Management of Gout

A 57-Year-Old Man With a History of Podagra, Hyperuricemia, and Mild Renal Insufficiency

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Gout is an ancient disease. Despite significant advances in the understanding of its risk factors, etiology, pathogenesis, prevention, and treatment, millions of people with gout experience repeated attacks of acute arthritis and other complications. The incidence of gout is increasing, most likely reflecting increasing rates of obesity and other lifestyle factors, including diet. Comorbid conditions that often accompany gout, including chronic kidney disease and diabetes mellitus, present challenges for the management of gout. Using the case of Mr R, a 57-year-old man with a history of podagra, hyperuricemia, and mild renal insufficiency, the diagnosis and treatment of gout are discussed. For those with moderate to severe gout, urate-lowering treatment can eliminate acute attacks of arthritis and prevent complications. In the near future, it is likely that new risk factors for gout will be identified and new ways of preventing and managing this common disease will become available.

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DR DELBANCO: Mr R is a 57-year old man with a history of podagra (acute first metatarsal-phalangeal joint pain and swelling), hyperuricemia, and mild chronic kidney disease. An immigrant from Eastern Europe, Mr R worked as an engineer and is now retired. He lives with his wife and has several children. For many years, he has been a patient at a hospital-based primary care practice. He has a 60-pack-year history of smoking but does not abuse alcohol or other drugs. He has no family history of gout, but his grandfather and father had renal disease of uncertain etiology.

In 1993, Mr R experienced his first episode of podagra and was treated with indomethacin and an "injection into my toe." Five years later, his first measurement of uric acid was 7.7 mg/dL. Over the next 10 years, recurrent episodes of podagra were accompanied by uric acid levels as high as 9 mg/dL. Treatment with colchicine caused diarrhea without pain relief. He has adamantly refused further colchicine treatment. A consulting rheumatologist recommended that he use ibuprofen as his principal medication during acute episodes. In 2006, his serum creatinine level was first elevated to 1.3 mg/dL (with an estimated glomerular filtration rate of 57 mL/min/1.73 m^2); it later increased to 1.5 mg/dL but stabilized more recently at 1.3 mg/dL. He has had microalbuminuria, most recently with an albumin-creatinine ratio of 442 mg/g (normal range, <30 mg/g). Aside from the presence of 2 cysts, kidney size and architecture were unremarkable on ultrasound and computed tomography.

At the time of the elevation in creatinine, Mr R started therapy with allopurinol, 100 mg/d, which he continues. His uric acid levels range between 6 and 7 mg/dL. He has never had physical stigmata of gout other than intermittent swelling, redness, and pain in his great toe. He has not had recurrent symptoms since initiating allopurinol.

CME available online at www.jamaarchivescme.com and questions on p 2154.

Mr R has long-standing obesity. His height is 68 in (173 cm); weight, 258 lb (116 kg); and body mass index (calculated as weight in kilograms divided by height in meters squared), 39.2. His blood pressure has been mildly elevated. He has a long history of hyperlipidemia. Currently, his low-density lipoprotein cholesterol level is 172 mg/dL (ideal range, <129 mg/dL). He currently takes rosuvasta-

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tin. In 2000, he also developed symptomatic coronary artery disease that led to the placement of 2 stents. In 2007, polydipsia, polyuria, and weight loss heralded the onset of diabetes mellitus, with hemoglobin A_{1c} levels of 15%, glucose levels above 500 mg/dL, and glycosuria. The symptoms and abnormal test results resolved rapidly with metformin therapy, and currently he takes no hypoglycemic agents and has normal hemoglobin A_{1c} levels.

At the time of the conference, physical examination was unremarkable except for obesity. Mr R had no joint abnormalities and there were no visible tophi. In addition to the medications to manage gout and hyperlipidemia, he was taking aspirin, amlodipine, and ramipril.

