IN PRACTICE

Management of Hyperuricemia and Gout in CKD

Angelo L. Gaffo, MD, and Kenneth G. Saag, MD, MSc

INDEX WORDS: Management; hyperuricemia; gout; chronic kidney disease.

CASE PRESENTATION

A 55-year-old man with history of kidney transplantation 3 years ago because of diabetic nephropathy has severe tophaceous gout. He has been unable to tolerate treatment with allopurinol because of worsening skin rashes. His last serum creatinine level was 2.3 mg/dL (203.3 μmol/L). Current medications include tacrolimus, mycophenolate mofetil, and prednisone at a dose of 20 mg/d orally. He presents to the emergency department with red, hot, swollen, and painful knees and wrists. His temperature is 99.5°F, gouty tophi are evident in the hands, and a peripheral-blood white blood cell count is 12.5 × 10^3/μL with 90% polymorphonuclear leukocytes without band forms. An aspirate of one of his knees shows 40,000 nucleated cells with 50% polymorphonuclear leukocytes. Abundant intracellular negatively birefringent needle-shaped crystals are observed under polarized microscopy.

INTRODUCTION

Hyperuricemia has been associated with worsening kidney function, metabolic syndrome, and hypertension. Although the clinical implications of these findings are not yet fully clear, serum urate level may become an additional risk factor to screen for and treat in patients under evaluation or at risk of these conditions. Gout, the clinical manifestation of the deposition of monosodium urate crystals in joints, has become more prevalent in Western populations and specific groups of patients, including those with solid-organ transplants. The management of gout becomes especially challenging in patients with decreased kidney function because some gout therapies have a greater rate of adverse events and drug interactions in these patients.

DEFINITIONS AND PATHOPHYSIOLOGICAL CHARACTERISTICS OF HYPERURICEMIA AND GOUT

Uric acid (or urate) is the end product of purine metabolism in humans and several other higher primates. Accumulation of urate beyond its excess solubility point (6.8 mg/dL [404 μmol/L]) defines hyperuricemia, a necessary, but not sufficient, factor for the development of gout, the disease state characterized by tissue deposition of monosodium urate crystals and its associated symptoms.

Urate is synthesized in the liver from purine compounds provided by diet and the endogenous pathway of purine synthesis de novo. It then is released into the circulation almost exclusively in its soluble form (monosodium urate), which is readily available for filtration in the proximal tubules of the kidney.

Hyperuricemia develops because of either overproduction (excretion > 600 mg/d in urine; accounting for 10% to 15% of hyperuricemia cases) and underexcretion (excretion < 330 mg/d; ~85% to 90% of hyperuricemia cases). Both overproduction and underexcretion could be primary, such as in inherited enzymatic disorders of urate production (hypoxanthine-guanine phosphoribosyl transferase defect or phosphoribosylpyrophosphatase synthetase overactivity) or the condition known as familial juvenile hyperuricemic nephropathy. The latter underexcretion disorder...
has been described in Japanese families and is caused by a defect in the autosomal dominant gene encoding uromodulin. This same defect seems responsible for medullary cystic kidney disease type 2. How a uromodulin defect affects urate reabsorption is unclear, but alterations in permeability of the renal loops affecting the countercurrent gradients in a manner similar to diuretics have been postulated as a possible mechanism. Secondary or acquired causes of overproduction and underexcretion are caused by excessive purine turnover (diet or malignancies), medications, and toxins. For an expanded list of causes of hyperuricemia, see Table 1.

After nearly complete filtration in the glomerulus, urate undergoes extensive reabsorption in the proximal tubule, largely mediated by the recently characterized organic anion transporter URAT-1. URAT-1, located in the luminal aspect of the renal proximal epithelial cell, mediates the reabsorption of luminal urate in exchange for intracellular anions (e.g., lactate and nicotinamide). The important role that URAT-1 has in the physiological process and management of hyperuricemia has been clarified by several findings: most drugs that are uricosuric (probenecid, losartan, sulfinpyrazone, benz bromarone, and high doses of salicylate) act by inhibiting URAT-1 from the luminal side, such urate-retentive compounds as pyrazinamide act as exchange anions for urate at the level of URAT-1, and finally, individuals with inherited mutations in the URAT-1 coding gene SLC22A12 have a clinical syndrome characterized by hypouricemia, uricosuria, and renal failure. Japanese families with a lower frequency of gout, apparently secondary to being heterozygous for a less active form of URAT-1, also have been reported. A second urate-transporter (UAT-1) has been described and is more widely distributed in tissues than URAT-1, but its exact role in the renal handling of uric acid has not been clarified (Fig 1B).

After the first round of reabsorption, a second cycle of secretion and further reabsorption occurs in the distal portions of the proximal tubule. These final steps determine net urate excretion; typically 8% to 12% of the initially filtered load (Fig 1A).

