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

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Introduction
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 (1,2). Tissue deposition of monosodium urate monohydrate crystals in supersaturated extracellular fluids of the joint, and certain other...
Significance & Innovations

- Patient education on diet, lifestyle, treatment objectives, and management of comorbidities is a recommended core therapeutic measure in gout.

- Xanthine oxidase inhibitor (XOI) therapy with either allopurinol or febuxostat is recommended as the first-line pharmacologic urate-lowering therapy (ULT) approach in gout.

- Serum urate level should be lowered sufficiently to durably improve signs and symptoms of gout, with the target <6 mg/dl at a minimum, and often <5 mg/dl.

- The starting dosage of allopurinol should be no greater than 100 mg/day and less than that in moderate to severe chronic kidney disease (CKD), followed by gradual upward titration of the maintenance dose, which can exceed 300 mg daily even in patients with CKD.

- Prior to initiation of allopurinol, rapid polymerase chain reaction–based HLA–B*5801 screening should be considered as a risk management component in subpopulations where both the HLA–B*5801 allele frequency is elevated and the HLA–B*5801–positive subjects have a very high hazard ratio (“high risk”) for severe allopurinol hypersensitivity reaction (e.g., Koreans with stage 3 or worse CKD and all those of Han Chinese and Thai descent).

- Combination oral ULT with 1 XOI agent and 1 uricosuric agent is appropriate when the serum urate target has not been met by appropriate dosing of an XOI.

- Pegloticase is appropriate for patients with severe gout disease burden and refractoriness to, or intolerance of, appropriately dosed oral ULT options.

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Dr. Dinesh Khanna has received consultant fees, speaking fees, and/or honoraria (less than $10,000 each) from Novartis and Ardea and (more than $10,000 each) from Takeda and Savient, and has served as a paid investment consultant for Guidepoint. Dr. Puja P. Khanna has received speaking fees (less than $10,000) from Novartis and (more than $10,000) from Takeda, and has served on the advisory board for Novartis. Dr. Pillinger has received speaking fees and/or honoraria (less than $10,000 each) from the RA Investigator Network, NY Downtown Hospital, Winthrop Hospital, and Einstein College of Medicine. Dr. Perez-Ruiz has received consultant fees, speaking fees, and/or honoraria (less than $10,000 each) from Novartis, Menarini, and Savient, and (more than $10,000) from Ardea. Dr. Liote has received consultant fees, speaking fees, and/or honoraria (less than $10,000 each) from Novartis Global, Novartis France, and Ipsen, and has served as a paid investment consultant for Gerson Lehrman Group. Dr. Choi has served on the advisory boards (less than $10,000 each) for Takeda, URL, and Savient. Dr. Singh has received consultant fees, speaking fees, and/or honoraria (less than $10,000 each) from Ardea, Savient, Allergan, and Novartis, and (more than $10,000) from Takeda, and has received investigator-initiated grants from Takeda and Savient. Dr. Dalbeth has received consultant fees, speaking fees, and/or honoraria (less than $10,000 each) from Takeda, Ardea, and Novartis, has received research funding from Fonterra, and holds a patent from Fonterra for milk products for gout. Dr. Niyyar has received honoraria (less than $10,000) from the American Society of Nephrology. Dr. Kerr has served as a study investigator (more than $10,000 each) for Savient and Nuon. Dr. Edwards has received consultant fees, speaking fees, and/or honoraria (less than $10,000 each) from Savient, Takeda, Ardea, and Regeneron, and (more than $10,000) from Novartis, and has given expert testimony for Novartis. Dr. Mandell has received consultant fees, speaking fees, and/or honoraria (less than $10,000 each) from Savient, Novartis, and Pfizer. Dr. Schumacher has received consultant fees (less than $10,000 each) from Pfizer, Regeneron, West-Ward, and Ardea, and (more than $10,000) from Novartis. Dr. Terkeltaub has received consultant fees (less than $10,000 each) from Takeda, Savient, Ardea, BioCryst, URL, Regeneron, Pfizer, Metabolex, Nuon, Chugai, EnzymeRx, Ajanta, Anadys, Celgene, Isis, and Prescription Solutions, and (more than $10,000) from Novartis, has received grant support from the VA San Diego Healthcare System and the NIH, and has served as a paid investment consultant for Leerinck Swann, Medacorp, and Guidepoint.

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Gout is one of the most common rheumatic diseases of adulthood, with a self-reported prevalence in the US recently estimated at 3.9% of adults (~8.3 million people) (6). The prevalence of gout has risen in many countries (e.g., New Zealand) and especially in the US over the last few decades, mediated by factors such as an increased prevalence of comorbidities that promote hyperuricemia, including hypertension, obesity, metabolic syndrome, type 2 diabetes mellitus, and chronic kidney disease (CKD) (7–10). Other factors in the rising prevalence of gout include certain dietary trends and widespread prescriptions of thiazide and loop diuretics for cardiovascular diseases (11). Many gout patients, including the growing subset of elderly patients affected with gout, have complex comorbidities and medication profiles that complicate overall management (12). Long-term morbidity and impairment of sites, mediates most of the clinical and pathologic features of gout. Typically, the disease initially presents as acute episodic arthritis. Gout also can manifest as chronic arthritis of 1 or more joints (1,2). 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 (3–5). Renal manifestations of gout include urolithiasis, typically occurring with an acidic urine pH (1,2). 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.

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health-related quality of life are now better appreciated in many gout patients, particularly those with multiple co-morbidities and/or chronic gouty arthritis (13,14). Despite advanced understanding of the molecular bases of hyperuricemia and gouty inflammation and the extensive practice experience of many providers, substantial quality of care gaps exist in gout management (15). Moreover, significant shortfalls in patient education and adherence have been identified in gout (16). On behalf of the American College of Rheumatology (ACR), we were charged with developing systematic non-pharmacologic 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 (anaglesic 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 (17).

There are multiple lines of epidemiologic and experimental evidence that hyperuricemia, via the effects of excess soluble urate, may play a role in some human renal, cardiovascular, and metabolic comorbidities also frequently associated with gout (7–10). We did not address pharmacologic management of asymptomatic hyperuricemia due to a paucity of prospective, randomized, controlled human research trials in that area (18).

We were charged by the ACR with developing gout recommendations based on evidence as available, at an international level, for rheumatologists and other health care providers, including other subspecialists, primary care practitioners, nurse practitioners, physician assistants, and allied health professionals. The ACR requested that we apply the established RAND/University of California at Los Angeles (UCLA) Appropriateness Method (19) to generate recommendations, and we engaged a diverse international panel of experts. Creating a novel classification of gout as a disease, new gout diagnostic criteria, or a definition of treatment outcomes was beyond the scope of this work. Instead, we generated multifaceted case scenarios to elucidate decision making based primarily on clinical and laboratory test-based data that can be obtained on a gout patient in an office practice setting.

Guidelines for gout management have been generated in the last decade, at the national or multinational society level and independent of industry sponsorship, by the European League Against Rheumatism (EULAR) (20,21), the Dutch College of General Practitioners (22), the Japanese Society of Gout and Nucleic Acid Metabolism (23), and the British Society for Rheumatology (BSR) (24). Moreover, the National Institute for Health and Clinical Excellence single technology appraisal process has been applied to ULT in gout patients receiving febuxostat (25). New guidelines were requested by the ACR, since the understanding of gout risk factors has been greatly augmented by recent clinical research (12). Moreover, ULT options recently increased via clinical development and drug regulatory agency approval of new pharmacologic agents (febuxostat and the biologic drug pegloticase) (26,27). New imaging approaches for gout that can detect radiographic changes of early disease not visualized by plain radiography (e.g., high-resolution ultrasound, dual-energy computed tomography [CT]) (28,29) are being investigated for impact on gout diagnosis, assessment of disease burden and severity, and choices and effectiveness of management. Developments such as these are considered in the work of this committee, which was built on several key assumptions (Table 1).

The ACR gout guidelines are designed to emphasize safety and quality of therapy and to reflect best practice, as evaluated by a diverse group of experts that examined the level of evidence available at the time. Importantly, societal cost of health care and cost and cost-effectiveness differences between therapies are excluded from analysis by the RAND/UCLA Appropriateness Method (19) (Table 1). Individual results of this work are designated as “recommendations” rather than guidelines, in order to reflect the nonprescriptive nature of decision making evaluated by experts and based on available evidence at the time. The recommendations cannot substitute for individual-

### Table 1. Key assumptions in the process applied to develop the recommendations

| 1. Recommendations were developed using the RAND/University of California at Los Angeles methodology, which assesses level of evidence and safety and quality, but does not take comparisons of cost and cost-effectiveness of therapies into consideration. |
| 2. The guidelines focused on clinically-based decision making in common scenarios and not on rare case presentations. |
| 3. Multiple scenarios were developed for acute treatment and chronic gout for voting purposes and are NOT meant to be disease classification criteria for gout. |
| 4. The project did not list specific drug choices, contraindications, and dosing in the presence of comorbidities associated with gout or with potential drug–drug interaction. These decisions are left with the practitioner, based on evaluation of the risk/benefit ratio when prescribing each therapy, the drug dosing and safety labeling, and other widely available databases and accessible sources of general medical information about potential drug-related adverse reactions. |
| 5. When a particular drug is not recommended, it does not imply that it is contraindicated. Similarly, if a hierarchy or sequence of a treatment is recommended, it does not necessarily imply that an agent lower in the hierarchy or sequence is indicated. |
| 6. It is assumed that the diagnosis of gout was correct before initiation of any management option. |
| 7. It is not always possible for the task force panel to reach a consensus on a case scenario (see Supplemental Figure 3 for examples of voting scenarios, available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/). |
ized direct assessment of the patient, coupled with clinical decision making by a competent health care practitioner. Treatment recommendations also assume appropriate attention to potential drug interactions (e.g., with anticoagulants, aspirin, and amoxicillin) and effects of comorbidities such as diabetes mellitus and renal, cardiac, gastrointestinal, and hepatic disease (Table 1). The motivation, financial circumstances, and preferences of the gout patient play a very important role. Moreover, the recommendations for gout management presented here are not intended to limit or deny third party payor coverage of health care costs for groups or individual patients with gout.

