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HYPERURICEMIA AND GOUT:

MANAGEMENT CHALLENGES AND SOLUTIONS

SUPPLEMENT EDITOR:

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SUPPLEMENT

HYPERURICEMIA AND GOUT:
MANAGEMENT CHALLENGES AND SOLUTIONS FOR THE NONRHEUMATOLOGIST

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Confessions of a goutophile:
Despite its treatability, gout remains a problem

In the spirit of full disclosure, I am a nonrecovering goutophile. Recent advances have even furthered my enthusiasm for the study of gout and boosted my optimism for improved management of patients with this disorder.

A curious clinical course that finally yields to insights

For years I have been fascinated by the clinical course of the gout—the explosive onset of attacks coupled with their spontaneous resolution. Attacks have been viewed as a relatively simple response to urate crystals, in contrast to the complex cascades that follow auto-antigen stimulation. Until recently, however, the nuances of the response to urate crystals were poorly defined. Several laboratories have contributed to our understanding of the mechanisms triggering the acute attack via activation by various cytokines of specific intracellular pathways involving inflammasomes. Models to explain the self-resolving nature of the attacks have also been developed.

For our patients, the concept that hyperuricemia plays a direct role in the development of hypertension and the progression of chronic kidney disease has been revitalized. Molecular studies have refined our insights into the renal handling of uric acid; we better understand how estrogen, diabetes, and certain medications affect renal uric acid reabsorption. Epidemiologic analyses, animal models of hyperuricemia, and human interventional studies have reintroduced urate as an etiologic agent in cardiovascular disease.

The development of new agents for the treatment of hyperuricemia (a less immunogenic uricase preparation and a nonpurine inhibitor of xanthine oxidase) has stoked interest in—and funding for—research related to patients with hyperuricemia and gout.

Effective diagnosis and treatment: Achievable but not widespread

Gout can be definitively diagnosed by documenting the presence of urate crystals in the synovial fluid from affected joints. Most attacks of gouty arthritis can be readily and safely treated, assuming that attention is paid to the patient's comorbid conditions. There is continuing discussion about which gouty patients need to have their urate levels reduced, but once the decision is made to treat, most patients can be effectively managed with urate-lowering therapies that will reduce the frequency of attacks and shrink tophi. So why does gout remain a problem?

Reviews of physician practice patterns and focus-group discussions show that despite the high prevalence of hyperuricemia and gouty arthritis, we do a suboptimal job at managing patients with these conditions. Conversations with clinical rheumatologists reveal the shared perception that gout often is misdiagnosed (or goes undiagnosed) because of failure to examine synovial fluids for crystals. There is an overreliance on serum urate levels to diagnose gout, despite the well-recognized lack of sensitivity and specificity of this measure. Plus, interpretation of the serum urate level is complicated by the fact that laboratory "normal" ranges typically include serum urate values above the biological solubility of urate (~ 6.8 mg/dL).

It also seems that even when the decision is made to treat hyperuricemia, treatment is frequently suboptimal because of limited use of appropriate serum urate targets (ie, levels less than ~ 6.0 mg/dL), insufficient monitoring of the urate level, and overly conservative drug escalation.
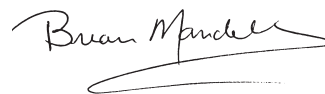
In other words, education in the management of gout and hyperuricemia is sorely needed.

A supplement conceived with nonspecialist feedback

In an effort to understand the difficulties faced by nonspecialists in managing patients with gout and hyperuricemia, I and several other rheumatologists with a special interest in clinical gout and continuing medical education took part in a symposium on this topic in Scottsdale, Ariz., on October 5, 2007. We made presentations to a group of invited internists and family practice physicians and gained feedback from them during breakout sessions that followed our talks.

This supplement is based on the series of formal talks presented at the symposium. The talks were transcribed and the authors developed their transcripts into the articles presented here, taking care to draw on questions and feedback from the breakout sessions to best address the educational needs of nonrheumatologists.

On behalf of my fellow authors, I hope we have succeeded in producing a readable and practical supplement that meets many of those needs and facilitates effective management of our patients with gout and hyperuricemia.

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The pathogenesis of gout

◼ ABSTRACT

An elevated serum urate level, together with local factors, can result in the deposition of urate crystals into the joints. Once crystals are deposited into a joint, they can be released into the joint space and initiate an inflammatory cascade causing acute gouty arthritis. These acute flares resolve, but the crystals remain in the joint. The way to ultimately correct the underlying metabolic problem of hyperuricemia and the crystal deposition is to lower the serum urate level and dissolve the crystal deposits. This will stop both the acute attacks and the progressive joint damage.

◼ KEY POINTS

A serum urate level of approximately 6.8 mg/dL is the concentration at which urate crystals begin to precipitate. The higher the urate level, the more likely that crystals will deposit into joints.

Local factors that combine with hyperuricemia to contribute to the development of gout are trauma, irritation, reduced temperature, and prior joint disease.

Because acute attacks of gout typically resolve spontaneously, especially early in the disease course, evaluating the efficacy of acute therapies can be difficult.

Lowering the serum urate to less than 6 mg/dL will dissolve crystals out of the joints, ultimately preventing acute gout attacks and joint damage.

A serum urate level greater than approximately 6.8 mg/dL, the saturation point of urate in biological fluids, is the underlying cause of gout. Hyperuricemia, along with other factors (detailed below), over time can result in the deposition of monosodium urate crystals into the joints. Gouty attacks are thought to occur by the abrupt release of these crystals into the joint space, where they may initiate an acute inflammatory reaction recognized as acute gouty arthritis. The acute attack is self-limited, but crystals remain in the joint and low-grade, often subclinical, inflammation persists even between acute attacks. Although acute attacks can be treated with anti-inflammatory medications, the underlying cause of the disease can be treated only by lowering the serum urate level.

◼ CRYSTAL DEPOSITION AND THE DEVELOPMENT OF GOUT

Asymptomatic hyperuricemia is not a disease but rather is the underlying factor that can predispose to gout. A serum urate level of approximately 6.8 mg/dL is the concentration at which monosodium urate crystals begin to precipitate.[1,2] Although this level is based on in vitro studies, it suggests a reasonable biological threshold for clinicians assessing patients for hyperuricemia. It should be noted that there are often no manifestations of gout during an extended period of hyperuricemia even though urate crystals are beginning to deposit into joints. The higher the serum urate level, the more likely that crystals will deposit into joints.

Predisposition is not causation

In the Normative Aging Study, 22% of men who had serum urate levels greater than 9 mg/dL developed gout during a 5-year period—a much higher rate than among men with serum urate levels less than 9 mg/dL.[3] Nevertheless, a full 78% of the men in this study with serum urate levels greater than 9 mg/dL did *not* develop gout over the 5-year period, illustrating that while hyperuricemia predisposes to gout, it does not automatically cause gout.

Contributing factors beyond serum urate

Other factors, when combined with hyperuricemia, contribute to crystal deposition and the development of gout.

Trauma or irritation. Patients with hyperuricemia tend to have monosodium urate crystal deposition at

FIGURE 1. Synovial tissue of a patient with acute gout. Note the dilated vessels, representing the throbbing, hot, erythematous joint, and the large numbers of neutrophils.

FIGURE 2. The synovium between acute gout attacks, viewed under polarized light. Two small micro-tophi and mononuclear cells are apparent, but there is no acute inflammatory response.
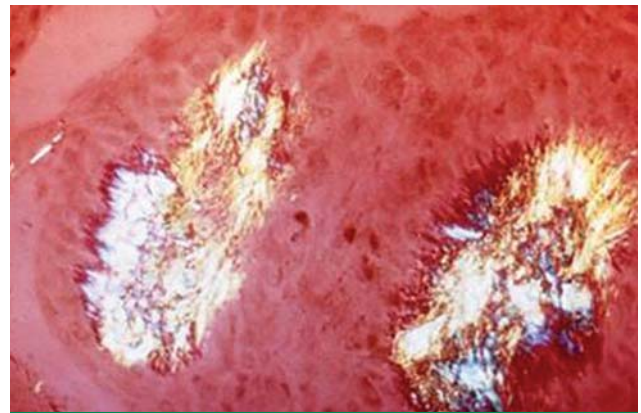
sites of trauma or irritation. The first metatarsophalangeal joint is often affected, at least in part because it is a site of mechanical stress. Likewise, mechanical irritation from leaning on the elbow may cause crystals to deposit in the olecranon bursa.

Lower temperatures favor crystal deposition,[1,4] which may explain why the helix of the ear and the foot are often sites of crystal deposition and tophus development. Both temperature and mechanical effects probably play a role in crystal deposition, however, as gouty attacks tend to occur at the first metatarsophalangeal joint, not at the interphalangeal joints of the foot, which are at a lower temperature.

Previous disease. Crystals also deposit with an increased incidence in previously diseased joints. The Heberden node is a good example.[5] A patient with osteoarthritis in the fingers may experience dramatically increased pain and swelling because of a gout flare superimposed on an osteoarthritic joint.

■ ACUTE GOUTY ARTHRITIS

In some patients, the deposited monosodium urate crystals will be released into the joint space and cause the dramatic acute inflammatory response of acute gouty arthritis. Crystals are believed to be released either by some metabolic change, such as an increase or decrease in serum urate level, or by mechanical trauma. In the joint space, synovial lining cells appear to be the first to phagocytize the crystals.[6] This sets into motion the formation of a complex called the inflammasome, which releases IL-1 beta, one of the most important mediators

of the acute attack.[7] It stimulates the release of chemokines, other cytokines, prostaglandins, and a variety of other proinflammatory molecules.[8] The chemokines attract neutrophils into the synovial tissue and the synovial fluid. Neutrophil influx into the joint is a key feature of an acute attack of gout **(Figure 1)**.

Gout flares may resolve spontaneously

Clinicians should be aware that gout attacks initially subside spontaneously.[9] Because acute attacks of gout typically resolve with or without treatment, especially early in the course of the disease,[10] it can be difficult to evaluate which treatments actually are effective against acute attacks.

