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How Would You Manage This Patient With Gout?

Grand Rounds Discussion From Beth Israel Deaconess Medical Center

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Gout is the most common form of inflammatory arthritis. In 2012, the American College of Rheumatology (ACR) issued a guideline, which was followed in 2017 by one from the American College of Physicians (ACP). The guidelines agree on treating acute gout with a corticosteroid, nonsteroidal anti-inflammatory drug, or colchicine and on not initiating long-term urate-lowering therapy (ULT) for most patients after a first gout attack and in those whose attacks are infrequent (<2 per year). However, they differ on treatment of both recurrent gout and problematic gout. The ACR advocates a "treat-to-target" approach, and the ACP did not find enough evidence to support this approach and offered an alternative strategy that bases intensity of ULT on the goal of avoiding recurrent gout attacks ("treat-to-avoid-symptoms") with no monitoring of urate levels. They also disagree on the role of a gout-specific diet. Here, a general internist and a rheumatologist discuss these guidelines; they debate how they would manage an acute attack of gout, if and when to initiate ULT, and the goals for ULT. Lastly, they offer specific advice for a patient who is uncertain about whether to begin this therapy.

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Mr. P is a 63-year-old man with hypertension and stage 3 chronic kidney disease (CKD). He was diagnosed with gout in June 2014 when he presented with redness, warmth, and tenderness of his left great toe. Uric acid (UA) level was 8.5 mg/dL. He was treated with acetaminophen. Nonsteroidal anti-inflammatory drugs (NSAIDs) were contraindicated because of the CKD. Symptoms recurred a month later, at which time he was treated with 40 mg of prednisone daily for 3 days. He eliminated consumption of alcoholic beverages, shellfish, and red meat to minimize purines. One month later he had another attack and again was treated with prednisone.

Mr. P did well through 2015. In 2016, he had 2 flares, which were treated with prednisone. His primary care physician recommended starting allopurinol, but Mr. P deferred to minimize his number of daily medications. Instead, he continued to receive as-needed colchicine and further restricted his diet.

During 2017, Mr. P. had 6 or 7 episodes of left great toe discomfort. He took 0.6 mg of colchicine twice daily for 3 days, and the discomfort resolved. His most recent UA level was 7.5 mg/dL and creatinine level was 1.7 mg/dL.

Mr. P's medical history is otherwise noteworthy for benign prostatic hypertrophy, as well as knee and low back pain. His medications include doxazosin and lisinopril. He has no known allergies. He is married and works as a medical specialist in a hospital radiology department. He exercises regularly and does not smoke.

ABOUT BEYOND THE GUIDELINES

Beyond the Guidelines is a multimedia feature based on selected clinical conferences at Beth Israel Deaconess Medical Center (BIDMC). Each educational feature focuses on the care of a patient who "falls between the cracks" in available evidence and for whom the optimal clinical management is unclear. Such situations include those in which a guideline finds evidence insufficient to make a recommendation, a patient does not fit criteria mapped out in recommendations, or different organizations provide conflicting recommendations. Clinical experts provide opinions and comment on how they would approach the patient's care. Videos of the patient and conference, the slide presentation, and a CME/MOC activity accompany each article. For more information, visit www.annals.org/GrandRounds.

This article is based on the Department of Medicine Grand Rounds conference held on 10 May 2018.

MR. P'S STORY

I was first diagnosed with gout in 2014. The base of my left toe was so painful I could hardly walk. The next day I made an appointment to see my doctor, and she

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diagnosed gout. She treated the first episode with a standard treatment of rest, ice, and elevating the foot. I can't take any NSAIDs, so she suggested Tylenol.

That year I had 4 episodes of gout. I resorted to prednisone for 2 of them because they lasted a few days and I couldn't get relief using the standard treatment. Then in 2016, I had 3 more episodes. I resorted to taking prednisone in 2 of those cases. Besides taking prednisone, I discussed taking allopurinol with my physician. I was a little hesitant about taking another drug, so I thought I would wait and see if the dietary management that I started would help control the uric acid and the episodes of gout. But if the frequency of attacks increased, I agreed to try allopurinol. I started to really manage my diet, eliminating alcohol, shellfish, and beef and drinking a lot of water.

