The Year in Gout: 2012-2013
A Walk Through the 2012 ACR Gout Treatment Guidelines

Daria B. Crittenden, M.D., and Michael H. Pillinger, M.D.

Abstract
In 2012 the American College of Rheumatology (ACR) established its first-ever gout treatment guidelines. These guidelines address whom to treat, how to treat, and lifestyle and medication changes to make when treating patients with gout. In this manuscript, we review the ACR guidelines, with special attention to the issues of treating to target, and when and how to prevent attacks during urate-lowering therapy. Given that the quality of gout treatment in the USA is often suboptimal poor, these guidelines have the potential to improve the health of millions of gout sufferers in the USA and around the world.

Gout, sometimes underestimated as a minor affliction, has more recently been revealed as a significant public health problem. Multiple epidemiologic studies have suggested that gout incidence and prevalence have been on the rise for at least four decades, and since the 1970s, gout appears to have increased two to fourfold among the United States population.1 Recent studies confirm that gout poses a significant health and economic burden. Gout patients are likely to suffer multiple comorbidities, including those contributing to the metabolic syndrome,2,3 and gout is associated with increased risk of mortality.4,5 Compared with non-gout populations, gout patients add significantly to national health care costs in terms of dollars consumed and productivity lost,6 with higher costs in gout patients with more frequent attacks.7 Nonetheless, and despite a reasonable armamentarium of anti-gout medications, gout tends to be poorly treated in the USA and elsewhere.8,9 Reasons for inadequate gout treatment include poor patient understanding of their disease, physician failure to develop targeted treatment plans, and (much less commonly) failure of available therapies.

Against this background, the American College of Rheumatology (ACR) recently released its first-ever gout treatment guidelines.10,11 These guidelines, intended to assist rheumatologists as well as primary care physicians and other health care providers, have the potential to set the standard and improve gout care nationwide. Given the potential importance of these guidelines, we here devote our annual “Year in Gout” to a “walk” through the ACR gout treatment guidelines. The highlights of the recommendations are outlined in Table 1 and discussed in more depth below, where we also acknowledge unresolved or controversial issues raised by the guidelines.

The RAND-UCLA Methodology
The ACR gout guidelines were developed using RAND-UCLA methodology. RAND-UCLA provides a strictly-defined process for incorporating available evidence and physician expertise to arrive at the most objective recommendations possible at a given point in time. Consistent with the RAND-UCLA method, the ACR principle investigators first identified and convened two separate committees—a Core Expert Panel (CEP) and a Task Force Panel (TFP). The CEP conducted a systematic review of the literature for the areas under study and used the results to generate scientific evidence reports. The CEP also created a detailed set of case scenarios that would frame the topics about which decisions were to be made (Fig. 1).

Once generated, the scientific evidence reports and case scenarios were passed along for consideration by the TFP.
Applying both the scientific evidence reports and their own expertise, each member of the TFP voted privately on each case scenario. These votes were followed by a round of face-to-face discussion, in order to address any points upon which committee consensus was not fully clear, followed by a re-vote. Any recommendation that scored a median vote of 7 or above (benefit outweighs risk of treatment) on a 10-point Likert scale and received no dissenting votes of 3 or below (risk clearly outweighs benefit) was advanced to the status of a recommendation. Once recommendations were generated, these were rated as to the strength of the evidence supporting them (A = supported by multiple randomized controlled trials; B = supported by randomized trials or non-randomized studies; C = supported by expert opinion, case studies, or standard of care). An important rule to bear in mind regarding the RAND-UCLA methodology is that the cost of a treatment is never considered in the recommendations. Additionally, by the determination of the committee, patient comorbidities or potential drug interactions relevant to an individual patient were not considered in the case scenarios addressed, mainly owing to the complexity that this would engender. However, the practicing physician is expected to account for these considerations during his or her own decision-making processes.