A number of factors have been identified to explain how inflammation in acute attacks can be spontaneously suppressed. Crystals may dissolve or become sequestered in the tissue. Monocytes mature into macrophages, changing their responsiveness to urate crystals, and can begin to produce anti-inflammatory cytokines. In addition, some proteins that exude into the joint space with the attack, such as apolipoprotein B, can coat the crystals and reduce their inflammatory properties.[11]

Crystals persist during intercritical periods

Following an acute attack, the symptoms of gouty arthritis may be gone, but the crystals are still present in the joint. Therefore, the patient remains at risk for continued flares and progressive disease.[12] The crystals that remain in the joint are often associated with a low-grade persistent inflammation.[13] It is not known why these crystals that remain in the joint fluid between attacks, some of which are phagocytized by white cells, do not initiate the whole cascade of inflammation. The reason may be related to the number of crystals present, their protein coating, or the nature of the resident synovial cells. Crystals may also persist as micro-tophi in the synovium **(Figure 2)**. The

FIGURE 3. Large, cystic joint erosions producing an overhanging edge (circled area) characteristic of chronic gouty arthritis.

key point is that low-grade inflammation persists and crystals remain in the joint, which can lead to progressive disease.[14]

ADVANCED GOUT

Clinicians treating patients with gout need to prevent the development of chronic, destructive arthritis and the overt, large tophaceous deposits of advanced gout. Over time, even in the absence of flares, deposited crystals and inflammation can lead to the development of clinically evident joint damage and erosions that can be seen on radiographs **(Figure 3)** or magnetic resonance imaging.[15]

INTERVENTIONS MUST NORMALIZE URATE LEVEL

Acute gout attacks can be treated with anti-inflammatory drugs, but the disease can and often will continue to progress unless the serum urate level is normalized. Two studies of patients whose serum urate levels were successfully reduced to less than 6 mg/dL showed that crystals began to be depleted from the patients' joint fluid, which should ultimately prevent the risk of progressive gouty arthritis.[12,16] Perez-Ruiz and colleagues have shown that tophi can be dissolved by decreasing the serum urate level.[17] When tophi are present, aiming for even lower levels of serum urate, such as 4 to 5 mg/dL, may help to promote more rapid dissolution of crystals.[17]

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Clinical manifestations of hyperuricemia and gout

■ ABSTRACT

Biologically significant hyperuricemia occurs when serum urate levels exceed urate solubility, ie, at approximately 6.8 mg/dL. At serum urate levels above this threshold, manifestations of chronic crystal deposition, including gouty arthritis, may occur, although asymptomatic hyperuricemia often persists for many years without progression. Intercritical asymptomatic periods follow the resolution of acute gout flares, but crystals remain in the joint during these intervals and further deposition may continue silently. Ultimately this may lead to persistent attacks, chronic pain, and, in some patients, joint damage.

■ KEY POINTS

Clinically significant hyperuricemia includes serum urate levels that fall within the population-defined "normal" range of many clinical laboratories.

There is no reliable way to predict the likelihood that gout will develop in a given hyperuricemic patient. Treatment of asymptomatic hyperuricemia is not generally recommended.

Untreated, an initial acute gout attack resolves within 3 to 14 days. Subsequent attacks tend to last longer and may involve more joints.

Chronic gout can mimic rheumatoid or psoriatic arthritis.

U ric acid—urate in most physiologic fluids—is an end product of purine degradation. The serum urate level in a given patient is determined by the amount of purines synthesized and ingested, the amount of urate produced from purines, and the amount of uric acid excreted by the kidney (and, to a lesser degree, from the gastrointestinal tract).[1] A major source of circulating urate is the metabolized endogenous purine. Renal excretion is likely determined by genetic factors that dictate expression of uric acid transporters, as well as by the presence of organic acids, certain drugs, hormones, and the glomerular filtration rate. A small minority of patients will have increased production of urate as a result of enzymopathies, chronic hemolysis, or rapidly dividing tumors, psoriasis, or other disorders characterized by increased turnover of cells.

Humans do not have a functional enzyme (uricase) to break down urate into allantoin, which is more soluble and readily excreted. There may have been genetic pressures that explain why functional uricase was lost and why humans have relatively high urate levels compared with other species.[2] If higher levels of serum urate are clinically detrimental, one would think that humans could have evolved an efficient way to excrete it. Instead, we excrete uric acid inefficiently as a result of active reabsorption in the proximal renal tubule. We have higher levels of serum urate than most other species, and we are predisposed to develop gouty arthritis and perhaps other sequelae of hyperuricemia, including hypertension, the metabolic syndrome, and coronary artery disease.

■ CLINICALLY SIGNIFICANT HYPERURICEMIA VS LAB-DEFINED HYPERURICEMIA

Clinically significant hyperuricemia is a serum urate level greater than 6.8 mg/dL, although the population-defined "normal" urate level indicated by the clinical laboratory is higher. At levels above 6.8 mg/dL, urate exceeds its solubility in most biological fluids.

The reality that clinically significant hyperuricemia often differs from laboratory-defined hyperuricemia is underappreciated. **Figure 1** presents findings from a patient

Discordance between lab-defined 'normal' serum urate values and clinical findings

Laboratory report:

Serum urate

Value: 7.8 mg/dL

Low: 3.0 mg/dL

High: 8.0 mg/dL

FIGURE 1. Although this patient's serum urate concentration of 7.8 mg/dL was above the solubility level for urate, it was within the laboratory's range of normal values (left). Nevertheless, gout was confirmed in this patient by aspiration of a forearm tophus that accompanied his asymptomatic intradermal tophus shown here.

Photograph reprinted from Mandell BF, Cleve Clin J Med 2002; 69:720.

I saw in clinic. The patient's serum urate level was 7.8 mg/dL, which was within the laboratory's indicated range of normal values despite being above the solubility level for urate. The patient was referred for evaluation of "refractory arthritis," but he had gout, which we confirmed by aspiration of a forearm tophus (an intradermal tophaceous deposit from the same patient is shown in **Figure 1**). Gout had not been considered a likely diagnosis because of his "normal" urate value.

■ SERUM URATE CAN VARY BY SEX, AGE, DIET

Men generally have higher serum urate levels than premenopausal women; serum urate levels increase in women after menopause. For years these findings were attributed to an estrogen effect, but the mechanism was not well understood. Recently a specific transporter (urate transporter 1 [URAT1]) has been identified in the proximal tubule of the kidney[3] that seems primarily responsible for the reabsorption of uric acid. Estrogen has a direct effect on the expression of this transporter. It also seems that the hypouricemic effects of probenecid and losartan, as well as the hyperuricemic effects of organic acids and high insulin levels, may be mediated via modulation of URAT1 activity.

Urate values tend to be lower in children, and urate levels are generally affected only modestly by diet.[4] Epidemiologic studies, however, have linked increased ingestion of red meats and low ingestion of dairy foods with an increased incidence of gout.[5] Acute alcohol ingestion can cause fluctuations in the serum urate levels and may precipitate acute gout attacks.

■ HYPERURICEMIA LEADING TO GOUT

Urate concentrations greater than 6.8 mg/dL may result in the deposition of urate crystals in the tissues around joints and in other soft tissue structures (tophi). Why this occurs in only some patients is not known. Crystals, when mobilized from these deposits, can provoke the acute gouty flare. The tophi are not usually hot or tender. Biopsy of a tophus reveals a chronic granulomatous inflammatory response around the sequestered crystals. However, the tophi are not inert; the uric acid can be mobilized by mass action effect if the urate in surrounding fluid is reduced. If tophi are adjacent to bone, erosion into bone may occur.

■ CLINICAL PROGRESSION OF HYPERURICEMIA AND GOUT: FOUR STAGES OF A CHRONIC DISEASE

Although there is significant heterogeneity in the expression of gout, we can conceptualize a prototypic progression from asymptomatic hyperuricemia to chronic gouty arthritis.

Stage 1: Asymptomatic hyperuricemia. At a serum urate concentration greater than 6.8 mg/dL, urate crystals may start to deposit. During this period of asymptomatic hyperuricemia, urate deposits may directly contribute to organ damage. This does not occur in everyone, however, and at present there is no evidence that treatment is warranted for asymptomatic hyperuricemia.

Stages 2 and 3: Acute gout and intercritical periods. If sufficient urate deposits develop around joints, and if the local milieu or some trauma triggers the release of crystals into the joint space, a patient will suffer acute attacks of gout. These flares are self-resolving but are likely to recur. The intervals between attacks are termed "intercritical periods." During these periods, crystals may still be present at a low level in the fluid, and are certainly present in the periarticular and synovial tissue, providing a nidus for future attacks.

Stage 4: Advanced gout. If crystal deposits continue to accumulate, patients may develop chronically stiff and swollen joints. This advanced stage of gout is relatively uncommon but is avoidable with therapy.

Progression is variable

The progression from asymptomatic hyperuricemia to advanced gout is quite variable from person to person. In most people it takes many years to progress, if it does so at all. In patients treated with cyclosporine following an organ transplant, the progression can be accelerated, although the reasons are not fully understood.

■ ASYMPTOMATIC HYPERURICEMIA: TO TREAT OR NOT TO TREAT?

Clues for predicting the likelihood that an individual patient with asymptomatic hyperuricemia will develop articular gout are elusive. Campion and colleagues pre-

sented data on men without a history of gout who were grouped by serum urate level and followed over a 5-year period.[6] The higher the patient's urate level, the more likely that he would have a gouty attack during the 5 years. In this relatively young population of hyperuricemic men (average age of 42 years), less than 30% developed gout over this short period.

The dilemma is how to predict who is most likely to get gout and will benefit from early urate-lowering treatment, and who will not. Currently, clinicians have no reliable way of predicting the likelihood of gout development in a given hyperuricemic patient. A history of organ transplantation, the continued need for diuretics, an extremely high urate level, alcohol ingestion, low dietary consumption of dairy products, high consumption of meat and seafood, and a family history of gout at a young age suggest a higher risk of gouty arthritis. At present, treatment of asymptomatic hyperuricemia in order to prevent gouty arthritis is not generally recommended.