When hyperuricemia ensues, the probability of having an acute gout flare depends on the urate concentration in the tissue or joint and other predisposing factors, such as low pH, low temperature, previous trauma to the joint, and lack of joint mobility (e.g., during sleep; perhaps by increasing water reabsorption and urate concentration). Monosodium urate crystals are capable of activating both the humoral and cellular arms of the immune system and are potent stimulators of neutrophil recruitment and adhesion, possibly through the action of interleukin 8, the neutrophil chemotactic factor CXCR2, or stimulation of macrophage activation with granuloma formation. A recent hypothesis for initiation of the inflamm-
tory process induced by monosodium urate crystals is through activation of intracellular innate-immunity receptors known as nucleotide-binding oligomerization domain–like receptors. These promote activation of inflammatory caspases and multiprotein complexes known as inflammasomes, which in turn induce the production of interleukin 1β (IL-1β) by activated macrophages upregulating nuclear factor κB (NF-κB) and interleukin 8.16

RISK FACTORS ASSOCIATED WITH THE DEVELOPMENT OF GOUT

Hyperuricemia

The importance of hyperuricemia in the prediction of subsequent risk of gout was confirmed in the Normative Aging study,17 a cohort of 2,046 men observed for 15 years. The risk of gout followed a gradient depending on the initial serum urate level. With an initial level greater than 9 mg/dL (>535 μmol/L), the annual incidence rate was 4.9%. When the initial level was 7.0 to 8.9 mg/dL (416 to 529 μmol/L), the annual incidence rate was 0.5%, but it decreased to 0.1% with urate levels less than 7.0 mg/dL (<416 μmol/L). The importance of hyperuricemia as the strongest risk factor for gout is not only limited to the initial diagnosis, as shown in a recent prospective study,18 in which low serum uric acid levels predicted freedom from recurrence of gout flares in patients who had discontinued urate-lowering therapy.

Diet and Alcohol

The effect of diet as a risk factor for hyperuricemia and gout has been clarified by recent epidemiological evidence. In a cross-sectional study of 14,809 Third National Health and Nutrition Examination Survey (NHANES III) participants (1988-1994), total meat and seafood consumption was associated with greater serum uric acid levels. However, dairy intake was associated with lower serum uric acid levels. Surprisingly, protein intake had no independent association with urate levels.19 In a prospective analysis of 47,150 participants in the Health Professionals Follow-up Study,20 the risk of incident gout was studied in groups stratified by quintiles according to their intake of food and nutrients. Similar to NHANES III, individuals with greater intake of seafood and meat had greater risk of the development of gout. Dairy food intake appeared to be protective, and total protein with purine-rich vegetables (eg, spinach and lentils) had no independent effect on gout risk.

Using the same databases, the role of alcoholic beverages has been better elucidated. Cross-sectional data from NHANES III showed that beer and liquor were associated with greater serum urate levels. However, moderate levels of wine intake were not associated with serum urate levels.21 Results again were similar in the Health Professionals Follow-up Study.22 Finally, an internet-based case-cross-
over study of 197 volunteers found that alcohol intake within the preceding 24 hours increased the risk of gout flares.23

Medications and Toxins

Many medications and chemical compounds influence renal handling of uric acid. Aspirin appears to have a dual effect on serum urate levels; high levels of intake (>3 g/d) are uricosuric and lower intake (1 to 2 g/d) promotes urate retention.24,25 More recent studies of the effects of the doses commonly used for cardiovascular protection (75 to 81 mg) found a small, but significant, effect in promoting urate retention.26 Diuretics (both loop and thiazides) are associated with greater serum urate concentrations, possibly through volume contraction and concurrent stimulation of urate reabsorption at the level of the URAT-1 receptor in the proximal tubules.27 A recent case-control study has challenged this traditional view, postulating that the association between diuretics and gout is confounded by the conditions associated with diuretic use; namely, hypertension, heart failure, and myocardial infarction.28

Cyclosporine is a widely used drug for immunosuppression posttransplantation and, to a lesser degree, in patients with other autoimmune diseases. It has been strongly associated with the development of hyperuricemia and gout.5 However, the mechanism for cyclosporine’s strong association with hyperuricemia is unclear and may include an inhibitory effect on urate secretion,29 stimulation of urate reabsorption,30 or through a decreased glomerular filtration rate.31 Tacrolimus also commonly is used in transplantation immunosuppressive regimens and has been reported to increase serum urate levels in a manner similar to cyclosporine.32 However, data from the US Renal Data System in combination with Medicare claims data suggest that it may induce less clinical gout in kidney transplant recipients (hazard ratio for cyclosporine versus tacrolimus, 1.24; 95% confidence interval, 1.06 to 1.45).33 Other drugs and toxins associated with hyperuricemia and gout include lead, pyrazinamide, ethambutol, and niacin.34

