.

Evaluation of Therapeutic Outcomes

Follow-up of patients with gout depends on the frequency of attacks and on the medications used to treat symptoms. For a patient who is experiencing a first attack of gout, long-term therapy is generally not indicated; however, patients having a first attack should be educated about the likelihood of recurrence and what to do if another attack occurs. Approximately 60% of patients have a second attack within the first year, and 78% have a second attack within 2 years. Only 7% of patients do not have a recurrence within a 10-year period.[39]

Baseline blood work for patients receiving ULT chronically should include kidney function (serum creatinine), liver enzymes (aspartate aminotransferase, alanine aminotransferase), complete blood count, and electrolytes. There is generally no need to recheck these laboratory parameters for patients undergoing acute therapy with an NSAID or colchicine of limited duration. However, for patients requiring long-term therapy or prophylaxis, they should be rechecked every 6 to 12 months or as clinically indicated. For patients suspected of having an acute attack of gouty arthritis, it is reasonable to check a serum uric acid concentration, particularly if it is not the first attack and a decision is to be made regarding initiation of prophylactic therapy. However, clinicians should be mindful that acute gouty arthritis can occur in the presence of normal serum uric acid concentrations.[1] During titration of ULT, serial uric acid measurements should be obtained; once the urate target is achieved, uric acid should be monitored periodically (every 6-12 months).[10] This monitoring regimen is recommended not only to insure appropriate dosing of ULT, but also to serve as an assessment of patient adherence given the known adherence issues with ULTs.[10] Because of the high rates of comorbidities associated with gout, including diabetes mellitus, CKD, hypertension, obesity, coronary heart disease, heart failure, and stroke, an elevated uric acid concentration or an acute attack of gout should prompt evaluation for these related comorbidities and implementation of appropriate risk reduction measures.[81] Additionally, clinicians should look for possible underlying causes of hyperuricemia that may be actionable, such as medications (eg, diuretics, niacin, calcineurin inhibitors), obesity, malignancy, and alcohol abuse. Nonpharmacologic options include encouraging patients to exercise, lose weight, and reduce their consumption of alcohol and syrup-sweetened sodas. Periodic follow-up is necessary to address progress on these goals.

CONCLUSION

Hyperuricemia can be asymptomatic without complications, or it may lead to acute attacks of gouty arthritis, chronic gout, and uric acid nephrolithiasis. Treatment of asymptomatic hyperuricemia is not recommended, although lifestyle modifications (eg, weight loss, reduction of alcohol intake, control of blood pressure) should be encouraged to help reduce serum urate and improve overall health.

Acute gouty arthritis responds well to short courses of NSAIDs, colchicine, or corticosteroids to treat the underlying inflammatory response. The management of uric acid nephrolithiasis includes hydration and alkalinization of the urine. Prevention of recurrent gouty arthritis or recurrent

nephrolithiasis, as well as the treatment of chronic gout, requires hypouricemic therapy with either a xanthine oxidase inhibitor, uricosuric, or a combination of both therapies. Allopurinol is the ULT with the strongest safety and efficacy profile, making it the first-line choice for prevention of gout attacks in patients needing prophylactic therapy who do not have contraindications. Finally, anti-inflammatory prophylaxis with colchicine, NSAID, or an oral corticosteroid is indicated during the initiation of ULT to prevent the development of acute gout due to the rapid mobilization or urate.

ABBREVIATIONS

ACR	American College of Rheumatology
ACP	American College of Physicians
ACTH	adrenocorticotropic hormone
CKD	chronic kidney disease
CNS	central nervous system
COX-2	cyclooxygenase-2
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
GI	gastrointestinal
GLUT9	glucose transporter 9
HGPRT	hypoxanthine-guanine phosphoribosyltransferase
IL-1	interleukin-1
MSU	monosodium urate
NSAID	nonsteroidal anti-inflammatory drug
PNP	purine nucleoside phosphorylase
PRPP	phosphoribosyl pyrophosphate (synthetase)
SURI	selective uric acid reabsorption inhibitor
ULT	urate-lowering therapy
URAT1	urate transporter 1
USP	United States Pharmacopeia

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SELF-ASSESSMENT QUESTIONS

1. Which course of action is recommended in patients with asymptomatic hyperuricemia?

A. Initiate treatment with urate-lowering therapy such as allopurinol or feboxustat

B. Initiate treatment with a nonsteroidal anti-inflammatory drug

C. Initiate treatment with colchicine

D. Recommend lifestyle measures to reduce serum urate level

2. Which of the following individuals would have the highest risk of developing gout?

A. An obese, 60-year-old male

B. A pre-menopausal, 40-year-old female

C. A physically active, 30-year-old male

D. A 45-year-old female with serum uric acid <7 mg/dL (416 µmol/L)

3. Which of the following is the most likely site for an acute attack of monoarticular gouty arthritis?

A. First metatarsophalangeal joint

B. Ankle

C. Heel

D. Knee

4. The American College of Rheumatology recommends which approach to lower risk of gout flares in patients who are candidates to receive urate-lowering therapy?