Materials and methods

Project design, development of recommendations, and grading of evidence. The overall design of the project is schematized in Supplemental Figure 1 (available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658). The RAND/UCLA consensus methodology, developed in the 1980s, incorporates both Delphi and nominal group methods (19,30), and was successfully used to develop other guidelines commissioned by the ACR. The purpose of this methodology is to reach a consensus among experts, with an understanding that published literature may not be adequate to provide sufficient evidence for day-to-day clinical decision making. The RAND/UCLA method requires 2 groups of experts: a core expert panel (CEP) that provides input into case scenario development and preparation of a scientific evidence report, and a task force panel (TFP) that votes on these case scenarios. Our CEP consisted of leaders for each domain (see Supplemental Figure 2, available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658). Pharmacologic approaches and diet, lifestyle, and nonpharmacologic measures (e.g., weight loss, exercise) were addressed within each domain. The CEP leaders communicated with an international panel of gout experts and the principal investigators (PIs; JD, PPK, DK, RT) to develop initial case scenarios that reflect broad differences in severity of the disease and its clinical manifestations. In addition, there were weekly interactive teleconferences between the domain leaders and PIs to refine case scenarios. Although a previous systematic review for gout has been performed by EULAR, as a prime example, we performed our own systematic review of pertinent literature. The resultant scientific evidence report was given to the TFP in conjunction with clinical scenarios representing differing degrees of disease activity. There were multiple questions of interest and alternative options presented for each case scenario.

By ACR mandate, the TFP had a majority of members without a perceived potential conflict of interest (COI), and had diverse experience and expertise, as described in detail in Supplemental Figure 2 (available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658). The TFP included 7 rheumatologists (including 1 Chair of Internal Medicine and 1 Internal Medicine Residency Training Program Director), 2 primary care physicians, a nephrologist, and a patient representative. There were 2 rounds of ratings, the first anonymous, with the members of the TFP instructed to rank each of the potential elements of the guidelines on a risk/benefit ratio is uncertain, and a vote of 1–3 on the Likert scale was rated as inappropriate (risks clearly outweigh the benefits), a vote of 4–6 was considered uncertain (risk/benefit ratio is uncertain), and a vote of 7–9 was rated as appropriate (benefits clearly outweigh the risks). Samples of votes taken and results are provided in Supplemental Figure 3 (available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658). Votes on case scenarios were translated into recommendations if the median voting score was graded 7–9 (appropriate) and if there was no significant disagreement, defined as no more than 1 of 3 of the votes graded as inappropriate for the scenario. The final rating was done anonymously in a 2-day face-to-face meeting, facilitated by an experienced moderator (NW). During the face-to-face TFP meeting, some case scenarios were clarified for content or verbiage and revoted on by the TFP.

The level of evidence supporting each recommendation was ranked based on previous methods used by the American College of Cardiology (31) and applied to recent ACR recommendations (32,33). Level A grading was assigned to recommendations supported by multiple (i.e., >1) randomized clinical trials or meta-analyses. Level B grading was assigned to the recommendations derived from a single randomized trial or nonrandomized studies. Level C grading was assigned to consensus opinion of experts, case

Clinical case descriptions. The 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). In generating these 9 fundamental clinical case scenarios, mild disease activity levels in each treatment group were meant to represent patients at the lowest disease activity level for which most clinicians would consider initiating or altering a specific med-
### ACR Guidelines for Gout Management: Part 1

**GOUT CASE SCENARIOS**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Toxoph or Tophi detected on Physical exam</th>
<th>Frequency</th>
<th>CASE SCENARIO NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermittent symptoms</td>
<td>NO</td>
<td>Infrequent Symptoms (≤1 attack/yr)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>NO</td>
<td>Frequent Symptoms (2–6 attacks/yr)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>NO</td>
<td>Very Frequent Symptoms (&gt;7 attacks/yr)</td>
<td>3</td>
</tr>
<tr>
<td>Intermittent symptoms</td>
<td>YES</td>
<td>Infrequent Symptoms (≤1 attack/yr)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>YES</td>
<td>Frequent Symptoms (2–6 attacks/yr)</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>YES</td>
<td>Very Frequent Symptoms (&gt;7 attacks/yr)</td>
<td>6</td>
</tr>
</tbody>
</table>

**Case scenarios for Chronic Tophaceous Gouty Arthropathy**

<table>
<thead>
<tr>
<th>Disease Severity</th>
<th>Characteristics</th>
<th>CASE SCENARIO NUMBER</th>
</tr>
</thead>
</table>
| Mild | • Simple chronic tophaceous gouty arthropathy  
• Affecting 1 joint  
• Scalp disease | 7 |
| Moderate | • Simple chronic tophaceous gouty arthropathy  
• Affecting 2–4 joints  
• Scalp disease | 8 |
| Severe | • Chronic tophaceous gouty arthropathy of ≥5 joints OR  
• ≥1 unstable, complicated, severe articular tophus or tophi | 9 |

**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 5 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); with clinically apparent high body urate burden was evaluated in case scenarios where there were no uric acid symptoms, 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 sulfisoxazole 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.

**Managing perceived potential COI.** Perceived potential COI was managed in a prospective and structured manner. Specifically, all participants intellectually involved in the project, whether authors or not, were required to fully and prospectively disclose relationships with pharmaceutical companies with a material interest in gout (see Supplemental Figure 2 and Appendix A, available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658). Disclosures were updated every 6 months, and for the PIs, CEP, and TFP, updated just prior to the face-to-face meeting. A summary listing of all perceived potential COI was disseminated to all participants in the project, and is available in Supplemental Appendix A (available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658). Based on the policies of the ACR, which are aligned with those of many medical societies, no more than 49% of the project participants could have a COI at any given time. It was required that the project PI (JDF) remain without perceived potential COI prior to and during the process.

**Results**

**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 treat-
ments 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) (34). 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 acetylsalicylic 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 overpro-

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**Figure 2.** Detailed pictorial representations of chronic arthropathy in chronic tophaceous gouty arthropathy (CTGA) case scenarios presented to the task force panel (TFP). A core element of our approach was to present the TFP and the readership with specifically detailed summaries of the CTGA case scenarios (case scenarios 7–9 in Figure 1B), including pictorial examples, to allow focus on clinical information that prompts management decisions. The photograph on the top left was provided by Dr. Robert Terkeltaub; the photographs on the top and bottom right were provided by Dr. Fernando Perez-Ruiz.

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**MILD Chronic Tophaceous Gouty Arthropathy (CTGA)**

(Stable, Simple Tophus Limited to 1 Joint (Scenario #7)

- Lack of drainage
- Lack of aggressive mass or connective tissue destructive effects
- Low risk of tophus infection
- Stable in size, or slow growth
- Lack of severe chronic, tophaceous joint inflammation

**MODERATE CTGA**

Stable, simple tophi affecting 2-4 joints (Scenario #8)

**SEVERE CTGA**

Numerous, Complicated, or Unstable Tophi (Scenario #9)

- Tophi affecting more than 4 joints
  OR
- One or more tophi demonstrating
  - Drainage
  - Aggressive mass or connective tissue destructive effects
  - High risk of infection
  - Very rapid growth
  - Severe, chronic tophaceous joint inflammation

**SEVERE CTGA Example**

CTGA of many joints
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 (“Comorbidity Checklist”) See Table 2
- Consider elimination of nonessential 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
  - Topus or tophi by clinical exam or imaging study
  - Frequent attacks of acute gouty arthritis (≥2 attacks/yr) C
  - CKD stage 2 or worse C
  - Past urolithiasis

TREAT TO SERUM URATE TARGET defined for individual patient

- 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

Select First Line ULT agent See Table 2, Figure 5

- Xanthine Oxidase Inhibitor (XOI):
  - Allopurinol A
  - Febuxostat A

- Alternative First Line ULT:
  - Probenecid B

Acute Gout Prophylaxis

- Initiate concomitant pharmacologic anti-inflammatory gout attack prophylaxis
  - See Part II of the Guidelines

TREAT TO TARGET Serum urate target achieved?

- Yes
  - Increase intensity of ULT
  - Re-evaluate serum urate
  - See Figure 5, Table 4

- No
  - Treat to target

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 II of the Guidelines C
- Continue to regularly monitor serum urate C and Monitor for ULT side effects C
- After palpable tophi and all acute and chronic gouty arthritis gout symptoms have resolved, continue all measures (including pharmacologic ULT) needed to maintain serum urate <6 mg/dL indefinitely
- Gout case scenarios, where referral to a specialist is considered, include: (i) Unclear etiology of hyperuricemia; (ii) Refractory signs or symptoms of gout; (iii) Difficulty in reaching target serum urate, particularly with renal impairment and a trial of XOI treatment; (iv) Multiple and/or serious adverse events from pharmacologic ULT

* Example of serum urate lowering drugs that might be nonessential in a given patient, and are generally used by a therapist agreed that divert clinical urate targets
- Basis for management of hyperuricemia
- Management recommendations for hyperuricemia remain, in discussion, and in a specific note, the TFP recognized the role of diuretic treatment in many patients with hyperuricemia, and cautioned against rapid cessation of diuretic treatment in patients with hypertension or renal impairment, as the loss of weight control of blood pressure is difficult to correct hypertension
- Colchicine initiation with colchicine or tocolubic, if it is not successful for gouty migraines
- Probepenicid and recommended as a first line or alternative that from XOI is not well tolerated
- CrCl = creatinine clearance

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 antiinflammatory prophylaxis of acute gout attacks, are developed further in Tables 2–4 and Figures 4 and 5, 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; CrCl = chronic kidney disease; CrCl = creatinine clearance.
The TFP recommended certain diet and lifestyle measures for the majority of patients with gout (evidence B and C for individual measures) (Figure 4). Many of the diet and lifestyle measures were recommended for decreasing the risk and frequency of acute gout attacks (12) and lowering serum urate levels, but the primary emphasis of the TFP recommendations in Figure 4 was on diet and lifestyle choices for promotion and maintenance of ideal health and prevention and optimal management of life-threatening comorbidities in gout patients, including coronary artery disease (35,36) and obesity, metabolic syndrome, diabetes mellitus, hyperlipidemia, and hypertension.

Dietary recommendations were grouped into 3 simple qualitative categories, termed “avoid,” “limit,” or “encourage” (Figure 4). This approach, with rare exceptions (37,38), reflected a general lack of specific evidence from prospective, blinded, randomized clinical intervention trials that linked consumed quantities of individual dietary components to changes in either serum urate levels or gout outcomes. Notably, the replication of hazardous lifestyle risk factors in a conventional clinical research trial would potentially pose both design and ethical difficulties. As such, the TFP deliberated on evidence regarding the impact of exposures to alcohol or purine-rich foods in a short timeframe. The evidence sources were epidemiologic studies of hyperuricemia and incident gout, including long-term prospective analyses (39–42) and internet-based case-crossover studies of specific exposures (43,44). The TFP recommended that gout patients limit their consumption of purine-rich meat and seafood (evidence B) (44) as well as high fructose corn syrup–sweetened soft drinks and energy drinks (evidence C), and encouraged the consumption of low-fat or nonfat dairy products (evidence B) (43) (Figure 4). The TFP voted to encourage vegetable intake in gout patients (evidence C) (Figure 4), having considered evidence in healthy subjects for lowered serum urate levels and urine uric acid excretion risk factors associated with dietary vegetable intake (43,45). However, there was no specific TFP vote on the question of avoidance of excess alcohol from food sources other than meat and seafood, such as vegetables and legumes, in gout patients (44). The TFP recommended reduced consumption of alcohol (particularly beer, but also wine and spirits) and avoidance of alcohol overuse in all gout patients (evidence B) (Figure 4). The TFP further recommended abstinence from alcohol consumption for gout patients during periods of active arthritis, especially with inadequate medical control of the disorder and in CTGA (evidence C) (46). Significantly, in discussion by the TFP, without a specific vote, the TFP recognized that diet and lifestyle measures alone provide therapeutically insufficient serum urate–lowering effects and/or gout attack prophylaxis for a large fraction of individuals with gout (12). For example, some clinical trials on diet and fitness have reported only an ~10–18% decrease in serum urate (43). In further discussion by the TFP, again without a specific vote, the TFP viewed this degree of serum urate level lowering as beneficial for all case scenarios, but insufficient to achieve an effective serum urate target in those with sustained hyperuricemia substantially above 7 mg/dl.

