2012 American College of Rheumatology Guidelines for Management of Gout. Part 1: Systematic Nonpharmacologic and Pharmacologic Therapeutic Approaches to Hyperuricemia

**Gout** is a disorder that manifests as a spectrum of clinical and pathologic features built on a foundation of an excess body burden of uric acid, manifested in part by hyperuricemia, which is variably defined as a serum urate level greater than either 6.8 or 7.0 mg/dl. Typically, the disease initially presents as acute episodic arthritis. Gout also can manifest as chronic arthritis of 1 or more joints. Tophi, mainly found in articular, periarticular, bursal, bone, auricular, and cutaneous tissues, are a pathognomonic feature of gout, and are detectable by physical examination and/or by imaging approaches and pathology examination. Renal manifestations of gout include urolithiasis, typically occurring with an acidic urine pH. Chronic interstitial nephropathy, mediated by monosodium urate monohydrate crystal deposition in the renal medulla, can occur in severe disease, but is currently considered to be an uncommon clinical manifestation of gout.

On behalf of the American College of Rheumatology (ACR), we were charged with developing systematic nonpharmacologic and pharmacologic recommendations for effective treatments in gout with an acceptable risk/benefit ratio. Our assignment was to focus on 4 specific domains in gout management. Two of these domains are addressed herein, i.e., urate-lowering therapy (ULT) and chronic gouty arthritis with tophaceous disease detected on physical examination (designated by the ACR with the terminology “chronic tophaceous gouty arthropathy” [CTGA] and specifically represented in the fundamental case scenarios 7–9 described herein). The remaining 2 domains (analgesic and antiinflammatory management of acute gouty arthritis and pharmacologic antiinflammatory prophylaxis of attacks of gouty arthritis) are addressed in part 2 of the guidelines as a separate article.

The task force panel (TFP) evaluated clinical scenarios with differences in frequency of acute gout symptoms and differences related to the presence or extent of chronic findings (tophi, synovitis) on physical examination, similar to what a clinician might see in a busy practice. Scenarios were divided into mild, moderate, and severe disease activity in each of 3 distinct “treatment groups” (Figures 1A and B).
**Figure 1.** Fundamental case scenarios evaluated by the task force panel (TFP). The TFP evaluated a broad spectrum of severity of gout, with presenting clinical information comparable to that encountered in practice. Scenarios were formulated iteratively by the core expert panel, as described in the text, and were not intended to serve as disease classification criteria. All case scenarios assumed that the diagnosis of gout was correct, and that there was some evidence of gout disease activity. Three distinct “treatment groups” for these recommendations, each with 3 case scenarios designed to succinctly represent clinically-based decision making and totaling 9 in all, are shown. The treatment group with intermittent attacks of acute gout but no tophi detected on physical examination was subdivided based on increasing yearly frequency of episodes of acute gouty arthritis of at least moderate to severe pain intensity (case scenarios 1–3; A). Gout associated with clinically apparent high body urate burden was evaluated in case scenarios where there were ≥1 tophi on physical examination, and either A, intermittently symptomatic acute gouty arthritis (case scenarios 4–6), or B, chronic joint symptoms due to synovitis attributable to gout or articular tophus or tophi in case scenarios 7–9 (the domain termed chronic tophaceous gouty arthropathy [CTGA]). Severity of case scenarios in the CTGA domain was distinguished by extent and characteristics of the tophi and chronic arthropathy, with variable inflammatory and deforming features detected on physical examination (see Figure 2).
Definitions of pharmacologic therapeutic agents.
Medication classes evaluated in the case scenarios were defined as follows: xanthine oxidase inhibitor (XOI) refers to allopurinol or febuxostat, and uricosuric agents were defined to include agents available in the US (probenecid and off-label use [as uricosuric therapy] of fenofibrate and losartan), but did not include sulfinpyrazone or benzbromarone. Other agents and modalities were self-explanatory.

Evaluation by the TFP of effectiveness of a given therapeutic option assumed that patients in the case scenarios received the maximum tolerated typical dose for a period of time sufficient to accurately assess therapeutic response, unless otherwise indicated.