A. Treat-to-target, goal serum urate <7 mg/dL (416 µmol/L)

B. Treat-to-target, goal serum urate <6 mg/dL (357 µmol/L)

C. Fixed dose, allopurinol 300 mg/day

D. Fixed dose, febuxostat 40 mg/day

5. Which of the following is a first-line therapy to treat an acute gout flare?

A. Adrenocortocotropic hormone

B. Prednisone

C. Allopurinol

D. High-dose colchicine

6. Which of the following agents is a preferred first-line urate-lowering therapy in patient with moderate-to-severe CKD?

A. Febuxostat

B. Pegloticase

C. Allopurinol

D. Probenecid

7. How long should prophylaxis for acute gout flare be given after initiation of urate-lowering therapy?

   A. 1-2 weeks

   B. 2-4 weeks

   C. 1-3 months

   D. 3-6 months

8. Which of the following is the most appropriate initial dosing strategy for colchicine used to treat an acute gout flare in patient with normal renal function?

   A. 0.6 mg one dose

   B. 0.6 mg hourly until symptoms subside

   C. 1.2 mg initially, followed by 0.6 mg one hour later

   D. 1.2 mg hourly until symptoms subside

9. In which of the following patient scenarios should urate-lowering therapy be initiated?

   A. After resolution of an initial gout flare in a 65-year-old male with no prior history of acute gout

   B. An 80-year-old female found incidentally to have hyperuricemia on labs conducted as part of her annual wellness physical.

   C. During an initial gout flare in a 75-year-old male found to have a serum urate of 10 mg/dL (595 µmol/L).

   D. After resolution of a gout flare in a 60-year-old female whose only other attack of gout was 5 years ago after initiating hydrochlorothiazide.

10. What is the best option for treatment of acute gouty arthritis of the great toe in a 65-year-old female with a past medical history significant for atrial fibrillation and who takes apixaban?

    A. Low-dose colchicine

    B. Febuxostat

    C. Intra-articular corticosteroid injection

    D. Indomethacin

11. Which of the following lifestyle modifications should be recommended in patients with gout, regardless of disease activity?

    A. Increasing dietary purine intake

    B. Adding vitamin C supplements

    C. Limiting alcohol intake

    D. Increasing consumption of high-fructose corn syrup products

12. Which of the following would be the most appropriate initial treatment option for a patient with uncontrolled diabetes, and no other past medical history, experiencing a polyarticular attack of acute gout?

    A. Prednisone 40 mg daily for 5 days, then taper by 10 mg every 3 days until off

B. Naproxen 250 mg TID until resolved

C. Colchicine 1.2 mg initially, then 0.6 mg hourly until symptoms have resolved or diarrhea occurs

D. Triamcinolone 40 mg × 1 dose intra-articularly

13. Which of the following is the best option for a patient with gout taking allopurinol 300 mg daily with a serum uric acid level of 7.4 mg/dL (440 µmol/L)?

A. Add febuxostat 40 mg daily

B. Add probenecid 500 mg daily

C. Add fenofibrate 145 mg daily

D. Increase the allopurinol dose to 400 mg daily

14. Which of the following is the best option for a patient of Southeast-Asian descent who carries the *HLA-B*58:01* variant and who presents with a history of three gout attacks in the past year and a current serum uric acid level of 8.4 mg/dL (500 µmol/L). The patient has no other significant PMH.

A. Initiate allopurinol 50 mg daily plus colchicine 0.6 mg daily

B. Initiate febuxostat 40 mg daily plus colchicine 0.6 mg daily

C. Initiate pegloticase 8 mg IV every two weeks daily plus colchicine 0.6 mg daily

D. Urate-lowering therapy not indicated

15. Which of the following should be recommended for a patient with monoarticular acute gouty arthritis unable to take oral medications?

A. Pegloticase

B. Topical naproxen

C. Methylprednisolone 40 mg IM

D. Heating pad

SELF-ASSESSMENT QUESTION-ANSWERS

1. **D.** For patients with asymptomatic hyperuricemia, the American College of Rheumatology recommends against initiating urate-lowering therapy in patients with asymptomatic hyperuricemia, since the benefits would not outweigh potential treatment costs or risks for most patients. Lifestyle measures designed to reduce serum urate concentrations should be recommended.