■ ACUTE GOUT FLARES: PAINFUL, UNPREDICTABLE, HIGHLY LIKELY TO RECUR

Acute flares of gouty arthritis are characterized by warmth, swelling, redness, and often severe pain. Pain frequently begins in the middle of the night or early morning. Many patients will describe awakening with pain in the foot that is so intense that they are unable to support their own weight. Patients may report fever and a flulike malaise. Fever and constitutional features are sequelae of the release of cytokines such as tumor necrosis factor, interleukin-1, and interleukin-6 following phagocytosis of crystals and activation of the intracellular inflammasome complex.[7] Untreated, the initial attack will usually resolve in 3 to 14 days. Subsequent attacks tend to last longer and may involve more joints or tendons.

Where flares occur

It has been estimated that 90% of first attacks are monoarticular. However, the first recognized attack can be oligoarticular or even polyarticular. This seems particularly true in postmenopausal women and in transplant recipients. Gout attacks initially tend to occur in the lower extremities: midfoot, first metatarsophalangeal joint, ankle, or knee. Over time, gout tends to include additional joints, including those of the upper extremities. Axial joints are far less commonly involved. The initial (or subsequent) attack may be in the instep of the foot, not a well-defined joint. Patients may recall "ankle sprains," often ascribed to an event such as "stepping off the curb wrong," with delayed ankle swelling. These may have been attacks of gout that were not recognized by the patient and thus not reported to his or her physician. Bunion pain may be incorrectly attributed to gout (and

vice versa). Therefore, we need to accept the limitations of historical recognition of gout attacks.

Acute flares also occur in periarticular structures, including bursae and tendons. The olecranon bursa, the tendons around the ankle, and the bursae around the knee are among the locations where acute attacks of gout can occur.

Risk of recurrence and implications for treatment

Based on historical data, the estimated flare recurrence rate is approximately 60% within 1 year after the initial attack, 78% within 2 years, and 84% within 3 years. Less than 10% of patients will not have a recurrence over a 10-year period. Untreated, some patients with gout will continue to have attacks and accrue chronic joint damage, stiffness, and tophi. However, that does not imply that published outcome data support treating every patient with urate-lowering therapy following an initial gout attack or even several attacks. There are no outcome data from appropriately controlled, long-term trials to validate such a treatment approach. Nonetheless, in some gouty patients, if hyperuricemia is not addressed, morbidity and joint damage will accrue. The decision as to when to intervene with urate-lowering therapy should be individualized, taking into consideration comorbidities, estimation of the likelihood of continued attacks, the impact of attacks on the patient's lifestyle, and the potential complications of needing to use medications to treat acute attacks.

■ INTERCRITICAL PERIODS: CRYSTAL DEPOSITION CONTINUES SILENTLY

Immediately after an attack of gout, patients may be apt to have another if anti-inflammatory therapy is not provided for a long enough period, ie, until several days after an attack has completely resolved. Subsequently, there may be a prolonged period before another attack occurs. During this time, uric acid deposits may continue to increase silently. The factors that control the rate, location, and degree of ongoing deposition in a specific patient are not well defined. Crystals may still be found in the synovial fluid of previously involved joints until the serum urate level is reduced for a significant period to a level significantly less than 6.8 mg/dL.[8]

■ ADVANCED GOUT: DIFFERENTIATION FROM RHEUMATOID ARTHRITIS IS KEY

Tissue stores of urate may continue to increase if hyperuricemia persists at biologically significant levels (> 6.8 mg/dL). Crystal deposition can cause chronic polyarthritis. Some patients, especially as they age, develop rheumatoid factor positivity. Chronic gout, involving multiple joints, can mimic rheumatoid arthritis. Patients can develop subcutaneous tophi in areas of friction or

FIGURE 2. Multiple tophi overlying both knees in a patient with unrecognized gout.

trauma. These tophi, as well as periarticular ones, can be mistaken for rheumatoid nodules. It is unclear why only some people with hyperuricemia develop tophi. The presence of urate crystals in the aspirate of a nodule (tophus) or synovial fluid will distinguish gout from rheumatoid arthritis. Radiographs can also be of diagnostic use.

Unlike radiographic findings in rheumatoid arthritis, in gout there is a prominent, proliferative bony reaction, and tophi can cause bone destruction away from the joint. There may be a characteristic "overhanging edge" of proliferating bone surrounding a gout erosion (see Figure 3 in preceding article by Schumacher, page S4). These radiographic findings, although distinct from those of rheumatoid arthritis, can be confused with psoriatic arthritis, which also can be erosive with a proliferative bone response. Gout, however, is less likely to cause joint space narrowing than is either psoriatic arthritis or rheumatoid arthritis.

Intradermal tophi **(Figure 1)** are asymptomatic and frequently not recognized, yet are not that rare in severe untreated gout. Such tophi may be particularly common in transplant patients and appear as white or yellowish deposits with the overlying skin pulled taut.

■ POSTSCRIPT: GOUT IS NOT SO EASILY RECOGNIZED AFTER ALL

There seems to be an impression that gout is easily diagnosed, and routinely and readily managed. Both the data and real-world clinical experience suggest the opposite, however. **Figure 2** shows the knees of a patient at the time of initial referral to my institution's rheumatology unit in 2006 for chronic joint pain. His tophaceous gout had not been recognized.

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Epidemiology of gout

■ ABSTRACT

The incidence and prevalence of gout are rising, likely as a result of a changing pattern of risk factors. At-risk populations are growing, due to the fact that people are living longer. Longevity and current dietary and lifestyle choices have also contributed to increased rates of co-morbidities associated with hyperuricemia and gout. The use of medications to treat such comorbidities also plays a role in some cases of gout. While dietary and lifestyle modification may be useful as adjunctive measures, such changes do not replace pharmacologic treatments for gout or associated comorbidities.

■ KEY POINTS

Although gout is more common in men, the diagnosis of gout should still be considered in women, particularly postmenopausal women.

Use of diuretics is a significant risk factor for gout.

Patients with hypertension, diabetes, hyperlipidemia, chronic kidney disease, or the metabolic syndrome are at increased risk for developing gout. Vigilance for gout is especially indicated in patients with metabolic syndrome.

Both the incidence and the prevalence of gout appear to be increasing worldwide.[1,2] Risk factors for the development of gout are related to our increasing longevity, dietary and lifestyle changes, and an increased prevalence of comorbid conditions. Patients with conditions such as hypertension, diabetes, cardiovascular disease, and the metabolic syndrome have an increased risk of developing hyperuricemia and gout,[1,2] and such conditions are frequently managed by primary care physicians. This paper discusses how these conditions, along with diet, alcohol intake, and lifestyle, contribute to the increasing prevalence of hyperuricemia and gout.[1]

■ PREVALENCE AND INCIDENCE: BOTH ARE RISING

The Third National Health and Nutrition Examination Survey (NHANES III) estimated the prevalence of gout in the US population to be 5.1 million between 1988 and 1994.[3] Data from a US managed care claims database revealed an increase in gout prevalence from 2.9 cases per 1,000 persons in 1990 to 5.2 cases per 1,000 persons in 1999.[4] Other studies indicate that gout is becoming more prevalent in societies such as New Zealand and Taiwan as well as in the United States.[5,6]

The NHANES III data show that gout affected more than 3 million men aged 40 years or older, and 1.7 million women aged 40 years or older, in the period from 1988 to 1994.[3] The estimated prevalence of gout among men aged 40 years or older makes this disease more common than rheumatoid arthritis and the most common form of inflammatory arthritis in adult men.[7–9]

The incidence of gout is also increasing. The Rochester Epidemiology Project estimated the incidence of gout in Rochester, Minn., for two 2-year periods: 1977–1978 and 1995–1996.[2] They found the age- and sex-adjusted annual incidence of gout to be higher in 1995–1996 (62.3 cases per 100,000 persons) than in 1977–1978 (45.0 cases per 100,000 persons). The annual incidence of primary gout (ie, in persons without exposure to diuretics) was more than twice as high in the more recent period than in the period 2 decades earlier, and this difference was significant both before ($P < .001$) and after ($P = .002$) adjustment for age and sex of the cohorts. As detailed in **Figure 1**, this investigation found that the incidence of gout was greater in men than in women and increased with advancing age in both sexes.[2]
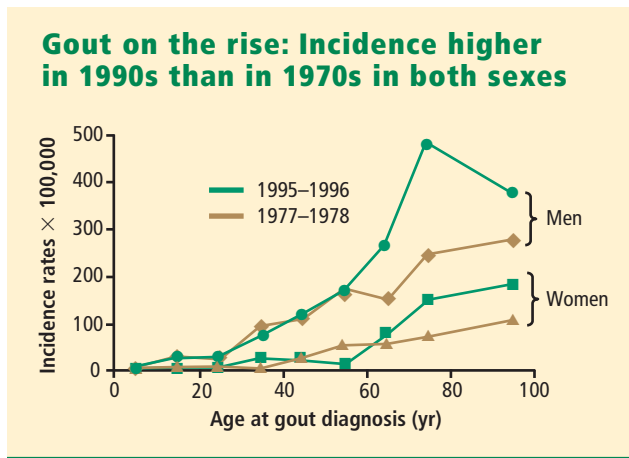
FIGURE 1. The incidence of gout in Rochester, Minn., in recent and remote 2-year periods according to age at diagnosis.

Reprinted, with permission, from *Journal of Rheumatology* (Arromdee E, et al. J Rheumatol 2002; 29:2403–2406).

