

THE JOURNAL OF FAMILY PRACTICE

JFP Find it

JFPOnline only
 PubMed

LOG-O

[Home](#) | [Current Issue](#) | [Past Issues](#) | [Reprints](#) | [Subscriptions](#) | [CME](#) | [Supplements](#) | [eNewsletters](#)

 PDF version

Can't open the PDF? [Click here](#) for help.

June 2010 (Vol. 59, No.6)

June 2010 · Vol. 59, No. 06 Suppl: S1-S8

WHAT DO I NEED TO KNOW ABOUT GOUT?

MICHAEL A. BECKER, MD

Professor Emeritus of Medicine, Department of Medicine, Rheumatology Section, The University of Chicago Medical Center, Chicago, Illinois

GARY E. RUOFF, MD

Clinical Professor of Family Practice, Department of Family Practice, Michigan State University College of Medicine, East Lansing, Michigan, Director of Clinical Research, Westside Family Medical Center, Kalamazoo, Michigan

LEARNING OBJECTIVES

After completing this activity, the primary care clinician will be better able to:

1. Identify the risk factors and comorbidities that contribute to and exacerbate acute gout flares
2. List the criteria for establishing a diagnosis of gout in the primary care setting
3. Distinguish between treatments for acute gout flares and chronic gout
4. Cite the data supporting which patients with chronic gout should be treated with urate-lowering medication and with which class of agents

ARCHIVES

- >> [Applie](#)
- >> [Audio](#)
- >> [Author](#)
- >> [Clinica](#)
- >> [Editori](#)
- >> [Family Round](#)
- >> [Guidel](#)
- >> [Hospit](#)
- >> [InfoPo](#)
- >> [Instan](#)
- >> [Online](#)
- >> [Origin](#)
- >> [Patien](#)
- >> [Photo](#)
- >> [Photo](#)
- >> [Practic](#)
- >> [PURLs](#)

MY ARTIC

FEAT

SUPPLE

WEBC

AUDI

Family pr

related lir

5. Establish goals for achieving, sustaining, and monitoring clinically meaningful urate lowering and means for optimizing patient adherence to long-term urate-lowering treatment

TARGET AUDIENCE

Family physicians and clinicians who have an interest in treating patients with gout

SPONSOR DISCLOSURE STATEMENT

As a continuing medical education provider accredited by the Accreditation Council for Continuing Medical Education (ACCME), it is the policy of the Primary Care Education Consortium (PCEC) to require any individual in a position to influence educational content to disclose the existence of any financial interest or other personal relationship with the manufacturer(s) of any commercial product(s).

PCEC clinical staff have provided financial disclosures and have no conflicts of interest to resolve related to this activity.

The medical accuracy reviewer for this activity, Louis Kuritzky, MD, disclosed that he is on the advisory board for Takeda Pharmaceuticals North America, Inc.

The CME reviewer for this activity, Allan Wilke, MD, has no real or apparent conflicts of interest to report.

Dr Becker disclosed that he is on the advisory board for BioCryst Pharmaceuticals, Inc, Novartis, Regeneron Pharmaceuticals, Inc., Savient Pharmaceuticals, Inc., Takeda Pharmaceuticals North America, Inc., and URL Mutual Pharma.

Dr Ruoff disclosed that he is on the advisory board and speakers bureau of Takeda Pharmaceuticals North America, Inc.

CONFLICT OF INTEREST STATEMENT

When individuals in a position to control content have reported financial relationships with one or more commercial interests, PCEC works with them to resolve such conflicts to ensure that the content presented is free of commercial bias. The content of this activity was vetted by the following mechanisms and modified as required to meet this standard:

- Content peer review by an external topic expert
- Content peer review by an external CME reviewer
- Content validation by internal PCEC clinical editorial staff

OFF LABEL DISCLOSURE STATEMENT

In accordance with ACCME guidelines, the faculty authors have been asked to disclose discussion of unlabeled or unapproved uses of drugs or devices during the course of the activity.

ACCREDITATION STATEMENT

The Primary Care Education Consortium is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

This activity has been planned and implemented in accordance with the Essentials and Standards of the Accreditation Council for Continuing Medical Education through the Primary Care Education Consortium.

The Primary Care Education Consortium designates this educational activity for a maximum of 1.0 *AMA PRA Category 1 Credit™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Release date: June 1, 2010

Expiration date: June 1, 2011

MEDIUM

Text publication in the form of a journal article.

SPONSORSHIP STATEMENT

This activity is sponsored by the Primary Care Education Consortium.

SUPPORTER STATEMENT

This activity is supported by an educational grant from Takeda Pharmaceuticals North America, Inc.

METHOD OF PHYSICIAN PARTICIPATION

To receive CME credit, please read the journal article and, upon completion, go to: www.pceconsortium.org/GoutSupplement to complete the online evaluation to receive your certificate of completion.

CASE STUDY. *Mr Hartman is a 52-year-old white male who is being seen by his primary care physician.*

“Good morning, Mr Hartman. I know that you’re here today so we can check your blood pressure. But my nurse tells me you had considerable difficulty walking from the waiting room. Why are you having such difficulty walking?”

