



# My Treatment Approach to Gout

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## Abstract

Gout is the most common form of inflammatory arthritis in the United States. Nevertheless, gout remains misunderstood, misdiagnosed, underdiagnosed, and undertreated. Several new recommendation and guideline documents regarding the management of gout have been published in the past few years. New diagnostic modalities, such as ultrasound and dual-energy computed tomography, are now available. Newer treatment options exist, and older agents and their interactions are now better understood. This review addresses these recent diagnostic and therapeutic developments and describes our management protocol with the aim of providing the clinician with a pragmatic approach to gout management.

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**G**out is the most common form of inflammatory arthritis in the United States, affecting 4% of the population,<sup>1</sup> and its prevalence has been increasing.<sup>2</sup> Its prevalence has also increased in other countries, which has been attributed to a westernized lifestyle, more comorbidities, and improved life expectancy.<sup>3</sup> Most patients with gout are obese and have coexisting hypertension and renal disease.<sup>4</sup> Unfortunately, gout remains misdiagnosed, underdiagnosed, and undertreated.<sup>5-8</sup>

New guidelines and recommendations have addressed the diagnosis and treatment of gout.<sup>9-11</sup> Advances have been made in the diagnostic imaging of gout with ultrasound (US) and dual-energy computed tomography (DECT). More data on older medications are now available, and new medications have been approved to treat gout.<sup>12</sup> The care of most patients with gout is managed by primary care providers; less than 10% of patients are referred to rheumatologists.<sup>13</sup> This review addresses the recent diagnostic and therapeutic developments, guidelines, and recommendations, along with our management protocol. We aim to provide the clinician with a pragmatic approach to gout management.

### MAKING A DIAGNOSIS

Confirmation of monosodium urate (MSU) crystals on polarized microscopy is the gold standard for diagnosis of gout. The presence of intracellular crystals is diagnostic of an acute flare, although extracellular crystals can

exist in the synovial fluid between attacks. A red, hot, and swollen great toe may be the most common presentation of acute gout; however, gout does not always present in this manner. The possibility of gout in nonmetatarsophalangeal joints and a polyarticular presentation must always be considered.

### Diagnosis by Criteria

Gout is usually diagnosed clinically because most patients are seen in primary care practices, where lack of facilities and time hamper synovial fluid aspiration. For example, arthrocentesis was performed in only 8% of patients with suspected gout first seen in an emergency department,<sup>14</sup> and it is unlikely that the use of arthrocentesis will increase substantially in the immediate future. **Because of these real-world limitations, a diagnostic rule for acute gout was proposed and then validated for primary care settings.<sup>15,16</sup>** Seven clinical variables were used in the calculation (Table 1). Caveats to note are that the study included only monoarticular arthritis, and the diagnoses were dependent on the evaluating physician's expertise. Therefore, atypical presentations may have been missed.

The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) have also proposed clinical classification criteria for gout because of the low utilization of synovial analysis (these classification criteria are not intended to be diagnostic criteria).<sup>17</sup> The ACR/EULAR criteria have as an entry criterion the occurrence of acute arthritis in a peripheral joint

or bursa, such as the metatarsophalangeal (MTP), ankle, or olecranon bursa. The presence of MSU crystals in synovial fluid was determined by ACR/EULAR to be a sufficient criterion to establish a diagnosis without further scoring. When synovial fluid is not available, clinical features, serum uric acid level, and imaging findings (US and DECT) are used to make the diagnosis. The ACR/EULAR calculator has sensitivity of 92% and specificity of 89% and is accessible at <http://goutclassificationcalculator.auckland.ac.nz>.

When time, resources, or both are limited, these criteria (ACR/EULAR and the diagnostic rule) may be useful to identify gout. Atypical presentations or lack of response to treatment should trigger comprehensive testing, including synovial fluid aspiration, use of US or DECT, closer patient follow-up, or referral to a rheumatologist, or a combination. If an infection is considered, whether alone or concomitantly with gout, synovial fluid aspiration must be performed by a qualified individual, and appropriate referrals must be made. A diagnosis of gout should always be considered in any person with an atypical, seronegative inflammatory arthritis. Examining the synovial fluid for crystals should be an essential step in the evaluation of any inflammatory arthritis.

### Hyperuricemia and Gout

Not all patients with hyperuricemia develop gout. In the United States, 21% of the population have hyperuricemia, and 4% have gout.<sup>1</sup> The 5-year cumulative incidence of gout was 0.5% in men with uric acid levels of 6 mg/dL or less (to convert to  $\mu\text{mol/L}$ , multiply by 59.485) and 30.5% in those with levels of 10 mg/dL or higher.<sup>18</sup> Uric acid levels may fluctuate and possibly decrease during an acute episode, but if normal, measuring uric acid 2 to 3 weeks after an acute attack has resolved will provide an accurate baseline and may aid in establishment of the diagnosis.<sup>19,20</sup> Acute gout cannot be excluded by the presence of a normal serum urate level.