MR R: HIS VIEW

I heard of gout through my friends; actually, the name was podagra. It was taken lightly at that point years ago. First time I received the attack on my toe was probably 20 years ago. When I went to the hospital, they said once you have it you always will have it, and I had a very hard time accepting that I will have some sickness or illness in my body that I will not be able to get rid of. My friends told me about podagra as being a rich man's sickness. If you live well and eat well, podagra will be unavoidable; it identifies with well-lived men, but I don't think that there is any truth to that. It's a legend, I guess, or that's how they explained it. It was a sharp pain, as in needles sticking into the joints on my toe to the point that at first you may ignore it, but half an hour later it started to test my tolerance. So the attack was so severe, pain-wise, that I had to go to the hospital for a remedy.

If I saw an expert and had a chance to ask him a question regarding gout, the first thing that would come to my mind is, is there any remedy or medicine or injection that will relieve the pain immediately or in a short time frame? That pain is very severe and it's almost not tolerable. So I think for people who have gout, immediate relief is extremely important. And then I would ask the expert, is there a permanent solution for keeping uric acid in balance in your body, whether it's by food intake or through nature, instead of medicine?

AT THE CROSSROADS: QUESTIONS FOR DR SHMERLING

Does Mr R have gout? How should acute attacks of gout be treated? How should attacks of gout be prevented? Which urate-lowering therapy is best, and how should it be prescribed? How should gout be monitored? When should the patient with gout be referred to a specialist? What do you recommend for Mr R?

DR SHMERLING: Gout is an old disease. The first description of what was almost certainly gout dates back to the Egyptians in 2600 BC.[1] Hippocrates called it "the unwalkable disease," and for good reason. The prototypic acute inflammation of the first metatarsal-phalangeal joint (podagra) can make walking—and almost every other activity—unthinkable.

Although much about its pathophysiology is well understood, much about gout remains mysterious. For example, even though a number of risk factors for the development of gout are well established, it is unclear why it afflicts some people and spares others, even when the unaffected share risk factors. It is also not clear why acute gout attacks are self-limited or why gout attacks can be triggered by a decreasing level of serum uric acid.

Gout is caused by monosodium urate crystals precipitating and depositing in the joints and other tissues. Hyperuricemia is a key pathophysiologic predisposition, although most people with hyperuricemia never develop gout. A complex interplay of genetics, diet, medications, comorbidities, and inflammatory response clearly contributes to the risk of developing gout and to its course (FIGURE).

A recent study of twins found that genetic factors play a major role in the risk of developing hyperuricemia, while the risk of gouty arthritis was largely driven by environmental influence.[2] Recent genome association studies have identified genetic variants, including the *ABCG2* gene, that encode for variants in urate exporters that regulate renal urate excretion and an increased risk of hyperuricemia and gout.[3]

Impaired renal excretion of uric acid (perhaps related to defective urate transporters across membranes of the proximal tubules[4]), overproduction of uric acid, consumption of dietary purines (that are metabolized to uric acid), or a combination of these underlie an individual's hyperuricemia. Though a number of genetic mutations predispose to hyperuricemia, the usefulness of genetic testing in the management of gout is unknown and is not standard practice.

Gout is common, affecting nearly 4% of US adults (8.3 million people). Its prevalence is increasing,[5] probably owing to lengthening life span, increasing rates of comorbidities (eg, chronic kidney disease, obesity, and type 2 diabetes), diuretic use, dietary choices, and use of certain medications, such as cyclosporine.[6-8]

Mr R has a number of risk factors and comorbidities typical of individuals with gout.[9] He is male, older than 30 years, and obese and has chronic kidney disease, hypertension, diabetes mellitus, cardiovascular disease, and hyperuricemia. His presentation (recurrent podagra) is typical for gout, as is his intermittent adherence to urate-lowering therapy.[10] Motivation to take daily medications during asymptomatic periods (intercritical gout) often wanes with time.

DIAGNOSIS OF GOUT

Ideally, the diagnosis of gouty arthritis is established through analysis of joint fluid or a tophaceous deposit. The identification of negatively birefringent, needle-shaped crystals, typical of monosodium urate crystals, by polarized microscopy is diagnostic. However, criteria and guidelines also acknowledge that a diagnosis of gout can be made solely based on clinical presentation without synovial fluid examination

(TABLE 1).[11-15] Dual-energy computed tomography[16] or ultrasound[17] may be useful to suggest a diagnosis of gout, but further study is needed before these tests are routinely used.