**Recommendations**

**General and Dietary Considerations for Gout Patients**

The TFP first—and emphatically—endorsed that all gout patients should follow a number of general recommendations aimed at a healthy lifestyle, including weight loss for obese patients, a healthy overall diet, regular exercise and activity, smoking cessation, and regular and adequate hydration. The committee made several recommendations regarding dietary changes to promote appropriate serum urate concentrations. The TFP recommended avoidance of high purine organ meats (e.g., liver, sweetbreads), beverages or foods sweetened with high-fructose corn syrup (thus endorsing implicitly a role for fructose in hyperuricemia), and alcohol overuse (i.e., more than two drinks per day for males, more than one drink per day for females).

Among the items to limit were meat, shellfish, some seafood, sweetened fruit juices (but not fruit), table sugar and salt, and again, alcohol. Finally, the TFP supported the intake of vegetables (making no specific exception for high purine vegetables) and recommended increased consumption of low- or non-fat dairy products since recent evidence suggests that these may have urate-lowering or anti-inflammatory effects.

The TFP also recommended that patients be assessed for a “checklist” of comorbidities commonly seen in gout patients, because these may contribute to or be affected by hyperuricemia (e.g., chronic kidney disease) or point to a modifiable risk to the patient (e.g., hyperlipidemia). The TFP additionally recommended the identification of medications that may be contributing to hyperuricemia (e.g., thiazide diuretics) and consideration of their substitution with alternative therapies on a case-by-case basis.

**Treatment of Acute Gout Attacks**

The TFP affirmed that acute gout attacks should be pharmacologically treated, and that treatment should ideally be initiated within 24 hours of the onset of the attack. The TFP recommended that, if the attack is mild to moderate in severity, monotherapy is appropriate. If the attack is severe, combination therapy may be considered. The committee supported the use of various traditional anti-inflammatory agents—NSAIDs at anti-inflammatory doses (including COX-2-selective inhibitors), oral glucocorticoids (0.5 mg/kg/day for 5 to 10 days or 2 to 5 days followed by a taper), and colchicine (1.2 mg followed by 0.6 mg 1 hour later, with the option of continuing daily lower dose colchicine until the attack resolves). Intra-articular steroids with or without oral therapy was also recommended, as was IM triamcinolone (60 mg) followed by oral prednisone. If the patient was already on prophylaxis with colchicine and had also used the acute gout colchicine regimen in the past 14 days, the TFP recommended selecting a different anti-inflammatory. For patients who are NPO, the committee supported the use of IV or IM methylprednisolone, 0.5 to 2 mg/kg, repeated as needed, with subcutaneous ACTH as an alternative consideration.
As noted earlier, the TFP did not consider the impact of comorbid conditions on the selection of any acute gout medication (e.g., systemic steroid use being relatively contraindicated in a patient with diabetes) or the drug-interactions that might influence the choice of gout anti-inflammatory medication (e.g., dose-reduction or avoidance of colchicine when the patient is taking cytochrome P450 3A4 or P-glycoprotein inhibitors, such as clarithromycin, various calcium-channel blockers, and so forth). These considerations were referred to the judgment of the treating physician.