### Gout in Women and Young Persons

Estrogen protects women from gout because of its association with enhanced renal excretion of uric acid,<sup>21</sup> and estrogen in hormone replacement therapy has a similar effect.<sup>22</sup> Gout occurs in only 0.2 per 1000 cases of women younger

**TABLE 1. Diagnostic Rule in Patients With Monoarthritis<sup>a,b</sup>**

Variable	Points
Male sex	2
Previous arthritis attack	2
Onset within 1 d	0.5
Joint erythema	1
First MTP joint involved	2.5
Hypertension or $\geq 1$ CVD variable	1.5
Serum uric acid $>5.88$ mg/dL	3.5
Category	Total points
95% of patients do not have gout. Consider alternative diagnoses.	$\leq 4$
Insufficient basis for diagnosis. Consider arthrocentesis if possible; otherwise, careful follow-up.	5-7
85% of patients have gout.	$\geq 8$
<sup>a</sup> CVD = cardiovascular disease; MTP = metatarsophalangeal.	
<sup>b</sup> SI conversion factor: To convert serum uric acid values to $\mu\text{mol/L}$ , multiply by 59.485.	

than 45 years.<sup>23</sup> Women with gout tend to be older and have more comorbidities, such as obesity and kidney disease, compared with men. Diuretic use as opposed to dietary triggers is more common in women than in men with gout.<sup>24</sup> Elderly women, particularly those taking diuretic agents, may have an initial polyarticular presentation, upper extremity—dominant disease, or tophi that may be confused with rheumatoid nodules.<sup>25,26</sup> Tophi may also be present in Heberden nodes.

Approximately 25% of patients with gout have a family history. However, in patients with early-onset gout (age  $<25$  years), 80% have a family member with gout.<sup>27</sup> These patients should be referred to a rheumatologist for further evaluation and management.

## ROLE OF IMAGING

### Radiography and Computed Tomography

Radiographs usually have negative findings but can be used to rule out fractures. Disease 5 to 10 years<sup>28</sup> after onset may show tophi and typical erosions, called rat bite erosions, which have overhanging edges.<sup>29</sup> Joint space is preserved until later in the course of the disease. Conventional computed tomography is not used in the routine diagnosis of gout, but it is excellent for identifying erosions.<sup>30</sup>

### Ultrasonography

Ultrasound is a well-accepted, safe, noninvasive, nonionizing, portable, and relatively

inexpensive imaging modality. Typical sonographic findings in gout are the double-contour sign, tophi, and the snowstorm sign. Ultrasound is more sensitive than radiography for identifying erosions.<sup>31</sup> A meta-analysis showed that pooled sensitivity and specificity for the double-contour sign on US were 83% and 76%, respectively, and for tophi, 65% and 80%, respectively.<sup>32</sup> Results of a large multicenter study showed more than 90% specificity for US in clinically symptomatic joints, and specificity remained high in cases without tophi, MTP swelling, or tenderness.<sup>33</sup> Ultrasound is useful in the evaluation of acute monoarticular or oligoarticular disease. In 1 long-term study of arthritis in the first MTP, the initial impression was gout in 98% of the patients, but only 77% were confirmed to have gout. Thus, although the MTP is the most common joint involved and may appear to have gout, gout is not always the correct diagnosis.<sup>34</sup> Ultrasound also facilitates assessing the effectiveness of urate-lowering therapy (ULT) because the tophi and double-contour sign regress with successful treatment.<sup>35</sup>

Ultrasound is a valuable tool for guiding arthrocentesis of synovial fluid. In 1 study of primary care internists, US-guided aspiration was successful in 93% vs 52% of patients when palpation was used.<sup>36</sup> Ultrasound also facilitates local corticosteroid injections into an affected joint. Also, US guidance can be used for dry needling, a technique used for aspirating MSU crystals in an asymptomatic joint in a patient without a synovial effusion but with suspected gout.<sup>37</sup>

The double-contour sign should be differentiated from a cartilage-interface sign, which is dependent on the angle of insonation. In 1 study, 29% of patients with asymptomatic hyperuricemia had evidence of MSU deposition.<sup>38</sup> However, patients with gout tend to have more erosions and synovitis than asymptomatic patients with hyperuricemia and MSU deposition.<sup>39</sup> Some concern has been expressed about differentiating gout from calcium pyrophosphate deposition disease; however, recent findings showed that the double-contour sign and tophi retain high specificity and allow for differentiation between the 2 diagnoses.<sup>33</sup>

Although US is a convenient tool for assessing gout, it does not replace

arthrocentesis as the test of choice.<sup>40</sup> It also does not exclude a diagnosis of infection, which requires clinical judgment and arthrocentesis. The use of US should increase because more programs now offer training in US as a part of graduate medical education.<sup>41</sup> However, its point-of-care availability, time constraints for the provider performing the procedure, availability of US-trained providers or radiologists, and a sonographer's skill may be limiting factors in a general community practice.

### Dual-Energy Computed Tomography

DECT is based on the principle of different attenuation of substances being dependent on their density, atomic number, and photon beam energy. Exposure to 2 different photon beam energies allows differentiation of substances.<sup>42</sup>

Regarding MSU deposition, DECT is as sensitive as US for the lower extremity and more sensitive than US for the upper extremity, the latter perhaps due to more complex anatomy that may not be easily accessible by US.<sup>43</sup> DECT can image MSU deposits in anatomically inaccessible areas, such as tendons, which are not easily amenable to aspiration. DECT identified gout in 30% of patients who had negative results for crystals in synovial fluid because the MSU deposition was not intra-articular.<sup>44</sup> Also, DECT will identify any underlying erosions but not any coexisting synovitis.

DECT and US compare well. In 1 study, DECT and US were comparable, but some false-negative results were associated with DECT. In this study, there was 85.7% concordance between synovial fluid analysis and DECT findings.<sup>45</sup> Another study reported DECT to be more specific than US, although small deposits were not always identified.<sup>46</sup> DECT was also not useful for diagnosing acute, new-onset disease or for diagnosing gout when advanced osteoarthritis was present in knee joints.<sup>44</sup> DECT was found to have 64% sensitivity for detecting nontophaceous gout and 100% for overt tophi.<sup>47</sup> However, artifacts mimicking MSU crystals may occur around nail deposits with DECT.<sup>48</sup> In addition, the sensitivity was lower when DECT was used solely for clinically symptomatic joints. DECT may also miss tophi that lack

density,<sup>49</sup> and machine parameter settings can produce false-negative results.