“Dr Kim, I have terrible pain in my ankle, and it’s swollen, too. The last time this happened, a few months ago, it took a week or so for the pain to improve. Sometimes the pain is in my ankle, and sometimes in my foot, but mostly in my big toe. I thought maybe it was just a case of bursitis.”

“Mr Hartman, this kind of pain is not something you should have to endure. Maybe there is something we can do about it. Let’s start by taking a look at your feet and ankles.”

■ INTRODUCTION

Similar to Mr Hartman, many patients with gout present with an acute attack (flare) of gouty arthritis. In its early stages, gout is a chronic, often silent disorder that is punctuated by acute, extremely painful arthritic flares. Over time, untreated or insufficiently treated gout may progress, with more frequent flares and formation of urate crystal deposits (tophi) and associated chronic, deforming arthritis (gouty arthropathy). About 20% of patients with gout have urinary tract stones and can develop an interstitial urate nephropathy.

Gout (also called *urate crystal deposition disease*) is characterized by reduced renal clearance or, less frequently, an overproduction of uric acid. When the serum urate acid (sUA) level persistently exceeds 6.8

mg/dL, extracellular fluids become saturated and hyperuricemia occurs.¹ Hyperuricemia is also very common among adult men and postmenopausal women, most of whom remain asymptomatic with respect to gout throughout their lives. Nevertheless, hyperuricemia is the major risk factor for gout because it predisposes to urate crystal formation and deposition, particularly in and around joints and in other soft tissue structures. The symptoms and signs of gout result from acute and chronic inflammatory responses of the body to urate crystal deposits. Although any joint may be affected, the metatarsophalangeal (MTP) joint of the great toe (podagra) is the first joint affected in half of all cases.^{2,3}

One major goal in the management of gout is to treat the pain of acute flares aggressively with anti-inflammatory agents to reduce flare intensity and duration. In addition, most patients with gout eventually require long-term treatment with urate-lowering therapy (ULT) to reverse the chronic urate crystal deposition and to prevent recurrent flares that can cause permanent joint damage.

■ COMORBIDITIES ASSOCIATED WITH GOUT AND HYPERURICEMIA

Patients with gout have unusually high frequencies of serious comorbidities⁴⁻⁷ (TABLE 1). Consequently, recognition and treatment of comorbidities and risk factors should be considered a part of gout management.⁸ The association with comorbid disorders also extends to patients with asymptomatic hyperuricemia, as hyperuricemia—with or without gout—is a recognized risk factor for these comorbidities.⁹ But since there is currently no definitive evidence that asymptomatic hyperuricemia causes these comorbidities, ULT is not recommended for patients with asymptomatic hyperuricemia.⁸ In contrast, gout is a highly treatable, crystal-induced consequence of hyperuricemia, and patient education combined with long-term urate lowering by lifestyle changes and/or urate-lowering medication can lead to more successful outcomes.¹⁰

ULT is not recommended for patients with asymptomatic hyperuricemia.

TABLE 1

Comorbidities associated with gout⁴⁻⁷

Comorbidities
<ul style="list-style-type: none"> • Metabolic syndrome <ul style="list-style-type: none"> – obesity – Hyperlipidemia – Diabetes or insulin resistance • Hypertension • Cardiovascular disease <ul style="list-style-type: none"> – Thromboembolic disorders <ul style="list-style-type: none"> • Myocardial infarction • Stroke • Peripheral artery disease – Congestive heart failure • Chronic kidney disease

■ RISK FACTORS

The sUA level is the most important modifiable risk factor for gout development.¹¹ Other modifiable risk factors include obesity, diet, moderate to heavy alcohol intake, and hypertension. Nonmodifiable risk factors for gout include male gender, increasing age, and African-American race.^{4,8,11-17} Foods high in meat and seafood content can elevate sUA levels and increase the risk for gout.^{8,12} Intake of high fructose corn syrup, found in sweetened soft drinks and fruit juices, also increases sUA levels.^{14,15} Beer and, to a lesser degree, distilled alcohol—but not modest wine intake—increase gout risk.^{4,13} Certain medications, including thiazide and loop diuretics, low-dose aspirin (eg, 325 mg/d), cyclosporine (especially in organ transplant recipients), niacin, pyrazinamide, and ethambutol, can also increase sUA levels.¹⁶ Conversely, weight loss and increased intake of low-fat dairy products are associated with reduced sUA levels and rates of incident gout.^{12,17}

■ PRESENTATION OF THE ACUTE GOUT FLARE

An acute gout flare often begins at night and produces a joint that is red, hot, swollen, and intensely tender to touch or movement. There is usually no fever, rash, or other sign of systemic illness during a flare. If left untreated, the flare usually peaks within 24 to 48 hours and then gradually subsides within 7 to 10 days, especially early in the course of the disease.

Involvement of 2 or more joints is uncommon in early flares, but polyarticular involvement and involvement of hands and more proximal joints are more likely as gout progresses and flares become more frequent. Women presenting with gout are most often postmenopausal and substantially older at onset than men.¹⁸ Possibly because of preexisting joint damage from osteoarthritis (OA), flares involving multiple joints in the upper extremities are a more common feature in early gout in women than in men.