Core recommendations for pharmacologic 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). Many of the diet and lifestyle measures were recommended for decreasing the risk and frequency of acute gout attacks (12) and lowering serum urate levels, but the primary emphasis of the TFP recommendations in Figure 4 was on diet and lifestyle choices for promotion and maintenance of ideal health and prevention and optimal management of life-threatening comorbidities in gout patients, including coronary artery disease (35,36) and obesity, metabolic syndrome, diabetes mellitus, hyperlipidemia, and hypertension.

Clinical evaluation of gout disease activity and burden. The TFP recommended clinical evaluation of gout disease symptom severity and burden in individual patients by history and a thorough physical examination for symptoms of arthritis and signs such as tophi and acute and chronic synovitis (evidence C). To be actionable by clinicians, the authors without a specific TFP vote suggested that clinicians can work with patients to record and estimate the number per year and severity (17) of acute attacks of gouty arthritis per year.

Core recommendations for pharmacologic ULT, including the serum urate target. Here, and with all other recommendations for drug therapy in parts 1 and 2 of the 2012 ACR guidelines for gout, the recommendations assumed a lack of contraindications, intolerance, serious adverse events, or drug–drug interactions for given agents.
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 XOI therapy with either allopurinol or febuxostat as the first-line pharmacologic approach (evidence A). The panel did not preferentially recommend either XOI over the other XOI drug. In doing so, the TFP weighed the lack of published safety data for febuxostat in the setting of stage 4 or worse CKD. Probenecid was recommended as an alternative first-line pharmacologic ULT option in the setting of contraindication or intolerance to at least 1 XOI 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 that pharmacologic ULT could be started during an acute gout attack, provided that

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### Specific Recommendations:

**GENERAL HEALTH, DIET, AND LIFESTYLE MEASURES FOR GOUT PATIENTS**

- **Avoid**
  - Organ meats high in purine content (e.g., sweetbreads, liver, kidney)
  - High fructose corn syrup-sweetened sodas, other beverages, or foods
  - 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
  - Any alcohol use in gout during periods of frequent gout attacks, or advanced gout under poor control

- **Limit**
  - Serving Sizes of: Beef, Lamb, Pork; Seafood with high purine content (e.g., sardines, shellfish)
  - Servings of naturally sweet fruit juices; Table sugar, and sweetened beverages and desserts; Table salt, including in sauces and gravies
  - Alcohol (particularly beer, but also wine and spirits) in all gout patients

- **Encourage**
  - Low-fat or non-fat dairy products
  - Vegetables

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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” intake was not intended to advocate excesses in consumption of specific dietary items. There was a lack of TFP voting consensus on: Cherries and Cherry Products, Ascorbate (In Supplements or Foods), Nuts, 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.
tive antiinflammatory management has been instituted (evidence C). 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 A). The TFP weighed this measure as particularly useful to monitor adherence, given that poor adherence to ULT is a common problem in gout patients (16).

The TFP recommended that the goal of ULT is to achieve a serum urate level target at a minimum of <6 mg/dl in all gout case scenarios (evidence A). Moreover, the TFP recommended that the target serum urate level should be lowered sufficiently to durably improve signs and symptoms of gout, including palpable and visible tophi detected by physical examination, and that this may involve therapeutic serum urate level lowering to below 5 mg/dl (evidence B).

Recommendations specific to allopurinol dosing and pharmacogenetics. The TFP recommended that the starting dosage of allopurinol should be no greater than 100 mg per day (evidence B) (47), consistent with prior Food and Drug Administration (FDA) and EULAR guidelines (21). The rationale of the TFP was that a low allopurinol starting dose could reduce early gout flares after ULT initiation (26), and partly as a component of risk management with respect to the potential for severe hypersensitivity reaction to allopurinol (47), discussed in further detail below. The TFP recommended gradual upward titration of the allopurinol maintenance dose every 2–5 weeks to an appropriate maximum dose for gout, in order to treat to the serum urate target appropriate for the individual patient (evidence C). The TFP weighed robust evidence that allopurinol monotherapy at doses of 300 mg or less daily failed to achieve the serum urate level target of <5 mg/dl (48,49) in more than half of the subjects with gout. The TFP reviewed small studies in which the allopurinol dose was titrated above 300 mg daily in gout with overall success in achieving the serum urate target (49,50). Importantly, in doing so, the TFP also recommended that the maintenance dosage of allopurinol can be raised above 300 mg per day, even in those with renal impairment, provided there is adequate patient education and regular monitoring for drug hypersensitivity and other adverse events, such as pruritis, rash, and elevated hepatic transaminases, as well as attention to potential development of eosinophilia (evidence B).

The TFP next considered the issue of measures to reduce the incidence of severe allopurinol hypersensitivity reactions, here termed allopurinol hypersensitivity syndrome (AHS). TFP discussion recognized the potential for hospitalization and severe morbidity and the reported mortality rate of 20–25% in AHS (51,52). The estimated incidence of AHS is ~1:1,000 in the US, and its spectrum includes not only Stevens-Johnson syndrome and toxic epidermal necrolysis, but also systemic disease with a clinical constellation of features such as eosinophilia, vasculitis, rash, and major end-organ disease (53). Concurrent thiazide use and renal impairment have been implicated as risk factors for AHS (50,54,55).

Table 3. Core recommendations in the use of allopurinol and uricosuric ULT in gout*

<table>
<thead>
<tr>
<th>Allopurinol</th>
<th>Uricosuric ULT in gout*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting dosage should be no greater than 100 mg/day for any patient, and start at 50 mg/day in stage 4 or worse CKD (evidence B).</td>
<td>Probenecid is the first choice among uricosuric agents for ULT monotherapy (evidence B).</td>
</tr>
<tr>
<td>Gradually titrate maintenance dose upward every 2–5 weeks to appropriate maximum dose in order to treat to chosen SUA target (evidence C).</td>
<td>In gout patients with a creatinine clearance &lt;50 ml/minute, probenecid is not recommended as first-line ULT monotherapy (evidence C).</td>
</tr>
<tr>
<td>Dose can be raised above 300 mg daily, even with renal impairment, as long as it is accompanied by adequate patient education and monitoring for drug toxicity (e.g., pruritis, rash, elevated hepatic transaminases; evidence B).</td>
<td>Use of agents other than probenecid with clinically significant uricosuric effects, such as fenofibrate and losartan, can be therapeutically useful as components of a comprehensive ULT strategy.</td>
</tr>
<tr>
<td>Prior to initiation, consider HLA–B*5801 in selected patients, specifically in subpopulations at higher risk for severe allopurinol hypersensitivity reaction (e.g., Koreans with stage 3 or worse CKD, and Han Chinese and Thai irrespective of renal function).</td>
<td>History of urolithiasis contraindicates first-line uricosuric urate-lowering monotherapy (evidence C).</td>
</tr>
<tr>
<td>Continue to monitor urinary uric acid during.</td>
<td>Elevated urine uric acid indicative of uric acid overproduction contraindicates uricosuric ULT.</td>
</tr>
<tr>
<td>Consider urine alkalization (e.g., with potassium citrate) with monitoring of urine pH, in addition to increased fluid intake, as a risk management strategy.</td>
<td>= chronic kidney disease;</td>
</tr>
</tbody>
</table>

The TFP next considered the issue of measures to reduce the incidence of severe allopurinol hypersensitivity reactions, here termed allopurinol hypersensitivity syndrome (AHS). TFP discussion recognized the potential for hospitalization and severe morbidity and the reported mortality rate of 20–25% in AHS (51,52). The estimated incidence of AHS is ~1:1,000 in the US, and its spectrum includes not only Stevens-Johnson syndrome and toxic epidermal necrolysis, but also systemic disease with a clinical constellation of features such as eosinophilia, vasculitis, rash, and major end-organ disease (53). Concurrent thiazide use and renal impairment have been implicated as risk factors for AHS (50,54,55). A widely employed risk management strategy has been a non–evidence-based algorithm for allopurinol maintenance dosing, calibrated to renal impairment (evidence C) (56); importantly, the TFP did not recommend this strategy.

In their evaluation of the allopurinol starting dose as a component of risk management strategy, the TFP first weighed evidence that the highest risk of severe allopurinol hypersensitivity reaction is in the first few months of therapy. A recent case–controlled retrospective analysis of AHS and allopurinol starting dose (47) further supported the aforementioned recommendation by the TFP of a starting dose of allopurinol of no more than 100 mg daily, and the TFP recommendation of an even lower starting dose of allopurinol (50 mg daily) in stage 4 or worse CKD (evidence B).
Figure 5. Case scenario–specific escalation of pharmacologic urate-lowering therapy (ULT) in gout, including approach to refractory disease. The figure, which accompanies Table 4, shows task force panel (TFP) recommendations for patients with continuing gout disease activity and focuses on escalating pharmacologic ULT measures, particularly for refractory disease. Each of the fundamental case scenarios is considered. Case scenario numbering of 1–9 refers to those gout clinical scenarios specifically detailed in Figures 1A and B above. The chronic tophaceous gouty arthropathy (CTGA) case scenarios numbered 7–9 are additionally shown in photographs in Figure 2. These recommendations specifically assume that for each case scenario: 1) the serum urate target needed to achieve improved gout signs and symptoms has not yet been achieved, 2) appropriate nonpharmacologic ULT measures have been applied, and 3) appropriate treatment and antiinflammatory prophylaxis are employed for attacks of acute gouty arthritis. Evidence grades for individual TFP votes to recommend that are shown here are summarized in the text. In the figure, the decision-making symbol indicates therapeutic appropriateness, with indicative of either a therapeutically inappropriate measure or one with uncertain risk/benefit ratio. The decision-making symbol indicates that the TFP recommended this therapeutic measure as appropriate only in specific conditions in a clinical scenario, marked by the symbol § or ¶ that refers to particular circumstances described below the figure. CKD = chronic kidney disease; ESRD = end-stage renal disease; XOI = xanthine oxidase inhibitor.