For patients with suspected acute gouty arthritis, the most important alternative considerations are infectious arthritis, calcium pyrophosphate deposition disease (pseudogout), and spondyloarthropathy (BOX). Their joint manifestations may be identical, so joint aspiration may be as important to rule out another condition as it is to confirm gout.

Patients with gout usually have hyperuricemia, but a normal uric acid level does not exclude the possibility of gout. In one study, about one-third of patients with gout at initial presentation had a serum uric acid level less than 8.0 mg/dL and 14% had a level less than 6.0 mg/dL.[18] (To convert uric acid to micromoles per liter, multiply by 59.485.) Coupled with the observation that most patients with hyperuricemia never develop gout,[19] uric acid measurement as a diagnostic test is neither sensitive nor specific.

TREATMENT OF GOUT ATTACKS

The treatment of acute gouty arthritis has long relied on 3 options[20]: nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, and corticosteroids.

A reasonable first choice is an NSAID with a rapid onset of action. Indomethacin and ketorolac are common choices in urgent care settings. Many patients with gout have ab-

Figure. Metabolic Pathways of Uric Acid, Its Role in the Pathogenesis of Gout, and Key Mediators of Monosodium Urate (MSU) Crystal–Induced Inflammation

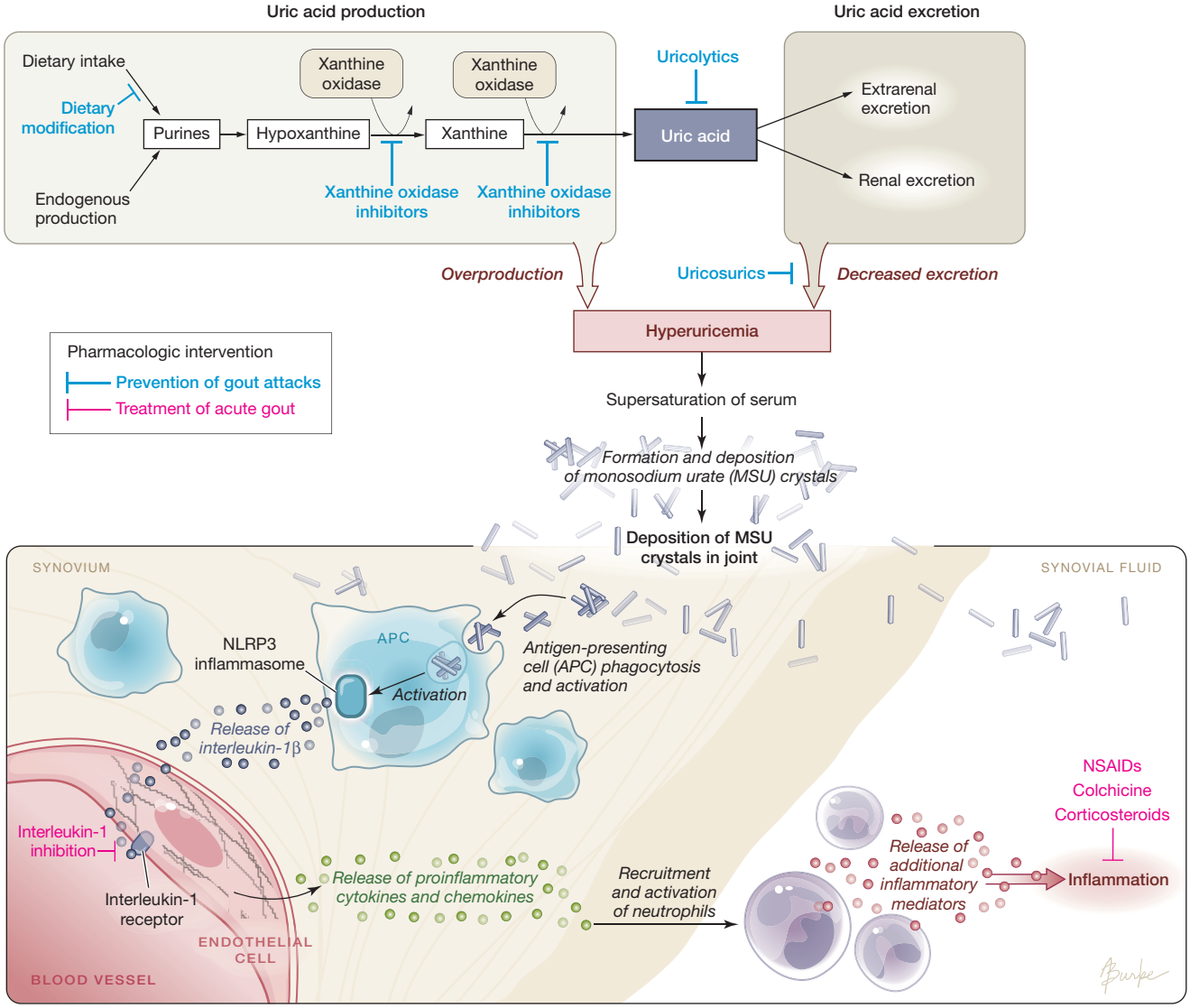

Table 1. Clinical Features of Gout

	Clinical Features	
	New-Onset Gout	Long-standing Gout
Typical patient	Hyperuricemia, postmenopausal women, men aged >30 y	Elderly men or women
Onset of attacks	Acute	Acute, subacute, or chronic
Joint distribution	Monoarthritis	Monoarthritis, oligoarthritis, or polyarthritis
Joints affected	Toe (especially first metatarsal-phalangeal), mid foot, ankle	Any joint but especially digits, mid foot, ankle, knee, wrist
Symptom duration	3 to 5 days, self-limited	5 days to weeks
Associated findings	Fever, elevated white blood cell count, elevated inflammatory markers	Tophi (eg, subcutaneous nodules or radiographic erosions)

solute or relative contraindications to NSAIDs (eg, hypertension, chronic kidney disease, gastropathy), but most patients with gout tolerate these drugs well.