### Advanced Imaging: Summary

No perfect imaging modality exists for diagnosing gout.<sup>50</sup> The choice of imaging type may be governed by availability and experience of available operators and the clinical context. Both US and DECT are considered in the ACR/EULAR classification criteria for gout diagnosis. However, they provide evidence of MSU deposition only (unless coexisting synovitis and erosions seen on US and erosions seen on DECT suggest more active disease), and this finding must be interpreted in the context of the clinical situation to make a diagnosis of gout. It is not our practice or recommendation to image every patient with suspected gout with US or DECT to detect MSU deposition but to use it when there is diagnostic uncertainty or lack of treatment response. Initially, when used, US may be the preferred method because of its lower cost, better availability, and lack of associated radiation.<sup>30,43</sup> In contrast, DECT is limited by higher cost, radiation, restricted availability, and lack of portability. Also, US and DECT can be used synergistically to identify patients with hydroxyapatite deposition.<sup>51</sup> Table 2 gives suggestions for choosing DECT vs US.

### Some Thoughts on Diagnosing Gout

Ideally, a diagnosis of gout should be confirmed by synovial fluid analysis. Realistically, this may not be possible in many practices, and we encourage using the ACR/EULAR approach for making a

clinical diagnosis. In our practice, we strive to obtain a synovial analysis whenever possible by using US guidance, if necessary. If not, we ask the patient to contact us during an acute flare for an evaluation and arthrocentesis.

### INDICATIONS FOR TREATMENT

Patients who have 2 or more acute attacks per year, the presence of palpable tophi or tophi confirmed by radiography, stage 2 or greater chronic kidney disease (CKD), or a history of urolithiasis merit treatment for hyperuricemia according to the ACR guidelines.<sup>9</sup> Also, ULT could be considered in patients who have gout at a younger age (<40 years), uric acid levels higher than 8 mg/dL, or coexisting diseases such as hypertension, cardiovascular disease (CVD), or heart failure according to the EULAR recommendations.<sup>11</sup> This recommendation was based on evidence-based studies reporting gout-related increases in CVD mortality and kidney impairment. In contrast, recent guidelines from the American College of Physicians recommended against initiating ULT for patients with fewer than 2 attacks per year or in patients after their first gout attack and suggest a treat-to-avoid-symptoms strategy.<sup>52</sup> However, evidence does not exist to support the latter, and these recommendations have been opposed by the rheumatology community.<sup>53</sup> We do not advocate a treat-to-avoid-symptoms strategy unless a patient declines ULT or it is contraindicated because this strategy ignores the consequences of ongoing urate deposition, negates an understanding of pathophysiology, and

**TABLE 2. Choice of Advanced Imaging Technique<sup>a</sup>**

Ultrasound	Dual-energy computed tomography
Recent-onset acute disease	Nonacute disease
Easily accessible anatomical location	Inaccessible anatomical areas/complex anatomy
Single-joint disease	Multi-joint disease/assessment of disease burden
Guidance for diagnostic aspiration	No identifiable target for aspiration
Dry needling guidance for diagnosis	Unsuccessful aspiration
Guidance for therapeutic injection	Resistant disease and unconfirmed diagnosis or atypical disease
Differentiation between soft-tissue masses (eg, tophus vs rheumatoid nodule)	Women with Bouchard and Heberden nodes with suspicion of underlying gout
Patient wants to avoid exposure to radiation	Patient has chronic inflammatory arthritis. Concern for underlying or coexisting gout

<sup>a</sup>Choices are not mutually exclusive.

discounts years of clinical experience. The patient should be involved in deciding the level of treatment aggressiveness. Treatment for asymptomatic hyperuricemia is not currently recommended, pending further evidence, although Japanese guidelines recommend treating such patients.<sup>54</sup>

### PRINCIPLES OF MANAGEMENT

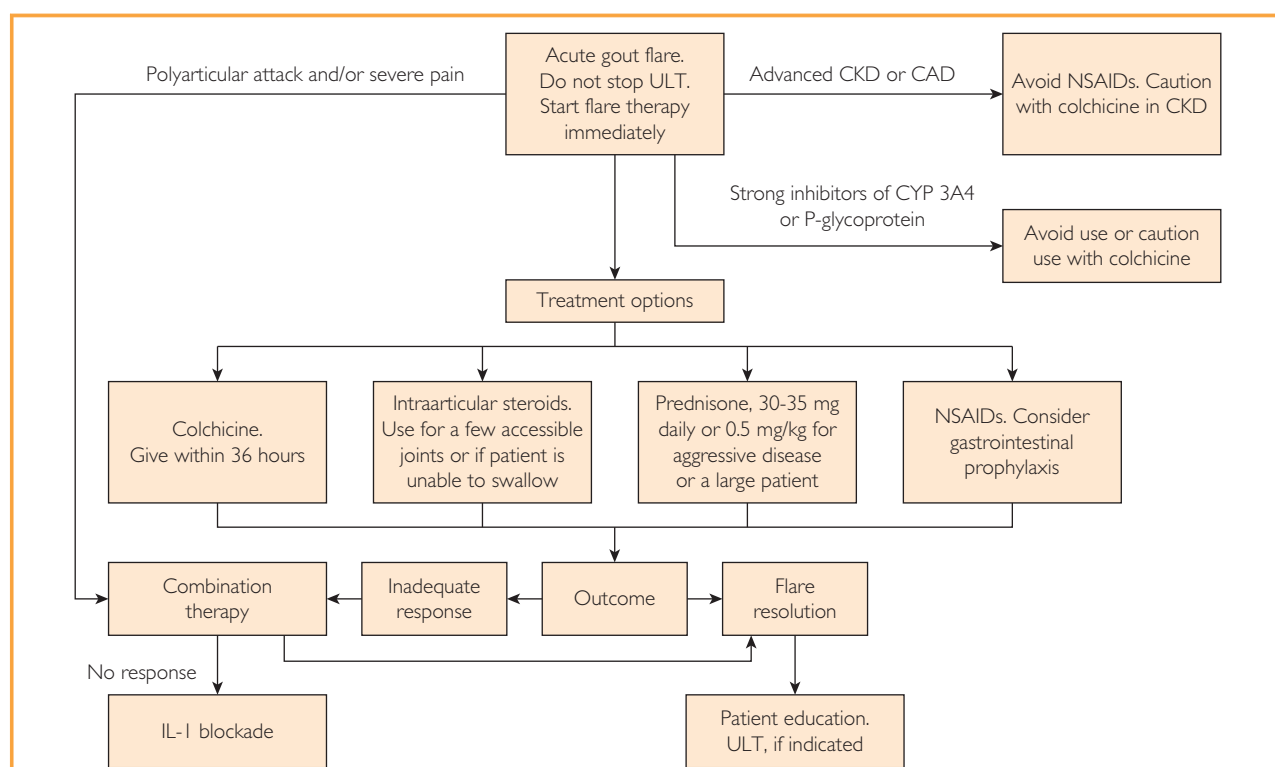
Gout management has 3 principles: treatment of acute attacks, prevention of gout flares, and treatment of hyperuricemia. The choice of medication is dictated by the coexisting medical conditions.