■ RISK FACTORS FOR GOUT DEVELOPMENT

Sex and age

Figure 2 presents the prevalence patterns for gout by age and sex in a large general practice–based population database from the United Kingdom in a recent year (1999).[6]

Men have higher serum urate levels than women do, which increases their risk of developing gout. Development of gout before age 30 years is overwhelmingly more likely in men than in women.[7,9,10] The prevalence of gout in men increases with advancing age and peaks between ages 75 and 84 years.[6] Women have an increased risk of developing gout after menopause; the risk begins to rise at about age 45 years with the decrease in estrogen levels.[10,11] The incidence of gout becomes approximately equal between the sexes after age 60 years.[10,12]

It is important for clinicians to bear these factors in mind when taking the patient history and considering gout in the differential diagnosis. Although gout is more common in men, the diagnosis of gout should still be considered in women, particularly postmenopausal women.[10,11]

Medications

The use of diuretics is a significant risk factor for the development of gout. Diuretic use results in increased reabsorption of uric acid in the kidney, leading to hyperuricemia.[1,7,10,13] If reasonable, an alternative antihypertensive agent should be prescribed. Low-dose aspirin, commonly prescribed for cardioprotection, also increases urate levels slightly in elderly patients,[14] but should not be discontinued if indicated. Cyclosporine, which increases tubular reabsorption of urate,[1] can result in a type of rapidly ascending gout that frequently is polyarticular.[1,15] This is often encountered in transplant patients taking cyclosporine as an immunosuppressant.

Hyperuricemia is also seen in patients taking pyrazinamide, ethambutol, and niacin. Physicians should be aware of the risks and benefits of prescribing any of these drugs to a patient with gout and consider that they may precipitate a gout flare in a previously unaffected patient.

Comorbidities

Primary care physicians regularly see patients with hypertension, diabetes, hyperlipidemia, chronic kidney disease, cardiovascular disease, and the metabolic syndrome. As patients with these comorbidities are at an increased risk for developing gout,[1,10,11] it may be beneficial in these patients to inquire whether they have had any bouts of arthritic pain and periodically evaluate the serum urate level (which is no longer included on chemistry profiles).

Choi et al reviewed the NHANES III data to evaluate the relationship between gout and the metabolic syndrome.[11] The prevalence of the metabolic syndrome in study participants with gout was greater than 60%, whereas the prevalence in participants without gout was only about 25%. Metabolic syndrome prevalence increased with age, such that it was present in more than 70% of participants with gout aged 40 years or older **(Figure 3)**. Vigilance in regard to this particular association is essential for optimal patient care.

Obesity/high body mass index

Obesity and high body mass index significantly contribute to the risk of developing gout.[13,16] Choi and colleagues observed that the risk of gout is very low for men with a body mass index between 21 and 22 but is increased threefold for men whose body mass index is 35 or greater.[13] Obesity is associated with increased serum urate levels attributable to increased urate production and decreased renal urate excretion. A weight loss program may reduce the risk of gout by decreasing urate levels over time.[13,16]

Diet and alcohol consumption

A study by Choi and colleagues found that high intake of alcohol (beer more so than hard liquor or wine) and a diet rich in meat (particularly red meat, wild game, or organ meat) and seafood (particularly shellfish and some larger saltwater fish) increase the risk for developing gout.[17,18] Purine-rich vegetables, which were previously eliminated in low-purine diets, were found not to have any association with hyperuricemia and did not increase the risk of gout.[17,18] Frequent consumption of dairy products was found to slightly reduce the risk of gout and hyperuricemia.[17,18]

Although manipulation of diet and alcohol consumption alone rarely achieves the desired degree of serum urate reduction, adherence to changes in diet and

Gout prevalence: Higher in men, and fueled by advancing age up to the mid-80s
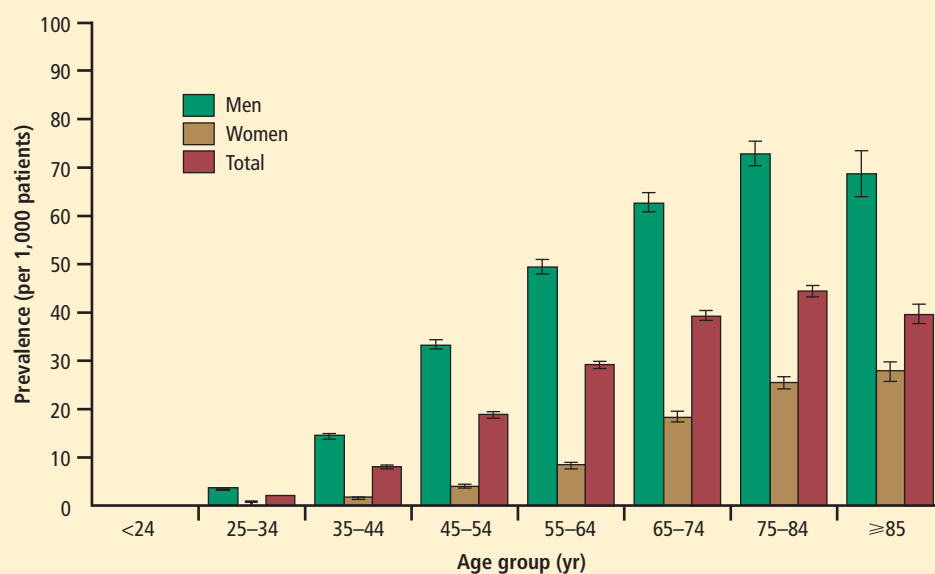
FIGURE 2. The prevalence of gout, stratified by age and sex, per 1,000 patients in the United Kingdom enrolled in the UK General Practice Research Database, a physician-validated electronic medical record.

Reprinted from *Annals of Rheumatic Diseases* (Mikuls TR, et al. Ann Rheum Dis 2005; 64:267–272) with permission from the BMJ Publishing Group.

Gout associated with higher prevalence of metabolic syndrome across age groups

FIGURE 3. Prevalence of the metabolic syndrome, by age, in adults with and without gout in the Third National Health and Nutrition Examination Survey (NHANES III). Based on data reported by Choi et al.[11]

alcohol intake will reduce flares of gout and assist in lowering serum urate levels.
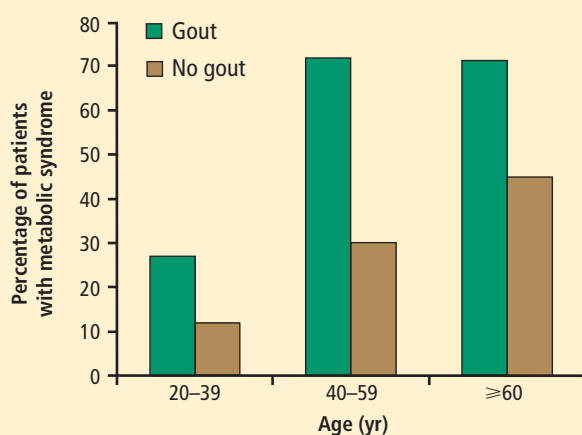
CONCLUSIONS

Diet, alcohol consumption, and lifestyle choices can increase the risk of developing gout, but making recom-

mended lifestyle changes does not replace pharmacologic treatments for existing gout or associated comorbidities. Furthermore, very few patients are likely to follow through with lifestyle changes such as weight reduction and a low-cholesterol diet.[19–21] Therefore, physician awareness of the factors that contribute to the development of gout is important, as is identification of at-risk patients before they develop manifestations of the disease. Increased vigilance in monitoring serum urate levels and monitoring for gout development in at-risk patients may help to improve the standard of care for gout.

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The role of hyperuricemia and gout in kidney and cardiovascular disease

ABSTRACT

Elevated serum urate levels are recognized as leading to gouty arthritis, tophi formation, and uric acid kidney stones. While serum urate elevations have long been associated with renal disease, they are not usually considered to have a causal role in kidney dysfunction. However, recent epidemiologic studies have identified serum urate elevations as an independent risk factor for chronic kidney disease. Hyperuricemia has also been found to be an independent risk factor for cardiovascular disease and hypertension. An animal model of mild hyperuricemia has shed new light on a potential mechanism of microvascular changes leading to endothelial dysfunction, a precursor to both coronary artery disease and hypertension. Additional animal studies and recent epidemiologic findings have provided further evidence that soluble urate is a risk factor for nonarticular disease.

KEY POINTS

Hyperuricemia significantly increases the risk of renal failure and end-stage renal disease.

Larger, more rigorous trials are under way to assess preliminary findings suggesting that urate-lowering therapy might normalize blood pressure in hypertensive adolescent patients.

Use of urate-lowering therapies to treat hyperuricemia is not currently supported in patients with kidney disease, heart disease, or hypertension in the absence of gout or uric acid kidney stones.

Hyperuricemia is a metabolic problem that has become quite common over the past several decades. The main clinical issues associated with hyperuricemia are gouty arthritis, gouty tophi, and uric acid kidney stones. For decades, these have been the main indications for lowering serum urate levels. Well-established nonarticular associations of hyperuricemia in gout include chronic kidney disease, coronary artery disease, and hypertension.[1] Recent animal studies and epidemiologic studies have shed new light on the relationship between urate and comorbid disease processes. This article describes our evolving understanding of the association of hyperuricemia and gout with kidney disease, hypertension, and cardiovascular disease, and also reviews the kidney's role in regulation of urate levels in the body.

SOURCES, DISTRIBUTION, AND ELIMINATION OF URATE

Uric acid is the end product of purine metabolism in humans. Sources of purine are either endogenous, from de novo synthesis and nucleic acid breakdown (approximately 600 mg/day), or exogenous, from dietary purine intake (approximately 100 mg/day).[2] In the steady state, this daily production and ingestion of approximately 700 mg of uric acid is balanced by daily elimination of an equal amount of uric acid from the body. Approximately 30% of this daily loss is through the gut, with subsequent bacterial intestinal uricolysis. The other 70% (roughly 500 mg daily) needs to be excreted by the kidneys.