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Gout is a chronic disease that, if untreated, typically occurs in 4 phases: (1) asymptomatic hyperuricemia, (2) acute gout flares, (3) intercritical periods (asymptomatic periods between acute gout flares), and (4) chronic, usually tophaceous, gout. As described previously, the cumulative incidence of gout is significantly increased in individuals with greater serum urate levels.17 Typically, acute gout flares present as warmth, swelling, erythema, and pain of abrupt onset in the involved joint, with symptoms peaking during 8 to 12 hours. Nighttime presentations are common, with fever, chills, and malaise usually part of the initial presentation, particularly in patients with polyarticular flares.35 In the elderly, atypical presentations may include delirium. The most commonly involved joints are in the feet, with the first metatarsophalangeal eventually involved in more than 90% of cases; ankles; knees; elbows; wrists; and fingers.36 The predilection for the lower extremities is believed to be caused by the lower temperatures in these joints, which favors the precipitation of uric acid crystals. Extra-articular sites also commonly are involved, including bursae (the olecranon and prepatellar bursae are the most commonly affected sites) and tendon sheaths.37 The first attack usually is monoarticular and involves the first metatarsophalangeal in 50% of cases. Common precipitants of gout flares include acute illness (trauma, sepsis, and surgery), alcohol abuse, starvation, excessive intake of certain food groups, and medications. In addition to thiazides and cyclosporine, initiation of allopurinol therapy can predispose to acute attacks.6 Untreated attacks frequently resolve spontaneously during 3 to 10 days, sometimes with exfoliation of the overlying skin.

End-stage renal disease (ESRD) appears to attenuate gout onset and recurrence of acute gouty arthritis. In a group of 13 patients with ESRD and a previous diagnosis of gouty arthritis (with an average of 2 attacks/y), after initiation of hemodialysis therapy, 9 patients did not have recurrence of attacks at all, and in the other 4, the frequency decreased by half despite still being hyperuricemic.38

The clinical course of gout is characterized by freedom from symptoms during the intercritical period. However, as the disease progresses, the length of these intercritical periods shortens. It is not uncommon to recover monosodium urate
crystals from aspirates of a previously affected joint during the intercritical period.⁹

Chronic gout is characterized by the unremitting nature of the symptoms, destructive arthritis, and the identifiable deposition of solid urate in tissues (tophi). At this stage, the involved joints are persistently uncomfortable, stiff, and swollen. Chronic gout could mimic other inflammatory arthropathies, such as rheumatoid arthritis. Superimposed acute flares may still occur and usually are polyarticular and additive. Tophi appear as a function of the duration of untreated hyperuricemia,⁴⁰ usually developing over extensor surfaces (forearms and the Achilles tendon) and pressure points, more commonly in the fingers, wrists, knees, and olecranon bursae.

The diagnosis of gout is strongly supported by the combination of a classic clinical presentation (monoarthritis and tophi) along with hyperuricemia and clinical response to colchicine, nonsteroidal anti-inflammatory drugs (NSAIDs), or glucocorticoids. However, it is very important to emphasize that each of these criteria is imperfect, and the diagnosis can be firmly established only by aspiration of negatively birefringent needle-shaped monosodium-urate crystals from an affected joint, bursae, or nodule suspicious of being a tophi.

Classic gout presentations can be mimicked by other inflammatory and infectious conditions, mainly septic arthritis (Box 1). Clinical differentiation between these conditions can be difficult in patients who are immunosuppressed, elderly, or have multiple comorbid conditions. In these settings, both conditions can be polyarticular and associated with such prominent systemic manifestations as fever, chills, and confusion. It is important to note that both entities can coexist in the same patient: A recent study found that of 265 joint aspirates containing gout or pseudogout crystals in a large university hospital emergency department, 4 (1.5%) also had positive culture results for bacteria.⁴¹ The patients these positive cultures belonged to had multiple comorbid conditions. Septic arthritis also can present in patients with established gout, mimicking a new flare of the disease. For this reason, Gram stain and cultures are necessary as part of the workup of synovial fluid aspirated from a patient in whom gout is suspected.

Measurement of serum urate has been found to be an unreliable predictor of gout flares and should not be used to this purpose. Up to 40% of cases of acute gout occur in the setting of normouricemia.⁴² Further diminishing the predictive value of serum urate level for gout diagnosis, hyperuricemia is frequent in the general population and can be present in the setting of acute arthritis secondary to rheumatoid disease, psoriasis, infection, or other inflammatory arthropathies. Other ancillary investigations, such as measurement of urine urate excretion and plain radiographs, have a limited role in diagnostic and management decisions.