■ DIAGNOSIS

The diagnosis and treatment of gout remains challenging,¹⁸ in part because of the significant heterogeneity in the expression of gout¹ and the overlap in the symptoms of a gout flare with other rheumatic conditions. Hyperuricemia alone is insufficient to establish a diagnosis of gout because sUA measurement lacks specificity and, in acute flares, sensitivity.⁴ Measurement of sUA levels at least 2 weeks after a flare subsides is more reliable.

Hyperuricemia alone is insufficient to diagnose acute gout.

The gold standard for gout diagnosis is the demonstration of monosodium urate (MSU) crystals in synovial fluid or in an aspirate of a tophus.^{4,19,20} However, primary care physicians do not often aspirate an exquisitely painful joint in a patient with known gout or during an acute flare; this is routinely done by rheumatologists. In the majority of patients, a reasonably accurate presumptive diagnosis can be made based on the presence of multiple clinical features typical of gout. These include:

- Very rapid development of pain, swelling, and tenderness in a single joint
- Flare in a distal lower extremity joint, particularly the podagra⁴
- A history of multiple prior flares of monoarticular inflammatory arthritis involving lower extremity joints
- Complete resolution of acute flares within a few days to 2 weeks

- Soft tissue or cartilage (eg, pinna, olecranon bursa) lesions in locations suggesting tophi.¹⁰

Other suggestive features include:

- A patient history of urolithiasis
- A family history of gout
- The presence of multiple risk factors for gout
 - Obesity
 - Hypertension
 - Use of urate-elevating medications

Except after several years of the disease, when erosive or tophaceous changes can be seen, standard radiography is usually more helpful in ruling out other diagnoses (eg, infection, calcium pyrophosphate crystal deposition disease [pseudogout], or articular or fibrocartilage calcification [chondrocalcinosis]), than in contributing to a gout diagnosis.

■ DIFFERENTIAL DIAGNOSIS

Distinguishing gout from the many other diseases that cause joint pain is important for successful treatment. In acute flares, the most important alternative diagnosis to exclude is a septic arthritis, which is most often a sign of serious systemic infection that, if undiagnosed, may prove fatal or lead to rapid and irreversible joint destruction. Early in the course of gout, flares are not usually accompanied by fever or leukocytosis. In more advanced gout, these systemic features are more frequent; in this setting, efforts to exclude infection, including synovial fluid aspiration, with Gram stain and culture of synovial fluid and blood are important.¹⁸ An acute gout flare can also be mistaken for cellulitis because the signs of gouty inflammation often spread well beyond the confines of the affected joint. Resolution of this issue often depends on identification of joint swelling and effusion that permit joint fluid aspiration and analysis.

Later, gout that has not followed the classical pattern of recurrent acute flares or where polyarticular flares have occurred might suggest rheumatoid arthritis (RA) or OA. OA is not usually accompanied by signs of acute joint inflammation but, particularly in the elderly, gout flares can emerge in joints damaged by ongoing OA, such as OA nodes in the interphalangeal joints of the hands. Early gout rarely resembles RA, but erosive gouty arthropathy, particularly when accompanied by tophi resembling rheumatoid nodules, can mimic RA. Pseudogout may present in an acute form indistinguishable from gout flare; radiographs often show chondrocalcinosis.² Finally, another consideration in the differential diagnosis of gout is stress or silent traumatic bone fracture.

■ TREATMENT PRINCIPLES FOR ACUTE FLARES

Treatment of acute gout flares centers on early initiation of anti-inflammatory therapy to target the cascade of inflammatory events initiated by urate crystals.²¹⁻²³ The goal is to provide rapid pain relief and improve patient function, rather than lower the sUA level. Because acute flare treatment has no impact on crystal formation or deposition, there is no impact on the progression of gout. However, if ULT was previously initiated, it should be continued through the acute flare. Patients should be provided with a medication plan to treat acute flares at home and instructed to continue treatment until the flare has resolved.

Lowering the sUA level is not a treatment goal for the acute flare. However, if ULT was previously initiated, it should be continued through the acute flare.

■ PHARMACOLOGIC OPTIONS FOR ACUTE FLARES

The main classes of anti-inflammatory therapy include nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, and corticosteroids.³ None of these agents has demonstrated superior efficacy. A 2008 Cochrane review found inconclusive evidence to support the use of corticosteroids over other medications for the treatment of acute gout flares.²⁴ In fact, a recent study involving patients with gout arthritis (N=118) found comparable pain relief with prednisolone 35 mg once daily or naproxen 500 mg twice daily.²⁵ Similarly, an evidence-based review of anti-inflammatory therapy indicates that NSAIDs and colchicine provide similar outcomes.⁸ In separate placebo-controlled studies of both NSAIDs and colchicine, the number of patients needed to treat (NNT) was 3, indicating that patient-specific factors and drug adverse event profiles are important considerations.⁸ Local application of ice, rest, and elevation are also helpful adjunctive therapies.

NSAIDs

Since the efficacy among the NSAIDs appears similar,⁸ the decision to use an NSAID may depend on a patient's concurrent medications, comorbidities, and prior tolerability. NSAIDs are best avoided in patients with a peptic ulcer disease or gastritis. NSAIDs, including the cyclooxygenase-2 (COX-2) inhibitors, are also associated with an increased risk of serious cardiovascular and thrombotic events, myocardial infarction, and stroke.