Table 4. Summary of recommendations for case scenarios of refractory disease in gout (Figure 5), including combination oral ULT and use of pegloticase*

<table>
<thead>
<tr>
<th>CASE SCENARIOS 1-9</th>
<th>No tophi on exam</th>
<th>≤ 1 Tophus on exam</th>
<th>≥ 1 Tophus on exam</th>
<th>Intermittent Symptoms</th>
<th>CTGA</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHARMACOLOGIC ULT ESCALATION: MEASURE</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>SINGLE AGENT XOI titrated to maximum appropriate dose</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(Alternative if XOI contra-indicated or not tolerated: Probenecid)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum urate target not achieved, continuing disease activity</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Add URICOSURIC* to XOI with both agents titrated to maximum appropriate dose</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Serum urate target not achieved, continuing disease activity</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PEGLOTICASE</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* Finding of a tophus or tophi on imaging study, or CKD Stage 2-5, or ESRD, are appropriate indications for first line pharmacologic ULT in Scenario 1.

1 Failure of combination XOI and uricosuric therapy at maximum appropriate doses is an acceptable indication for consideration of Pegloticase therapy in Scenario 5.

* Uricosuric ULT choices in combination with XOI inhibitor therapy can include probenecid, or off-label use of losartan or fenofibrate.

** Table 4. Summary of recommendations for case scenarios of refractory disease in gout (Figure 5), including combination oral ULT and use of pegloticase**

- Attempt upward dose titration of 1 XOI to respective maximum appropriate dose (evidence A)
- Febuxostat can be substituted for allopurinol or vice versa in the event of drug intolerance and adverse events, and such a substitution should be considered after initial failure of upward dose titration of 1 XOI (evidence C)†
- Effective therapeutic options include addition of a uricosuric agent (e.g., probenecid, fenofibrate, or losartan) to an XOI drug (evidence B) or vice versa (evidence C)
- Pegloticase is appropriate for patients with severe gout disease burden and refractoriness to, or intolerance of, conventional and appropriately dosed ULT (evidence A)‡
- Pegloticase therapy is not recommended as first-line ULT agent for any case scenarios
- LACK OF CONSENSUS: appropriate duration of pegloticase therapy relative to intended and achieved decrease in symptoms and signs of gout, including decrease in tophus size

* ULT = urate-lowering therapy; XOI = xanthine oxidase inhibitor.
† Important drug label information includes that febuxostat and allopurinol should not be used in combination with each other.
‡ Important drug label information includes that pharmacologic oral ULT agents should be discontinued during the course of pegloticase therapy to avoid masking the loss of a pegloticase serum urate-lowering effect associated with an increased risk of pegloticase infusion reactions.
The TFP also weighed the rapidly emerging area of pharmacogenetics to screen for AHS (53,57,58), and recommended that, prior to initiation of allopurinol, HLA–B*5801 testing should be considered in select patient subpopulations at an elevated risk for AHS (evidence A). Those with HLA–B*5801 and of Korean descent with stage 3 or worse CKD (HLA–B*5801 allele frequency ~12%), or of Han Chinese or Thai extraction irrespective of renal function (HLA–B*5801 allele frequency ~6–8%), have been highlighted in the literature as prime examples of subjects at high risk for AHS, marked by HLA–B*5801 hazard ratios of several hundred (59–61). Such high-risk individuals were recommended to be prescribed an alternative to allopurinol if HLA–B*5801 positive (evidence A).

The TFP recommended that the HLA–B*5801 screening be done by the rapid, widely available polymerase chain reaction (PCR)–based approach (evidence A) that, in only ~10% of tests, requires more cumbersome followup HLA–B*5801 sequencing for inconclusive results. Significantly, the TFP did not recommend universal HLA–B*5801 allopurinol screening. Current evidence informing this TFP decision included that whites with an HLA–B*5801 prevalence of ~2% had a substantially lower HLA–B*5801 hazard ratio and negative predictive value of the test than in the aforementioned Asian subpopulations (53,58,62).

Recommendations specific to primary uricosuric urate-lowering monotherapy.

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 asis (63,64). Specific TFP recommendations for risk management in uricosuric ULT also included initial measurement and monitoring of urine uric acid, and that an elevated urine uric acid level indicative of uric acid overproduction contraindicates uricosuric ULT. There was no TFP consensus on assay of undissociated urine uric acid, or use of Simkin’s Index and similar calculation on spot urine, in risk management in uricosuric therapy (63). The TFP did recommend that when initiating uricosuric ULT, patients should also be instructed to increase fluid intake and consider urine alkalinization (e.g., with potassium citrate; evidence C for all) (63), but no quantitative parameters were voted on for these measures, in view of lack of evidence.

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). In doing so, the TFP, in limited voting scenarios, first considered the potential role of imaging in the evaluation of disease burden and clinical decision making on ULT gout. The TFP recommended the utility of high-resolution ultrasound, CT, or dual-energy CT (evidence B) to detect tophi, and the utility of plain radiographic findings consistent with tophi (such as characteristic bone erosion; evidence C). The TFP also voted that the ultrasound “double contour sign” was consistent with nontophaceous urate crystal deposition on the surface of articular cartilage (evidence B). However, the TFP did not recommend use of the double contour sign as a sufficient indicator for initiating or increasing the intensity of ULT, given that the sign was detected in joints of ~25% subjects with asymptomatic hyperuricemia in a recent study (65). Conversely, in a recent study, the double contour sign was not universally 33% of subjects in an ultrasound survey of multiple joints in each subject) in patients with early gout not receiving ULT (66).

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). The TFP further recommended, and broadly so in the 9 case scenarios, that if upward titration of the initial XOI agent was not tolerated or did not achieve the serum urate target, substitution of another XOI was an appropriate first-line option (evidence B).

Notably, the TFP recommended probenecid and other agents with clinically significant uricosuric effects, such as fenofibrate and losartan, as therapeutically useful in a comprehensive ULT program in refractory disease (evidence B). Specifically, the TFP recommended a combination oral ULT approach (i.e., 1 XOI agent [allopurinol or febuxostat] and 1 uricosuric agent [probenecid, fenofibrate, or losartan being the currently available agents in the US]) as an option when the serum urate target has not been met across the 9 case scenarios (evidence B) (67–69) (Figure 5 and Table 4).

Last, the TFP recommended pegloticase as appropriate only in the case scenarios with severe gout disease burden and refractoriness to, or intolerance of, appropriately dosed oral ULT options (evidence A) (Figure 5 and Table 4). In 2 large placebo-controlled randomized clinical trials, pegloticase 8 mg every 2 weeks was effective in reducing the serum uric acid level to <6 mg/dl in 42% of patients versus 0% in the placebo group at 6 months (27). In addition, 45% of patients receiving pegloticase 8 mg every 2 weeks had complete resolution of 1 or more tophi versus 8% in the placebo group, with significant improvement in chronic arthropathy and health-related quality of life. Importantly, the TFP did not recommend pegloticase as a first-line ULT for any case scenarios. The TFP also did not
achieve consensus on the appropriate duration of pegloticase therapy once decreased symptoms and signs of gout, including decrease in size (or resolution) of tophi on clinical examination, had been achieved.

Discussion

We present the first ACR evidence- and consensus-based pharmacologic and nonpharmacologic management recommendations for gout, the product of a formal group consensus process. The thorough systematic review of the literature essential to this project was timely. Comparable gout guidelines independently (i.e., not developed with pharmaceutical company support) assembled at the level of national and multinational rheumatology societies in the last decade by EULAR and the BSR did not comprehensively evaluate newer evidence and therapies, including febuxostat and pegloticase (21,24). The ACR-sponsored work presented here in part 1 of the guidelines focused on systematic disease management and urate-lowering measures in all gout patients and in refractory disease, including CTGA. The work first addressed core aspects of patient education, which includes discussion with the patient of the role of uric acid excess in gout and as key long-term treatment target, and impacts heavily on ULT treatment adherence and ultimate efficacy (34). Based on the existing evidence in patients with gout, the TFP was able to generate a set of diet and lifestyle recommendations for gout, but the recommendations are dominated or superseded, for good reason, by diet and lifestyle recommendations for life-threatening comorbidities common in gout patients, such as atherosclerosis, diabetes mellitus, and hypertension. There was only limited advice on specific serving sizes and quantities, as was the case for prior gout recommendations of this nature (21). Clearly, more research is needed in diet and lifestyle modifications for gout, especially for direct intervention studies (34).

The TFP also recommended that all gout patients have a thorough clinical evaluation of disease activity and burden, and appropriate attention to possible etiologies of hyperuricemia in each patient, with potential modification of secondary causes of hyperuricemia such as comorbidities and specific medications that elevate serum urate. However, the TFP did not vote on specific indications for employing imaging studies to assess disease burden or treatment responses in gout. This issue should be updated in the next few years, as more studies appear on the use of high-resolution ultrasound and dual-energy CT that may inform disease classification and prognosis in gout, and as more outcomes data emerge on ULT-induced alterations in imaging findings of gout (70).

Specific TFP recommendations on indications for pharmacologic ULT initiation were accompanied by novel TFP recommendations that either allopurinol or febuxostat is appropriate as the first line of pharmacologic ULT, although the issue of allopurinol nontitration in comparison to clinical trial designs for these agents was recognized. Probencicad was recommended as an alternative first-line therapy if at least 1 XOI drug was contraindicated or not tolerated, but probencicad monotherapy was not recommended as a first-line approach in those with a creatinine clearance less than 50 ml/minute. In discussion, TFP reservations on probenecid included lack of data on long-term safety and efficacy in stage 3 CKD (given that creatinine clearance <50 ml/minute was an exclusion criterion in some studies [48,69]). Reservations also included multiple drug interactions, the ~9% risk of urolithiasis, and the complexity of risk management in dose escalation of probenecid ULT as a monotherapy. There was an unexpected lack of TFP consensus on ideal approaches to monitor uric acid excretion to lessen the risk of urolithiasis risk management during probenecid ULT as monotherapy.

Treating to a serum urate target was evaluated in detail. The TFP consolidated previous EULAR and BSR recommendations (21,24), here recommending that serum urate should be lowered in patients with gout to achieve, at a minimum, a serum urate level <6 mg/dl. In those with greater disease severity and urate burden, such as those with tophi detected on physical examination and with CTGA, the TFP recommended that the serum urate level may need to be lowered below 5 mg/dl to achieve better outcomes data emerge on ULT-induced alterations in specific tophi. The TFP also made the novel recommendation that rapid PCR-based HLA–B*5801 screening should be considered as a risk management component in subpopulations where both the HLA–B*5801 allele frequency is elevated and the HLA–B*5801–positive subjects have a very high hazard ratio (“high risk”) for severe allopurinol hypersensitivity reaction (e.g., Koreans with stage 3 [or worse] CKD and all those of Han Chinese and Thai descent). It is anticipated that additional high-risk subpopulations for AHS will be identified in future studies.