#### Acute Attack Management

Medications for managing an acute attack include nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, and corticosteroids. For most patients, these medications relieve 50% of symptoms.<sup>55</sup> For maximal effectiveness, therapy should be initiated early, preferably within 24 hours of an acute attack onset. Ice, applied topically, is a useful adjunct.

Ongoing ULT should not be interrupted. [Figure 1](#) gives a general overview of our protocol of acute gout management.

No particular NSAID or cyclooxygenase inhibitor is preferred over another. Naproxen, indomethacin, and sulindac have been approved for treatment of acute episodes of gout.<sup>10</sup> In resistant or severe cases, a drug from a different class should be added. Combination therapy with 2 different classes of agents should be initiated in the case of a severe attack or for polyarticular disease ( $\geq 4$  joints).<sup>10</sup> Combinations of an NSAID and an oral corticosteroid should be avoided owing to the additive adverse effects. However, intra-articular corticosteroids may be used in combination with any class of drugs. Typically, NSAIDs are given at the full dose for the first 3 days of the acute attack and then at a lower dose over 4 to 7 days, tailored as per the clinical response (eg, naproxen, 750-1000 mg daily for 3 days and then 500-750 mg for 4-7 days).<sup>55</sup> Studies have found that indomethacin and naproxen have equivalent



**FIGURE 1.** Acute gout management. CAD = coronary artery disease; CKD = chronic kidney disease; CYP 3A4 = cytochrome P450 3A4; IL-1 = interleukin-1; NSAID = nonsteroidal anti-inflammatory drug; ULT = urate-lowering therapy.

efficacy to prednisone (35 mg/d) over a short course, although NSAIDs may have more adverse effects.<sup>56,57</sup> A recent randomized controlled trial comparing prednisone with indomethacin in the emergency department reported similar clinical effectiveness for the treatment of acute gout.<sup>58</sup> This finding supports the use of prednisone as a first-line agent when adverse effects concerns or contraindications preclude the use of NSAIDs. NSAIDs should be avoided in patients with CKD, coronary artery disease, or gastroesophageal reflux disease and in those taking oral anticoagulants. Prophylaxis with a proton pump inhibitor may be needed. Cyclooxygenase inhibitor therapy may be used in carefully selected patients. When any of these medications are prescribed, a patient's blood cell count and renal and hepatic function should be assessed periodically.

Prednisone is the prototypical corticosteroid used for acute gout management. It can be administered in several ways. One schedule is 30 to 35 mg daily for 5 days.<sup>11</sup> For severe cases, a dose of 0.5 mg/kg for 5 to 10 days may be used and then stopped without tapering.<sup>10</sup> This higher dose may also be used for individuals with a high body mass index. Another regimen is 30 to 60 mg daily for 2 days and then tapering by 5 to 10 mg every 2 days, for a total of 10 to 14 days.<sup>33</sup> Methylprednisolone dose packs may also be prescribed. When 1 or 2 joints are involved, intra-articular corticosteroids may be considered. We use methylprednisolone for injection of small or superficial joints and triamcinolone for larger joints, such as the knee or ankle. Clinical judgment should be exercised with respect to the possibility of septic arthritis in a joint, and fluid should be sent for analysis as well as a Gram stain and bacterial culture. If the findings are equivocal, an arthrocentesis should be performed to exclude infection, and a corticosteroid should be injected 48 hours later provided that the cultures show negative findings. Patients with a nothing-by-mouth instruction can be given intra-articular injections, intramuscular triamcinolone (60 mg), intravenous methylprednisolone (0.5-2 mg/kg), or subcutaneous adrenocorticotropic hormone (25-40 IU), with dosing repeated as clinically indicated.<sup>10</sup> Glucocorticoids must be used with caution for patients with

congestive heart failure, diabetes mellitus, and hypertension. Reflux prophylaxis should be considered, and if it is used long-term, osteoporosis prevention should be pursued. For patients with heart failure (particularly symptomatic or decompensated), dexamethasone may be used because of its lower mineralocorticoid effect.<sup>33</sup>