### EPIDEMIOLOGICAL CHARACTERISTICS

Gout is a common diagnosis in the United States. According to the most recent estimate by the National Arthritis Data Workgroup using 1996 data from the National Health Interview Survey and NHANES, 3 million adults older than 18 years had gout in the past year, and gout has been diagnosed at some point in the lives of 6.1 million adults older than 20 years.⁴³ The incidence of gout has been increasing over the decades: the Rochester Epidemiology Project estimated an age- and sex-adjusted annual incidence rate for primary gout of 45/100,000 for the city of Rochester, MN, in the study period 1977 to 1978. The same analysis reported the incidence rate to have increased to 63.2/100,000 in 1995 to 1996.⁴⁴ Gout is the most common inflammatory disease in men older than 40 years, exceeding rheumatoid arthritis in this demographic group.⁴⁵

Worldwide, gout frequency and time trends are heterogeneous. It is unclear whether these variations occur because of true differences in frequencies or differences in gout definitions and

<table>
<thead>
<tr>
<th>Box 1. Differential Diagnosis for an Acute Gout Flare</th>
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<tbody>
<tr>
<td>Septic arthritis</td>
</tr>
<tr>
<td>Localized trauma</td>
</tr>
<tr>
<td>Crystalline deposition arthritis</td>
</tr>
<tr>
<td>Calcium pyrophosphate dihydrate (pseudogout)</td>
</tr>
<tr>
<td>Calcium oxalate</td>
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<tr>
<td>Calcium hydroxypatite (calcific periarthritis)</td>
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<tr>
<td>Inflammatory arthritis or tendinitis</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
</tr>
<tr>
<td>Reactive arthritis</td>
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<tr>
<td>Neuropathic osteoarthropathy</td>
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methods of data collection. A report of the UK General Practice Research Database shows that the incidence of gout was relatively constant (at 11.9 to 18.0/10,000 patient-years) in 1991 to 1999.46 However, a survey estimating the prevalence of gout in the United Kingdom in 1993 reported that the prevalence of gout had tripled since the 1970s (from 3 to 9.5/1,000).4 A high prevalence of gout has been noted in Malayo-Polynesians (1.7%)47 and New Zealand Maoris (8.8%).48 Conversely, a relatively low gout prevalence is seen in residents of coastal China (0.36%).49

There is a paucity of data regarding the prevalence of gout in individuals with CKD before dialysis therapy. Frequencies of gout in 493 Japanese patients more than 2 years before initiating dialysis therapy were 15.1% for men and 4.1% for women.50 This decreased to 7.7% for men and 0.6% for women within 2 years of starting dialysis therapy. The frequency in the 2 years soon after beginning dialysis therapy and in the following 2 years continued to decrease for men to 3.4% and 1.2% and for women to 0% in both cases, respectively (Fig 2).

The frequency of gout clearly increases after kidney transplantation. Incidence and prevalence rates vary considerably depending on the post-transplantation immunosuppressive treatment. In patients on cyclosporine-based regimens, gout incidence varies between 3.5 and 28/100 patients as opposed to 0 to 8 for patients on azathioprine and no cyclosporine regimens.5 The overall cumulative incidence of new-onset gout in the US population has been reported at 7.6% using data from the US Renal Data System,33 and a recent report found an overall prevalence of gout as high as 23% in New Zealand patients after kidney transplantation.51

**MANAGEMENT**

Management goals in gout differ depending on the setting and stage of the disease. In patients with acute gout, pharmacological treatment is aimed at resolving the prominent pain and inflammation. In the intercritical periods, the goal is to maintain serum urate at subsaturation levels, preventing the development of tophi and recurrence of new attacks through prophylactic management. Agents available for management of gout are listed in Table 2.

![Figure 2. Frequency of gouty arthritis in 493 patients with end-stage renal disease (ESRD). The frequency of gouty arthritis diminishes as patients advance in the process of worsening chronic kidney disease, ESRD, and dialysis. (Reproduced with permission from Ohno et al.50)](image)

<table>
<thead>
<tr>
<th>Clinical Setting</th>
<th>Drug Family</th>
<th>Use in Chronic Kidney Disease</th>
<th>Use in Dialysis Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute gout flares and prophylaxis of new flares</td>
<td>Nonsteroidal anti-inflammatory drugs</td>
<td>Contraindicated</td>
<td>If needed, use with caution</td>
</tr>
<tr>
<td></td>
<td>Colchicine</td>
<td>If needed, use with great caution because of risk of myopathy and neuropathy; commonly used dosing regimens, 0.6 mg orally every other day or 3 times/wk</td>
<td>Avoid if possible</td>
</tr>
<tr>
<td></td>
<td>Glucocorticoids</td>
<td>Generally well tolerated with reasonable short-term safety if infection has been ruled out; long-term safety issues are common</td>
<td>Same as in chronic kidney disease</td>
</tr>
<tr>
<td></td>
<td>Cosyntropin</td>
<td>Generally considered safe</td>
<td>Generally considered safe</td>
</tr>
<tr>
<td>Long-term urate lowering in patients with gout</td>
<td>Xanthine-oxidase inhibitor: allopurinol</td>
<td>Optimal dosing uncertain; risk of allopurin hypersensitivity syndrome; can initiate therapy at 50-100 mg/d with gradual dose escalation (eg, every 2 wk) to a target serum urate ≤ 6.0 mg/dL</td>
<td>Optimal dosing uncertain; risk of allopurinol hypersensitivity syndrome; can initiate therapy at 50-100 mg every other day (better given post dialysis) with gradual dose escalation (eg, every 2 wk) to a target serum urate ≤ 6.0 mg/dL</td>
</tr>
<tr>
<td></td>
<td>Uricosuric agents: probenecid, sulfinpyrazone, benzbromarone</td>
<td>Ineffective at glomerular filtration rates ≤ 50 mL/min</td>
<td>Ineffective</td>
</tr>
</tbody>
</table>
Management of Acute Gout Flares

It is important to emphasize that the success in aborting attacks of acute gout is dependent on how early the pharmacological management is initiated and whether it is continued for an appropriate time. As a general rule, long-term urate-lowering therapy should not be initiated until joint inflammation has completely resolved. Patients should be educated that resolution of an acute flare does not constitute a cure for the disease.