Colchicine may be effective, though less so if symptoms have been present for more than 24 to 36 hours. Diarrhea is a common adverse effect; after his poor experience, Mr R refused to consider even low doses of the drug. A recent randomized, double-blind trial[21] comparing high-dose and low-dose colchicine (4.8 mg over 6 hours vs 1.8 mg over 1 hour) found that the low-dose regimen was as effective and caused less toxicity. However, the response rate at 24 hours was relatively low in both groups (about 38% in the low-dose group and 33% in the high-dose group).

Of note, generic colchicine was removed from the US market recently as part of the US Food and Drug Administration's (FDA's) program to take unapproved drugs through its approval process. Brand-name colchicine is currently $5.82 per pill, while generic colchicine was only $0.56 per pill before it was withdrawn from the market. The resumption of sales of generic colchicine is eagerly anticipated.

Effective corticosteroid treatment can include a short course of low- to medium-dose prednisone (eg, 30-40 mg/d, discontinued over 5-10 days) or intra-articular or parenteral corticosteroid injection (such as intramuscular triamcinolone). Although adverse effects of corticosteroids are always a concern, the self-limited nature of acute gout attacks requires only short-term use and, as a result, a generally acceptable rate of toxicity. A Cochrane review published in 2008[22] concluded that corticosteroids and NSAIDs appear to have similar efficacy for patients with acute gout, though the studies were of limited quality. When monotherapy is ineffective, short-term combination therapy (eg, colchicine and an NSAID) can provide relief.

A novel treatment approach currently under investigation for acute gouty arthropathy is interleukin 1 inhibition. This follows advancing insights into the interactions between monosodium urate crystals and the cryopyrin (NLRP3) inflammasome[23] (Figure). Although limited studies suggest that these drugs (including anakinra, canakinumab, and rilonacept) might be effective to prevent or treat acute gout, they are not yet approved for this purpose, must be given by injection, and are quite expensive. The future role of interleukin 1 inhibitors for acute gouty arthritis is unclear.

A limited number of controlled trials have compared treatments for acute gout (eTable 1; available at http://www.jama.com).[21,24-31] Most document improvement with corticosteroids and NSAIDs and find little difference among them.

I believe NSAIDs should be considered the drug of first choice for acute gout, but comorbidities, concomitant medication use, cost, and patient preference weigh heavily on individual patient choice.