Colchicine for an acute gout episode is given at a dose of 1.2 mg, followed by another dose of 0.6 mg in 1 hour. After 12 hours, 0.6 mg can be given once or twice daily until the flare resolves.<sup>10</sup> This regimen is as effective as the former, standard high-dose regimen and has fewer associated adverse effects.<sup>59</sup> This newer regimen is most effective if used within 36 hours of the onset of the acute attack.<sup>10</sup> It may not be effective if the flare has been ongoing for 72 hours or more, and it should be continued for the duration of the flare. Patients with established gout who are educated about their disease can use the pill-in-the-pocket strategy, where they self-administer colchicine at the earliest sign of a flare.<sup>11</sup>

It is imperative to look for comorbid conditions and concomitant medications in gout management in general and with colchicine use in particular. One study reported that one-third of patients taking colchicine had 1 contraindication to it, and more than 90% had at least 1 contraindication to NSAIDs.<sup>60</sup> The safety of colchicine in patients with a glomerular filtration rate (GFR) less than 30 mL/min has not been established; thus, for those patients, colchicine is best avoided.<sup>11</sup> The most commonly reported adverse effect is gastrointestinal toxicity. Bone marrow suppression, cardiac toxicity, and arrhythmias can also occur. Myotoxicity is rare but a particular problem in patients undergoing transplant and taking colchicine. Periodic creatine kinase monitoring should be considered for patients whose GFR is less than 50 mL/min.<sup>61</sup> Enhanced myotoxicity can occur with concomitant statin use.<sup>62</sup> Recent recommendations from the American Heart Association suggested careful monitoring for muscle-related toxicity when statins and colchicine are given together, and dose reductions of simvastatin, atorvastatin, and lovastatin may need to be considered.<sup>63</sup> A patient with renal insufficiency taking a statin drug may be at higher risk for such toxicity. Vigilance should also

be exercised in patients with underlying hepatic disease.

Several drugs interact with colchicine. Colchicine should not be given or should have the dosage reduced in patients taking a concomitant P-glycoprotein or a moderate to strong inhibitor of cytochrome P450 3A4. These agents include cyclosporine, tacrolimus, clarithromycin, erythromycin, verapamil, diltiazem, and ketoconazole. Cyclosporine, for example, can cause neuromyopathy within weeks of its use with colchicine.<sup>64</sup> In contrast, azithromycin, a macrolide, is safe to use.<sup>65</sup> Modified colchicine dosing regimens have been addressed elsewhere.<sup>65</sup> The blood cell count and renal and hepatic function should be assessed periodically.

The interleukin-1 (IL-1) inhibitors anakinra (100 mg for 3 days) and canakinumab (a single 150-mg dose) may be used subcutaneously when the typically prescribed agents are contraindicated.<sup>11</sup> Infection is a contraindication to the use of IL-1 inhibitors. The IL-1 inhibitors are safe in renal disease, although anakinra should be given every other day if the patient's creatinine clearance is less than 30 mL/min/1.73 m<sup>2</sup> (to convert to mL/s/m<sup>2</sup>, multiply by 0.0167). However, in clinical practice, the cost and required insurance approvals limit their use. The best use for IL-1 inhibitors currently is for hospitalized patients with acute polyarticular gout where multiple comorbidities contraindicate the use of NSAIDs or systemic corticosteroids.

### Acute Attack Prophylaxis

Anti-inflammatory prophylaxis is always indicated when initiating ULT because flares are increased during the initial phase of urate lowering. Educating patients about flares and about adequate treatment methods is important for patient compliance and successful long-term gout management. Prophylaxis should be started along with or just before initiating ULT. Our practice is to start prophylaxis a week before ULT is begun. This decision should be made in consultation with the patient, considering the potential adverse effects of these medications. In a study undertaken in a gout clinic, patients were found to do well without prophylaxis for gout flare when they were thoroughly educated about

the disease and when allopurinol use was started at lower doses and titrated slowly.<sup>66</sup> This regimen may not be applicable in routine care settings or in patients with a high urate level. Prophylaxis should be continued as long as there is a recent (within the past 3 months) gout flare, chronic gouty synovitis (within the past 3 months), or the presence of tophi. If no recent gout flare or gouty synovitis is present, prophylaxis can be continued for 6 months or, alternatively, for 3 months after a sustained target uric acid level is achieved in a patient who never had tophi; or for 6 months in patients who had tophi that resolved and whose target uric acid level was achieved and sustained.<sup>10</sup>

Colchicine or a low-dose NSAID is the preferred prophylactic agent.<sup>10</sup> In clinical practice, colchicine may be preferred over NSAIDs to minimize adverse effects. Colchicine prevents or lowers the frequency of flares in 80% to 85% of patients.<sup>67</sup> We use a dose of 0.6 mg daily, but a twice-daily dose may also be used. Low-dose NSAIDs, such as naproxen (250 mg twice daily) should be used with concomitant gastrointestinal prophylaxis. If these 2 classes of drugs cannot be used, low-dose prednisone ( $\leq 10$  mg) may be given,<sup>10</sup> with appropriate consideration for the possible adverse effects on the gastrointestinal system and bones. The colchicine dose should be reduced to 0.3 mg daily if the patient's GFR is less than 30 mL/min. The dosage for patients undergoing dialysis is 0.3 mg twice weekly, but this dosage needs to be monitored carefully because colchicine is essentially nondialyzable.<sup>68</sup> The IL-1 antagonists (eg, canakinumab or riloncept) may be used for prophylaxis if standard agents cannot be used.