The TFP also made the novel recommendation that allopurinol was addressed at length, since allopurinol is the most commonly prescribed ULT worldwide. First, TFP recommendations reinforced both the previous EULAR guidelines (21) and FDA guidance for risk management to initiate allopurinol at no more than 100 mg daily, and to start allopurinol at 50 mg daily in patients with stage 4 or worse CKD. Second, the TFP recommended steady upward titration of allopurinol soon after initiation, accompanied by adequate patient education and monitoring for drug toxicity. Recent clinical trial evidence that allopurinol doses of 300 mg or less daily fail to achieve target serum urate in the majority of gout patients informed the TFP recommendation that, with appropriate risk management, allopurinol can be advanced above 300 mg daily to achieve the serum urate target, including in patients with CKD. The TFP, for all degrees of renal impairment, did not recommend the AHS risk management strategy of Hande et al (56), in which a non-evidence-based algorithm for allopurinol maintenance dosing had been calibrated to renal impairment. However, the authors, without a specific TFP vote, are concerned about the lack of long-term safety data for allopurinol dosing above 300 mg daily, particularly with significant renal impairment, which is associated with increased allopurinol toxicity (50,71).

The TFP also made the novel recommendation that rapid PCR-based HLA–B*5801 screening should be considered as a risk management component in subpopulations where both the HLA–B*5801 allele frequency is elevated and the HLA–B*5801–positive subjects have a very high hazard ratio (“high risk”) for severe allopurinol hypersensitivity reaction (e.g., Koreans with stage 3 [or worse] CKD and all those of Han Chinese and Thai descent). It is anticipated that additional high-risk subpopulations for AHS will be identified in future studies.

The TFP also made the novel recommendation that allopurinol was addressed at length, since allopurinol is the most commonly prescribed ULT worldwide. First, TFP recommendations reinforced both the previous EULAR guidelines (21) and FDA guidance for risk management to initiate allopurinol at no more than 100 mg daily, and to start allopurinol at 50 mg daily in patients with stage 4 or worse CKD. Second, the TFP recommended steady upward titration of allopurinol soon after initiation, accompanied by adequate patient education and monitoring for drug toxicity. Recent clinical trial evidence that allopurinol doses of 300 mg or less daily fail to achieve target serum urate in the majority of gout patients informed the TFP recommendation that, with appropriate risk management, allopurinol can be advanced above 300 mg daily to achieve the serum urate target, including in patients with CKD. The TFP, for all degrees of renal impairment, did not recommend the AHS risk management strategy of Hande et al (56), in which a non-evidence-based algorithm for allopurinol maintenance dosing had been calibrated to renal impairment. However, the authors, without a specific TFP vote, are concerned about the lack of long-term safety data for allopurinol dosing above 300 mg daily, particularly with significant renal impairment, which is associated with increased allopurinol toxicity (50,71).
a combination therapy (24). Significantly, for combination with an XOI drug, the TFP recommended not simply probenecid, but also as alternatives, other medications with less marked uricosuric effects (fenofibrate and losartan). However, the authors recognize that the published data are limited. The authors believe that ongoing and further studies will help understand how to optimize combinations of uricosuric agents with XOI therapy to decrease the risk of uricosuric-induced urolithiasis, while increasing the velocity of size reduction of body urate stores and tophi (67).

Based on results of placebo-controlled trials in study populations with particularly severe gout, the TFP recommended pegloticase as a third-line agent in distinct case scenarios of refractory disease with failure of appropriately dosed oral ULT, including in CTGA. Clinical trials directly comparing pegloticase to appropriate maximally dosed first- and second-line oral medication regimens of the agents recommended here would be of interest in severe gout, including CTGA.

Limitations of the ACR gout guidelines include the quality and quantity of evidence evaluated. For part 1 of the gout guidelines, the majority of evidence reviewed, upon which recommendations were based, was level C, with less than 20% level A evidence. For ULT clinical trials, study designs comparing allopurinol to febuxostat, where both agents are titrated to attempt to achieve the serum urate target, would be more informative than past trials (26,72,73). Another issue was variability in end points and outcome measures (e.g., gout attack frequency, serum urate, tophus size reduction, and health-related quality of life) in the clinical trials reviewed. Moreover, there are likely differences in “real-world” patients compared to those in most large industry-sponsored clinical trials. Clearly, further studies are needed in both the ULT and CTGA domains of gout.

The RAND/UCLA methodology utilized for this project did not allow us to address the important clinical practice and societal implications of treatment costs, which clearly impact patient and provider preferences for gout management options recommended by the TFP as effective. For example, the authors recognize the potential cost issues of the ULT recommendations presented, since, for example, febuxostat is substantially more expensive than allopurinol or probenecid. We note that a recent single technology appraisal with cost analysis done by an independent evidence review group of the National Institute for Health and Clinical Excellence concluded that febuxostat should be recommended for ULT in gout only in patients with contraindications or intolerance to allopurinol (25). Conversely, PCR-based HLA-B*5801 pharmacogenetics screening for allopurinol is a one-time test and relatively inexpensive, but raises new questions about the added costs to gout management, particularly for populations where the risk of AHS is low (53,57,58). Last, third-line ULT with pegloticase is an expensive biologic therapy approach for gout, and additional biologic agents for gout therapy are currently being developed and investigated. Cost-effectiveness trials and analyses are particularly timely for emerging therapies in gout.

The ACR guidelines for ULT in gout presented herein, and for treatment and antiinflammatory prophylaxis of gouty arthritis presented in a separate article (part 2 of the guidelines) (17), 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.

Therapies that were approved after the original literature review, or diet and lifestyle measures studied after the original literature review, are not included.

We thank Ms Amy Miller and Ms Regina Parker of the ACR for administrative support and guidance. Drs. Jennifer Grossman (UCLA), Michael Weinblatt (Brigham and Women’s Hospital, Harvard Medical School), Ken Saag (University of Alabama, Birmingham), and Ted Ganiats (University of California, San Diego) provided valuable guidance on the objectives and process. Rikke Ogawa (UCLA) provided greatly appreciated service as a medical research assistant.

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.


REFERENCES


34. Rees F, Jenkins W, Doherty M. Patients with gout adhere to curative treatment if informed appropriately: proof-of-concept observational study. Ann Rheum Dis 2012; E-pub


42. Choi HK, Curhan G. Soft drinks, fructose consumption, and


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Guidelines and recommendations developed and/or endorsed by the American College of Rheumatology (ACR) are intended to provide guidance for particular patterns of practice and not to dictate the care of a particular patient. The ACR considers adherence to these guidelines and recommendations to be voluntary, with the ultimate determination regarding their application to be made by the physician in light of each patient’s individual circumstances. Guidelines and recommendations are intended to promote beneficial or desirable outcomes but cannot guarantee any specific outcome. Guidelines and recommendations developed or endorsed by the ACR are subject to periodic revision as warranted by the evolution of medical knowledge, technology, and practice.

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Introduction
In response to a request for proposal from the American College of Rheumatology (ACR), our group was charged with developing nonpharmacologic and pharmacologic guidelines for treatments in gout that are safe and effective, i.e., with an acceptable risk/benefit ratio. These guidelines for the management and antiinflammatory prophylaxis of acute attacks of gouty arthritis complement our article on

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Significance & Innovations

- An acute gouty arthritis attack should be treated with pharmacologic therapy, initiated within 24 hours of onset.
- Established pharmacologic urate-lowering therapy should be continued, without interruption, during an acute attack of gout.
- Nonsteroidal antiinflammatory drugs (NSAIDs), corticosteroids, or oral colchicine are appropriate first-line options for treatment of acute gout, and certain combinations can be employed for severe or refractory attacks.
- Pharmacologic antiinflammatory prophylaxis is recommended for all gout patients when pharmacologic urate lowering is initiated, and should be continued if there is any clinical evidence of continuing gout disease activity and/or the serum urate target has not yet been achieved.
- Oral colchicine is an appropriate first-line gout attack prophylaxis therapy, including with appropriate dose adjustment in chronic kidney disease and for drug interactions, unless there is a lack of tolerance or medical contraindication.
- Low-dose NSAID therapy is an appropriate choice for first-line gout attack prophylaxis, unless there is a lack of tolerance or medical contraindication.

Guidelines to treat hyperuricemia in patients with evidence of gout (or gouty arthritis) (1).

Gout is the most common cause of inflammatory arthritis in adults in the US. Clinical manifestations in joints and bursa are superimposed on local tissue deposition of monosodium urate crystals. Acute gout characteristically presents as a self-limited attack of synovitis (also called “gout flare”). Acute gout attacks account for a major component of the reported decreased health-related quality of life in patients with gout (2,3). Acute gout attacks can be debilitating and are associated with decreased work productivity (4,5).

Urate-lowering therapy (ULT) is a cornerstone in the management of gout (1) and, when effective in lowering serum urate, is associated with a decreased risk of acute gouty attacks (6). However, during the initial phase of ULT, there is an early increase in acute gout attacks, which has been hypothesized due to remodeling of articular urate crystal deposits as a result of rapid and substantial lowering of ambient urate concentrations (7). Acute gout attacks attributable to the initiation of ULT may contribute to nonadherence in long-term gout treatment, as reported in

In order to systematically evaluate management of acute gouty arthritis, we generated multifaceted case scenarios to elucidate decision making based primarily on clinical and laboratory test–based data that can be obtained from a gout patient by both nonspecialist and specialist health care providers in an office practice setting. This effort was not intended to create a novel classification system of gout or new gout diagnostic criteria, since such endeavors are

Prior gout recommendations and guidelines, at the independent (i.e., non–pharmaceutical industry sponsored) national or multinational rheumatology society level, have
been published by the European League Against Rheumatism (EULAR) (9,10), the Dutch College of General Practitioners (11), and the British Society for Rheumatology (BSR) (12). The ACR requested new guidelines in view of the increasing prevalence of gout (13), the clinical complexity of management of gouty arthritis imposed by comorbidities common in patients with gout (14), and increasing numbers of treatment options via clinical development of agents (15–17). The ACR charged us to develop these guidelines to be useful for both rheumatologists and other health care providers on an international level. As such, this process and resultant recommendations involved a diverse and international panel of experts.

In this article, we concentrate on 2 of the 4 gout domains (1) that the ACR requested for evaluation of pharmacologic and nonpharmacologic management approaches: analgesic and antiinflammatory management of acute attacks of gouty arthritis and pharmacologic antiinflammatory prophylaxis of acute attacks of gouty arthritis. Part 1 of the guidelines focused on systematic nonpharmacologic measures (patient education, diet and lifestyle choices, identification and management of comorbidities) that impact hyperuricemia, and made recommendations on pharmacologic ULT in a range of case scenarios of patients with disease activity manifested by acute and chronic forms of gouty arthritis, including chronic tophaceous gouty arthropathy (1). Each individual and specific statement is designated as a “recommendation,” in order to reflect the nonprescriptive nature of decision making for the hypothetical clinical scenarios.