Primary principles of management for all gout case scenarios.
The TFP generated recommendations for a systematic nonpharmacologic and pharmacologic management approach intended to be applicable to all patients with gout, which is summarized in Figure 3.
This was based on the assumption that the diagnosis of gout was correct before initiation of management. The approach highlighted patient education on the disease and treatments and their objectives, and initiation of diet and lifestyle recommendations, including the particular role of uric acid excess in gout and as the key long-term treatment target (evidence B). The TFP also recommended, on a case-by-case basis, careful consideration of potential elimination of serum urate-elevating prescription medications that might be nonessential for the optimal management of comorbidities (e.g., hypertension, hyperlipidemia, or major organ transplant) in a given patient. Prime examples of urate-elevating medications are thiazide and loop diuretics, niacin, and calcineurin inhibitors (evidence C). However, the TFP, without a specific vote, recognized the particular benefits of thiazides for blood pressure control and outcomes in many patients with hypertension. Although low-dose acetysalicylic acid (aspirin _325 mg daily) elevates serum urate, the TFP did not recommend discontinuation of this modality as cardiovascular disease prophylaxis in gout patients. In discussion, without a specific vote, the TFP viewed the relative risks specifically attributable to the modest effects of low-dose aspirin on serum urate as negligible in gout management.
The TFP recommended that clinicians consider causes of hyperuricemia for all gout patients, and recommended a specific comorbidity checklist (evidence C) (Table 2). In doing so, the TFP specially recommended consideration, and if indicated, medical evaluation of certain agents and disorders that cause uric acid underexcretion or overproduction, which thereby could merit laboratory investigations such as urinalysis, renal ultrasound, a complete blood cell count with differential cell count, or urine uric acid quantification, as indicated. In this context, the TFP specifically recommended screening for uric acid overproduction (by urine uric acid evaluation) in patient subsets with gout clinical disease onset before age 25 years (evidence C) or a history of urolithiasis (evidence C).
The TFP provided guidance for referral to a specialist, with caution to avoid appearing self-serving. Although limited by the absence of outcomes data on potential benefits of referral.
Establish Diagnosis of Gout

Baseline Recommendations for Patients with Diagnosis of Gout
- Patient education, with initiation of diet, lifestyle recommendations. See Figure 4
- Consider secondary causes of hyperuricemia ("Co-morbidity Checklist"). See Table 2
- Consider elimination of non-essential prescription medications that induce hyperuricemia
- Clinically evaluate gout disease burden (palpable tophi, frequency and severity of acute and chronic symptoms and signs)

Indications for Pharmacologic ULT
Any patient with established diagnosis of gouty arthritis and:
- Tophus or tophi by clinical exam or imaging study
- Frequent attacks of acute gouty arthritis (≥ 2 attacks/y)
- CKD stage 2 or worse
- Past uncontrolled

If Pharmacologic ULT is indicated
- The minimum serum urate target is <6 mg/dL
- Serum urate lowering below 5 mg/dL may be needed to improve gout signs and symptoms

TREAT TO SERUM URATE TARGET defined for individual patient
- Select First Line ULT. See Table 3, Figure 5
  - Xanthine oxidase inhibitor (XOI):
    - Allopurinol
    - OR Febuxostat
  - Alternative First Line ULT:
    - Probenecid

Acute Gout Prophylaxis
- Initiate concomitant pharmacologic anti-inflammatory gout attack prophylaxis. See Part 2 of the Guidelines

TREAT TO TARGET
Serum urate target achieved?
- Yes
- No
  - Increase intensity of ULT
  - Re-evaluate serum urate

Long-Term Management of Gout:
- Continuing gout attack prophylaxis if there are ongoing gout symptoms and/or signs (≥ 1 tophus on physical exam). See Part 2 of the Guidelines
- Continue to regularly monitor serum urate and Monitor for ULT side effects
- After palpable tophi and all acute and chronic gouty arthritis gout symptom episodes have resolved, continue all measures (including pharmacologic ULT) needed to maintain serum urate <6 mg/dL indefinitely.

Figure 3. Baseline recommendations and overall strategic plan for patients with gout. This algorithm summarizes overall treatment strategies and flow of management decisions for gout. Certain elements, including nonpharmacologic and pharmacologic measures, the approach to refractory disease, and treatment and anti-inflammatory prophylaxis of acute gout attacks, are developed further in Tables 2-4 and Figures 2 and 2, and in part 2 of the guidelines, as referenced in the figure. Evidence grades (A-C, as indicated) are summarized for each task force panel (TFP) recommendation, and the text discusses in detail each aspect of clinical decision making. ULT = urate-lowering therapy; CKD = chronic kidney disease; CrCl = creatinine clearance.
Core recommendations for nonpharmacologic ULT measures in gout. The TFP recommended certain diet and lifestyle measures for the majority of patients with gout (evidence B and C for individual measures) (Figure 4).

![Specific Recommendations: General Health, Diet, and Lifestyle Measures for Gout Patients#](image)

<table>
<thead>
<tr>
<th><strong>Avoid</strong></th>
<th><strong>Limit</strong></th>
<th><strong>Encourage</strong></th>
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<tbody>
<tr>
<td>• Organ meats high in purine content (e.g., sweetbreads, liver, kidney)</td>
<td>• Searing sizes of: Beef, Lamb, Pork</td>
<td>• Low-fat or non-fat dairy products</td>
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<td>• High fructose corn syrup-sweetened sodas, other beverages, or foods</td>
<td>• Servings of naturally sweet fruit juices</td>
<td>• Vegetables</td>
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<tr>
<td>• Alcohol overuse (defined as more than 2 servings per day for a male and 1 serving per day for a female) in all gout patients</td>
<td>• Table sugar, and sweetened beverages and desserts</td>
<td>• Alcohol (particularly beer, but also wine and spirits) in all gout patients</td>
</tr>
<tr>
<td>• Any alcohol use in gout during periods of frequent gout attacks, or advanced gout under poor control</td>
<td>• Table salt, including in sauces and gravies</td>
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*Without a specific task force panel (TFP) vote, adherence to diets for cardiac health and control of co-morbidities such as obesity, metabolic syndrome, diabetes, hyperlipidemia, and hypertension was stressed for gout patients, as appropriate.