### Hyperuricemia Treatment

Lowering the uric acid level is important to prevent long-term joint damage and tophus development. [Figure 2](#) provides a general overview of our protocol for managing chronic gout. Treatment of hyperuricemia is lifelong because recurrence eventually occurs once ULT is stopped.<sup>69</sup> Recent data suggest that ULT may be started during an acute flare.<sup>70,71</sup> However, until more data are available regarding initiating ULT during a flare, the strategy remains to wait for the flare to resolve.<sup>11,33,55</sup> Discussing the potential for

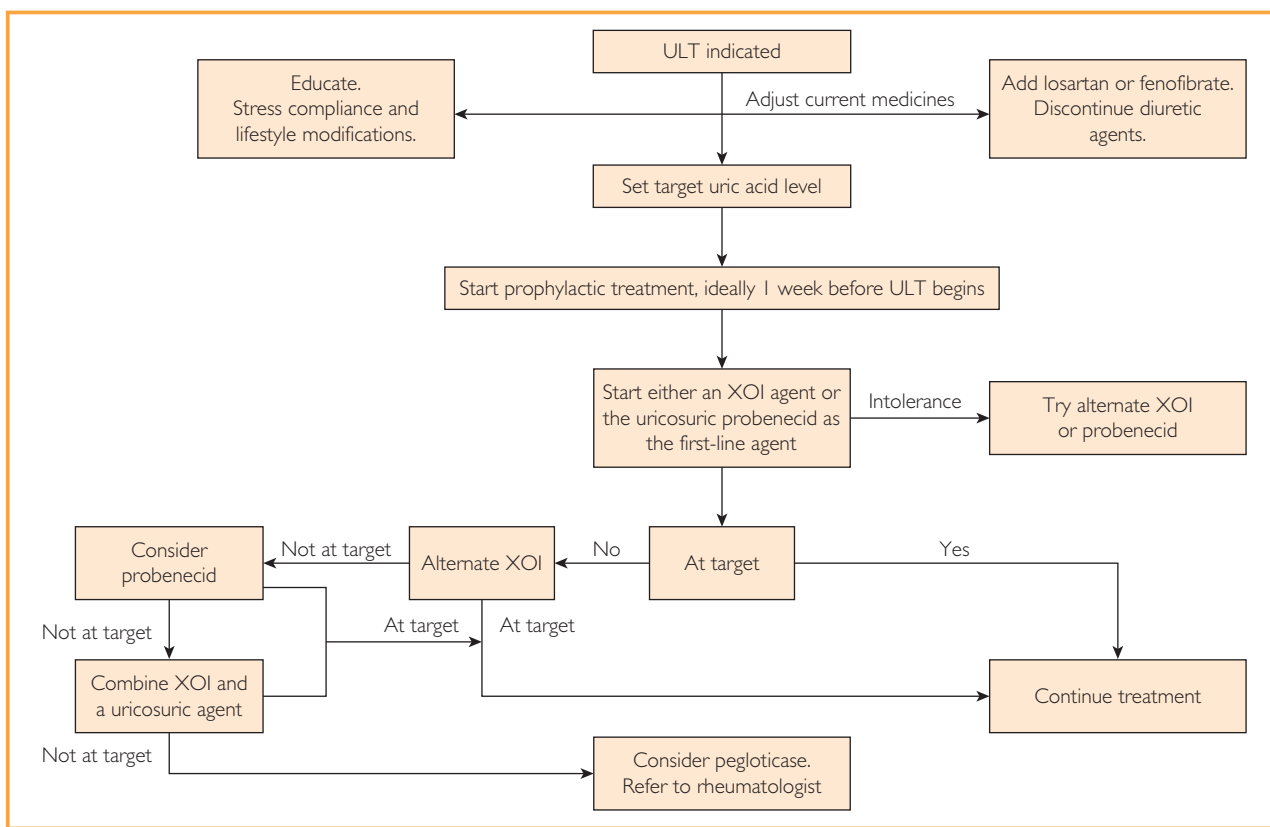
lifelong treatment with a patient may also be more fruitful when the patient is pain free. In general, the target uric acid level should be less than 6 mg/dL; for patients with tophi, the level should be less than 5 mg/dL.<sup>11</sup> Sustained uric acid levels lower than 3 mg/dL should be avoided because some evidence suggests that uric acid may be neuroprotective.<sup>72,73</sup> In our consulting practices, we have found that the most common error in managing gout is not lowering the level of serum uric acid adequately—to a level below the crystallization threshold. Therefore, we support treating to target urate levels as an effective clinical strategy.

**Xanthine Oxidase Inhibitors**

Xanthine oxidase inhibitors (XOIs), including allopurinol and febuxostat, are the mainstays of ULT. When XOIs are used, periodic monitoring of blood cell counts and renal and hepatic function is necessary. Uric acid should be monitored every 4 weeks until the target

urate level is reached and then every 6 months. Xanthine oxidase inhibitors are contraindicated in patients taking azathioprine or its metabolites. The concomitant use of allopurinol and febuxostat is not recommended.<sup>33</sup> It is thought that no additive benefit is gained because both agents compete for the same receptor.<sup>74</sup> With combination therapy, xanthinuria could also occur. However, 1 case report described successful combination of the 2 XOIs.<sup>75</sup> No single XOI is preferred, although allopurinol is more cost-effective. Patients should be informed about the possibility of increased flares with the initiation of ULT.