So that the voting panel could focus on gout treatment decisions, a number of key assumptions were made, as described in part 1 of the guidelines (1). Importantly, each proposed recommendation assumed that correct diagnoses of gout and acute gouty arthritis attacks had been made for the voting scenario in question. For treatment purposes, it was also assumed that treating clinicians were competent, and considered underlying medical comorbidities (including diabetes mellitus, gastrointestinal disease, hypertension, and hepatic, cardiac, and renal disease) and potential drug toxicities and drug–drug interactions when making both treatment choices and dosing decisions on chosen pharmacologic interventions. The RAND/UCLA method requires 2 groups of experts: a core expert panel (CEP) that provides input into case scenario development, and a task force panel (TFP) that votes on the case scenarios (1). A systematic review of pertinent literature was performed concurrently, and a scientific evidence report was generated. This evidence report was then given to the TFP, in conjunction with a variety of clinical scenarios and clinical decision-making questions.

Materials and methods

Utilizing the RAND/UCLA methodology (18), we conducted a systematic review, generated case scenarios, developed recommendations, and graded the evidence.

Design: RAND/UCLA Appropriateness Method overview. The RAND/UCLA method of group consensus was developed in the 1980s, incorporates both Delphi and nominal group methods (18), and has been successfully used to develop other guidelines commissioned by the ACR. The purpose of this methodology is to reach a consensus among experts, with an understanding that published literature may not be adequate to provide sufficient evidence for day-to-day clinical decision making. The RAND/UCLA method requires 2 groups of experts: a core expert panel (CEP) that provides input into case scenario development, and a task force panel (TFP) that votes on the case scenarios (1). A systematic review of pertinent literature was performed concurrently, and a scientific evidence report was generated. This evidence report was then given to the TFP, in conjunction with a variety of clinical scenarios and clinical decision-making questions.

The diverse TFP, totaling 11 people, consisted of rheumatologists in a community private practice (CK), a health maintenance organization practice (GL), and a Veterans Affairs practice (GK); a rheumatology physician–scientist inflammation researcher (BR); a rheumatologist with expertise in clinical pharmacology (DEF); a rheumatologist gout expert that is an Internal Medicine Residency Director (NLE); a rheumatologist gout expert that is a Chair of Internal Medicine (BM); 2 primary care internal medicine physicians (DJ, SAY); a nephrologist (VN); and a patient representative (SK) (1). There were 2 rounds of ratings, the first anonymous, with the members of the TFP instructed to rank each potential element of the guidelines on a risk/benefit Likert scale ranging from 1–9, followed by a face-to-face group discussion with revoting. A vote of 1–3 on the Likert scale was scored as inappropriate, where risks clearly outweigh the benefits; a vote of 4–6 was (“lack of consensus”), where the risk/benefit ratio is uncertain; and a vote of 7–9 was scored as , where benefits clearly outweigh the risks. Case scenarios were translated into recommendations, where the median voting scores were 7–9 on the Likert scale (“appropriate”), and if there was no significant disagreement, defined as no more than one-third of the TFP voting below the Likert scale level of 7 in the question. The final rating was done anonymously in a 2-day face-to-face meeting led by an experienced internal medicine physician moderator (NW).

Systematic review. PubMed and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched to find all articles on gout with the help of an experienced librarian. PubMed is a database of medical literature from the 1950s to the present. CENTRAL includes references from PubMed, Embase, and the Cochrane Review Groups’ specialized registers of controlled trials and hand search results. We used search terminology (hedge) based on the Cochrane Highly Sensitive Search Strategy for identifying
randomized trials. The hedge was expanded to include articles discussing research design, cohort, case-control, and cross-sectional studies. Limits added to the hedge include English language and the exclusion of “animal only” studies. The searches for all 4 domains were conducted simultaneously and therefore included terms for hyperuricemia and other gout-related issues. Conducted on September 25, 2010, the search retrieved 5,830 articles from PubMed and CENTRAL. The review was divided into 3 stages: titles, abstracts from manuscripts, and entire manuscripts. At each stage, each title, abstract, or manuscript was included or excluded using prespecified rules, as described (1). Of the 5,830 titles, 192 duplicate titles and 82 non-English titles were excluded, with an additional 3,729 titles excluded based on exclusion criteria, leaving 1,827 titles, of which another 1,699 were excluded in the abstract phase. A total of 128 manuscripts remained that were further categorized into pharmacologic and nonpharmacologic studies (1). Subsequently, we updated our systematic review by repeating the search with the same criteria to include any articles that were published between September 25, 2010 and March 31, 2011, and we hand searched recent meeting abstracts from the ACR and EULAR for any randomized controlled trials that were yet to be published. The supplemental search resulted in 4 additional manuscripts and 5 meeting abstracts on pharmacologic agents, some of which were subsequently published and then reevaluated for evidence grade. Finally, there were 41 manuscripts on nonpharmacologic modalities (such as diet, alcohol, exercise, etc.) that included both retrospective and prospective studies, but all were excluded, since none were randomized controlled studies on interventions in gout patients. There were 87 manuscripts on pharmacologic agents for the treatment of patients with gout. Of these, 47 were randomized controlled trials and included in the evidence report, whereas the remaining 40 uncontrolled trials were excluded. A total of 21 manuscripts on ULT were separately addressed (1).

For this article (part 2 of the guidelines), a total of 30 manuscripts and 5 meeting abstracts were assessed, with 26 manuscripts and 2 meeting abstracts on acute gout and 4 manuscripts and 3 meeting abstracts on prophylaxis included in the evidence report and evaluated by the TFP.

Case scenarios. Through an interactive, iterative process, the CEP developed unique case scenarios of acute gouty attacks with varied treatment options, and the type of attack by severity, duration, and extent of the attack. The objective was to represent a broad spectrum of attacks that a clinician might see in a busy practice. For the case scenarios, the severity of acute gout differed based on self-reported worst pain on a 0–10 visual analog scale (VAS) (19,20). Pain ≤4 was considered mild, 5–6 was considered moderate, and ≥7 was considered severe (19,20). Case scenarios also varied by duration of the acute gout attack; we divided this into early (<12 hours), well established (12–36 hours), and late (>36 hours). Case scenarios also varied in the number of active joints involved: 1 or a few small joints, 1 or 2 large joints (ankle, knee, wrist, elbow, hip, or shoulder), and polyarticular involvement (defined as either acute arthritis involving 3 separate large joints, or acute arthritis of 4 or more joints, with arthritis involving more than 1 “region” of joints). Joint regions were defined as: forefoot (metatarsal joints and toes), midfoot (tarsal joints), ankle/hindfoot, knee, hip, fingers, wrist, elbow, shoulder, or other (Figure 1). The management strategies presented were developed for case scenarios involving gouty arthritis, but the intent was that acute bursal inflammation due to gout (e.g., in the prepatellar or olecranon bursa) and small joint involvement would have comparable recommendations for overall management strategies.

Developing recommendations from votes by the TFP and grading the evidence. A priori recommendations were derived from only positive results (median Likert 7). In the text below, all recommendations derived from TFP votes are denoted by an accompanying evidence grade. In addition to TFP vote results, the panel provided some statements based on discussion (not votes). Such statements are specifically described as discussion items (rather than TFP-voted recommendations) in the Results. We also comment on specific circumstances where the TFP did not vote a particularly important clinical decision-making item as appropriate (i.e., the median of 6 or there was a wide dispersion of votes 7). Samples of voting scenarios and results are shown in Supplemental Figure 1 (available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658).

The level of evidence supporting each recommendation was ranked based on previous methods used by the American College of Cardiology (21) and applied to other recent ACR recommendations (22,23): level A grading was assigned to recommendations supported by more than 1 randomized clinical trial, or 1 or more meta-analyses; level B grading was assigned to the recommendations derived from a single randomized trial, or nonrandomized studies; and level C grading was assigned to consensus opinion of experts, case studies, or standard of care.

Managing perceived potential conflict of interest (COI). Potential COI was managed in a prospective and structured manner (1). All of the participants intellectually involved in the project, whether authors or not, were required to fully disclose their relationships with any of the companies with a material interest in gout, listed in Supplemental Appendix A (available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658). Disclosures were identified at the start of the project and updated every 6 months. A summary listing of all perceived potential COI is available in Supplemental Appendix A (available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658).

Based on the policies of the ACR, no more than 49% of the project participants were permitted to have COI at any given time, and a majority of the TFP was required to have no perceived potential COI. It was further required that the project principal investigator (JDF) remain without per-
ceived potential COI during the guideline development process, and for an additional 12 months afterward.

Results

General principles for treatment of the acute attack of gouty arthritis ("acute gout" management)

marizes the overall recommendations on treatment of an acute gouty arthritis attack. The TFP recommended that an acute gouty arthritis attack should be treated with pharmacologic therapy (evidence C), and that treatment should be preferentially initiated within 24 hours of onset of an acute gout attack (evidence C). The latter recommendation was based on consensus that early treatment leads to better patient-reported outcomes. The TFP also recommended continuing established pharmacologic ULT without interruption during an acute attack of gout (evidence C), i.e., do not stop ULT therapy during an acute attack. The TFP also recommended patient education, not simply on dietary and other triggers of acute gout attacks, but also providing the patients with instruction so that they can initiate treatment upon signs and symptoms of an acute gout attack, without the need to consult their health care practitioner for each attack (evidence B) (24). Moreover, fundamental patient education includes discussion that gout is caused by body excess of uric acid, and that only effective ULT is potentially “curative” (evidence B) (24).