In humans, plasma urate is freely filtered at the glomerulus, but the fractional excretion of the filtered uric acid is less than 10%. This demonstrates a dominance of reabsorptive processes in humans, and these processes are handled primarily by the selective urate transport protein known as URAT1 in the proximal convoluted tubules. In normouricemic individuals, there is a balance between
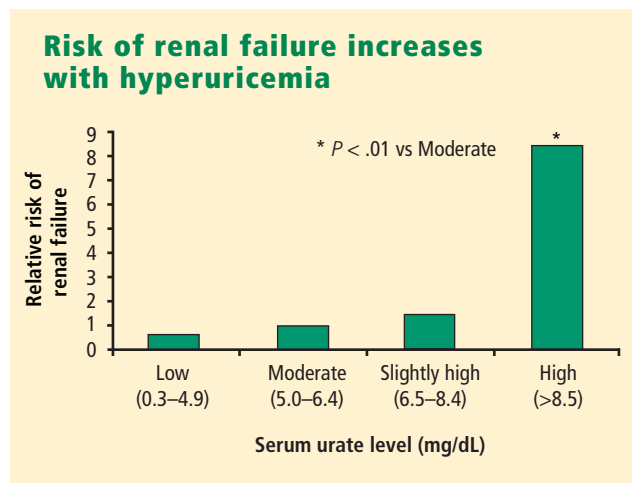
Risk of renal failure increases with hyperuricemia

FIGURE 1. Risk of renal failure in a prospective cohort study of 49,413 Japanese men stratified into quartiles by serum urate level. Risk was calculated relative to the quartile with "moderate" serum urate levels.[5]

the daily production and ingestion of uric acid and the daily excretion of it. In most patients with primary hyperuricemia and gout, the fractional excretion of uric acid by the kidneys is relatively diminished, resulting in an imbalance of uric acid homeostasis, and serum urate exceeds saturability (6.8 mg/dL at physiologic temperature and pH). As this imbalance persists over years and decades, the miscible serum uric acid pool expands and urate may be deposited as part of an insoluble urate pool in the joints and soft tissues, referred to as tophi.

In the past, most investigators have focused on the destructive and proinflammatory role of insoluble deposited urate crystals, but new evidence is accumulating that rising levels of soluble urate in body fluids may also be harmful and lead to kidney disease, hypertension, and cardiovascular disease.

■ RENAL MANIFESTATIONS OF HYPERURICEMIA

Urate is strongly associated with renal disease but traditionally has not been considered to have a causal role in kidney dysfunction. The exceptions have been uric acid kidney stones and the acute uric acid nephropathy associated with chemotherapy and tumor lysis syndrome. New epidemiologic studies in humans, as well as an animal model of mild hyperuricemia leading to microvascular changes in the glomerular afferent arterioles, shed new light on a possible direct role of urate in the genesis of idiopathic chronic kidney disease.

Longstanding reluctance to implicate urate in kidney disease

Significant impairment of renal function was reported in up to 40% of patients with gout in studies conducted

before the advent of effective urate-lowering therapies.[3,4] In these older studies, renal failure was the eventual cause of death in 18% to 25% of patients with gout.[3,4] However, any primary causal relationship for urate in this very high incidence of kidney disease was questioned for decades in light of the many other conditions and factors associated with hyperuricemia and gout that may contribute to kidney disease, such as hypertension, diabetes mellitus, alcohol abuse, nonsteroidal anti-inflammatory drug use, and lead toxicity.

Recent epidemiologic studies establish the connection

More recently, two large prospective population studies from Japan examined the relationship between serum urate level and development of kidney disease using multiple covariate analysis to adjust for age, blood pressure, body mass index, proteinuria, hematocrit, hyperlipidemia, fasting glucose, and serum creatinine.[5,6]

Tomita et al investigated the relationship between urate levels and various health hazards in a prospective cohort study that followed 49,413 male Japanese railroad workers aged 25 to 60 years for an average of 5.4 years.[5] They found a strong association between serum urate level and renal failure, even when adjusted for covariate effects, with high urate levels (> 8.5 mg/dL) conferring a greater than eightfold increase in the risk of renal failure relative to moderate urate levels (5.0 to 6.4 mg/dL) **(Figure 1)**.

Similarly, Iseki et al screened 48,177 Japanese adults and calculated the cumulative incidence of end-stage renal disease (ESRD) according to quartiles of baseline serum urate levels for each sex.[6] Mean baseline serum urate levels were 6.4 ± 1.4 mg/dL in men and 4.8 ± 1.1 mg/dL in women. The calculated incidences of ESRD per 1,000 screenees were 1.22 for men without hyperuricemia (urate < 7.0 mg/dL) versus 4.64 for men with hyperuricemia (urate ≥ 7.0 mg/dL) **(Figure 2)**. For women, the incidences per 1,000 screenees were 0.87 for those without hyperuricemia (urate < 6.0 mg/dL) versus 9.03 for those with hyperuricemia (urate ≥ 6.0 mg/dL) **(Figure 2)**. The researchers concluded that hyperuricemia was associated with a greater risk of ESRD even after adjustment for comorbidities. They also suggested that lowering urate levels to within "normal range" may reduce the population burden of ESRD.[6]

■ ASSOCIATION OF HYPERTENSION AND HYPERURICEMIA

The strong association between hypertension and hyperuricemia has been recognized for more than a century. In his original description of essential hypertension in 1879, Frederick A. Mohamed noted that many of his subjects came from gouty families.[7] Studies from the 1950s and 1960s showed the prevalence of hyperuricemia in hyper-

tensive subjects to be between 20% and 40%.[8,9] The prevalence of hypertension among gouty patients is between 25% and 50%.[10] In 1972, Kahn et al found that a rising level of serum urate is an independent risk factor for hypertension.[11] A year later, Klein et al demonstrated a linear relationship between serum urate level and systolic blood pressure in both black and white subjects.[12]

Six large epidemiologic studies published over the past 7 years have found that serum urate level predicts the later development of hypertension.[13–18] The most recent of these is the Normative Aging Study,[18] which showed that the serum urate level independently predicts the development of hypertension when using age-adjusted and multivariate models that include body mass, abdominal girth, alcohol use, serum lipid levels, plasma glucose level, and smoking status.

A potential mechanism emerges

No clear causal or mechanistic link between elevated serum urate and the development of hypertension was evident until a rat model of mild hyperuricemia was found to be associated with the development of an initial salt-insensitive hypertension that was reversible with restoration of normal urate levels.[19] However, if the urate-induced hypertension was allowed to persist, the rat would develop a salt-sensitive hypertension that was irreversible even if normouricemia was reestablished.[19]

This mechanism was tested in a small pilot study of 5 children with previously untreated essential hypertension who received monotherapy with allopurinol for 1 month.[20] All 5 children had substantial drops in their continuously monitored ambulatory blood pressure, and 4 of the 5 developed normal blood pressure (as assessed by continuous monitoring). After the allopurinol was stopped, the blood pressure of all 5 children rebounded to baseline levels.[20] A larger blinded, randomized, placebo-controlled crossover trial using the same intervention with similar results has been presented recently at national meetings.[21]

■ ASSOCIATION BETWEEN CARDIOVASCULAR DISEASE AND HYPERURICEMIA

There is considerable documentation that urate levels correlate with many recognized cardiovascular risk factors, including age, male gender, hypertension, diabetes mellitus, hypertriglyceridemia, obesity, and insulin resistance. Because of these relationships, the observed association between serum urate elevations and cardiovascular disease was considered to be "epiphenomenal" and not causal. Many older epidemiologic studies that demonstrated the increased cardiovascular risk associated with higher urate levels used traditional statistical techniques that could not prove the "independence" of urate as a risk factor.[22]
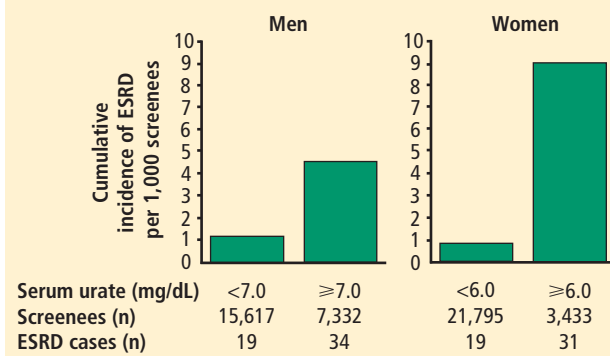
FIGURE 2. Cumulative incidence, over a 7-year period, of end-stage renal disease (ESRD) according to baseline serum urate level in a screened cohort of Japanese men and women.[6]

Reprinted from *American Journal of Kidney Diseases* (Iseki K, et al. Significance of hyperuricemia as a risk factor for developing ESRD in a screened cohort. Am J Kidney Dis 2004; 44:642–650), copyright 2004, with permission from Elsevier.

An independent effect is finally documented

Three studies published in the past several years demonstrate an independent risk relationship between hyperuricemia and cardiovascular disease, including acute myocardial infarction.[23–25]

Multivariate regression analysis of the Multiple Risk Factor Intervention Trial (MRFIT) database demonstrated hyperuricemia to be an independent risk factor for acute myocardial infarction.[23]

Similarly, the Italian Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) study showed that after adjustment for age, sex, diabetes, serum lipid levels, serum creatinine, left ventricular hypertrophy, blood pressure, and diuretic use, serum urate levels in the highest quartile were associated with increased risk of all cardiovascular events (relative risk [RR] = 1.73) and fatal cardiovascular events (RR = 1.96) compared with urate levels in the second quartile.[24]

Finally, follow-up of 4,385 participants in the Rotterdam Study over an average of 8.4 years revealed that high urate levels were a strong predictor of both myocardial infarction and stroke, even after adjustment for other vascular risk factors.[25]

■ CONCLUSIONS

Based on the preponderance of recent epidemiologic studies, it appears that an elevated serum urate level is an independent risk factor for kidney disease, hypertension, and cardiovascular disease. The precise mechanisms for urate-induced tissue injury remain unclear, and no large study to date has convincingly demonstrated

that lowering serum urate levels can prevent or lessen the risk of these potentially severe complications of hyperuricemia.

It should also be emphasized that the treatment of hyperuricemia with medications such as allopurinol or probenecid is currently not indicated in patients with hypertension, kidney disease, or heart disease. The use of these agents is supported only in the treatment of gout, the treatment of uric acid kidney stones, and the prevention of tumor lysis syndrome.