Allopurinol remains the principal treatment for ULT but is underused. We hope that the ensuing discussion will make prescribers more comfortable with appropriate allopurinol use. With allopurinol dosing, the approach should be to start low and go slow. For normal renal function, the starting dose is 100 mg daily, increasing by 100 mg every 4 weeks depending on the urate



**FIGURE 2.** Chronic gout management. ULT = urate-lowering therapy; XOI = xanthine oxidase inhibitor.



level.<sup>9,11</sup> Patients with chronic stage IV renal disease or worse should start by taking 50 mg daily. A common error in gout management is to stop the dosing increase at 300 mg even if the target serum urate level has not been achieved. Commonly, the average dose required to reach a target uric acid level is 400 mg.<sup>76</sup> However, dosages can be increased to 800 mg daily even in patients with renal disease.<sup>76</sup> Some physicians may feel uncomfortable doing so in patients with CKD, especially when febuxostat is available.<sup>77</sup> Because of genetic polymorphisms, some people may be allopurinol resistant.<sup>78</sup> Attempts to safely maximize allopurinol dosing should not be abandoned, especially if cost or intolerance issues limit the use of febuxostat. Careful monitoring, however, is necessary.

Allopurinol hypersensitivity syndrome, which is rare, typically occurs within 60 days of a patient starting therapy<sup>79</sup> and has a mortality rate of approximately 25%.<sup>80</sup> Renal dysfunction and thiazide diuretic agents are risk factors for allopurinol hypersensitivity. The syndrome is more likely in persons of Korean descent with CKD of stage III or higher or those of Thai or Han Chinese ethnicity. Before being prescribed allopurinol, a patient of these ethnic origins should have baseline genetic screening for HLA-B\*5801.<sup>9</sup> Approximately 20% of patients develop a rash if they take amoxicillin or ampicillin along with allopurinol. Monitoring should include laboratory evaluations, including for eosinophilia, and clinical evaluations, including for rash. Patients should be educated to stop taking the medicine if they develop pruritus, which can indicate an impending reaction. When doses are higher than 300 mg daily, they should be split to mitigate gastrointestinal adverse effects.

Febuxostat is given in 40 and 80 mg doses, although doses up to 120 mg have been approved in Europe. The dose of febuxostat may be increased in 2 weeks if uric acid levels do not decline.<sup>55</sup> New data suggest that febuxostat is safe for patients with moderate to severe renal disease.<sup>81,82</sup> Febuxostat is not cross-reactive with allopurinol, although vigilance is still recommended.<sup>83,84</sup> Approximately 2% to 4% of users may develop a rash from febuxostat.<sup>33</sup> Transaminitis, diarrhea, and nausea may occur. Some concern has been expressed

about the cardiovascular safety of febuxostat, but this is an area of ongoing research.<sup>85</sup> Of note, the European Union recommends against using febuxostat in patients with CVD or heart failure.<sup>86</sup> Our practice has been to use it carefully in such patients.

### Uricosuric Medications

The underexcretion of uric acid is the cause of hyperuricemia in most patients, and probenecid is the standard uricosuric agent used to treat hyperuricemia.<sup>87</sup> However, probenecid is underused compared with XOIs, and its required twice-daily doses may cause compliance issues for patients. Probenecid is contraindicated in patients with nephrolithiasis or a creatinine clearance less than 30 mL/min/1.73 m<sup>2</sup>; it is also contraindicated in those who excrete excess urate (determined by 24-hour urinalysis for uric acid). Adequate hydration is important for patients taking probenecid because the risk of kidney stones is 9% to 11%.<sup>55</sup> For patients who require probenecid in the setting of a history of renal stones, alkalization of the urine should be considered with sodium bicarbonate or potassium citrate. A typical starting dose for probenecid is 250 mg twice daily, which can be increased to 2000 to 3000 mg daily. Probenecid can be used in combination with XOIs or as an alternative first-line agent.<sup>9</sup> Its ability to alter the serum levels of many medications, including NSAIDs,  $\beta$ -lactam antibiotics, methotrexate, and heparin, must be considered when it is prescribed.

Lesinurad, another uricosuric agent, was approved recently for use in combination with any XOI; the dose (200 mg/d) should be given in the morning. Lesinurad should not be used as monotherapy because of possible adverse effects on the kidneys.<sup>12</sup> If the XOI is withheld, so should lesinurad. Renal function requires careful monitoring, but lesinurad can be used in patients with a history of nephrolithiasis. One review reported that patients enrolled in various trials had increased levels of creatinine, although the increased levels resolved in most patients by their final follow-up visit.<sup>88</sup> It should not be started if the creatinine clearance is less than 45 mL/min/1.73 m<sup>2</sup> and should be halted if the creatinine level rises to more than 2 times the pretreatment value. Common adverse

effects are headaches, influenza, and gastroesophageal reflux. Clinical experience is lacking at present.

### Pegloticase

Pegloticase is a powerful pegylated uricase that converts uric acid to the more soluble allantoin and is recommended for gout that is refractory to other ULTs, as well as to combination therapy with a uricosuric agent.<sup>9,11</sup> Pegloticase is highly effective at reducing uric acid levels and the tophaceous burden. Glucose-6-phosphate dehydrogenase deficiency is a contraindication to its use. It is given intravenously at a dose of 8 mg every 2 weeks. During treatment with pegloticase, multiple gout flares are common because of the rapid decline in uric acid levels. Prophylaxis should be maintained and started for an acute gout attack a week before the pegloticase infusions. Patients should be premedicated to prevent infusion reactions. Infusion reactions due to antibody formation result from pegloticase in 40% of patients and are preceded by loss of the urate-lowering response.<sup>89,90</sup> Therefore, preinfusion uric acid levels should be evaluated, and if they are increasing or at or above 6 mg/dL, further infusions should be withheld. To help prevent masking of an increase in uric acid level, concomitant ULT cannot be given to patients taking pegloticase. Long-term management and the duration of treatment with pegloticase are unclear. An open-label extension study with mean follow-up of 25 months did not report any new safety signals, and the target uric acid level was achieved in 55% of the patients.<sup>90</sup> Switching to an oral ULT has been suggested once the tophi resolve.<sup>11</sup> Pegloticase has a narrow indication and is used essentially as a debulking therapy in persons with severe tophaceous gout. The care approach to a patient with refractory gout is given in [Table 3](#).