Colchicine

Colchicine is effective in reducing the pain and clinical symptoms associated with an acute gout flare, with an NNT of 3 and 2, respectively, compared with placebo.²⁶ Oral colchicine use in acute gout flare has traditionally involved administration hourly or every other hour until the earliest occurrence of pain relief, gastrointestinal toxicity (usually abdominal pain, diarrhea, nausea, or vomiting), or ingestion of a prespecified dose. Under these circumstances, the benefit-to-risk ratio for colchicine in acute gout is very low.⁸ A recent trial in acute gout flares found that low-dose colchicine (1.8 mg over 1 hour) had equivalent efficacy, compared with high-dose colchicine (4.8 mg over 6 hours); both were more efficacious than placebo ($P=.005$ and $P=.034$ vs placebo, respectively).²⁷ In contrast, the incidence of diarrhea did not differ significantly in the low-dose and placebo groups (23% and 16%, respectively), but was significantly greater in the high-dose group (77%; 19% rated severe). These results led to the approval by the US Food and Drug Administration of a low-dose colchicine-only product in 2009.²⁸ A prophylactic colchicine dose of 0.6 mg once or twice daily 12 hours after acute dosing has also been approved.

Colchicine is not dialyzable and is contraindicated in renal patients on dialysis, as well as patients receiving P-glycoprotein or strong cytochrome P450 3A4 inhibitors, as severe colchicine toxicity may result. For patients with acute gout and severe renal or liver impairment, a single course of low-dose colchicine can be given, but no further colchicine should be given for at least 2 weeks.²⁹

Corticosteroids

The use of an oral corticosteroid, such as prednisone 20 to 40 mg once or twice daily, is rapidly effective in reducing the pain of an acute gout flare. Treatment tapered over 10 days to 2 weeks is generally recommended when oral corticosteroids are used and, particularly, when the patient has had many prior flares or has recently had more frequent flares. Reduction in the corticosteroid dose can be started as symptomatic improvement occurs, first with removal of afternoon dosing (if given), with the aim of avoiding “rebound” flares of gout upon steroid withdrawal. In the experience of one of the authors (M.A.B.), such rebound flares occur most often in patients with a history of multiple prior gout attacks and a recent acceleration in flare frequency.

The underlying concern about rebound flares is that such events may prompt the use of even higher doses of corticosteroids, which, if tapered rapidly, will lead to still another flare, with the unfortunate endpoint being a patient on long-term, high-dose steroid treatment that is increasingly difficult to withdraw. Except in the case of a coexisting or undiagnosed septic arthritis,³⁰ the short-term use of a corticosteroid may be preferable to that of an NSAID in older adults because the side effects of NSAIDs are more pronounced in this population.³⁰

■ TREATMENT PRINCIPLES FOR CHRONIC GOUT

Flare prophylaxis

Although preventive treatment of asymptomatic hyperuricemia in the absence of gout is not indicated, ULT should be initiated in a patient with progressive gout to protect against future gout flares and to minimize or reverse joint, bone, and soft tissue damage. Silent urate crystal deposition can be prevented only by reducing the sUA level to a subsaturating range that allows urate crystal dissolution. The sUA goal range for patients with gout is <6.0 mg/dL.⁸ With prolonged successful achievement and maintenance of this goal range, acute gout flares diminish in frequency or disappear, and tophi resolve. In the case of tophi, rates of resolution are inversely related to the sUA level maintained in therapy.³¹ Because the benefits of ULT are not immediately apparent and, in most instances, occur over many months to several years, it is important to reinforce adherence to the treatment program, especially in light of the fact that a transient but substantial increase in the risk for recurrent gout flare occurs following initiation of ULT. This paradox may be observed during treatment with any urate-lowering agent and appears to reflect changes in the relationship of deposited urate crystals with the inflammatory processes that result in gout symptoms.

Two key actions are necessary to assure that flares early in ULT do not compromise ongoing treatment. The first is to prepare the patient for this possible occurrence, and the second is to provide prophylactic therapy with colchicine or an NSAID, which can prevent up to 80% of flares.^{32,33} As noted above, colchicine flare prophylaxis at a dose of 0.6 mg once or twice a day (depending on renal function and patient tolerance) is recommended for a period of 6 months from the time of initiation of urate-lowering medication.^{32,34} Similar evidence to support the efficacy of NSAID prophylaxis is not available, despite substantial use of NSAIDs for this purpose.

■ URATE-LOWERING TREATMENT

There is no consensus about the frequency or severity of flares that warrant ULT. Although a single gout

flare does not constitute an indication to treat, about 60% of patients will experience a recurrence within 1 year of the initial attack and 78% within 2 years.¹ Fewer than 10% of patients will be flare free in 10 years.¹ Conversely, about three-quarters of patients with gout will become candidates for long-term ULT within a few years of onset of gout symptoms. Other indications for urate-lowering therapy in patients with symptomatic gout are listed in **TABLE 2**.⁸

TABLE 2**Indications for urate lowering in symptomatic gout^{a8}**

• Frequent or disabling acute gout flares
• Tophaceous gout (soft tissue or bony)
• Gout with renal function impairment
• Gout with urolithiasis
• Uric acid overproduction and urinary overexcretion (>1000 mg daily)
• Radiation or chemotherapy for lymphoma or leukemia
^a Treating asymptomatic hyperuricemia of any serum urate acid level to prevent gout or the comorbid disease associated with gout is controversial but generally not recommended.