PREVENTION OF GOUT ATTACKS

There are 3 general approaches to preventing gout attacks: risk factor modification, anti-inflammatory medication, and urate-lowering medication.

Risk Factor Modification

It is reasonable to recommend that all patients with a history of gout take measures to modify risk factors, although clinical trials demonstrating the efficacy of this approach have not been performed. Strategies to reduce risk factors include loss of excess weight and dietary changes. Because the consumption of alcohol (particularly beer), fructose, meat, and seafood are risk factors for hyperuricemia and an increased incidence of gout,[32-34] moderation in their intake may help prevent future attacks of gout. A tight correlation exists between the increasing incidence of gout and increasing consumption of fructose.[7,35] The link may be related to increased adenine catabolism induced by fructose in sweeteners, including sucrose and high-fructose corn syrup.[36] Conversely, milk and coffee intake are inversely associated with gout risk.

Anti-inflammatory Medications

For patients at high risk of gout attacks, including those who are beginning urate-lowering therapy, NSAIDs or colchicine are highly effective and commonly prescribed. However, these agents have no effect on uric acid levels and do not prevent joint damage, renal stones, or the formation and growth of tophi. For these reasons, long-term monotherapy with colchicine or an NSAID is discouraged for patients who are appropriate candidates for urate-lowering treatment.

Urate-Lowering Medications

Lowering the uric acid burden in the body dramatically reduces the risk of gout flare and can protect joints from damage by limiting or even reversing tophus formation. Pharmacologic treatment to lower uric acid is typically reserved for patients with gout who have frequent attacks (eg, more than 2 or 3 episodes per year); severe recalcitrant or polyarticular attacks; tophi; or kidney stones. Chronic kidney disease (stage 2 or worse) was also included as an indication for urate-lowering treatment for patients with gout in the recently released American College of Rheumatology (ACR) guidelines.[37]

The importance of delaying urate-lowering medication until an acute attack has resolved may have been overemphasized in the past.[37] As long as an anti-inflammatory prophylactic agent (eg, low-dose NSAID or colchicine) is concomitantly administered, urate-lowering treatment may begin during or after an attack of gouty arthritis.

A principal tenet of urate-lowering therapy is the importance of achieving adequate uric acid suppression[14,38]; in this regard, Mr R's treatment falls short. The target level of uric acid should be well below 6.8 to 7.0 mg/dL, the level at which plasma is saturated in humans. Targets vary according to published guidelines,[15,38] ranging from 5.0 mg/dL to 6.0 mg/dL or even lower if necessary to eliminate signs and symptoms of gout. The ACR recently released guidelines with similar "treat to target" recommendations.[37]

Options for lowering uric acid include xanthine oxidase inhibitors that impair uric acid synthesis, uricosurics that encourage the renal elimination of uric acid, and "uricolytics" (drugs that dissolve uric acid).

Inhibitors of Uric Acid Synthesis. Allopurinol, the inhibitor of uric acid synthesis that Mr R is taking, is in my view the drug of choice to lower uric acid. It is highly effective when properly dosed. Although it has a range of dosing options, the most commonly prescribed dosage is 300 mg/d. However, this dosage may be too low to suppress uric acid adequately in a majority of patients.[39] One study found that among individuals with gout and preserved renal function who were receiving 300 mg/d of allopurinol, only 24% met the target level of suppressed uric acid (which was 5 mg/dL in this study).[40]

Low initial dosing of allopurinol may be better tolerated. Recent guidelines from the European League Against Rheumatism and the ACR recommend a maximum starting dosage of 100 mg/d for all patients receiving this drug.[14,37]

A nomogram[41] recommending restricted dosing of allopurinol in the setting of renal dysfunction has never been validated. Recent studies suggest that even among patients with chronic kidney disease, a low starting dosage,[42] with gradual dosage escalation to reduce uric acid to less than 6.0 mg/dL, is effective and well tolerated.[43] The maximal FDA-approved dosage of allopurinol is 800 mg/d, though dosages above 600 mg/d are rarely necessary.