Nonsteroidal Anti-inflammatory Drugs

Multiple oral and parenteral nonselective NSAIDs have been proved as effective therapies for patients with acute gout. High dosages are used in the first 3 to 4 days, followed by maintenance with standard dosages for a total of 7 to 10 days. These agents should be used cautiously because of the gastric, renal, cardiac, hematologic, and hepatic toxicities of NSAIDs. Close monitoring or complete avoidance of NSAIDs is recommended in elderly patients, users of warfarin, and those with significant cardiac, renal, or hepatic dysfunction.

In patients with acute gout, etoricoxib and lumiracoxib are two cyclo-oxygenase 2–selective inhibitors that have similar efficacy, but fewer drug-related adverse effects in comparison to indomethacin. Neither agent is available in the United States, but 2 studies suggest that these cyclo-oxygenase 2 inhibitors may be useful for the management of acute gout in patients unable to tolerate nonselective NSAIDs. Scheduled maintenance doses of NSAIDs are an alternative for prevention of acute flares in the intercritical period, although there is no evidence from controlled trials to support this approach.

Colchicine

Colchicine interferes with microtubule assembly and, through this mechanism, with neutrophil phagocytosis and chemotaxis. It is particularly effective in controlling symptoms of an acute gout flare when administered within the first 24 hours after symptom onset. The commonly advocated dosage of 0.6 mg orally every hour until “symptom resolution or diarrhea” (to a maximum of 6 mg in 12 hours) very often is limited by such prominent gastrointestinal side effects (in addition to diarrhea) as nausea, vomiting, and abdominal pain. This approach has progressively fallen out of favor. Of added concern, adverse reactions to colchicine are more common in patients with kidney disease. It is important to note that several inflammatory arthropathies other than gout can have complete or partial response to this drug; accordingly, improvement after colchicine therapy should not be considered diagnostic of gout. Intravenous colchicine has been linked to multiple deaths and its use is strongly discouraged, particularly in individuals with kidney disease.

Colchicine is being used more commonly as a prophylactic agent to prevent flares. Dosages commonly used in this setting are 0.6 to 1.2 mg/d orally; however, dosages should be decreased when colchicine is used in the setting of kidney dysfunction. Gastrointestinal side effects, including diarrhea, nausea, and vomiting, also can be present at these lower doses. With long-term use, neutropenia, neuropathy, and vacuolar myopathy can develop. These often insidious side effects may fully or partially resolve with discontinuation of the drug.

Glucocorticoids and Corticotropin

In view of the increasing frequency of comorbid conditions in patients with acute gout flares that may preclude colchicine or NSAID use, glucocorticoids are increasingly used to treat patients with acute gout in this setting. When patients present with a confirmed gout flare involving 1 or 2 large joints, aspiration of synovial fluid followed by intra-articular injection of a long-acting glucocorticoid may be an effective option. Patients who are good candidates for this approach are those in whom clinical presentation, medical history, and laboratory studies make the possibility of septic arthritis minimal.

Typical doses used to manage acute gout flares are exemplified by prednisone at 20 to 60 mg/d or its steroid equivalent. Dose reductions should be more gradual than those typically provided by premeasured “dose-packs,” with an extended treatment course during the 10 to 14 days. Prednisolone in combination with acetaminophen was proved equivalent in effectiveness to indomethacin with acetaminophen, but associated with fewer adverse events based on a recent randomized controlled trial. Adverse effects associated with glucocorticoids, albeit a valid
concern, are less worrisome given the relatively short-term courses needed to control acute symptoms. In patients with recurrent acute flares or chronic gout managed with frequent doses of glucocorticoids, adverse effects may predominate.

Corticotropin shares the same profile of indications as systemic glucocorticoids: polyarticular flares in which NSAIDs are not effective or contraindicated. However, corticotropin is more costly compared with generic glucocorticoids and not as widely available. Its mechanism of action seems to be through stimulation of endogenous adrenal hormones; however, direct anti-inflammatory effects at the affected site also have been postulated. Corticotropin is available for subcutaneous or intramuscular administration, and a single dose of 40 IU is rapid, efficient, and well tolerated, even in patients using moderate doses of oral glucocorticoids. Adverse effects include mild hypokalemia, fluid retention, hyperglycemia, and the development of rebound arthritis; the latter is controlled by administration of prophylactic low-dose colchicine (if possible).