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The gout diagnosis

◼ ABSTRACT

Synovial fluid aspiration and analysis is the gold standard for making the diagnosis of gout but is not always performed when indicated in clinical practice. In clinical situations when joint aspiration simply cannot be performed, a presumptive (or clinical) diagnosis of gout may be made in consultation with published recommendations and criteria from expert societies. A thorough patient history and physical examination are critical to a presumptive diagnosis of gout, as is serum urate measurement at the time of an acute attack and at follow-up 2 weeks later.

◼ KEY POINTS

If the serum urate level was not elevated when measured during an acute attack of arthritis, it will likely be elevated at 2-week follow-up if the patient does indeed have gout.

Gouty tophi are typically found in the olecranon bursa, whereas rheumatoid nodules are usually located on the extensor surface of the forearm.

Urate crystals of gout are negatively bifringent and fine and needlelike in shape, whereas the crystals of pseudogout are weakly positively birefringent and rhomboid.

Gout and septic arthritis can coexist; when the differential diagnosis includes septic arthritis, joint aspiration is required.

Until criteria for the presumptive diagnosis of gout are validated, clinicians should become familiar with the technique of joint aspiration.

The presence of urate crystals in synovial fluid is the gold standard for diagnosing gout,[1] yet clinicians—both primary care physicians and rheumatologists—may not routinely perform synovial fluid analysis even when evaluating a patient who presents with an acute inflammatory arthritis.[2] This paper discusses the various reasons why this is so and reviews several important resulting clinical issues: how a presumptive diagnosis of gout is made, when to measure the serum urate level, and special considerations in the differential diagnosis.

◼ SYNOVIAL FLUID ANALYSIS: WHY IS THE GOLD STANDARD NOT MORE ROUTINE?

When synovial fluid containing monosodium urate crystals of gout is viewed under a polarizing microscope, bright yellow needlelike negatively birefringent crystals are seen[3] **(Figure 1A)**. Since synovial fluid analysis is the definitive method for diagnosing gout, why then is synovial fluid aspiration not performed routinely in clinical practice?

Occasionally, the aspirated joint does not appear to contain any joint fluid and the clinician may be concerned about the possibility of a "dry tap." Other possible reasons include lack of experience with synovial fluid aspiration and evaluation, or limited access to the polarizing microscopes used to examine synovial fluid. Time is another factor; in a busy primary care practice, where patients are usually seen approximately every 7 to 11 minutes, there may not be time to aspirate a joint. The urgency of fluid examination is another issue, as synovial fluid must be examined immediately, since the crystals can become smaller, less numerous, and less birefringent with time.[4]

◼ THE CLINICAL, OR PRESUMPTIVE, DIAGNOSIS

In the appropriate clinical scenario, a presumptive diagnosis of gout can be made on the basis of typical clinical features and the presence of hyperuricemia.[1,2]

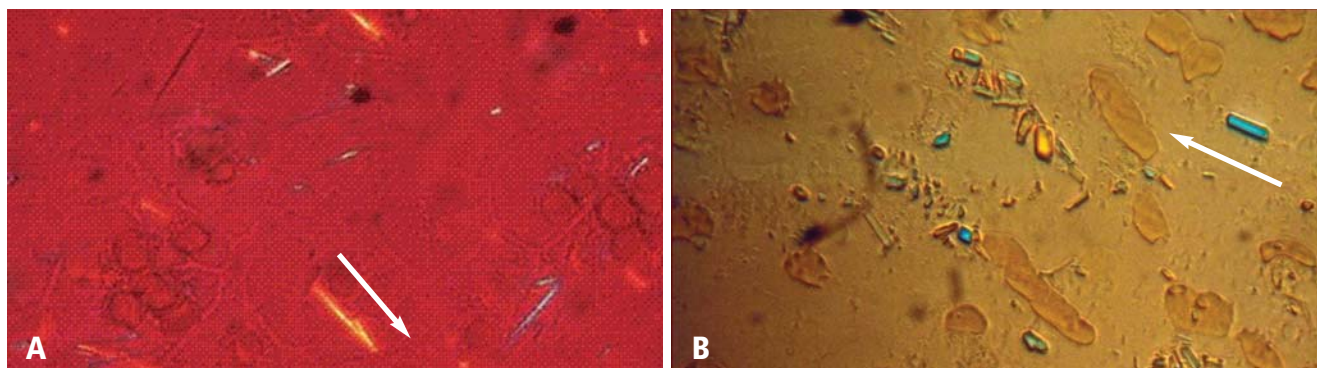### Expert societies offer guidance, but no validation studies to date

Evidence-based recommendations for the diagnosis of gout from the European League Against Rheumatism (EULAR) state that in acute attacks, the rapid development of severe pain, swelling, and tenderness that peaks within 6 to 12 hours, especially with overlying erythema,

FIGURE 1. (A) Monosodium urate crystals of gout appear as fine yellow needlelike crystals that are negatively birefringent under compensated polarized light. **(B)** In contrast, crystals of calcium pyrophosphate dihydrate (CPPD) crystal deposition disease are rhomboid in shape and weakly positively birefringent under compensated polarized light. Arrows alongside the crystals indicate the direction of the compensator.

Images courtesy of Brian F. Mandell, MD, PhD.

is highly suggestive of crystal inflammation although not specific for gout.[5] These recommendations further state that for typical presentations of gout (such as recurrent podagra [gouty pain in the great toe] with hyperuricemia), a clinical diagnosis alone is reasonably accurate.[5]

In 1977, the American College of Rheumatology (ACR) published its preliminary criteria for the diagnosis of acute gout, as outlined in **Table 1**.[6] It concluded that any of the following is highly suggestive of gout:[6]

- The presence of urate crystals in joint fluid
- A tophus containing urate crystals
- Fulfillment of 6 or more of the criteria in **Table 1**.

No subsequent studies have been published on the validity or usefulness of any of these diagnostic criteria.

What must inform the presumptive diagnosis

Both the EULAR recommendations and the ACR criteria state that although the gold standard for diagnosing gout is the presence of urate crystals on synovial fluid analysis, a clinical diagnosis of gout can be made on the basis of certain patient criteria. This clinical, or presumptive, diagnosis of gout should be made based on the following:

- A careful patient and family history, including questions regarding comorbid conditions frequently associated with gout (such as hypertriglyceridemia, diabetes, coronary heart disease, hypertension, and the metabolic syndrome) and whether the patient has had previous similar episodes of acute joint pain and swelling in the absence of trauma
- Thorough identification of all current medications, some of which may be associated with hyperuricemia
- A thorough physical examination.

■ THE PHYSICAL EXAMINATION FOR GOUT

Examination of patients with a history suggestive of gout should include not only the joints but also the extensor surface of the forearms and feet. When patients are seen for a visit and gout is suspected, they should be instructed to remove their shoes and socks and roll up their sleeves to allow examination for evidence of tophi, which would suggest a past history of gouty arthritis. The ear, knee, and olecranon bursa are other common sites for tophi,[3] so patients should also be asked to roll up their pants and sleeves and remove any head coverings.[7] In the late stages of gouty arthritis, multiple joints may be involved, which can cause the condition to be confused with other diagnoses such as psoriatic arthritis or erosive osteoarthritis.[7]

■ ACUTE PRESENTATIONS OF GOUT

The typical gout presentation is remarkable for very intense pain that often occurs at night when the extremities are colder. Precipitation of urate in the distal extremities can occur when the extremities are horizontal and tend to become cold.[8]

Approximately 90% of initial gout attacks are monoarticular, leaving only 10% of cases that are oligoarticular or polyarticular.[7] If more than one joint is involved, especially if the patient has a family history suggestive of gout or takes a medication that causes hyperuricemia, gout should be considered in the differential diagnosis even if the patient denies having a prior gout attack.

Frequently, patients will call their primary care physician during a gout attack but are not be able to schedule an appointment until after the attack has resolved. When possible, patients should be seen during the attack to confirm whether the attack is due to gout. A diagnosis of gout should not be made over the phone when a patient describes pain in the great toe, as only 50% of initial gout attacks occur in the great toe[7] and it is not known what proportion of acute pain episodes in the great toe are attributable to gout. The most common cause of pain in the great toe is osteoarthritis.

1	More than 1 attack of acute arthritis
2	Maximum inflammation develops within 1 day
3	Monoarthritis attack
4	Redness over joints
5	First metatarsophalangeal joint painful or swollen
6	Unilateral first metatarsophalangeal joint attack
7	Unilateral tarsal joint attack
8	Tophus (proven or suspected)
9	Hyperuricemia
10	Asymmetric swelling within a joint on radiography
11	Subcortical cysts without erosions on radiography
12	Monosodium urate monohydrate microcrystals in joint fluid during attack
13	Joint fluid culture negative for organisms during attack

FIGURE 2. Swollen, erythematous ankle and first metatarsophalangeal joints during an acute attack of gout.

the patient presents with acute joint pain.

It has been argued that a reduction in joint pain and swelling after the use of colchicine confirms a diagnosis of gout. However, other conditions—such as tendonitis, calcium pyrophosphate dihydrate (CPPD) crystal deposition disease (pseudogout),[3] and rheumatoid arthritis (RA)—can also improve after treatment with colchicine.[1]

Be vigilant for fever
Another consideration in making a clinical diagnosis of gout is the association with a low-grade fever; these patients may feel as if they have the flu.[8] Acute gout may also cause a high fever and an elevated white blood cell (WBC) count;[3] in this situation, synovial fluid aspiration must be performed to exclude septic arthritis, either alone or in the presence of gouty arthritis. In situations where septic arthritis is suspected, an emergency visit to a rheumatologist is indicated for synovial fluid aspiration to be performed, as gout and sepsis can coexist.[5] In such instances, Gram staining and culture of the synovial fluid should still be performed even if monosodium urate crystals are identified.[5]

■ MEASUREMENT OF SERUM URATE LEVELS
Measuring serum urate levels during an acute attack, treating the acute attack with anti-inflammatory medications, and reevaluating the patient in the office 2 weeks after the acute attack are all recommended in the management of a patient with gout. If the serum urate level was not elevated during the acute attack, it is likely to be elevated 2 weeks later if the patient has gout.[10] Elevated levels of serum urate during the intercritical periods are predictive of future gout attacks.[11] Measuring serum urate during the initial attack and then 2 weeks later yields two serum urate levels that can be compared to assist in considering a presumed diagnosis of gout. A study by Rigby and Wood concluded that in patients

Gout can also occur in the ankle or forefoot[7] (**Figure 2**) and may appear to be cellulitis.[1] In this instance, a prior history of a gouty attack, a family history of gout, an exposure to cold, binge drinking, or a history of hyperuricemia is suggestive of a gout diagnosis, but not definitively so.