Case Vignettes

What would you do in the following situations? Would you start pharmacologic urate-lowering therapy?

1. LW is a 48-year-old male who has experienced 3 acute flares, each lasting 6 to 10 days, over the past 14 months. Despite moderate pain, LW is able to perform his necessary daily functions. LW has no evidence of kidney disease or cardiovascular disease (CVD).
2. AG is a 53-year-old female who has experienced 3 flares over the past 2 years. Her most recent flare lasted 5 weeks, causing severe pain that prevented her from working. AG has no evidence of kidney disease or CVD.
3. PY is a 42-year-old female who has experienced 2 flares over the past 9 months. Each flare caused only mild pain and lasted 10 to 14 days. Her serum creatinine level has risen from 0.9 mg/dL 13 months ago to 1.7 mg/dL now. She has no evidence of CVD, but a small tophus is observed on her left great toe.
4. DK is a 54-year-old male who has experienced 2 flares over the past 10 months. Although each flare was accompanied by moderate pain and some difficulty walking, DK was able to work. He is taking lisinopril/ hydrochlorothiazide for hypertension. He has no evidence of kidney disease.

In the absence of other indications mandating pharmacologic urate lowering (**TABLE 2**), and with the agreement of the patient, infrequent and mild gout flares can be managed with anti-inflammatory medications, in conjunction with attempts at lifestyle adjustments that may lower sUA levels and thus, reduce the likelihood of recurrent flares. This symptomatic treatment approach can be followed until flare frequency or severity, overt evidence of urate crystal deposition (tophi), or patient preference dictates the need for urate-lowering drug treatment. However, more advanced gout, as evidenced by tophi or chronic

gouty arthropathy, radiographic changes in erosive or tophaceous gout, or gout with chronic kidney disease or recurrent uric acid urolithiasis are clear indications for the initiation of urate-lowering pharmacologic therapy.⁸

Based on these considerations, urate-lowering therapy probably would not be recommended in case 1, but would be recommended in cases 2 and 3. In case 3, a workup for worsening renal function should also be undertaken. Urate-lowering therapy might be initiated in case 4, but an alternative approach would be to replace the thiazide diuretic with an alternative antihypertensive agent. In each of these cases, it would be important to take into consideration and respect the patient's opinion on this issue, based on an educated understanding of the benefits and risks of long-term urate-lowering therapy and the impact of gout on the patient's lifestyle.

■ PHARMACOLOGIC OPTIONS FOR CHRONIC GOUT: SPECIFIC URATE-LOWERING AGENTS

Allopurinol

Allopurinol (Zyloprim, generics) reduces the production of uric acid by blocking xanthine oxidase, the enzyme catalyzing the final steps in uric acid synthesis. Allopurinol should be started at a daily dose of 100 mg/d (50 mg/d in patients with estimated creatinine clearance [CrCl] of 30 to <60 mL/min) and increased in 100 mg increments every 2 to 4 weeks until the sUA goal range (<6.0 mg/dL) is achieved or the maximum dose of 800 mg is reached.³⁵ In patients with normal renal function, the full effect of a given dose of allopurinol is achieved within 1 to 2 weeks (up to 3 weeks in patients with renal impairment); therefore, sUA levels can be monitored every 2 to 4 weeks during titration. Once the goal-range sUA level is achieved, maintenance screening should be performed every 3 months for the next 6 months and then once or twice yearly.

Although about half of current patients treated with allopurinol fail to reach goal-range sUA levels on 300 mg/d,^{36,37} <5% of prescriptions for allopurinol are for doses >300 mg/d.³⁸ Dosing guidelines aimed at reducing allopurinol exposure in patients with impaired renal function have long been used³⁹ but they reduce urate-lowering efficacy,⁴⁰ and a benefit of these guidelines in reducing the severity of allopurinol adverse events on patient outcomes is now questioned.^{41,42}

Intolerance to allopurinol occurs in 10% to 15% of patients and is generally mild and readily reversible. The precise incidence of allopurinol hypersensitivity reactions is uncertain (estimates range from 0.2 to 4 per 1000 treated patients), but severe cutaneous reactions or allopurinol hypersensitivity syndrome are frequently life threatening or fatal,^{41,43} and are more common in patients with moderate chronic renal disease that is treated with diuretics. Allopurinol interacts with many drugs, some of which (6-mercaptopurine, azathioprine, and theophylline) should not be used with allopurinol.⁴¹

Probenecid

Probenecid is the only potent uricosuric drug available in the United States for urate lowering and is used in <5% of patients with gout, largely for those with an intolerance or contraindication to the use of allopurinol.⁸ There are several explanations for this:

- Probenecid treatment involves twice-daily dosing

- Uricosuric agents are not indicated in patients with gout who overproduce uric acid (10%) or who have a history of uric acid or calcium oxalate urolithiasis (20%)
- Probenecid loses much of its efficacy when the CrCl is <60 mL/min
- Drug-drug interactions are common, such as with penicillin antibiotics, methotrexate, sulfonyleureas, and ketorolac
- Allopurinol has been the dominant urate-lowering agent in use for more than 40 years

Probenecid is initiated at 250 to 500 mg daily and increased until the goal range sUA level of <6.0 mg/dL is achieved, usually with 1 to 2 grams daily. Hydration with at least 2 liters (8 glasses) of fluid per day is advised, particularly early in treatment when there is a risk for urinary stone formation due to increased uric acid clearance. Flushing, dizziness, nausea, and vomiting are among the adverse events observed with probenecid.

Febuxostat

Febuxostat (Uloric), a more selective xanthine oxidase inhibitor than allopurinol, is indicated for the chronic management of hyperuricemia in adults with gout.³⁴ Febuxostat is initiated at 40 mg once daily and increased to the maximum dose of 80 mg twice daily if an sUA level <6.0 mg/dL is not achieved after 2 weeks. Dose reduction of febuxostat is unnecessary in patients with a CrCl \geq 30 mL/min.^{44,45} Efficacy and safety in patients with more severe renal impairment or with severe liver disease remain to be established.

The efficacy of febuxostat 40 and 80 mg once daily for 28 days was demonstrated in 116 adults with gout and baseline sUA levels \geq 8.0 mg/dL.⁴⁶ By day 7, sUA levels <6.0 mg/dL were achieved by 50% and 59% of the patients receiving febuxostat 40 or 80 mg, respectively, and 3% of those receiving placebo (P <.001 for each comparison vs placebo). By day 28, the proportion of patients achieving sUA levels <6.0 mg/dL was 56%, 76%, and 0%, respectively (P <.001 for each comparison vs placebo). Diarrhea and liver function test abnormalities were the most frequent adverse events associated with febuxostat in this brief study (25% and 8%, respectively). Subsequent trials have demonstrated the superiority of febuxostat 80 mg/d in lowering sUA levels, compared with febuxostat 40 mg/d⁴⁵ or allopurinol 300 mg/d.^{36,44,45} The latter doses showed equivalent urate-lowering efficacy. The safety profiles of febuxostat (40 mg and 80 mg) and allopurinol (300 mg, or 200 mg in moderate renal impairment) showed no significant differences, most importantly in liver function test abnormalities and severe cardiovascular events.

As with allopurinol, febuxostat is contraindicated in patients receiving 6-mercaptopurine, azathioprine, or theophylline.³⁴ The most common adverse event with febuxostat is liver function abnormalities (incidence of 6.6% with 40 mg and 4.6% with 80 mg). Nausea, arthralgia, and rash are the next most frequently reported adverse events, with a low incidence (<1.6%) overall.³⁴ The cost of febuxostat 40 mg is \$5.00, compared with \$0.18 for generic allopurinol 300 mg and \$1.76 for Zylprim 300 mg (source: www.drugstore.com).

■ STRATEGIES TO IMPROVE PATIENT ADHERENCE

Development of a patient care plan

Patients with gout should be asked whether or how many flares have occurred since the last visit. To accomplish this, patients should be encouraged to record the duration and severity of flares, even if they

are successfully managed at home. In addition, vigilance of office staff for patients experiencing an acute gout flare should be encouraged, as in the case cited in this article.

Optimal treatment of patients with gout requires patient education about both the disease and the goals of pharmacologic and nonpharmacologic treatment options.^{8,47} Considerations for an optimal treatment care plan are shown in **TABLE 3**.^{8,38,47}

TABLE 3

Care plan for a patient with gout^{8,38,47}

	Acute flare	Chronic gout
Goals	<ul style="list-style-type: none"> To recognize and manage acute flare To treat pain as quickly as possible 	<ul style="list-style-type: none"> To prevent future flares To slow and reverse joint and soft tissue damage
Educational points	<ul style="list-style-type: none"> Promote patient self-management for very early recognition and treatment of acute flare symptoms Provide an action plan and a means to record flare number, duration, and intensity as well as medication for treating acute flares at home Provide guidance on when to call the clinic during a flare and what to do if acute treatment is not effective Provide guidance on the most likely adverse drug reactions 	<ul style="list-style-type: none"> Discuss the silent phases of the disease (between flares) and the importance of monitoring sUA levels and continued adherence with ULT Inform patients that initiation of ULT may increase the early risk for acute flare, and provide flare prophylaxis for at least 6 months Remind patients that acute flares during treatment should be treated with anti-inflammatory medications but to continue ULT for long-term flare prevention Provide guidance on lifestyle modifications to reduce sUA levels Provide guidance on the most likely adverse drug reactions

sUA, serum uric acid; ULT, urate-lowering therapy.