Box. Distinguishing Features of Gout Mimics

Septic arthritis: positive synovial fluid Gram stain and culture

Calcium pyrophosphate deposition disease: synovial fluid crystal examination demonstrating typical polymorphic, positively birefringent crystals; joint distribution (especially wrist, knee) with chondrocalcinosis on radiograph

Spondyloarthropathy: absence of crystals in synovial fluid, associated features (eg, colitis, psoriasis)

Rheumatoid nodules (vs tophus): lack of crystals in synovial fluid, anatomic location, pathologic examination

Osteomyelitis (vs tophaceous erosion): osteopenia, lack of characteristic "overhanging edge"; aspiration or biopsy may be necessary

Severe adverse effects are rare, although hypersensitivity reactions associated with allopurinol use, including Stevens-Johnson syndrome, can be life threatening. The risk of such reactions has long been considered idiosyncratic or, perhaps, related to underlying kidney disease,[41,42] but more recent studies suggest a genetic predisposition.[44]

Unlike allopurinol, febuxostat is not a purine analog, so those who are allergic to allopurinol may tolerate febuxostat. In studies to date, febuxostat is well tolerated among patients with mild or moderate kidney disease. Febuxostat and allopurinol have not been compared in a head-to-head trial allowing appropriate up-titration of allopurinol. As a result, it is not clear that either drug has an advantage among patients with normal renal function or mild to moderate chronic kidney disease.

Uricosurics. Uricosuric drugs, such as probenecid, are less appealing options than urate-lowering treatments because they are not effective in the setting of renal dysfunction and are contraindicated in patients with prior nephrolithiasis. However, probenecid has an excellent safety profile.

Probenecid is the only uricosuric commonly prescribed for gout in the United States, but others, such as benzbromarone and sulfinpyrazone, are available elsewhere. In addition, fenofibrate,[45] vitamin C,[46] losartan,[47] and moderate- to high-dose aspirin[48] also have uricosuric properties, although they are not commonly used for this purpose. The evidence base supporting their use for gout is limited.

Uricolytics. Uricase is an uricolytic enzyme that keeps uric acid levels low in most mammals. However, this enzyme was lost during human evolution. The FDA recently approved pegloticase, which is uricase combined with polyethylene glycol to lengthen its half-life. It is indicated as a urate-lowering treatment for symptomatic patients with gout in whom appropriate dosages of other standard treatments have failed or were not tolerated. Trials suggest that infusions every 2 weeks can be dramatically effective,[49] although cost, loss of benefit (possibly due to the generation

Table 2. Costs of Medications Used to Prevent or Treat Gout[60]

Medication	Dosage	Monthly Cost, $	Comments
Brand-name colchicine (Colcrys)[a]	0.6 mg/d	175	Brand-name colchicine is the only form currently available in the United States.
Generic colchicine[b]	0.6 mg/d	16.80	Withdrawn from the market in 2010 but may soon be available again.
Indomethacin[c]	50 mg 3 times daily for ≤10 d	19.20	Many other generic nonsteroidal anti-inflammatory drugs are available and effective; relative contraindications including gastropathy and kidney disease can be limiting among gout patients.
Prednisone[c]	5 mg (starting at 6 pills once daily; taper over 10 d)	1.28	If more than 2 or 3 tapers per year are required, urate-lowering therapy may be indicated.
Allopurinol	300-400 mg/d	18.00-25.20	Requires dose adjustment to achieve suppression of uric acid.
Probenecid	500-1000 mg twice daily	14.70- 29.40	Ineffective in setting of significant renal dysfunction.
Febuxostat	40 to 80 mg/d	212.10	Owing to higher costs, may be reserved for allopurinol failure or intolerance.
Pegloticase	8 mg intravenously every 2 wk	6182	If uric acid is not promptly suppressed, medication should be stopped.

[a] Cost shown is for continuous use for prophylaxis; can usually be stopped after 4 to 6 months.
[b] Currently unavailable; price shown is from prior to withdrawal from the market.
[c] May be taken intermittently; usually no more than 3 or 4 courses of treatment per year.

of antibodies), and infusion reactions, including anaphylaxis, suggest that the role of pegloticase may be limited.

Whichever urate-lowering treatment is chosen, education regarding disease course and appropriate medication use as well as regular follow-up are essential. Nonadherence is common[10,50] and contributes to a high but preventable burden of disease, as demonstrated by Mr R. He began taking allopurinol regularly only when he became convinced it would protect his kidneys (a notion that remains unproven).