■ SPECIAL CONSIDERATIONS FOR THE PRESUMPTIVE DIAGNOSIS OF GOUT

How long have acute attacks been occurring?
In a clinical scenario in which synovial fluid aspiration cannot be performed, the appropriateness of a presumptive diagnosis can be assessed by a discussion with the patient about how long he or she has been experiencing acute attacks of joint pain. If the attacks have occurred for more than 10 years, tophi will likely be present.[3] After even longer periods, gout may become polyarticular.[7] In postmenopausal women, the distal interphalangeal joints may be involved,[3] which may lead to a misdiagnosis of osteoarthritis, as these joints are typically affected by osteoarthritis.

Is the patient taking a urate-raising medication?
Certain medications have been associated with hyperuricemia, including cyclosporine and thiazide diuretics.[9] If a patient has been taking one of these medications, gout should be considered in the differential diagnosis if

FIGURE 3. (A) Rheumatoid nodules are firm and usually not movable but rather are attached to the extensor surface of the forearm. **(B)** Tophi appear as firm, gritty particles in the olecranon bursa.

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with low serum urate levels (< 4 mg/dL) 2 weeks following an inflammatory arthritis attack, a diagnosis of gout is unlikely.[12]

■ DIFFERENTIAL DIAGNOSIS OF GOUT

Rheumatoid arthritis

Patients with RA may present with nodules on their elbows, which can be mistaken for gouty tophi.[3] However, the differences between RA and gout are appreciated on careful physical examination. Rheumatoid nodules are firm and nontender on physical exam,[13] and usually are present on the extensor surface of the forearm **(Figure 3A)**, whereas gouty tophi are usually located in the olecranon bursa **(Figure 3B)**. In later stages of both RA and gout, the presentation can be that of a polyarticular inflammatory symmetric arthritis.[14] A misdiagnosis of RA may be made if the serum urate level is normal at initial presentation,[3] underscoring the importance of the followup visit 2 weeks after the attack. Serum urate levels are likely to be elevated after an attack, suggesting a clinical diagnosis of gout, per the EULAR recommendations,[5] if the attack occurred in the great toe. An elevated serum urate level alone is not sufficient to support a presumed diagnosis of gout.

CPPD crystal deposition disease (pseudogout)

CPPD crystal deposition disease, or pseudogout, must also be included in the differential diagnosis of gout. This disease usually occurs in joints previously affected by osteoarthritis or joints that have been injured in the past.[15] Attacks of CPPD crystal deposition disease commonly occur in the knee, in the wrist at the base of the thumb, or in the shoulder.[15] Radiographic examination may reveal a line of calcification along the cartilage outlining the joint.[15] Like gout, pseudogout attacks can occur spontaneously or after trauma, surgery, or a severe illness such as myocardial infarction or stroke.[16]

The presentation of pseudogout can be very similar to an acute attack of gout. The difference is seen when evaluating the crystals through a polarizing microscope. CPPD crystals are weakly positively birefringent **(Figure 1B)**, in contrast to the negatively birefringent crystals seen with gout **(Figure 1A)**.[7] If a polarizing microscope is not available, the crystals usually can be distinguished by their differing shapes: urate crystals are fine and needlelike, whereas CPPD crystals are rhomboid **(Figure 1)**.

Septic arthritis

When the differential diagnosis includes septic arthritis, the joint must be aspirated; a presumed diagnosis cannot be made. Among patients with an acute gouty attack, lowgrade fever is reported during the attack in 29% of gout patients and 38% of patients with CPPD crystal deposition disease.[14] Temperatures of 101°F or higher are not usually seen in patients with gout or CPPD crystal deposition disease and suggest an infection, although patients with septic arthritis may be afebrile, especially if they are taking immunosuppressive therapy or glucocorticoids, which can inhibit a febrile response. Synovial fluid analysis in patients with gout and septic arthritis can reveal WBC counts above 100,000 per mm^3, whereas synovial fluid WBC counts above 50,000 per mm^3 are more common in infection.

As noted earlier, gout and septic arthritis can coexist. In a patient presenting with a fever and a warm erythematous swollen joint, synovial fluid aspiration must be performed and evaluated for the presence of crystals *and* bacteria. The patient may require treatment for both causes of acute monoarticular arthritis.

In a patient undergoing renal dialysis, where gout or pseudogout can occur and where there is frequent intravascular manipulation, a septic joint can occur simultaneously.[3,14] In this situation, not only must joint aspiration be performed, but the synovial fluid also needs to be evaluated for both crystals and bacteria. Again, the patient may require treatment for both causes of acute monoarticular arthritis.

CONCLUSIONS

The gold standard for diagnosing gout remains synovial fluid aspiration and analysis. In clinical situations when joint aspiration cannot be performed, the EULAR recommendations[5] and the ACR criteria[6] provide guidance for making a clinical or presumptive diagnosis of gout. A thorough patient history—both personal and family—and physical examination are critical in making a presumed diagnosis of gout. If the patient presents during an acute attack, serum urate measurement may be useful in making a clinical diagnosis if it reveals an elevated level. When the patient returns for follow-up 2 weeks later, a second serum urate measurement should be taken to allow comparison of the two levels. If the serum urate level is elevated at the follow-up visit, the EULAR recommendations state that a clinical diagnosis of gout can be made if the patient had an acute attack of arthritis in the great toe.

As noted in the EULAR recommendations, the future research agenda should include validating the clinical manifestations of gout against a diagnosis established by identification of urate crystals on synovial fluid analysis.[5] Until this task can be completed, clinicians should become familiarized with the technique of joint aspiration so that in situations where a clinical or presumptive diagnosis of gout cannot be made—including cases where the differential diagnosis includes a septic joint—clinicians will be able to perform aspiration with confidence.

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The practical management of gout

◼ ABSTRACT

Gout management requires a comprehensive strategy that considers both acute and chronic aspects of the disease. Acute gout flares should be treated with anti-inflammatory agents as rapidly as possible. The underlying hyperuricemia may be treated with urate-lowering agents initiated at a time appropriate for the individual patient. Successful urate lowering ultimately prevents flares and disease progression and should be started immediately in patients with advanced or tophaceous disease. When urate-lowering therapy is initiated, anti-inflammatory prophylaxis should be used to reduce the risk of flares induced by abrupt changes in urate levels. Regular monitoring of serum urate can ensure therapeutic dosing of urate-lowering agents to achieve levels below 6 mg/dL, which are associated with a reduction in flares and tophi.

◼ KEY POINTS

A patient's comorbidities and other medications should guide the choice of anti-inflammatory agent for acute attacks.

NSAIDs are the treatment of choice for acute gout attacks; colchicine and corticosteroids are alternatives when NSAIDs are contraindicated.

Urate-lowering therapy to address underlying hyperuricemia is generally a lifelong commitment, as intermittent therapy can lead to recurrent gout flares.

To apropriately manage gout, it is important to distinguish between treatment of acute gout attacks and management of the underlying metabolic defect. While acute attacks are treated with anti-inflammatory agents, the underlying hyperuricemia must be addressed by lowering the serum urate concentration to levels that lead to prevention of acute flares, together with consideration of the contributing role of the patient's lifestyle factors and comorbidities. This article surveys treatment options for both acute gout attacks and the underlying hyperuricemic state, focusing on considerations to guide therapy selection and optimize prospects for treatment success.

◼ ACUTE GOUTY ARTHRITIS: ANTI-INFLAMMATORY AGENTS AND KEY ISSUES FOR THEIR USE

Acute attacks of gouty arthritis can be treated with any of several anti-inflammatory agents **(Table 1)**. The earlier anti-inflammatory treatment is started, the more rapidly the acute flare will subside. Adequate dosing and duration is important; treatment should be continued until the flare has resolved and then reduced in tapered doses for at least 2 to 3 days after all overt signs of inflammation are gone.

One of the most important considerations in selecting an anti-inflammatory medication is how the patient's comorbidities, such as renal disease, or concurrent medications may influence the choice of agent, as outlined in **Table 1**.

Nonsteroidal anti-inflammatory drugs (NSAIDs)
A number of NSAIDs are available to treat acute flares of gout.[1–3] When used at a full anti-inflammatory dose, all NSAIDs appear to be equally effective.

NSAIDs must be used cautiously in patients who have any of a number of comorbid conditions, as detailed in **Table 1**. If a patient is otherwise healthy—without significant renal, cardiovascular, or gastrointestinal disease—and has no history of aspirin allergy, NSAIDs are the treatment of choice for acute gout attacks. Use of a proton pump inhibitor can improve gastrointestinal tolerance of NSAIDs and reduce the likelihood of gastric bleeding but may not avoid other concerns. Indomethacin can cause headache or even confusion, particularly in the elderly.

Colchicine
Colchicine can be an effective alternative for acute therapy.[4,5] If a patient with previously documented gout can be coached to begin colchicine at the first hint of a

TABLE 1

Commonly used therapies for acute gout flares, and considerations to guide their use

Drug/class	Examples/dosage	Contraindications/reasons for caution in use	Drug interactions
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Indomethacin (50 mg 3 times daily) Naproxen (500 mg twice daily)	Severe heart failure, peptic ulcer disease, gastrointestinal bleeds, aspirin-induced or NSAID-induced asthma, renal impairment	Warfarin
Colchicine	0.6 mg 3 times daily*	Dialysis (contraindication), renal or hepatobiliary dysfunction	Cyclosporine, statins, macrolides
Corticosteroids	Prednisone (20–40 mg/day) Intra-articular methylprednisolone (20–40 mg)	Diabetes, infection	

* Adjust for creatinine clearance in patients with mild renal impairment.

gout attack, a full-blown attack often can be prevented. A colchicine regimen of 0.5 or 0.6 mg 3 times daily, although not well studied, may be effective while limiting the diarrhea, nausea, and vomiting that is predictable with hourly colchicine dosing.[6,7] Colchicine must be used cautiously in patients with renal or liver disease and is contraindicated in patients undergoing dialysis.[8]

Corticosteroids

Systemic corticosteroids are often used for polyarticular gout or in patients with contraindications to NSAIDs or colchicine.[9] When they are used in diabetic patients, glycemic control must be monitored, and an increased insulin dose can be prescribed temporarily until glucose levels normalize.