### Supplementary Medicines

Losartan is a mild uricosuric agent, but other angiotensin receptor blockers and angiotensin-converting enzyme inhibitors are not.  $\beta$ -Blockers confer an increased gout risk.<sup>91</sup> Fenofibrate lowers the uric acid level on average by 1.5 mg/dL.<sup>92</sup> Atorvastatin and simvastatin also lower uric acid levels, but hypouricemia was not found to be a class effect of statin therapies.<sup>93</sup>

### Nonpharmacologic Measures

Patients should be educated about gout. The provider should emphasize that gout is a lifelong condition, and the goal of treatment is to prevent flares and joint damage. Convincing patients to commit to lifelong pharmacologic therapy is not easy. In 1 study, the authors reported that 40% of the respondents preferred nonpharmacologic treatments.<sup>94</sup> The target levels for uric acid need to be set with the patient and reinforced at every visit. In 1 survey, only 14% of patients knew their target uric acid level.<sup>95</sup> In a report of a systematic review, adherence to treatment ranged from 10% to 46%.<sup>96</sup>

Patients also need to be educated about the importance of maintaining an acceptable weight and in avoiding certain foods, which can help control gout. Weight loss is important because adiposity contributes to hyperuricemia. Organ meat, red meat, and seafood with a high purine content, such as shellfish, anchovies, and sardines, cause hyperuricemia.<sup>9</sup> Consuming most forms of alcohol, particularly beer, increases uric acid levels in a dose-dependent manner; moderate wine consumption does not.<sup>97</sup> Fructose-containing drinks and soft drinks increase uric acid levels, but diet drinks do not.<sup>98</sup> Dairy proteins lower uric acid levels. Coffee consumption also

**TABLE 3. Approach to Resistant Gout**

Confirm diagnosis by aspiration of crystals.
Always consider alternative and coexisting diagnoses.
Ensure that patients are educated regarding gout and understand that gout is a chronic disease.
Emphasize weight reduction, diet moderation, and avoidance of acute flare triggers (eg, beer).
Account for comorbidities in choosing medications.
Ensure proper flare prophylaxis.
Provide acute, prompt, and appropriately dosed treatment of acute flares.
Withdraw, if feasible, medicines that contribute to hyperuricemia (eg, loop diuretics).
Add medications with hypouricemic properties to replace the hyperuricemic ones (eg, losartan to treat hypertension instead of hydrochlorothiazide).
Use the maximal permissible dosage for urate-lowering therapy. Be aware of potential allopurinol resistance.
Add an appropriate uricosuric agent, if possible.
Verify compliance with the patient and consider checking oxypurinol levels for allopurinol compliance.
Involve rheumatology consultants to manage care for patients with complex disease (eg, advanced kidney disease, previous transplant, unconfirmed diagnosis, intolerance to therapy, and refractory disease) and for consideration of treatment with pegloticase.

reduces uric acid and the risk of incident gout.<sup>99,100</sup> Purine-rich vegetables do not substantially increase uric acid levels,<sup>101</sup> and eating cherries can reduce gout attacks.<sup>102</sup> However, patients with gout should understand that diet and lifestyle changes do not obviate ULT. Data from 1 study of 30 patients reported that dietary interventions did not have a profound effect on uric acid levels.<sup>103</sup> However, they are certainly important from an overall health perspective, considering the risk associated with the typical metabolic profile of patients with gout.

### Specific Situations

Approximately 40% of patients with gout have CKD (at least stage II) and a reduced GFR,<sup>104</sup> which limits the use of medications such as NSAIDs and uricosuric agents. In this situation, colchicine, in renal-adjusted dosing, may be used for prophylaxis and treatment, but clinical judgment regarding risks and benefits should be individualized to the patient. Great caution must be exercised when using colchicine in patients undergoing dialysis because of its nondialyzable nature, although gout flare frequency typically declines in these patients because of hemodialysis.<sup>104</sup> Sevelamer, commonly used for patients with CKD to manage phosphate load, is hypouricemic.<sup>105</sup> Calcium pyrophosphate deposition disease arthropathy should remain part of the differential diagnosis for patients with CKD because of its association with hyperparathyroidism.

An increase in organ transplant has resulted in a concomitant increase in hyperuricemia and gout, primarily from the renal effects of immunosuppressive medications such as cyclosporine<sup>106</sup> and tacrolimus. Transplant patients with gout may develop tophi early after their transplant and in unusual sites, such as the spine and sacroiliac joints.<sup>107</sup>

Surgical management can be considered when there is infection, joint instability, or an entrapment neuropathy.<sup>108</sup> Without ULT, the tophi tend to recur.

### CONCLUSION

Effective management of gout requires a complete understanding of the disease process and its chronicity, as well as treatment by the providers, compliance by the patients, and

support by their caregivers. With the present patients, we must emphasize the lifelong nature of the disease and its negative health consequences if the disease is untreated. In this review, we provided suggestions based on the current literature and from our practice to help guide the practicing clinician in managing this challenging disease.

**Abbreviations and Acronyms:** ACR = American College of Rheumatology; CAD = coronary artery disease; CKD = chronic kidney disease; CVD = cardiovascular disease; DECT = dual-energy computed tomography; EULAR = European League Against Rheumatism; GFR = glomerular filtration rate; IL-1 = interleukin-1; MSU = monosodium urate; MTP = metatarsophalangeal; NSAID = nonsteroidal anti-inflammatory drug; ULT = urate-lowering therapy; US = ultrasound; XO = xanthine oxidase inhibitor

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