My doctor recommended I use colchicine when I thought a gout attack was coming on. I took it probably about 6 or 7 times, twice a day—once in the morning and once in the evening. I believe that that, as well as the dietary management, really helped the gout from coming on full strength.

I think it would be nice to know how often my uric acid level should be tested to see if any changes in my life are affecting that. Also, I would like to know how much effect diet has on lowering uric acid level as opposed to taking allopurinol or other drugs. Also, can physical activity help control gout?

See the **Patient Video** (available at Annals.org) to view the patient telling his story.

CONTEXT, EVIDENCE, AND GUIDELINES

Gout is caused by excess accumulation of monosodium urate crystals in joint fluid, cartilage, bones, tendons, and other sites. It is one of the most common forms of inflammatory arthritis—nearly 4% of U.S. adults (approximately 8.3 million persons) will receive a diagnosis of gout at some point in their lives (1). Gout is characterized by joint pain and swelling during acute attacks and can progress to chronic gout, which may be associated with deposits of UA crystals known as tophi (2).

On an annual basis, gout accounts for 7.2 million ambulatory visits and costs an estimated $1 billion, of which 61% is spent on medications (3). Available pharmacologic therapies include anti-inflammatory drugs (for example, NSAIDs, corticosteroids, colchicine) and urate-lowering therapy (ULT) (for example, allopurinol, febuxostat) (**Tables 1** and **2**) (4–6). Nonpharmacologic therapies include weight loss and exercise and gout-specific dietary therapy, such as reducing intake of red meat, shellfish, high-fructose corn sweeteners, and alcohol (4).

In January 2017, the American College of Physicians (ACP) published a guideline on managing acute and recurrent gout (4) based on a background evidence paper (6) and systematic evidence review by the Agency for Healthcare Research and Quality (2). The ACP guideline recommends a corticosteroid, NSAID, or colchicine for treatment of acute gout because high-quality evidence has found all 3 to be effective. The guideline recommends against initiating long-term ULT in most patients after a first gout attack and in patients with infrequent attacks (<2 per year) because it has not been adequately studied in those populations.

The ACP encouraged shared decision making about initiating ULT with patients who have recurrent gout (≥2 episodes per year) or problematic gout (that associated with tophi, CKD, or urolithiasis). Regarding ULT goals, the ACP concluded that evidence was insufficient to determine whether the benefits of escalating ULT to reach a serum urate target less than 6 mg/dL ("treat-to-target") outweighs the harms associated with repeated monitoring and medication escalation. The ACP noted an alternative strategy that bases ULT intensity on the goal of avoiding recurrent attacks ("treat-to-avoid-symptoms") without monitoring urate levels. It recommends that studies be done to compare these 2 strategies. Finally, the ACP concludes that evidence was insufficient to determine the efficacy of gout-specific dietary therapies.

Earlier, in 2012, the American College of Rheumatology (ACR) issued a guideline on management of

Table 1. Treatment of Acute Gout*

Agent, by Drug Class	Usual Dosage†	Harms and Adverse Effects
Anti-inflammatory drugs		
Nonsteroidal anti-inflammatory drugs		Dyspepsia, gastrointestinal ulceration and bleeding, renal dysfunction
Ibuprofen	800 mg orally 3 times/d	
Naproxen	500 mg orally twice/d	
Diclofenac	75 mg orally twice/d	
Indomethacin	50 mg orally 3 times/d	
Celecoxib	200–400 orally mg/d	
Corticosteroids		
Prednisone	30–40 orally mg/d	
Methylprednisolone	0.5–2.0 mg/kg of body weight intramuscularly	
Methylprednisolone acetate	20–80 mg intra-articularly	
Colchicine (generic)	1.2 mg orally, then 0.6 mg by same route 1 h later	Gastrointestinal effects (e.g., diarrhea, nausea, cramps, vomiting)

* Data from references 4–6.
† Derived from DynaMed Plus (www.dynamed.com) or the Agency for Healthcare Research and Quality report.