■ SUMMARY

Key points a primary care physician needs to know about gout are:

1. Although a reasonably accurate presumptive diagnosis of gout can be made based on the common clinical features of gout flares, especially when accompanied by hyperuricemia (sUA >6.8 mg/dL), the identification of MSU crystals in synovial fluid or tophi is required for definitive diagnosis.
2. An NSAID, colchicine, or corticosteroid is used to treat an acute flare. Allopurinol, probenecid, or febuxostat are eventually indicated in most patients to eliminate flares and to prevent or reverse complications of chronic gout, such as tophi and destructive joint disease.
3. Although there is no consensus about the frequency or severity of flares that warrant ULT, such therapy is indicated for patients with intolerable or debilitating symptoms or when signs of progressive gout are present.
4. Initiation of ULT should involve dose titration and monitoring of sUA to ensure that the sUA goal range (<6.0 mg/dL) is reached. During titration, the sUA level should be measured every 2 to 4 weeks to guide dose adjustment. Once the sUA goal range is achieved, it is sufficient to monitor sUA every 3 months for the next 6 months and then once or twice yearly thereafter.
5. Successful long-term gout management relies on 2 actions:
 - a. Customizing treatment based on patient preference, risk factors, comorbidities, and medication side effects to achieve and maintain sUA levels within the goal range; and
 - b. Providing ongoing patient education and reinforcement aimed at promoting long-term treatment adherence.

Take the CME Evaluation online: www.pceconsortium.org/GoutSupplement

REFERENCES

1. Mandell BF. Clinical manifestations of hyperuricemia and gout. *Cleve Clin J Med*. 2008;75(suppl 5):S5–S8.
2. Dore RK. The gout diagnosis. *Cleve Clin J Med*. 2008;75(suppl 5):S17–S21.
3. Kirby BS, McTigue JC, Edwards NL. Pain management in gout. *Curr Pain Headache Rep*. 2008;12:418–422.
4. Zhang W, Doherty M, Pascual E, et al; EULAR Standing Committee for International Clinical Studies Including Therapeutics. EULAR evidence based recommendations for gout. Part I: Diagnosis. Report of a task force of the Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis*. 2006;65:1301–1311.
5. Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. *N Engl J Med*. 2008;359:1811–1821.
6. Krishnan E. Gout and coronary artery disease: epidemiologic clues. *Curr Rheumatol Rep*. 2008;10:249–255.
7. Choi HK, Ford ES, Li C, et al. Prevalence of the metabolic syndrome in patients with gout: the Third National Health and Nutrition Examination Survey. *Arthritis*

- Rheum. 2007;57:109–115.
8. Zhang W, Doherty M, Bardin T, et al; EULAR Standing Committee for International Clinical Studies Including Therapeutics. EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis*. 2006;65:1312–1324.
 9. Becker MA, Jolly M. Hyperuricemia and associated diseases. *Rheum Dis Clin North Am*. 2006;32:275–293, v-vi.
 10. Becker MA, Chohan S. We can make gout management more successful now. *Curr Opin Rheumatol*. 2008;20:167–172.
 11. Saag KG, Choi H. Epidemiology, risk factors, and lifestyle modifications for gout. *Arthritis Res Ther*. 2006;8(suppl 1):S2–S8.
 12. Choi HK, Atkinson K, Karlson EW, et al. Purine-rich foods, dairy and protein intake, and the risk of gout in men. *N Engl J Med*. 2004;350:1093–1103.
 13. Choi HK, Atkinson K, Karlson EW, et al. Alcohol intake and risk of incident gout in men: a prospective study. *Lancet*. 2004;363:1277–1281.
 14. Choi HK, Curhan G. Soft drinks, fructose consumption, and the risk of gout in men: prospective cohort study. *BMJ*. 2008;336:309–312.
 15. Choi JW, Ford ES, Gao X, et al. Sugar-sweetened soft drinks, diet soft drinks, and serum uric acid level: the Third National Health and Nutrition Examination Survey. *Arthritis Rheum*. 2008;59:109–116.
 16. Caspi D, Lubart E, Graff E, et al. The effect of mini-dose aspirin on renal function and uric acid handling in elderly patients. *Arthritis Rheum*. 2000;43:103–108.
 17. Dessein PH, Shipton EA, Stanwix AE, et al. Beneficial effects of weight loss associated with moderate calorie/carbohydrate restriction, and increased proportional intake of protein and unsaturated fat on serum urate and lipoprotein levels in gout: a pilot study. *Ann Rheum Dis*. 2000;59:539–543.
 18. Rott KT, Agudelo CA. Gout. *JAMA*. 2003;289:2857–2860.
 19. Pascual E, Doherty M. Aspiration of normal or asymptomatic pathological joints for diagnosis and research: indications, technique and success rate. *Ann Rheum Dis*. 2009;68:3–7.
 20. Courtney P, Doherty M. Joint aspiration and injection and synovial fluid analysis. *Best Pract Res Clin Rheumatol*. 2009;23:161–192.
 21. Nuki G. Colchicine: its mechanism of action and efficacy in crystal-induced inflammation. *Curr Rheumatol Rep*. 2008;10:218–227.
 22. So A, De Smedt T, Revaz S, et al. A pilot study of IL-1 inhibition by anakinra in acute gout. *Arthritis Res Ther*. 2007;9:R28.
 23. Chen CJ, Shi Y, Hearn A, et al. MyD88-dependent IL-1 receptor signaling is essential for gouty inflammation stimulated by monosodium urate crystals. *J Clin Invest*. 2006;116:2262–2271.
 24. Janssens HJ, Lucassen PL, Van de Laar FA, et al. Systemic corticosteroids for acute gout. *Cochrane Database Syst Rev*. 2008;(2):CD005521.
 25. Janssens HJ, Janssen M, Van de Lisdonk EH, et al. Use of oral prednisolone or naproxen for the treatment of gout arthritis: a double-blind, randomized equivalence trial. *Lancet*. 2008;371:1854–1860.
 26. Schlesinger N, Schumacher R, Catton M, et al. Colchicine for acute gout. *Cochrane Database Syst Rev*. 2006;(4):CD006190.
 27. Terkeltaub RA, Furst DE, Bennett K, et al. High versus low dosing of oral colchicine