Table 1 Overview of ACR Gout Treatment Guidelines

<table>
<thead>
<tr>
<th>Topic Addressed by Guidelines</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>General recommendations for and assessment of any patient with gout</td>
<td>Education, lifestyle modification, assessment for gout comorbidities or hyperuricemia-inducing medications</td>
</tr>
<tr>
<td>When to treat an acute attack</td>
<td>Ideally within 24 hours of symptoms onset</td>
</tr>
<tr>
<td>How to treat an acute gout attack in a patient who can take oral therapy</td>
<td>• Mild to moderate attack: NSAIDs, systemic steroids, colchicine (within 36 hours of symptom onset); intra-articular steroids (when practical); IM triamcinolone followed by oral steroids also an option • Severe attack: consider combination therapy</td>
</tr>
<tr>
<td>When to start urate lowering therapy</td>
<td>Gout patient with any of the following: 1. two or more attacks in a year, 2. one attack and stage 2 kidney disease or worse, 3. tophi or tophus on exam or imaging, or 4. past urolithiasis</td>
</tr>
<tr>
<td>Target serum urate</td>
<td>Goal is &lt; 6.0 mg/dL, or &lt; 5.0 mg/dL if needed to improve signs and symptoms of gout, including tophi</td>
</tr>
<tr>
<td>Frequency of dose adjustment to reach serum urate during initial urate-lowering therapy</td>
<td>Every 2 to 5 weeks</td>
</tr>
<tr>
<td>Agents to use for urate-lowering therapy</td>
<td>1. Xanthine oxidase inhibitor (either allopurinol or febuxostat), 2. probenecid as alternative first-line therapy if a xanthine oxidase inhibitor cannot be used (assuming acceptable renal function and no evidence of urate overproduction), 3. combination xanthine oxidase inhibitor and uricosuric if target urate not reached on monotherapy, 4. pegloticase for severe gout when oral agents have failed or are contraindicated</td>
</tr>
<tr>
<td>Dose titration of allopurinol</td>
<td>Start at 100 mg daily (or 50 mg for stage 4 kidney disease) and titrate up to max dose of 800 mg; note that 300 mg dose is often insufficient and dose must be titrated up appropriately to reach the target</td>
</tr>
<tr>
<td>How long to give prophylaxis during urate-lowering therapy</td>
<td>Once there are no symptoms of gout (flares or tophi), continue prophylaxis for whichever of the following is longer: 1. 6 months total treatment, 2. 3 months after reaching target urate in a patient who had no tophi at baseline, or 3. 6 months after reaching target urate in a patient who had tophi at baseline</td>
</tr>
<tr>
<td>Agents to use for flare prophylaxis</td>
<td>Low-dose colchicine or NSAIDs; prednisone an option if the other agents are contraindicated or not tolerated</td>
</tr>
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</table>

As noted earlier, the TFP did not consider the impact of comorbid conditions on the selection of any acute gout medication (e.g., systemic steroid use being relatively contraindicated in a patient with diabetes) or the drug-interactions that might influence the choice of gout anti-inflammatory medication (e.g., dose-reduction or avoidance of colchicine when the patient is taking cytochrome P450 3A4 or P-glycoprotein inhibitors, such as clarithromycin, various calcium-channel blockers, and so forth). These considerations were referred to the judgment of the treating physician.

**Urate Lowering in Patients with Established Gout**

The TFP provided clear recommendations regarding when to start pharmacologic urate lowering, recommending that any patient with a diagnosis of gout should receive urate lowering therapy in of the following circumstances: 1. two or more attacks per year (which is more specific than the EULAR gout recommendations in 2006); 2. a single gout attack in the presence of stage 2 or worse chronic kidney disease; or 3. one or more tophi on clinical exam or imaging. Regarding treating earlier in chronic kidney disease patients, the TFP did not explain their rationale, which we speculate might relate to increased risk for gout in the setting of kidney disease or to recent evidence suggesting possible benefit of serum urate lowering to preserve renal function.\(^{14,15}\)

The TFP recommended that initial therapy to lower serum urate should consist of a xanthine oxidase inhibitor, either allopurinol or febuxostat, with no preference asserted. This may be considered controversial by some rheumatologists, given that allopurinol is a less expensive agent and may be equivalent in efficacy depending on the doses compared.\(^{16}\) If using allopurinol, the committee recommended that all patients be started on a dose of 100 mg (or 50 mg in patients with stage 4 or 5 kidney disease) with titration every 2 to 5 weeks to achieve the target urate, up
to a maximum dose of 800 mg. This stands in contrast to the common community practice of initiating allopurinol at 300 mg and maintaining that dose regardless of the urate response. Importantly, the TFP explicitly stated that allopurinol can be titrated above 300 mg in patients with renal disease (with appropriate monitoring), which has often been a subject of debate among providers. Based on several recent studies, the TFP also made the novel recommendation to undertake HLA testing prior to allopurinol initiation in Korean patients with chronic kidney disease stage 3 or worse, as well as in Han Chinese and Thai patients with or without chronic kidney disease, and to eschew allopurinol if the HLA haplotype B*5801 is present. These groups are significantly enriched for B*5801, which increases the hazard ratio for allopurinol hypersensitivity by several hundred fold.