Table 2. Urate-Lowering Treatment of Gout*

Agent, by Drug Class	Usual Dosage†	Harms and Adverse Effects
Uricosuric drug: Probenecid	500 mg orally twice/d	Rash, flushing, and nausea
Xanthine-oxidase inhibitors		
Allopurinol	Starting dose: 100 mg/d orally (lower dose if renal function is impaired); increase by 50–100 mg/d every few weeks	Rash and other potentially serious idiosyncratic reactions
Febuxostat	40–80 mg orally daily	Abdominal pain, diarrhea, and musculoskeletal pain

* Other urate-lowering medications approved by the U.S. Food and Drug Administration include lesinurad and pegloticase.
† Derived from DynaMed Plus (www.dynamed.com) or the Agency for Healthcare Research and Quality report.

gout (7, 8). The ACP and ACR guidelines agree on the treatment of acute gout. For the treatment of recurrent gout, although the ACR would offer ULT to a similar group of patients as the ACP, it endorses the "treat-to-target" strategy. It sets the goal for a UA level less than 6 mg/dL with the understanding that a further decrease below 5 mg/dL may be needed to reduce signs and symptoms. The ACR guideline also differs from the ACP's in recommending a gout-specific diet that avoids high-protein organ meat, high-fructose corn–sweetened sodas, and alcohol overuse and limits red meat, lamb, pork, and seafood.

CLINICAL QUESTIONS

To structure a debate between our discussants, we mutually agreed on the following key questions to consider when applying this guideline to clinical practice in general and to Mr. P in particular.

1. How would you manage an acute attack of gout?
2. How would you decide whether, and if so when, to initiate ULT?
3. How would you manage ULT: Would you "treat-to-avoid-symptoms" or "treat-to-target"?

DISCUSSION

A General Internist's Viewpoint (Dr. C. Christopher Smith)

Question 1: How would you manage an acute attack of gout?

While many acute gout flares subside without treatment in 7 to 14 days, most are associated with substantial pain. Given this, the management of acute gout requires prompt control as more rapid and complete resolution of symptoms is achieved the sooner treatment is begun (ideally in the first 24 hours). Strong evidence supports use of corticosteroids, NSAIDs, or low-dose colchicine (4, 7, 8).

Treatment options for acute gout are shown in the Table 1 (4–6). Colchicine is most effective if started within 24 hours. A low-dose regimen (1.2 mg followed by 0.6 mg 1 hour later) appears to be as effective as a high-dose regimen (4.8 mg over 6 hours) with fewer side effects (9). Different NSAIDs have similar efficacy (10, 11) and should be administered at relatively high doses until 1 to 2 days after the acute flare has resolved. Glucocorticoids have a similar efficacy to NSAIDs and may have fewer side effects (12, 13); however, they require a longer, tapering course to prevent rebound attacks. A usual regimen is 40 mg of prednisone daily until resolution begins, followed by a taper over 7 to 14 days. In patients unable to take oral medications who have 1 or 2 inflamed joints, intraarticular injection of glucocorticoids can be performed after infection has been excluded.

Given Mr. P's CKD, I would avoid NSAIDs and would use either glucocorticoids or colchicine to treat an acute flare.

Question 2: How would you decide whether, and if so when, to initiate ULT?

In approaching ULT, both nonpharmacologic and pharmacologic treatment should be discussed. Nonpharmacologic management focuses on dietary and lifestyle changes. While these changes have overall health benefits, several systematic reviews of randomized controlled trials have not demonstrated a reduction in gout symptoms (14, 15), and a gout-specific diet has not been demonstrated to be more effective than general dietary counseling.

I concur with the ACP and would offer ULT to patients such as Mr. P who have recurrent or problematic gout (4, 7, 8). As Mr. P has had recurrent flares despite dietary modifications, I would discuss the benefits and risks of ULT. Over time, it is likely that Mr. P will have increasing frequency of flares that will be more difficult to control, placing him at a greater risk for tophi, chronic arthritis, and joint damage. In addition, ULT may slow the progression of his kidney disease (16, 17).