Long-term Therapy for Hyperuricemia and Gout

The decision about initiating long-term therapy for hyperuricemia and gout prevention should be individualized. Currently, there is no evidence that treating patients with asymptomatic hyperuricemia alone is efficacious or cost-effective. However, very high serum urate levels place persons at a very high risk of incident gout, and at a minimum, lifestyle changes including a decrease in alcohol intake, dietary changes, and weight loss should be considered. After a single episode of acute gout, long-term urate-lowering therapy may not yet be indicated because joint damage is unlikely to occur in patients who remain asymptomatic. However, there is reasonable consensus that long-term therapy be advocated in patients with 2 or more flares per year.

When long-term therapy is agreed on, urate-lowering therapy should be intensified until the target goal of a subsaturation urate level at or about 6 mg/dL (357 μmol/L) is reached.

During the initiation of urate-lowering therapy, coadministration of colchicine, glucocorticoids, or NSAIDs may be needed to prevent rebound flares.

Xanthine Oxidase Inhibitors

Allopurinol is the preferred urate-lowering agent in view of its efficacy in overproducers and underexcretors of serum urate, relatively easy dosing regimen, low cost, and generally acceptable safety profile. Allopurinol and its metabolite oxypurinol are both substrates and inhibitors of xanthine oxidase, blocking the conversion of hypoxanthine to xanthine to uric acid (Fig 3) and decreasing serum and urinary urate levels.
The starting dose of allopurinol typically is 50 to 300 mg/d, with lower initial doses preferred because of a perceived lower incidence of rebound flares and hypersensitivity reactions. In addition, some patients may reach target serum urate goals with doses as low as 100 to 200 mg/d. Lower doses should be used in elderly patients and those with impaired kidney function. It is important to monitor serum urate levels regularly for dosage adjustments until the target concentration is reached. The most commonly used allopurinol dose of 300 mg/d achieves target serum urate concentrations in only 53% of patients, and dosages as high as 1,000 to 1,200 mg/d are used safely in many patients. However, before escalating the dose to very high levels, adherence should be assessed because as many of 50% of patients are nonadherent with the medication regimen, especially if they are having recurrent gout flares.

Adverse reactions from allopurinol generally are uncommon and most are mild. The most frequent toxicities are rash, such gastrointestinal intolerance as diarrhea, headache, and leukopenia. Rashes can be recurrent on reexposure to the drug and are an important cause of intolerance. Given the scarcity of treatment alternatives for certain patients, allopurinol desensitization protocols have been developed. Allopurinol hypersensitivity syndrome is an uncommon immune-mediated severe reaction with a mortality rate up to 20%. It is characterized by fever, rash, acute renal insufficiency, eosinophilia, hepatic injury, and vasculitis. Supporting a causative role for the accumulation of oxypurinol in this condition, in a case series of 78 patients, it was determined that at a creatinine clearance less than 10 mL/min (<0.17 mL/s), there is virtually no renal excretion of oxypurinol. Along the same lines, cases of allopurinol hypersensitivity have been linked to T-cell–mediated immune reactions to oxypurinol, possibly induced by certain HLA haplotypes. Renal impairment, diuretic use, and recent initiation of allopurinol therapy have been implicated as risk factors for the development of allopurinol hypersensitivity syndrome. Multiple drug interactions may be an additional limiting factor in the use of allopurinol; notably, allopurinol can increase drug levels of theophylline, warfarin, and azathioprine, with the latter often considered a contraindication to allopurinol use. Thiazide diuretics can inhibit allopurinol excretion and potentiate allopurinol toxicity. Finally, a high incidence of skin rashes has been described with the combination of ampicillin or amoxicillin with allopurinol.

Uricosuric Agents

Uricosuric drugs reverse the most common physiological abnormality in patients with gout; namely, underexcretion of uric acid (<800 mg/24 h of uric acid on a regular diet). Probenecid and sulfipyrazone are used internationally, and benzbromarone is available in many countries, but not in the United States. Other drugs with mild uricosuric effects include losartan and fenofibrate. Uricosuric agents likely act at the level of the URAT1 transporter in the proximal tubule. When used on ideal patient candidates, probenecid, sulfipyrazone, and benzbromarone can be successful 70% to 80% of the time in achieving optimal serum urate levels. However, several limitations are encountered when trying to use uricosurics in practice. First, they rapidly lose effectiveness as glomerular filtration rate (GFR) decreases to less than 30 mL/min (<0.5 mL/s). Second, their use is strongly discouraged in patients with a history of renal calculi because uricosuric agents may further promote nephrolithiasis. Last, their use is not recommended in elderly patients and those administered multiple medications because of multiple drug interactions. For example, probenecid has known interactions with azathioprine, rifampin, salicylates, penicillins, indomethacin, and heparin. Probenecid is the most widely used uricosuric. Usually initiated at a dosage of 500 mg orally twice daily, the dosage can be increased slowly up to 3 g/d. Adverse effects include gastrointestinal intolerance, rash, hepatotoxicity, acute gout attacks, nephrolithiasis, and nephrotic syndrome.