- for early acute gout flare: twenty-four-hour outcome of the first multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-comparison colchicine study. *Arthritis Rheum.* 2010;62:1060–1068.
28. Colcrys [prescribing information]. Philadelphia, PA: AR Scientific, Inc.; 2009.
 29. Terkeltaub RA. Colchicine update: 2008. *Semin Arthritis Rheum.* 2009;38:411–419.
 30. Singh H, Torralba KD. Therapeutic challenges in the management of gout in the elderly. *Geriatrics.* 2008;63:13–18, 20.
 31. Perez-Ruiz F, Calabozo M, Pijoan JI, et al. Effect of urate-lowering therapy on the velocity of size reduction of tophi in chronic gout. *Arthritis Rheum.* 2002;47:356–360.
 32. Borstad GC, Bryant LR, Abel MP, et al. Colchicine for prophylaxis of acute flares when initiating allopurinol for chronic gouty arthritis. *J Rheumatol.* 2004;31:2429–2432.
 33. Paulus HE, Schlosstein LH, Godfrey RG, et al. Prophylactic colchicine therapy of intercritical gout. A placebo-controlled study of probenecid-treated patients. *Arthritis Rheum.* 1974;17:609–614.
 34. Febuxostat (Uloric) for chronic treatment of gout. *Med Lett Drugs Ther.* 2009;51:37–38.
 35. Allopurinol [prescribing information]. Corona, CA: Watson Laboratories, Inc.; 2006.
 36. Becker MA, Schumacher HR Jr, Wortmann RL, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. *N Engl J Med.* 2005;353:2450–2461.
 37. Perez-Ruiz F, Alonso-Ruiz A, Calabozo M, et al. Efficacy of allopurinol and benzbromarone for the control of hyperuricaemia. A pathogenic approach to the treatment of primary chronic gout. *Ann Rheum Dis.* 1998;57:545–549.
 38. Sarawate CA, Brewer KK, Yang W, et al. Gout medication treatment patterns and adherence to standards of care from a managed care perspective. *Mayo Clin Proc.* 2006;81:925–934.
 39. Hande KR, Noone RM, Stone WJ. Severe allopurinol toxicity. Description and guidelines for prevention in patients with renal insufficiency. *Am J Med.* 1984;76:47–56.
 40. Dalbeth N, Kumar S, Stamp L, et al. Dose adjustment of allopurinol according to creatinine clearance does not provide adequate control of hyperuricemia in patients with gout. *J Rheumatol.* 2006;33:1646–1650.
 41. Chao J, Terkeltaub R. A critical reappraisal of allopurinol dosing, safety, and efficacy for hyperuricemia in gout. *Curr Rheumatol Rep.* 2009;11:135–140.
 42. Stamp L, O'Donnell JL, Zhang W, et al. Increasing allopurinol dose above the recommended range is effective and safe in chronic gout, including those with renal impairment. *Arthritis Rheum.* 2009;60(suppl):S768–S773.
 43. Arellano F, Sacristan JA. Allopurinol hypersensitivity syndrome: a review. *Ann Pharmacother.* 1993;27:337–343.
 44. Schumacher HR Jr, Becker MA, Wortmann RL, et al. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: a 28-week, phase III, randomized, double-blind, parallel-group trial. *Arthritis Rheum.* 2008;59:1540–1548.
 45. Becker MA, Schumacher HR, Espinoza LR, et al. The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: the CONFIRMS trial. *Arthritis Res Ther.* 2010;12:R63.
 46. Becker MA, Schumacher HR Jr, Wortmann RL, et al. Febuxostat, a novel

nonpurine selective inhibitor of xanthine oxidase: a twenty-eight-day, multicenter, phase II, randomized, double-blind, placebo-controlled, doseresponse clinical trial examining safety and efficacy in patients with gout. *Arthritis Rheum.* 2005;52:916–923.

47. Schumacher HR Jr, Chen LX. The practical management of gout. *Cleve Clin J Med.* 2008;75(suppl 5):S22–S25.

THE JOURNAL OF FAMILY PRACTICE ©2010 Quadrant HealthCom Inc.

[About Us](#) | [E-mail Alert](#) | [Advertising Information](#) | [Site Map](#) | [Privacy Statement](#) | [Contact Us](#) | [Author Guic](#)

Copyright 2012 THE JOURNAL OF FAMILY PRACTICE. All rights reserved.