Along with reviewing the potential benefits of ULT, I would want to better understand Mr. P's reluctance to starting it. Patients often have concerns about excessive medication use as well as cost of medications, office visits, and laboratory tests. While 2% to 5% of patients develop a mild rash with allopurinol, the more concerning reaction, allopurinol hypersensitivity syndrome, is far less common, occurring in approximately 1 out of 1000 patients treated (7). Individuals with HLA-B*5801 are at a higher risk, and populations with a high frequency of this allele should be screened, including individuals of Korean descent and especially those with stage 3 or worse CKD, and those of Han Chinese or Thai descent. Patients may also harbor a sense of guilt or embarrassment about gout as it has long been linked to obesity and excessive intake of food or alcoholic beverages. For most patients, the primary underlying cause of gout is genetically induced renal urate underexcretion. Thus, care must be taken to counteract the stigma that gout is self-inflicted (18, 19). In addition,

I would want to help Mr. P understand the long-term consequences of poorly controlled gout.

Another consideration in starting ULT is that rapid changes in UA levels can precipitate gout flares (20). Patients should be prescribed prophylactic therapy with low-dose colchicine or NSAIDs (21) concomitant with initiation of ULT. In recent trials (22, 23), the rate of acute attacks was doubled when prophylaxis was discontinued after 8 weeks; however, in a similar study that continued prophylaxis for 6 months, there was no increase in flares (24).

For Mr. P, I think the benefits of initiating ULT outweigh the risks. While both allopurinol and febuxostat reduce serum urate levels, I would recommend allopurinol given its lower cost and long-term safety profile (25) and would start prophylaxis with low-dose colchicine. If he chooses not to initiate ULT, I would regularly revisit the topic with him, especially if he has increasing frequency and intensity of flares or signs and symptoms of more severe disease, such as tophi, nephrolithiasis, or joint damage.

Question 3: How would you manage ULT: Would you "treat-to-avoid-symptoms" or "treat-to-target"?

Serum urate levels of approximately 6.8 mg/dL saturate extracellular fluid and allow crystal deposition, which triggers the inflammatory response that causes gout. A post hoc analysis combining data from 3 large trials comparing allopurinol to febuxostat (26) and several retrospective cohort studies (27–29) provide support for an association of lower urate levels and a reduction of gout attacks. Supported by these physiologic and observational data, the ACR and several other organizations recommend a treat-to-target approach (7, 8), targeting a UA level of less than 6 mg/dL in most patients and less than 5 mg/dL in those with greater disease severity, such as the presence of tophi.

The treat-to-target approach has a natural appeal. It sets measurable goals that both the physician and patient can follow. However, there have been no randomized trials to support it. While recognizing indirect evidence and biologic plausibility, the ACP found the strength of evidence to support this approach to be low (4) and could not conclude whether the benefits of a treat-to-target approach outweighed the potential harms of escalating ULT in asymptomatic patients. The ACP proposed an alternative strategy that adjusts ULT to prevent recurrent attacks (treat-to-avoid-symptoms). As some patients with serum urate levels above 6 mg/dL are asymptomatic and patients below this value have flares, the treat-to-avoid-symptoms approach is appealing because symptoms rather than laboratory values direct management decisions. Such an approach could reduce the need to monitor urate levels and prevent potentially unnecessary dose escalation in asymptomatic patients. Comparative effectiveness studies are needed to compare these 2 approaches and to determine gout-related and overall health outcomes.

Since we are routinely forced to make decisions without all the evidence we would like, my approach is somewhere between the ACP and ACR guidelines. I principally use the patient's clinical symptoms to manage ULT and utilize serum UA in certain circumstances. For Mr. P, after a careful discussion of risks, benefits, and costs, I would recommend the initiation of ULT. If he has no barriers to regularly measuring UA, I would assess UA levels and monitor signs and symptoms when making management recommendations; however, I would not feel compelled to make changes based on his UA level alone. For example, if during a visit Mr. P reports being asymptomatic for months and has had no signs or symptoms of advanced disease (such as tophi), I would be less inclined to adjust his dosing. On the other hand, if he were having flares or had evidence of tophi, I would further increase his dose even if his urate level was lower than 6 mg/dL. Finally, if Mr. P had financial or other barriers that limited regular laboratory monitoring without signs or symptoms of advanced disease, I would adjust his dose based solely on clinical symptoms.