Initial pharmacologic treatment of the acute attack of

The TFP recommended that the choice of pharmacologic agent should be based upon severity of pain and the number of joints involved (Figure 2). For attacks of mild/moderate gout severity (≤6 of 10 on a 0–10 pain VAS) particularly those involving 1 or a few small joints or 1 or 2 large joints, the TFP recommended that initiating monotherapy was appropriate, with recommended options being oral nonsteroidal antiinflammatory drugs (NSAIDs), systemic corticosteroids, or oral colchicine (evidence A for all therapeutic categories) (25–28) (Figure 2). The TFP also voted that combination therapy was an appropriate option to consider when the acute gout attack was characterized by severe pain, particularly in an acute polyarticular gout attack or an attack involving 1–2 large joints (evidence C) (Figure 2). The TFP did not rank one therapeutic class over another. Therefore, it is at the discretion of the prescribing physicians to choose the most appropriate monotherapy based on the patient’s preference, prior response to pharmacologic therapy for an acute gout attack, and associated comorbidities. Recommendations for appropriate combination therapy options are highlighted in Table 1 and discussed below. The TFP did not vote on case scenarios for specific renal or hepatic function impairment–adjusted dosing and individual contraindications or drug–drug interactions with pharmacologic therapies (29–31).
Figure 2. Overview of management of an acute gout attack. This algorithm summarizes the recommendations by the task force panel on the overall approach to management of an acute attack of gouty arthritis, with further details, as expanded in other figures and tables, referenced in the figure and discussed in the text. ULT = urate-lowering therapy; NSAID = nonsteroidal antiinflammatory drug; COX-2 = cyclooxygenase 2; GI = gastrointestinal; IL-1 = interleukin-1.
**Table 1. Task force panel (TFP) recommendations for combination therapy approach to acute gouty arthritis**

<table>
<thead>
<tr>
<th>Recommendation</th>
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<tr>
<td>Initial combination therapy is an appropriate option for an acute, severe gout attack, particularly with involvement of multiple large joints or polyarticular arthritis (evidence C).</td>
</tr>
<tr>
<td>Acceptable combination therapy approaches include: 1) colchicine and nonsteroidal antiinflammatory drugs (NSAIDs), 2) oral corticosteroids and colchicine, or 3) intraarticular steroids with all other modalities (evidence C).</td>
</tr>
<tr>
<td>For patients not responding adequately to initial pharmacologic monotherapy, adding a second appropriate agent is an acceptable option (evidence C)*</td>
</tr>
<tr>
<td>The TFP was not asked to vote on use of NSAIDs and systemic corticosteroids in combination, given core expert panel concerns about synergistic gastrointestinal tract toxicity.</td>
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* Assumes that the initial diagnosis of acute gout was correct, and that the lack of adequate response of acute gout was an appropriate first-line therapy option.

**NSAIDs.** For NSAIDs, the TFP recommended full dosing at either the Food and Drug Administration (FDA)– or European Medical Agency–approved antiinflammatory/analgesic doses used for the treatment of acute pain and/or treatment of acute gout (evidence A–C) (27,28,32–34) (Figure 3A). The FDA has approved naproxen (evidence A) (34,35), indomethacin (evidence A) (27,28,32,33), and sulindac (evidence B) (36) for the treatment of acute gout. However, analgesic and antiinflammatory doses of other NSAIDs may be as effective (evidence B and C). For cyclooxygenase 2 (COX-2) inhibitors, as an option in patients with gastrointestinal contraindications or intolerance to NSAIDs, published randomized controlled trials support the efficacy of etoricoxib (evidence A) and lumiracoxib (evidence B) (25,37,38), but these agents are not available in the US, and lumiracoxib has been withdrawn from use in several countries due to hepatotoxicity. A randomized controlled trial of a single comparison of celecoxib versus indomethacin (39) suggested effectiveness of a high-dose celecoxib regimen (800 mg once, followed by 400 mg on day 1, then 400 mg twice daily for a week) in acute gout. The TFP recommended this celecoxib regimen as an option for acute gout in carefully selected patients with contraindications or intolerance to NSAIDs (evidence B), keeping in mind that the risk/benefit ratio is not yet clear for celecoxib in acute gout.

The TFP did not reach a consensus to preferentially recommend any one specific NSAID as first-line treatment. The TFP did recommend continuing the initial NSAID inhibitor treatment regimen at the full dose (if appropriate) until the acute gouty attack completely resolved (evidence C). The option to taper the dose in patients with multiple comorbidities/hepatic or renal impairment was reinforced by the TFP, without specific TFP voting or more prescriptive guidance. Last, there was no TFP consensus on the use of intramuscular ketorolac or topical NSAIDs for the treatment of acute gout.

**Colchicine.** The TFP recommended oral colchicine as one of the appropriate primary modality options to treat acute gout, but only for gout attacks where the onset was no greater than 36 hours prior to treatment initiation (evidence C) (Figure 3B). The TFP recommended that acute gout can be treated with a loading dose of 1.2 mg of colchicine followed by 0.6 mg 1 hour later (evidence B) (10), and this regimen can then be followed by gout attack prophylaxis dosing of 0.6 mg once or twice daily (unless dose adjustment is required) 12 hours later, until the gout attack resolves (evidence C) (26). For countries where 1.0 mg or 0.5 mg rather than 0.6 mg tablets of colchicine are available, the TFP recommended, as appropriate, 1.0 mg colchicine as the loading dose, followed by 0.5 mg 1 hour later, and then followed, as needed, after 12 hours, by continued colchicine (up to 0.5 mg 3 times daily) until the acute attack resolves (evidence C). In doing so, the TFP rationale was informed by pharmacokinetics of the low-dose colchicine regimen, where the exposure to the drug in plasma becomes markedly reduced ~12 hours after administration in healthy volunteers (26). The TFP also evaluated prior EULAR recommendations on a colchicine dosing regimen for acute gout (0.5 mg 3 times daily) and the BSR-recommended maximum dosage for acute gout of

The algorithm in Figure 3B outlines recommendations for colchicine based on FDA labeling and TFP deliberations and votes, including specific recommendations for patients already receiving colchicine acute gout attack prophylaxis. For more specific prescriptive guidance, practitioners should consult the FDA-approved drug labeling, including recommended dosing reduction in moderate to severe chronic kidney disease (CKD) (40,41), and colchicine dose reduction (or avoidance of colchicine use) with drug interactions with moderate to high potency inhibitors of cytochrome P450 3A4 and of P-glycoprotein; major colchicine drug interactions include those with clarithromycin, erythromycin, cyclosporine, and disulfiram (30,31). Last, the TFP did not vote on use of intravenous colchicine, since the formulation is no longer available in the US, due to misuse and associated severe toxicity.

**Systemic and intraarticular corticosteroids and adrenocorticotropic hormone (ACTH).** When selecting corticosteroids as the initial therapy, the TFP recommended to first consider the number of joints with active arthritis. For involvement of 1 or 2 joints, the TFP recommended the use of oral corticosteroids (evidence B); the TFP additionally recommended the option of intraarticular corticosteroids for acute gout of 1 or 2 large joints (evidence B) (42) (Figure 3C). For intraarticular corticosteroid therapy in acute gouty arthritis, it was recommended that dosing be based on the size of the involved joint(s), and that this modality could be used in combination (Table 1) with oral corticosteroids, NSAIDs, or colchicine (evidence B) (42). Specific doses for intraarticular corticosteroid therapy in specific joints were not considered during TFP voting.

Where intraarticular joint injection is impractical (e.g., polyarticular joint involvement, patient preference, or injection of the involved joint site is not in the scope of the provider’s usual practice), the TFP recommended oral cor-
ticosteroids, prednisone, or prednisolone at a starting dosage of at least 0.5 mg/kg per day for 5–10 days, followed by discontinuation (evidence A) (28,43), or alternately, 2–5 days at the full dose, followed by tapering for 7–10 days, and then discontinuation (evidence C). Acknowledging current prevalence of usage, the TFP recommended, as an
appropriate option according to provider and patient preference, the use of an oral methylprednisolone dose pack for initial treatment of an acute attack of gout (evidence C).

The TFP also recommended, as appropriate in each case scenario, an alternative regimen of intramuscular single-dose (60 mg) triamcinolone acetonide, followed by oral prednisone or prednisolone (evidence C). However, there was no consensus by the TFP on the use of intramuscular triamcinolone acetonide as monotherapy. Last, the TFP vote also did not reach a consensus on use of ACTH (evidence A) for acute gout in patients able to take medications orally, but did consider ACTH in separate voting, as described below, for patients unable to take oral anti-inflammatory medications.

Initial combination therapy for acute gout. For patients with severe acute gout attack (≥7 of 10 on a 0–10 pain VAS) and patients with an acute polyarthritis or involvement of more than 1 large joint, the TFP recommended, as an appropriate option, the initial simultaneous use of full doses (or, where appropriate, a full dose of 1 agent and prophylaxis dosing of the other) of 2 of the pharmacologic modalities recommended above. Specifically, the TFP recommended the option to use combinations of colchicine and NSAIDs, oral corticosteroids and colchicine, or intra-articular steroids with any of the other modalities (evidence C). The TFP was not asked by the CEP to vote on use of NSAIDs and systemic corticosteroids in combination, given CEP concerns about synergistic gastrointestinal tract toxicity.

Inadequate response of an acute gout attack to initial therapy. There is a lack of a uniform definition of an inadequate response to the initial pharmacologic therapy for an acute attack of gouty arthritis (2,26,44). Clinical trials in acute gout have defined variable primary end points for therapeutic response, such as percent improvement in pain on a Likert scale or VAS. To define inadequate response for scenarios in this section, the CEP asked the TFP to vote on various percent improvement definitions at time points such as 24, 48, or 72 hours. The TFP voted that the following criteria would define an inadequate response of acute gout to pharmacologic therapy in case scenarios: either ≥20% improvement in pain score within 24 hours or ≥50% improvement in pain score ≥24 hours after initiating pharmacologic therapy.

For the scenario of a patient with an acute attack of gouty arthritis not responding adequately to initial monotherapy, the TFP advised, without a specific vote, that alternative diagnoses to gout should be considered (Figure 2 and Table 1). For patients not responding to initial therapy, the TFP also recommended switching to another monotherapy recommended above (evidence C) or adding a second recommended agent (evidence C). Use of a biologic interleukin-1 (IL-1) inhibitor (anakinra 100 mg subcutaneously daily for 3 consecutive days) would be considered for patients unable to take oral anti-inflammatory medications. If the patient fails to respond to the second agent, the TFP recommended using ACTH (evidence A) as described above for patients unable to take oral medications.

Figure 4. Acute gouty arthritis attack management in the nothing by mouth (NPO) patient. The figure schematizes options for management of acute gout in the patient unable to take oral antiinflammatory medications, and specific recommendations by the task force panel on decision making in this setting. ACTH intramuscular; NSAID = nonsteroidal antiinflammatory drug.
days; evidence B) (44,45) or canakinumab 150 mg subcutaneously (46,47) as an option for severe attacks of acute gouty arthritis refractory to other agents was graded as evidence A in the systematic review. Given a lack of randomized studies for anakinra (44,45) and the unclear risk/benefit ratio and lack of FDA approval for canakinumab (46,47) at the time this was written, the authors, independent of TFP discussion, assessed the role of IL-1 inhibitor therapy in acute gout as uncertain.

Case scenarios for the nothing by mouth (NPO) patient. Acute gout attacks are common in the in-hospital setting, where patients may be NPO due to surgical and medical conditions. In such a scenario, the TFP recommended intraarticular injection of corticosteroids for involvement of 1 or 2 joints (with the dose depending on the size of the joint; evidence B) (42) (Figure 4). The TFP also recommended, as appropriate options, intravenous or intramuscular methylprednisolone at an initial dose at 0.5–2.0 mg/kg (evidence B) (48).