A summary of selected controlled clinical trials for urate-lowering treatment is provided in eTable 2.[51-54]

CHOOSING A URATE-LOWERING THERAPY

The best urate-lowering drug is uncertain. In head-to-head trials of allopurinol and febuxostat,[52,55] the target uric acid level of less than 6.0 mg/dL was achieved in only 48% to 53% of participants treated with 80 mg/d of febuxostat (the FDA-approved maximal dosage) and in only 21% to 22% of those treated with 100 mg/d to 300 mg/d of allopurinol. Despite these results and aggressive marketing of febuxostat (a drug with an average wholesale price of $7.07 per dose in the United States, more than 8 times as much as generic allopurinol), allopurinol should not be considered inferior to febuxostat; optimal dosing of allopurinol was not allowed in these trials.

The new ACR guidelines recommend either allopurinol or febuxostat as first-line urate-lowering medication. However, these guidelines were created without considering cost, and a recent analysis favored allopurinol as the urate-lowering drug of choice when cost was taken into account.[56]

Until more useful studies are available, the most appropriate strategy in my view is to start with a low dose of allopurinol (eg, 100 mg/d), repeating measurements of uric acid every 3 to 6 weeks and gradually increasing the allopurinol dosage to achieve suppression of uric acid to 6 mg/dL or lower. Allopurinol is usually prescribed as monotherapy, although it can be added to probenecid.[51]

If a patient has contraindications or is nonresponsive to allopurinol, febuxostat or probenecid treatment should be considered. Uricase can be considered as a last resort.

Because urate-lowering medication may be associated with acute attacks of gout, preventive treatment (with low-dose colchicine or an NSAID) is appropriate for at least the first 6 months of urate-lowering treatment.[20] Some patients require a longer period of prophylaxis, especially if tophi are present. Flares of gouty arthritis are common during urate-lowering therapy (even with appropriate prophylaxis), so patients should be warned about this and advised to continue urate-lowering treatment despite the acute attack.

The few controlled trials of treatments to prevent acute gouty arthritis during urate-lowering treatment are summarized in eTable 3,[57-59] and costs of common and currently available gout medications are presented in TABLE 2.[60]

PATIENT MONITORING

Once the diagnosis of gout is established, regular follow-up is warranted. For patients with rare attacks that are easily treated (and for whom long-term urate-lowering treatment is not necessary), follow-up can be as needed. Monitoring should include occasional measures of renal function, blood counts, and tests of stool for occult blood to identify complications of gout (eg, obstructive uropathy), its treatment (eg, NSAID gastropathy), and common comorbidities (eg, hypertensive renal dysfunction). Monitoring should be more frequent if NSAIDs or colchicine are taken regularly. If there is concern about nephrolithiasis, urinalyses and 24-hour urinary uric acid measurement may be appropriate.

If urate-lowering treatment is prescribed, tests of renal and liver function, blood counts, and uric acid should be measured periodically, especially when a urate-lowering drug

has just been started. This is important both for monitoring the adequacy of uric acid suppression and for identifying toxic effects related to treatment. Once a stable treatment plan is in place, office visits and laboratory testing can be decreased to once or twice per year.

For patients starting a uricosuric, some experts recommend baseline and periodic testing of urinary uric acid levels to ensure that excretion is not too high (ie, >800 mg per 24 hours) because excessive uricosuria increases the risk of nephrolithiasis.

REFERRAL TO A SPECIALIST

Gout can usually be diagnosed and treated by a patient's primary care physician. However, referral to a rheumatologist should be considered when (1) symptoms persist and the diagnosis remains in question; (2) the primary care physician cannot perform the joint aspiration or injection that is warranted; (3) disease is not well controlled with standard treatment; or (4) medications are needed that the primary care physician does not prescribe (eg, pegloticase).

RECOMMENDATIONS FOR MR R

Frequent attacks are a clear indication for urate-lowering treatment. Therefore, I recommend for Mr R (1) education regarding risk factor modification, treatment goals, and prognosis; (2) reviewing the importance of medication adherence and treating with allopurinol to lower uric acid to less than 6.0 mg/dL (this may require higher than the current dose of allopurinol); (3) regular monitoring for adequacy of uric acid suppression and drug toxicity; and (4) prophylactic colchicine in a low dosage (such as 0.6 mg daily or every other day) if tolerated until his uric acid level is stable at or below the goal.