A Rheumatologist's Viewpoint (Dr. Robert H. Shmerling)

Question 1: How would you manage an acute attack of gout?

Gout flares can be treated with judicious use of NSAIDs, low-dose colchicine, or corticosteroid therapy (30–32). While minor side effects are common, the vast majority of patients can be safely and effectively treated. In some refractory cases, combination therapy (for example, colchicine and an NSAID) or off-label use of a biologic therapy (including IL-1 inhibitors, anakinra, or canakinumab) may be considered (32, 33).

Question 2: How would you decide whether, and if so when, to initiate ULT?

I agree with the ACR: ULT should be offered to individuals who are at the greatest risk for joint damage, repeated flares, and other complications. This includes patients who have frequent attacks (≥2 per year) (like Mr. P), tophi, or a history of nephrolithiasis. Although CKD (stage 2 or worse) is included as an indication for ULT, this strategy could lead to overtreatment, including initiation of ULT after a single attack. Polyarticular gout and attacks that do not respond promptly to therapy are relative indications as well. While allopurinol or febuxostat are considered first-line ULT for most patients, allopurinol is typically the first choice due to its lower cost and greater range of dosing options; in addition, a recent study raised concern that febuxostat may be accompanied by cardiovascular morbidity (25).

Long-term ULT is generally highly effective and well-tolerated. However, patient preference is important, since treatment is generally lifelong. Despite meeting criteria for ULT, some patients, such as Mr. P, prefer to treat symptoms as they develop rather than take a daily medication; others prefer to rely on nonpharmacologic options, such as weight loss and dietary changes (vitamin C, cherry juice, and a low purine or "anti-inflammatory" diet) (34, 35) to avoid the cost and

side effects of medications. However, rigorous clinical trials demonstrating the effectiveness of these options are not available, leading the ACP to make no specific recommendation regarding diet and lifestyle (15, 36, 37). The ACR, nevertheless, endorsed these approaches primarily because of their positive impact on prevention and management of comorbidities associated with gout, including coronary artery disease, diabetes, and obesity.

These steps, however, rarely allow for the discontinuation of ULT. For example, a patient who undergoes bariatric surgery, discontinues heavy alcohol use, and switches from a high- to low-purine diet might be able to lower UA enough to avoid or discontinue ULT. Unfortunately, nonpharmacologic approaches are often ineffective (38, 39) and those who discontinue ULT often have recurrent gout (40).

Mr. P asks how often his UA should be monitored to determine whether lifestyle changes alone are lowering his levels. I would recommend measuring UA every 6 to 12 months with the expectation that if gouty attacks recur and hyperuricemia persists, ULT should be reoffered. If periodic radiographs or other imaging demonstrates the development of joint damage over time, the impetus for ULT would be even greater. For patients on ULT with adequately suppressed UA, regular imaging is generally not warranted; however, if a patient has indications for ULT and declines, I would recommend radiographs at least yearly to detect the development of tophaceous erosions.

For Mr. P, gout flares have continued, leading him to require colchicine treatment. While this can relieve acute symptoms, urate deposition and irreversible joint damage and increasingly more frequent and prolonged flares are likely without ULT. This represents a missed opportunity to prevent suffering and other downstream consequences, such as missed work, loss of employment, and higher health care costs.

Question 3: How would you manage ULT: Would you "treat-to-avoid-symptoms" or "treat-to-target"?

The ACP and ACR answer this important question differently. I strongly favor the ACR's recommendation to adopt the treat-to-target strategy. If ULT is initiated, treatment should address the metabolic derangement responsible for the disease. A rational approach based on the pathophysiology of gout is to reduce serum UA levels well below those at which UA precipitates at normal human pH and temperature (approximately 6.8 mg/dL) by treating to target and aiming for a UA level less than 6.0 mg/dL. This allows the patient some "wiggle room" and is preferred because pH and temperatures vary throughout the body: Cool, distal sites (such as the great toe) may have lower temperature and pH than more proximal sites and may account for the propensity of such sites to develop gouty arthritis or tophi. If gout attacks recur despite suppression of UA to less than 6.0 mg/dL, a lower target (e.g., less than 5.0 mg/dL) may be appropriate; this is especially common for patients with tophaceous disease.