New Therapeutic Approaches

Febuxostat is an orally administered nonpurine selective inhibitor of xanthine oxidase that is metabolized through the liver and appears to be safer than allopurinol in patients with decreased kidney function. A phase 3 double-blind controlled trial against a fixed dose of 300 mg/d of allopurinol showed that febuxostat at doses of 80 and 120 mg/d was more effective at achieving the primary goal of a serum urate level of 6.0
mg/dL (357 μmol/L) at 3 months. Because increases in allopurinol dosage were not permitted in this research protocol, the comparative effectiveness of febuxostat against allopurinol dose titration in real practice is not yet known. Both drugs were effective in decreasing tophi size and gout flares at 52 weeks. Potentially attributable to its more profound and rapid decrease in serum urate levels, febuxostat induced gout flares on initiation of therapy (up to 70% of patients) despite adequate prophylaxis. Although now approved in Europe, concerns about the long-term safety of febuxostat given abnormal liver function test results and cardiovascular adverse outcomes during clinical trials have delayed its approval in the United States.

Urate oxidase (uricase) is a potent enzyme present in all mammals except higher primates and humans that converts uric acid into more soluble allantoin. Nonrecombinant (obtained from Aspergillus flavus) and recombinant (rasburicase; obtained from Saccharomyces cerevisiae) forms have been used effectively as intravenous infusions in the prevention and treatment of tumor lysis syndrome. The development of severe anaphylactic reactions, methemoglobinemia, and hemolytic anemia in glucose-6-phosphate dehydrogenase–deficient patients was reported with the nonrecombinant form and significantly decreased with the recombinant product. However, the short half-life of the intravenous infusion makes its use impractical for the routine management of gout despite its inarguable potency in decreasing uric acid levels. Off-label protocols in patients with severe tophaceous gout unable to receive allopurinol have been described.

A polyethylene glycol–linked uricase has been developed and reported to have a longer half-life and less immunogenicity than earlier uricase compounds. Phase 1 trials of both subcutaneous and intravenous forms of this drug have been conducted, showing less immunogenicity and better tolerability for the intravenous preparation. Adverse effects of this product in phase 1 and 2 clinical trials have included localized injection reactions and gout flares. Polyethylene glycol–linked uricase currently is undergoing phase 3 clinical trials to assess its effectiveness in the long-term management of gout.

**UNIQUE CONSIDERATIONS IN KIDNEY DISEASE**

**Hyperuricemia, Kidney Function, and Urate Nephropathy**

The observation that patients with gout have impaired kidney function dates back to the 1950s and 1960s, and this finding has been replicated since then. Several observational studies have described an association between increased serum urate levels with hypertension, decreased GFR, and progression to ESRD. In one study, serum urate level greater than 8.0 mg/dL (>476 μmol/L) conferred relative risks of developing ESRD of 2.9 in men and 10.4 in women compared with patients with serum urate less than this level. In addition, serum urate level has been associated with progression of kidney dysfunction in patients with other CKDs, such as immunoglobulin A nephropathy. Experimental models support this association; induction of mild hyperuricemia in rats with oxonic acid (a uricase inhibitor) resulted in renin-dependent hypertension, interstitial renal disease, glomerular hypertension, arteriolopathy, and endothelial dysfunction partially reversible by the administration of allopurinol. Notably, allopurinol and the new agent febuxostat can ameliorate systemic and glomerular hypertension in mildly hyperuricemic rats in models induced by oxonic acid and fructose. Finally, in a small prospective study of 54 hyperuricemic patients with CKD, therapy with allopurinol decreased the proportion of patients with deterioration of renal function or progression to dialysis dependence. All these data suggest that treatment of hyperuricemia may have a role in the management of CKD.

Hyperuricemia can clinically manifest in the kidney as deposition of uric acid crystals in the renal interstitium or collecting tubules or development of uric acid lithiasis. This conglomerate is known as urate or uric acid nephropathy with or without urolithiasis (some investigators make a distinction between the first 2 depending on whether deposition is in the interstitium or collecting tubules). The primary effect of uric acid crystals is to obstruct luminal flow, potentially promoting subsequent inflammation and fibrosis and eventual kidney function decrease. Urate crystal nephropathy appears to be common in
patients with gout, with frequencies up to 79% to 99% of patients described in autopsy studies. However, controversy exists because reports of the natural history suggest that the disease runs a benign and slowly progressive course without evidence of decreased life expectancy. Management of hyperuricemic patients with urate crystal nephropathy would involve urate lowering (ideally to less than the urate solubility point of 6.8 mg/dL [404 \mu mol/L]) with nonuricosuric agents along with adequate hydration.