The uricosuric agent probenecid was recognized as an alternative first-line agent for urate lowering in patients who could not tolerate or had a contraindication to at least one xanthine oxidase inhibitor. The TFP recommended that this agent not be given as first-line therapy to patients with a history of urolithiasis or with a creatinine clearance less than 50 ml/min (as the drug tends to be ineffective in these individuals); urate overproduction (as evidenced by elevated urine uric acid) is also a contraindication to probenecid. Probenecid administration should be accompanied by generous daily fluid intake as well as consideration of urine alkalinization to reduce stone risk.

Regardless of which agent is initiated, the committee recommended that all patients should be treated to a target serum urate level. This official treat-to-target recommendation stands as a clear guide for rheumatologists and other providers. At a minimum, this target should be no greater than 6.0 mg/dL. However, the TFP was explicit that a target serum urate of 5.0 mg/dL or even lower may be needed to control the signs and symptoms of gout in an individual patient, including the resolution of tophi. Should monotherapy with a xanthine oxidase inhibitor be insufficient to reach target, the TFP recommended the addition of a uricosuric agent, such as probenecid, losartan, or fenofibrate to the xanthine oxidase inhibitor. Should dual oral therapy not result in achievement of target urate level, the TFP’s recommendations varied with the severity of the patient’s disease. For patients on dual oral therapy at maximum acceptable doses who were still having frequent flares or those with unresolving chronic tophaceous arthropathy, the TFP recommended pegloticase. In cases in which a patient has more mild disease (e.g., no tophi and only rare attacks) but has nonetheless failed to reach the urate target, the TFP did not offer specific guidance, implying that monitoring on the “failed” urate lowering agents may be adequate.

Importantly, the guidelines recommend that urate lowering not be interrupted during gouty attacks, a frequent cause of gout management setbacks. On the other hand, initiation of urate lowering may be reasonable even in the middle of a gout attack if an appropriate anti-inflammatory regimen has been initiated, an approach that runs counter to previous teaching.

**Prophylaxis During Urate Lowering**

Initiation of urate-lowering therapy paradoxically causes an increased risk of gout flares, necessitating flare prophylaxis during this period. The ACR guidelines offer a set of recommendations regarding prophylaxis during initiation of urate-lowering therapy that should help standardize the approach of providers for improved care overall. However, the recommendations for selection of a drug for prophylaxis provide the clinician with considerable flexibility. The TFP recommended, as first-line prophylactic agents, the use of either low-dose colchicine or a low-dose NSAID with a proton pump inhibitor (or other equivalent protection against peptic ulcer disease) but noted that the supporting evidence was stronger for the choice of colchicine. If neither of these are considered appropriate (intolerance or lack of efficacy), low-dose prednisone of 10 mg per day or less may be considered.

Another clear and important recommendation concerned the appropriate duration of anti-inflammatory prophylaxis. If the patient continues to have any gout activity during urate-lowering therapy (gout attacks, tophi, or persistent chronic synovitis), then prophylaxis should continue. Once disease activity has resolved, prophylaxis should continue for the longer of either: 6 months total; 3 months after achieving appropriate serum urate target in non-tophaceous gout patients; or 6 months after achieving appropriate serum urate target for patients with a history of tophi that have resolved.

**Seeking Expert Guidance**

Because achieving a complete resolution of gout will not always be easy, the committee also provided guidelines for when a non-expert should seek help in gout management. Gout expert input should be sought, at minimum, when the cause of hyperuricemia is unclear, when gout signs or symptoms are refractory, when there is difficulty achieving serum urate target (especially in patients with chronic kidney disease), or when there are multiple or serious adverse events from therapy.

**Conclusion**

In sum, the ACR gout treatment guidelines provide a useful assemblage of available data and a codification of best-practices strategies applicable to most gout patients. They may be particularly useful for non-experts seeking to maintain a minimum standard of excellent care for their gout patients or wishing to distinguish between patients they can manage themselves and patients requiring rheumatologic input. Given the inadequate state of gout management at the present time, these guidelines have the potential to improve the health and well-being of millions of gout sufferers.
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References