In my view, there is no indication currently for the newer gout drugs, such as febuxostat or uricase. Although urate-lowering treatment is usually lifelong, patients who make major lifestyle changes could eventually discontinue treatment. With proper treatment, Mr R's prognosis is excellent.

QUESTIONS AND DISCUSSION

QUESTION: You mentioned that patients taking cyclosporine had an increased risk of gout. Why would an immunosuppressant, as transplant patients take, increase the risk of gout, when you would expect inflammation to be reduced?

DR SHMERLING: I had referred to cyclosporine treatment in particular as a medication that increases the risk of gout, but not all immunosuppressant medications increase the risk. The impact of cyclosporine (and related medications) is not related to immune suppression but, instead, is related to its effect on renal function and renal handling of uric acid. Cyclosporine contributes to hyperuricemia by reducing the glomerular filtration rate and renal tubular injury, both of which impair clearance of uric acid.[61]

QUESTION: You mentioned that with urate-lowering therapy, physicians should have a target uric acid level of less than 6 mg/dL. If the patient is taking allopurinol and experiencing no attacks of gouty arthritis but has a uric acid level of 7.0 or 8.0 mg/dL, why should we lower uric acid further?

DR SHMERLING: If the patient is a good candidate for urate-lowering therapy (eg, frequent attacks, tophi), it makes little sense to leave their uric acid above the physiologic saturation level because the risk of complications (eg, joint damage) is high. The logic here is a bit like with hemoglobin A_{1c} in patients with diabetes mellitus. If a patient with diabetes feels well but has a hemoglobin A_{1c} level of 9.0%, we recommend tighter blood glucose control because studies suggest that, in aggregate, patients with lower hemoglobin A_{1c} levels have less end-organ damage. A similar logic applies to uric acid suppression for patients with moderate to severe gout.[62]

QUESTION: Some people with toe pain think they have gout but have other problems instead, so I recommend they come in during an acute flare. But, you said that aspiration is not always necessary. How do you rule out other causes of toe pain without joint aspiration?

DR SHMERLING: It is true that there are many causes of toe pain other than gout. The most common is probably osteoarthritis. But, as with all diagnostic reasoning, it comes down to pretest probability, and that probability is driven by the clinical presentation, especially the mode of onset and the findings of acute inflammation on examination. If I am convinced that the patient has gout by his or her history and physical examination and I cannot offer a likely alternative diagnosis, I think aspiration can often be deferred. Also, the results of arthrocentesis may not be as useful as anticipated. If the synovial fluid demonstrates gout crystals, the patient should be treated for gout. But, given a high suspicion, the clinician may choose the same treatment without aspiration. If an attempt to aspirate the joint is made and no fluid is obtained (a frequent occurrence), the diagnosis remains unproven and the clinician may still treat the patient for gout. It is primarily when there is a clinical suspicion of infection or another diagnosis that would be treated differently that joint aspiration becomes critical. If aspiration is deferred, vigilant follow-up is warranted when gout is treated empirically, as clinical assessment is clearly not perfect.[63,64]

QUESTION: Could you say a word about the relationship between uric acid stones and gout?

DR SHMERLING: There has long been controversy about whether gout is bad for the kidneys. I was taught that while hyperuricemia and gout are often associated with renal dysfunction, gout was not the proximate cause of kidney disease and that obstructive uropathy, when present, was the real link between hyperuricemia and kidney disease. Although uric acid crystals can be found in the parenchyma of the kidneys of individuals who are hyperuricemic, it has

never been clear that these crystals were particularly harmful. More recent data, however, raise the possibility that hyperuricemia itself is associated with renal dysfunction (as well as hypertension and heart disease).[65,66] We need better evidence to sort this out. If future investigations make a compelling case that treating asymptomatic hyperuricemia significantly reduces the incidence of kidney disease or other cardiovascular problems, the practice could make a comeback.

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Online-Only Material: eTables 1 through 3 are available at http://www.jama.com.
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