**Hyperuricemia and Gout in Patients With CKD**

Multiple comorbid conditions leading to CKD, such as hypertension, metabolic syndrome, diabetes mellitus, heart failure, and hyperlipidemia, also are associated with hyperuricemia and make the management of gout more complex in this patient population. In cases of acute gout, NSAIDs for the most part are contraindicated in patients with impaired kidney function and/or heart failure. Colchicine is an alternative in selected cases and under close supervision given its high potential for neuropathy and myopathy, even after short courses of therapy, in patients with advanced kidney dysfunction. There are no safety data published about the commonly used every-other-day or thrice-weekly dosing regimens in patients with CKD, and it would appear safe to exclude patients with very advanced kidney dysfunction (creatinine clearance < 10 mL/min [<0.17 mL/s]) from using it altogether. Therefore, by default, systemic or intra-articular glucocorticoid therapy may be treatments of choice in many patients. However, it is important to emphasize that in patients with diabetes, closer follow-up of serum glucose levels with intensification of therapy may be needed. Of note, patients with CKD, particularly those on hemodialysis therapy, are among the patients most prone to septic arthritis. An effort should be undertaken to fully exclude this possibility before administering glucocorticoids, either systematically or intra-articularly. Finally, corticotropin also may be a safe alternative for management of acute gout attacks in this patient population.

The choice of urate-lowering agents is limited in patients with CKD. At creatinine clearance less than 50 mL/min (<0.83 mL/s), most uricosuric agents are largely ineffective. Allopurinol should be considered the current treatment of choice, and recommendations for dose adjustment and careful escalations in the setting of decreased kidney function exist, but have not been well validated. Patients with CKD are at greater risk of allopurinol hypersensitivity syndrome, even at very low doses. However, undertreatment and lack of clinical efficacy in the management of hyperuricemia and gout in this patient population are common. Intravenous recombinant uricase infusions recently have been reported as a possible safe alternative for the management of hyperuricemia in patients with renal failure.

**Hyperuricemia and Gout in Patients With Kidney Transplants**

As described, it is well established that the incidence of hyperuricemia and gout increases after solid-organ transplantation in general and in kidney transplant recipients in particular. Transplant recipients share many risk factors for hyperuricemia with the general population, but there also are other specific factors that predispose to gout. In a large retrospective cohort of kidney transplant recipients derived from Medicare claims data, use of cyclosporine (versus tacrolimus), greater body mass index, older age, and male sex were associated with the development of gout both early after transplantation and 1 year after transplantation. Delayed graft function was associated with increased risk shortly after transplantation, whereas decreased GFR at 1 year after transplantation was associated with later development of gout.

Calcineurin antagonists, such as cyclosporine and tacrolimus, increase serum urate levels by increasing serum urate reabsorption. The critical implication of azathioprine involves the elimination of its active metabolite 6-mercaptopurine. By inhibiting xanthine oxidase, allopurinol will decrease the metabolism of 6-mercaptopurine, significantly increasing levels and the resultant risk of toxicity. Accordingly, concurrent use of azathioprine and allopurinol should be avoided when possible, and the need to use...
allopurinol may necessitate a careful transition from azathioprine to mycophenolate mofetil for transplantation immunosuppression.133,134

For management of acute gout attacks, therapy with NSAIDs should be considered with caution in kidney transplant recipients. Colchicine may be considered, but an important interaction with cyclosporine that increases colchicine levels has been described. Colchicine myopathy has been reported with low doses and short duration of treatment in users of cyclosporine.135 Systemic or intra-articular glucocorticoids can be used safely in most cases, but as with patients with CKD and given the underlying immunosuppression, measures to rule out the possibility of a septic joint should be taken. Long-term urate lowering can be achieved with uricosurics (if kidney function is relatively well preserved) or allopurinol (in patients not receiving azathioprine).

CONCLUSION AND RECOMMENDATIONS

As the prevalence of CKD continues to increase, it is likely that management of hyperuricemia and gout will continue to be a challenge in these patients. Diet, polypharmacy, and lifestyle issues are important aspects to discuss with patients. Pharmacological therapies for patients with acute episodes of gout are relatively limited and include NSAIDs, colchicine, intra-articular or systemic glucocorticoids, and corticotropin. However, special attention should be given to specific contraindications to certain drugs (eg, NSAIDs and CKD) and the possibility of infectious arthritis, especially relevant in such complex patients as those with CKD or transplant recipients.

Intercritical (between acute gout flares) management of hyperuricemia can be accomplished with uricosurics or allopurinol. Allopurinol often is the treatment of choice for patients with chronic gout given its effectiveness, even in the setting of decreased GFR. However, caution should be exercised in this setting, with low starting doses and conservative dose escalations tailored to serum urate concentration. In the next years, new options for long-term management of hyperuricemia may become available, and these may allow us to offer alternatives for difficult-to-treat patient populations.

CASE REVIEW

The patient described at the beginning of this article was admitted for observation and initially managed with analgesia. Several hours later, synovial fluid obtained from his knees grew gram-positive cocci in clusters, later identified as methicillin-resistant Staphylococcus aureus. Management with antibiotics, repeated joint aspirations, and systemic glucocorticoids (while covered by antibiotics) led to symptomatic relief and eventual resolution of the acute flare. Long-term management of his gout will continue to be challenging as long as systemic glucocorticoids remain as one of the few available options, and until new agents become available.

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