* The TFP recommendation to “encourage” was not intended to advocate excessive consumption of specific dietary items. There was a lack of TFP voting consensus on: Choline and Choline Products. Aseraone (In Supplements or Foods). Note: Legumes. The TFP did not specifically vote on the question of limits on consumption of purine-rich vegetables and legumes.

Figure 4. Specific task force panel (TFP) recommendations on general health, diet, and lifestyle measures for gout patients. The TFP recommendations on nonpharmacologic measures for gout patients are shown, including a program of broad diet and lifestyle measures. The recommendations encompass measures not only for decreasing the risk and frequency of acute gout attacks and lowering serum urate, but also with a major emphasis on maintenance of ideal health and prevention and best practice management of cardiovascular and metabolic diseases. Dietary recommendations were grouped into 3 simple qualitative categories, termed “avoid,” “limit,” and “encourage,” reflecting a general lack of specific evidence from prospective, blinded, randomized clinical intervention trials linking consumed quantities of individual dietary components to changes in either serum urate or to gout signs and symptoms. Specific TFP votes on dietary components resulting in a “lack of consensus” are also cited. BMI = body mass index.
Core recommendations for pharmacologic ULT, including the serum urate target.
The TFP recommended gout with CKD stage 2–5 or end stage renal disease as an appropriate indication, by itself, for pharmacologic ULT (evidence C) in patients with prior gout attacks and current hyperuricemia. In pharmacologic ULT, certain treatment choices (e.g., probenecid) and drug dosing decisions (e.g., allopurinol) are impacted by the creatinine clearance. The TFP, without a direct vote, discussed and recognized the clinical value of accurate measurement of creatinine clearance, not simply the serum creatinine, in ascertaining the degree of renal impairment.

However, the scope of the project did allow for detailed prescriptive recommendations regarding specific ULT drug doses, usage of individual agents in the presence of a given degree of either renal impairment, or other comorbidities such as hepatic impairment.

TFP recommendations for pharmacologic ULT, shown graphically in Figure 3, included recommendation of XO1 therapy with either allopurinol or febuxostat as the first line pharmacologic approach (evidence A). The panel did not preferentially recommend either XO1 over the other XO1 drug. In doing so, the TFP weighed the lack of published safety data for febuxostat in the setting of stage 4 or worse CKD. Probencid was recommended as an alternative first-line pharmacologic ULT option in the setting of contraindication or intolerance to at least 1 XO1 agent (evidence B). However, the TFP did not recommend probenecid as a first-line ULT monotherapy in those with a creatinine clearance below 50 ml/minute.

The TFP recommended regular monitoring of serum urate (every 2–5 weeks) during ULT titration, including continuing measurements once the serum urate target is achieved (every 6 months; evidence C). The TFP weighed this measure as particularly useful to monitor adherence, given that poor adherence to ULT is a common problem in gout patients.

Recommendations specific to allopurinol dosing and pharmacogenetics
TFP recommendations for use of allopurinol in gout are summarized in Table 3.
Recommendations specific to primary uricosuric uratelowering monotherapy.
Under conditions where uricosuric monotherapy was employed as a primary ULT modality (Table 3), probenecid was recommended by the TFP as the first choice among uricosuric drugs currently available in the US (evidence B). The TFP recommended that a history of urolithiasis contraindicates first-line use of a potent uricosuric agent for ULT (evidence C), given that probenecid (and benzbromarone, which is unavailable in the US) was associated with an 9–11% risk of urolithiasis.

Recommendations on pharmacologic ULT decision making in gout, including case scenarios with mild, moderate, or severe disease activity or CTGA.

The TFP voted on clinical decision making in each of the 9 case scenarios when the serum urate target had not yet been met and under circumstances where gout remained symptomatic (i.e., where there were 1 or more continuing clinical signs and symptoms of gout, such as recent acute gout attacks, tophi, and chronic gouty arthritis) (Figure 5 and Table 4). For all 9 case scenarios when the serum urate target has not been met, the TFP recommended upward dose titration of 1 XOI (allopurinol or febuxostat) to the respective maximum appropriate dose for the individual patient (evidence A) (Figure 5 and Table 4). The maximum FDA approved dose of allopurinol is 800 mg daily, and for febuxostat is 80 mg daily. Given the request for an international frame of the gout guidelines by the ACR, the TFP recommended increasing febuxostat up to 120 mg daily, a dose approved in many countries outside the US, in the specific scenario of active disease refractory to appropriately dosed oral ULT (evidence A).
In summary, the ACR guidelines for ULT in gout presented herein will require updating as new evidence emerges for appropriate evaluation and management of gout advances and new medications achieve regulatory agency approval. Increased comparative studies of gout specific health-related quality of life impairment and disease activity outcomes for ULT agents and regimens evaluated here will be of particular interest, given cost, long-term safety, and other considerations such as cardiovascular disease outcomes. It is hoped that publication of these guidelines, along with effective patient education in gout treatments and the objectives and safety issues of management, will improve patient adherence, quality of care, and outcomes in management of gout.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Terkeltaub had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.


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