In clinical practice, some patients with suboptimal urate suppression may experience fewer acute attacks even while joint damage progresses. In addition, there may be other complications of hyperuricemia—a growing body of evidence links cardiovascular, renal, and overall mortality risk to hyperuricemia (41–43), although direct causation has not been demonstrated.

Rheumatologists in the U.S. have been trained to treat-to-target for decades. There is a wealth of experience with this approach, and it is generally well tolerated and highly effective (44, 45). The rationale of treating to target is sound: It makes little sense to administer doses of ULT that do not lower the UA below that at which it precipitates. Monitoring UA levels is the only way to know whether ULT has adequately suppressed levels. Recurrent attacks during ULT could occur because of expected fluxes in UA levels, nonadherence, underdosing, or ineffectiveness of the medication. Meanwhile, lack of attacks may provide a false sense of security, as an ill-timed attack may be imminent or tophaceous disease may develop while causing little or no symptoms. Without monitoring (and appropriate ULT dose adjustment), there is no way to know whether the goals of ULT are being achieved. The 2012 ACR guideline codified this strategy, recommending allopurinol (beginning with a dose of no more than 100 mg/d) or febuxostat, with uptitration every 2 to 5 weeks based on UA levels.

With the ACP treat-to-avoid-symptoms strategy, adjustments in ULT are presumably based on recurrent symptoms; therefore, the patient must endure attacks to "justify" uptitration. This reactive approach may have the advantage of administering lower doses of ULT than the treat-to-target strategy. However, the marginal benefit in lowering medication costs or toxicity is likely low, because generic ULT is available and toxicity is not highly dose-dependent with long-term treatment. The analogy to diabetes (in which driving blood sugar levels lower may cause harm) and anemia related to renal disease (in which driving hemoglobin levels higher may cause harm) are inappropriate because there is no known downside to keeping UA levels under the target of 6.0 mg/dL.

By either set of guidelines, Mr. P met criteria for ULT in 2014; as might be predicted, he continued to have gout flares in the absence of ULT. While we have no formal cost-effectiveness analyses comparing treat-to-target with treat-to-avoid-symptoms strategies, I believe Mr. P and others like him can benefit immensely from guidelines that proactively prevent complications rather than waiting for additional, avoidable suffering. The ACR and ACP guidelines are similar in many respects but the biggest difference—how to manage ULT—can profoundly impact quality of life. Until compelling evidence suggests otherwise, I believe the ACR got it right: Treating to target should be the standard approach.

SUMMARY

Gout is one of the most common forms of inflammatory arthritis. Acute attacks involve significant joint

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pain and swelling. Some patients progress to chronic gout, which may be associated with deposits of UA crystals known as tophi (2). Both discussants agree that acute gout should be treated with NSAIDs, corticosteroids, or colchicine. Similarly, neither would initiate ULT in patients after a first gout attack or in those with infrequent attacks (<2 per year).

They also agree that ULT should be considered for patients, such as Mr. P, who have recurrent attacks (≥2 per year) or those with problematic gout (gout associated with tophi, CKD, or urolithiasis). Both are concerned that without treatment, the frequency of flares may increase and the attacks may be more difficult to control and involve more joints, placing them at greater risk for tophi. They would try to address Mr. P's concerns about initiating ULT; however, if he remains reluctant they would recommend regularly revisiting this topic, especially if flares are increasing or signs and symptoms of more severe disease, such as the development of tophi, appear.

Our discussants disagree on treatment goals for ULT. Dr. Shmerling advocates the treat-to-target approach because it is based on the metabolic derangement responsible for gout and reduces serum UA to less than 6 mg/dL—the level at which it precipitates at normal human pH and temperature. If gout attacks recur despite suppression to this level, Dr. Shmerling would favor a lower target (such as <5 mg/dL). Furthermore, he states that there is no known harm of long-term UA suppression; treatment has an acceptable price tag; and, most important, this protocol avoids suffering, hospital admissions, and downstream costs.