Corticosteroids may also be injected directly into the joint, as this approach offers reduced risks compared with oral administration. Direct injection is especially useful in patients with attacks that involve only one or two joints.

■ TREATING THE UNDERLYING HYPERURICEMIA THROUGH URATE-LOWERING STRATEGIES

Terminating the acute flare manages gout symptoms but does not treat the underlying disease. Crystals often remain in the joint after flares have resolved. Addressing the underlying metabolic condition requires lowering serum urate levels, which can deplete crystals and reduce or prevent gout flares.

The goals of urate-lowering therapy are to reduce serum urate levels to less than 6 mg/dL in order to mobilize and deplete crystals with minimal toxicity.[10]

Role of lifestyle interventions

As discussed by Weaver earlier in this supplement (pages S9–S12), obesity and certain patterns of food and alcohol consumption can increase the risk of developing hyperuricemia and gout. In addition to weight loss, dietary changes—such as reducing intake of animal purines, high-fructose sweeteners, and alcohol, and increasing intake of vitamin C or bing cherries—may lower serum urate levels modestly (ie, by 1 or 2 mg/dL).[11–15] While lifestyle interventions may be all that is needed in some patients with early mild gout, such interventions gener-

ally do not replace the need for urate-lowering drug therapy in cases of existing gout. Accordingly, this discussion focuses on medications used to treat hyperuricemia in the United States: the xanthine oxidase inhibitor allopurinol and the uricosuric agent probenecid.

Initiating urate-lowering drug therapy

Chronic therapy should be discussed with the patient early in the course of the disease. Treatment recommendations need to be individualized based on the patient's overall health, comorbidities, and willingness to adhere to chronic treatment.

Initiation of urate-lowering therapy is appropriate to consider after the acute attack has fully resolved and the patient has been stable for 1 to 2 weeks. If a patient's serum urate level is very high (eg, > 10 mg/dL), urate-lowering therapy may be initiated even after a single attack, as progression is more likely to occur with higher levels. Treatment should be initiated long before tophi or persistent joint damage develop. If the patient already has objective radiographic evidence of gouty changes in the joints, or if tophi or nephrolithiasis are present when the patient is first seen, urate-lowering therapy should be started.

Concurrent low-dose anti-inflammatory prophylaxis

Abrupt decreases (or increases) in serum urate levels may precipitate gout flares. For this reason, anti-inflammatory prophylaxis should be used when urate-lowering therapy is initiated, as it can quickly reduce serum urate levels. Colchicine (0.6 mg once or twice daily)[8] or NSAIDs (eg, naproxen 250 mg/day) prescribed at lower than full anti-inflammatory doses may be used to prevent flares in this setting. When using long-term colchicine in a patient with renal disease, lower doses must be used and the patient should be monitored closely for reversible axonal neuromyopathy and vacuolar myopathy or rhabdomyolysis; the latter complication may be more frequent in patients taking concurrent statin or macrolide therapy. There are no controlled studies on the benefits and safety of prophylactic NSAID use in gouty patients with comorbidities.

Borstad et al documented in a placebo-controlled study that colchicine prophylaxis at the time of allopurinol initiation reduces flares but does not completely

TABLE 2
Considerations in using urate-lowering therapy

Agent	Considerations
Allopurinol	Effective in urate underexcretors and overproducers
	Renal function may require dose adjustment
	Drug interactions (eg, azathioprine); requires dose adjustment
	Target serum urate not always easily achieved; high doses may be necessary
	Rare but potentially fatal hypersensitivity syndrome
Uricosurics	Renal function (ineffective if creatinine > 2 mg/dL)
	Drug interactions (eg, aspirin)
	Target serum urate not always achieved
	Risk of nephrolithiasis in urate overproducers
	Fluid intake should be increased
	Twice-daily dosing required

abolish them.[16] From 0 to 3 months after therapy initiation, the mean number of flares was 0.57 in patients who received colchicine versus 1.91 in patients who received placebo (P = .022); from 3 to 6 months after initiation, the mean number of flares was 0 versus 1.05 in the respective patient groups (P = .033).[16]

Depending on the body's urate load, it may take many months to deplete crystals. There is evidence that prophylaxis should be used for at least 3 to 6 months to reduce the risk of mobilization flares.[16] Patients should be warned during this time that gout flares may still occur and should be treated promptly. Prophylaxis should continue longer in patients with tophi, often until the tophi have resolved.

Allopurinol
The xanthine oxidase inhibitor allopurinol works by blocking production of uric acid and can be used in any patient with gout (Table 2). When initiating allopurinol, the safest option is to start all patients on 100 mg/day and increase the dose gradually to attempt to lower the risk of mobilization flares. Achieving full therapeutic benefit, including a reduction in flares, frequently requires doses greater than the commonly used 300 mg/day.[17] The serum urate level should be monitored every 2 weeks during dose escalation until the level is less than 6 mg/dL. Once a stable level is established, the serum urate can be checked once or twice a year to ensure that therapeutic concentrations are maintained.

The rare but potentially fatal hypersensitivity syndrome is a concern with allopurinol. If a rash develops in a patient taking allopurinol, the drug should be discontinued, as rash can be a precursor of severe systemic hypersensitivity.

Renal function must be considered in allopurinol dosing, and treatment should always be initiated at lower doses in patients with renal disease.[18] However, recent reports indicate that allopurinol doses can be gradually and safely increased to an effective level that achieves a serum urate concentration of less than 6 mg/dL even in patients with reduced kidney function.[19,20]

Uricosurics
The uricosuric agent probenecid works by increasing the urinary excretion of urate.[10] Probenecid is commonly dosed at 500 mg twice daily, with a maximum daily dose of 2 g, in an attempt to reach the target serum urate level. Probenecid is unlikely to be effective if the patient's serum creatinine is greater than 2 mg/dL.[21]

When a uricosuric agent is used, a 24-hour urine urate measurement must be taken to identify and exclude urate overproducers (patients with more than 800 to 1,000 mg of uric acid in a good 24-hour collection), as such patients are at risk for uric acid kidney stones. Additionally, aspirin interferes with probenecid's effect on the renal tubules. The ideal candidate for uricosuric therapy has good kidney function, is not a urate overproducer, and is willing to drink 8 glasses of water a day to minimize the risk of kidney stones (Table 2).

Evidence supporting urate targets and continuous maintenance of urate reductions
If a serum urate level of less than 6 mg/dL is achieved and maintained, gout flares will be reduced and crystals can be depleted from inside the joint.[22–25] Additionally, the size of tophi can be reduced and their recurrence prevented.[26–28] Serum urate levels below 4 mg/dL can result in more rapid dissolution of tophi.[26]

Urate-lowering therapy with allopurinol or probenecid is generally a lifelong commitment. Intermittent therapy or cessation of therapy can lead to recurrent attacks.[21,28,29] In a randomized trial examining outcomes of continuous versus intermittent urate-lowering therapy with allopurinol, gout attacks were eliminated after about 2 years of therapy in patients who continuously received allopurinol, whereas they continued to recur beyond 2 years in patients who received allopurinol intermittently (ie, due to the way it was prescribed or nonadherence) (Figure 1).[29]

Patient commitment and education are essential
No treatment plan will succeed without the commitment of the patient, so discussion to determine the patient's willingness to commit to lifetime therapy is warranted. A number of surveys have shown that the rate of continued use of allopurinol after it is initially prescribed is less than 50%.[17] If the physician or nurse monitors adherence, however, treatment is more likely to be successful.[30]

Patients need more education about gout, as education may improve adherence and treatment success. Patient education material is available from the Arthritis Founda-
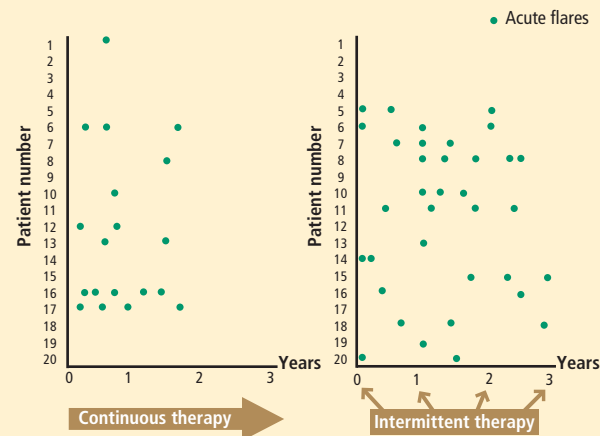
FIGURE 1. Frequency of acute gout flares in a randomized trial of patients with gout who received allopurinol either continuously (left) or on an intermittent basis (right).[29]

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tion (www.arthritis.org/disease-center.php) and the Gout & Uric Acid Education Society (www.gouteducation.org).

■ CONCLUSION

A comprehensive treatment strategy is critical to ensure ideal gout therapy. Acute flares should be addressed as rapidly as possible with an anti-inflammatory agent selected on the basis of the patient's comorbidities and other medications. Most patients require chronic urate-lowering therapy to deplete crystals from joints and prevent flares. Initiation of urate-lowering therapy should be considered early in the disease course, following resolution of the acute attack. Low-dose anti-inflammatory prophylaxis should be initiated when any urate-lowering therapy is started. Regular monitoring of serum urate will ensure effective dosing to achieve a target serum urate level of less than 6 mg/dL. Once urate deposits are depleted, acute flares should cease.

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