2. **A.** Obese persons are twice as likely as non-obese persons to have gout. Gout is rare in individuals with serum uric acid <7 mg/dL (416 µmol/L), and in younger adults (particularly pre-menopausal females).

3. **A.** The first metatarsophalangeal joint (great toe) is most often affected in an attack of acute gout, and then in order of frequency, the insteps, ankles, heels, knees, wrists, fingers, and elbows.

4. **B.** The American College of Rheumatology recommends a treat-to-target management strategy to achieve a serum urate target of <6 mg/dL (357 µmol/L) in patients receiving urate-lowering therapy, over a fixed-dose strategy.

5. **B.** Based on similar efficacy between agents, NSAIDs, glucocorticosteroids, or low-dose colchicine are all recommended as first-line therapy to treat an acute gout flare.

6. **C.** Allopurinol is the preferred first-line agent recommended by the American College of Rheumatology for urate-lowering therapy due to tolerability, safety, and lower cost, including patients with CKD. Lower starting doses help mitigate safety issues.

7. **D.** Anti-inflammatory prophylaxis should be given when initiating urate-lowering therapy, and it should be continued for at least 3 to 6 months after urate-lowering therapy is initiated. Shorter durations have been associated with flares upon cessation of prophylaxis.

8. **C.** Data submitted in support of the FDA approval of Colcrys showed that a lower dose of colchicine (1.2 mg initially, followed by a single 0.6-mg dose one hour later) was as effective as traditionally used higher doses, but better tolerated.

9. **C.** The American College of Rheumatology recommends starting urate-lowering therapy during an acute gout flare rather than risking the patient not returning for urate-lowering therapy initiation. Additionally, patients may be highly motivated to initiate therapy due to the symptoms related to their current flare. While it is traditionally recommended against starting urate-lowering therapy in patients who have their first gout flare, the American College of Rheumatology recommends it be considered in certain patients, including those with comorbid CKD (stage ≥3), serum urate concentration >9 mg/dL (535 µmol/L), or urolithiasis.

10. **A.** Colchicine, NSAIDs, or glucocorticoids are all appropriate first-line therapy for gout flare, with the choice of which agent determined by patient specific factors. In this scenario, the presence of apixaban and increased bleeding risk makes indomethacin less viable. Although intra-articular corticosteroid injection could be used, the difficulty in injecting the great toe makes this a less attractive option. Low-dose colchicine is the most appropriate agent in this case given lack of interaction with apixaban and likelihood of early resolution of symptoms with minimal exposure to the medication.

11. **C.** Lifestyle modifications are important to minimize the risk of gout flares. These include limiting alcohol intake, eating a diet low in purines and high-fructose corn syrup products, and losing weight. Vitamin C supplementation has limited evidence of effects on serum urate.

12. **B.** Prednisone would not be a good choice because it may worsen the already uncontrolled diabetes. Colchicine could be used, but the dosing listed is inappropriate. Because it is polyarticular, steroid injection is not feasible. Naproxen would be the best choice in this case.

13. **D.** The maximum dose of allopurinol is 800 mg daily. The dose should be optimized prior to considering dual therapy with a uricosuric therapy making choice D correct and choice B incorrect. Choice A is incorrect because febuxostat would be considered duplicate therapy when combined with allopurinol given that they are both xanthine oxidase inhibitors (XOIs). Fenofibrate does have urate-lowering properties; however, the effect is not as substantial as the effects of XOIs or uricosurics so it is not recommended as a standalone urate-lowering therapy. Furthermore, fibrates are not generally preferred for the management of lipid disorders according to most current lipid guidelines so fenofibrate is rarely indicated.

14. **B.** Allopurinol should be avoided in patients with the *HLA-B*58:01* variant due to increased risk of allopurinol hypersensitivity syndrome in these patients. Febuxostat is the preferred agent in these instances, especially if the patient is free from cardiovascular disease (the most serious concern limiting widespread febuxostat use). Pegloticase is reserved for patients with refractory disease due to high cost and limited information on successful long-term therapy. Choice D is incorrect because the patient has frequent gout attacks (> 2 per year) combined with elevated uric acid and, therefore, is a candidate for ULT.

15. **C.** For patients experiencing an acute attack of gout who cannot take oral medications, treatment with glucocorticoids (intramuscular, intravenous, or intra-articular) are recommended. Local ice therapy, not a heating pad, can be used as an adjuvant. Pegloticase is used to lower serum urate and would not be effective in relieving the pain from an acute gout attack.