Dr. Smith acknowledges that the treat-to-target approach has a natural appeal but notes that it is based on indirect evidence with no supporting data from randomized trials. He notes that there may be a place for the ACP's treat-to-avoid-symptom approach and urges that studies evaluate the comparative effectiveness of the 2 strategies. For now, he would find a path between them. He would principally use the patient's clinical symptoms to manage ULT and would measure serum UA under certain circumstances. For example, he would assess UA levels and monitor signs and symptoms when making management recommendations for patients who have no barriers to regular measurement. However, he would not feel compelled to make changes based on UA levels alone. For patients who had barriers that limited regular laboratory monitoring and who did not have signs or symptoms of advanced disease, he would adjust dosing based solely on clinical symptoms.

Finally, the guidelines and our discussants disagree on the role of diet and lifestyle change. The ACP found no evidence for gout-specific dietary therapy. Nevertheless, the ACR endorsed these therapies primarily because of their positive effect on management of comorbidities associated with gout, including coronary artery disease, diabetes, and obesity.

A transcript of the audience question-and-answer period is available in the **Appendix** (available at Annals.org). To view the entire conference video, including the question-and-answer session, go to Annals.org.

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FAST-TRACK REVIEW

Annals will consider manuscripts of high quality for expedited review and early publication (Fast Track) if they have findings that are likely to affect practice or policy immediately and if they are judged valid. We give priority to fast-tracking large clinical trials with clinical outcomes and manuscripts reporting results that are likely to have an immediate impact on patient safety. Authors wishing to fast-track their articles should contact Senior Deputy Editor Dr. Cynthia Murlow (e-mail, cynthiam@acponline.org) and provide an electronic version of their manuscript along with a request and justification for expedited review and, for trials, the protocol and registry identification number.

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Appendix: Comments and Questions

Dr. Tess: Thank you both for a great presentation. Patients with gout often have a lot of other comorbidities and medications. How does the likelihood of adherence play into your decision about whether to start urate-lowering therapy, and could lack of adherence actually cause more problems?

Dr. Shmerling: I would argue that adherence is a problem all across medicine. Any time a drug is prescribed, there is the chance that it will not be taken appropriately. Allopurinol taken intermittently can cause harm—it can wreak havoc on uric acid fluctuations, and gout attacks can be perpetuated that way. I think partial adherence (for example, just taking colchicine without urate-lowering therapy) is not great care for gout, so using generic medications as much as possible, understanding the patient's copay and insurance situation, and understanding what the barriers are to adherence are important strategies. We also have to look for interactions with other medications. Colchicine was taken off the generic list and put back onto the brand-name list, in part with the understanding that more testing would be done. With that change, we learned that colchicine has a lot of drug interactions. Side effects and drug interactions are important barriers to adherence.

Dr. Mark Zeidel: It makes perfect sense that there are 2 sets of guidelines: One is written by a group of people who see patients referred to them with gout, so providers like Rob are seeing people with staccato presentations of tophi and pain. On the other hand, a general internist may have a large number of patients who are not referred because their gout is easily treated, and guidelines geared toward these physicians might be less aggressive. In any event, I recall that the patient has a creatinine of 1.7. As a nephrologist, I am wondering if that has any effect on how aggressively we're going to control the uric acid.

Dr. Shmerling: I think the goals for urate suppression in a patient with renal failure are the same as for patients without renal failure. It just may be more difficult; they tend to be more hyperuricemic to start with. They may need higher doses of allopurinol, although it is hard to predict. Starting with lower doses, maybe 50 or 100 mg a day, and gradually increasing doses is often the plan. It is hard to predict what dose the patient will need to get the urate level under 6 mg/dL. Patients with renal failure tend to be the most difficult cases to control, so uric acid may need to be much lower than 6. If the level is less than 6 and symptoms continue, the goal may need to be less than 5.5 or even less than 5.

Dr. Smith: It's possible, and you had a slide about this in your presentation as well, that aggressive control of uric acid may help prevent the decline of renal function. The jury is still out, but there may be some benefits. When we look at trials and studies, the patients and the study design are often very different from what we see every day in the office. The patients Rob sees in his clinic are often different from the ones I see. The ones that I refer to Rob either are really complex and are failing things that we normally do and may have the ability to make it to more appointments. I do think this is a call for more data—we need to be very careful with what we see in the randomized trials and think very carefully about how to apply the lessons from the patients in those trials to the patients that we see every day.

Dr. Shmerling: I think the "goutologists" see this as a turf war and believe that we should have one, consistent set of guidelines created by experts—rheumatologists—and that our guidelines would apply to patients regardless of whether they are seen in primary care physicians or by specialists. But it's worth noting that 90% of the care is provided by primary care clinicians, and we need guidelines that apply broadly.

Dr. John Markis: I don't understand how any randomized controlled trial could ever answer the question of how chronic hyperuricemia affects renal function. That worries me far more. If I had this problem, I would be concerned about the long-term effect, year after year, of hyperuricemia on my kidneys. How do you know that the 1.7 wasn't in part contributed to by long-time hyperuricemia?

Dr. Shmerling: I feel a little odd answering that in front of a nephrologist who is world-renowned, but I think it's a fair point. Data are emerging that suggest hyperuricemia may be bad for the kidneys. But we also don't know definitively that lowering uric acid is good for the kidneys. So you could design a study of patients with moderate renal insufficiency and randomize them to receive allopurinol therapy or placebo for a certain period, and it is conceivable that you could get an answer. I don't think that we should rely on epidemiological data alone.

Dr. Smith: We also don't know that a uric acid level of 6 is really that much better than a uric acid level of 5 or 6.2. These are the questions that we need to try to answer more clearly.

Dr. Jacqueline Wolf: Going beyond the guidelines and looking at who gets gout, which is mostly men, with postmenopausal women not in that group, what would you say about your therapies and how you would tailor them for women? Why is it so much more common in men, and what can you do to affect that?

Dr. Shmerling: I would maybe take exception to the very first part of what you said. Age is a very powerful

predictor of gout. Postmenopausal women do get gout, and the older they get, the more gout they get, and they start to catch up with men. It is thought that estrogen has some effect on urate handling in the kidney (so I was taught), which is why premenopausal women, by and large, do not get gout. Men and women do get it at advanced ages. I don't think therapy should vary based on gender. I can't tell you why more men get more gout. Certainly the male gender, perhaps because of lack of estrogen, is a contributor to gout in younger men, but I am not sure why. We don't know why some men get it and others don't, even within one gender, much less in between them. There's still a lot of mystery. Our therapies are typically quite similar among men and women.

Dr. Smith: Adding to the mystery is the fact that if you look at hyperuricemia and gout, only a very small percentage of people who are hyperuricemic actually develop gout. Many people are walking around with supersaturated serum, but they don't develop gout. Why? There are lots of questions we don't know the answers to yet.

Dr. Reynolds: The data don't suggest that lifestyle modification alone is adequate to manage somebody like Mr. P's gout. You both alluded to quality of life as a major factor in your decision making with patients about whether or not to start them on medication. I am wondering if you think it's worth these patients trying to change their diet if it diminishes quality of life and is not adequate to control their symptoms.

Dr. Shmerling: The ACR endorsed the lifestyle changes, including dietary changes, not because of their effects on gout but because of their effects on health otherwise. So the recommendations around diet are typically better for other comorbidities as well. If a restrictive diet has a major impact on quality of life, I would suggest that allopurinol would be a much more powerful way to lower uric acid than avoiding certain foods. So, one possible advantage of urate-lowering therapy is that you can probably tell patients they can liberalize their diet and get away with it. Because if the uric acid is 5.5 or 5.8, dietary restriction may be less important—so that's an advantage. Quality of life and patient preference are important, so you need to include those issues in the decision making as well.

Dr. Smith: One concern about gout-specific diets is that if you eliminate purines, you often substitute with carbohydrates, which leads to other problems that we all recognize now. I do recommend dietary changes, but I wouldn't necessarily say, "Follow a gout-specific diet." I think weight loss, exercise, and a healthy lifestyle are very important, but not necessarily a gout-specific healthy lifestyle.

Dr. Reynolds: I worry that it distracts patients and that we spend a lot of time on diet, when we should be talking about medications.

Dr. Shmerling: I agree. In fact, recent studies have found that the DASH diet may be effective at lowering uric acid and risk of gout. We may learn that this approach is actually better than any purine-limiting or gout-specific diet (46, 47).