The TFP also recommended, as an appropriate alternative for the NPO patient, subcutaneous synthetic ACTH at an initial dose of 25–40 IU (evidence A) (49), with repeat doses as clinically indicated (for either ACTH or intravenous steroid regimens). There was no voting by the TFP on specific followup ACTH or an intravenous steroid dosing regimen, given a lack of evidence. In the scenario of the NPO patient with acute gout, there was no consensus on the use of intramuscular ketorolac or intramuscular triamcinolone acetonide monotherapy. Biologic IL-1 inhibition therapy remains an FDA-unapproved modality for NPO patients, without specific past evaluation in this population.

Critical drug therapy adverse event considerations in acute gout. It was not possible to evaluate every permutation of gout treatment and comorbid disease, given the constraints of the project. The treating clinician will need to carefully weigh the complexities of each unique patient. TFP discussions emphasized that potential drug toxicities due to comorbidities and drug–drug interactions are considerable in treatment of acute gout (30,31). Some examples include underlying moderate and severe CKD (NSAIDs, COX-2 inhibitors, colchicine), congestive heart failure (NSAIDs, COX-2 inhibitors), peptic ulcer disease (NSAIDs, COX-2 inhibitors, corticosteroids), anticoagulation or antiplatelet aggregation therapy (NSAIDs), diabetes mellitus (corticosteroids), ongoing infection or high risk of infection (corticosteroids), and hepatic disease (NSAIDs, COX-2 inhibitors, colchicine) (30,31).

Complementary therapies for acute gout attack. The TFP recommended topical ice application to be an appropriate adjunctive measure to 1 or more pharmacologic therapies for acute gouty arthritis (evidence B) (50). The TFP voted, as inappropriate, the use of a variety of oral complementary agents for the treatment of an acute attack (cherry juice or extract, salicylate-rich willow bark extract, ginger, flaxseed, charcoal, strawberries, black currant, burdock, sour cream, olive oil, horsetail, pears, or celery root).

Recommendations for pharmacologic antiinflammatory prophylaxis of attacks of acute gout

The TFP recommended pharmacologic antiinflammatory prophylaxis for all case scenarios of gout where ULT was initiated, given high gout attack rate frequencies in early ULT (evidence A) (51–54) (Figure 5). For gout attack prophylaxis, the TFP recommended, as a first-line option, use of oral colchicine (evidence A) (54,55). The TFP also recommended, as a first-line option (with a lower evidence grade than for colchicine), the use of low-dose NSAIDs (such as naproxen 250 mg orally twice a day), with proton-pump inhibitor therapy or other effective suppression therapy for peptic ulcer disease and its complications, where indicated (evidence C) (54).

In their evaluation of colchicine evidence in gout attack prophylaxis, the TFP specifically recommended low-dose colchicine (0.5 mg or 0.6 mg orally once or twice a day, with dosing further adjusted downward for moderate to severe renal function impairment and potential drug–drug interactions) (30) as appropriate for gout attack prophylaxis. The TFP did not vote on specific quantitative renal function impairment–adjusted dosing of oral colchicine. Since a pharmacokinetic analysis suggesting colchicine dose should be decreased by 50% below a creatinine clearance of 50 ml/minute is unpublished in peer-review form (41), specific quantitative colchicine dose adjustment in CKD is the decision of the treating clinician.

The TFP, in discussion without a specific vote, recognized the evidence that colchicine and low-dose NSAID prophylaxis fail to prevent all gout attacks in patient populations after initiation of ULT (51–54). As an alternative gout attack prophylaxis strategy in patients with intolerance or contraindication or refractoriness to both colchicine and NSAIDs, the TFP recommended use of low-dose prednisone or prednisolone (defined here as 10 mg/day) (evidence C). Nevertheless, concerns were raised in discussion among the TFP and by the other authors regarding particularly sparse evidence for efficacy of this low-dose strategy. Given the known risks of prolonged use of corticosteroids, the authors urge clinicians to be particularly attentive in reevaluating the risk/benefit ratio of continued corticosteroid prophylaxis as the risk of acute gout attack decreases with time in conjunction with effective ULT. The TFP voted the use of high daily doses (i.e., >10 mg daily) of prednisone or prednisolone for gout attack prophylaxis to be as inappropriate in most case scenarios, and there was a lack of TFP consensus for more severe forms of chronic tophaceous gouty arthropathy. Last, there was a lack of TFP consensus on the risk/benefit ratio for off-label use of biologic IL-1 inhibition (evidence A) (56,57) for antiinflammatory gout attack prophylaxis in patients who previously failed or had intolerance or contraindications to low doses of colchicine, NSAIDs, and prednisone or prednisolone for gout attack prophylaxis.

Duration of antiinflammatory prophylaxis of acute gout attacks. The TFP recommended to continue pharmacologic gout attack prophylaxis if there is any clinical evidence of continuing gout disease activity (such as 1 or
more tophi detected on physical examination, recent acute gout attacks, or chronic gouty arthritis), and/or the serum urate target has not yet been achieved (1). Specifically, the TFP voted to continue the prophylaxis for the greater of:

1) 6 months' duration (evidence A) (51,53,54), 2) 3 months after achieving the target serum urate level for the patient without tophi detected on physical examination (evidence B), or 3) 6 months after achieving the target serum urate

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**Figure 5.** Pharmacologic antiinflammatory prophylaxis of gout attacks and its relationship to pharmacologic urate-lowering therapy (ULT). The figure provides an algorithm for use of antiinflammatory prophylaxis agents to prevent acute gout attacks. The schematic highlights specific recommendations by the TFP on decision making on the initiation, options, and duration of prophylaxis relative to pharmacologic ULT therapy, relative to achievement of the treatment objectives of ULT. NSAIDs = nonsteroidal antiinflammatory drugs.
Discussion
Acute attacks of gout have a detrimental impact on the quality of life of the patient due to pain and dysfunction of affected joints, and acute gout can have a substantial economic and societal impact (58–60). Following a systematic review of the literature and use of a formal group assessment process, we provide the first ACR guidelines for the therapy and antiinflammatory prophylaxis of acute gout attacks.

The TFP recommended multiple modalities (NSAIDs, corticosteroids by different routes, and oral colchicine) as appropriate initial therapeutic options for acute gout attacks. The TFP was informed in part by recent direct comparison studies suggesting approximate equivalency of oral systemic corticosteroids with NSAIDs (28,43). Essentially, the TFP concluded, without a specific vote, that selection of treatment choice is that of the prescribing clinician, and to be based upon factors including patient preference, the patient’s previous response to pharmacologic therapies, associated comorbidities and, in the unique case of colchicine, the time since onset of the acute gout attack. The dosing adjustments and relative and absolute contraindications for NSAIDs and colchicine due to associated comorbidities (such as renal and hepatic impairment) and drug interactions were not addressed in these guidelines. There is published literature addressing these issues (30,31) such as quality indicators for safe use of NSAIDs (61–63), including ACR quality indicators for treatment of gout (64).

The TFP recommended a novel set of strict limitations on colchicine doses for acute gout, starting with no more than 1.8 mg over 1 hour in the first 12-hour period of treatment (evidence B) (26), a paradigm shift from widespread prior use of this drug in clinical practice (10,12), but in accordance with FDA guidance. Prior EULAR and BSR recommendations on colchicine dosing for acute gout (10,12) and colchicine low-dose regimen pharmacokinetics (26) informed the TFP recommendation of low-dose colchicine (at a maximum of 0.6 mg twice daily) as a continuation option for an acute gout attack, if started at least 12 hours following the initial low-dose regimen.

For patients with polyarticular joint involvement and severe presentations of gout in 1 or 2 large joints, the TFP recommended, as appropriate, certain first-line combination therapy approaches. Although there is a lack of published randomized controlled trial data to support these recommendations, a large survey of rheumatologists in the US has shown that combination therapy for acute gout is often employed (65).

With respect to antiinflammatory prophylaxis of acute gout attacks, low-dose colchicine or low-dose NSAIDs were recommended as acceptable first-line options by the TFP, with a higher evidence level for colchicine. The use of low-dose colchicine or an NSAID in gout attack prophylaxis is also recommended by EULAR (10). To date, in small clinical trials, low-dose daily oral colchicine was effective in preventing acute gout attacks (3,55), with supportive post hoc analyses in ULT trials (54). The efficacy of low-dose NSAIDs for gout attack prophylaxis also was described in the febuxostat clinical trial program (54); however, prophylaxis was not the primary focus of the trials. Importantly, recent clinical trials of ULT agents have shown substantial rates of acute gout attacks in the first 6 months after the initiation of ULT, even when prophylaxis with colchicine 0.6 mg daily or low-dose NSAID therapy is administered (51–54). It is noteworthy that the TFP recommended prednisone or prednisolone ≤10 mg daily as a second-line option for acute gout prophylaxis, with the caveat that there is a lack of published robust data for the use of low-dose oral prednisone for gout prophylaxis. More investigation is needed to improve management for this clinical problem. Assessment of modulation of cardiovascular event risks by colchicine prophylaxis or by NSAIDs (66) in patients with gout would be particularly relevant.

Limitations of the recommendations presented in this evidence, with approximately half based on level C evidence; this indicates the need for more studies in the aspects of gout management considered here. The process used here was limited by the current trial designs for assessment of acute gout therapies and prophylaxis of antiinflammatory pharmacologic agents in gout. For acute gout studies, most studies were on NSAIDs and involved an active comparator and noninferiority trial design. However, the majority of these studies failed to provide a noninferiority margin, which needs to be defined a priori to assess the validity of these trials. Although the majority of studies assessed pain as the primary outcome for the acute gout trials, there is a lack of a single uniform measure that precludes meta-analysis. Furthermore, there is a lack of consensus on what time period after initiation of therapy constitutes a primary response, since trials ranged from a few hours to 10 days. With the exception of recent analyses of biologic IL-1 inhibitors (56,57), there was a lack of robust clinical trials of gout attack prophylaxis using antiinflammatory pharmacologic agents. Also, the primary measure in these trials is the recurrence of self-reported acute gout attacks, an outcome that has not been validated using Outcome Measures in Rheumatology criteria (67). Efforts are underway to precisely define acute gout attack in gout clinical trials (68). Last, the RAND/UCLA methodology did not address important societal and patient preference issues on treatment costs and cost-effectiveness comparisons between medication choices for acute gout and pharmacologic prophylaxis of acute gout attacks. This is already a pressing question with respect to use of agents, including colchicine and COX-2 selective inhibitors, and would be expected to emerge as a larger issue if biologic IL-1 inhibitors, in late-stage clinical development after phase III studies at the time this was written, obtain regulatory approval for acute gout treatment and prophylaxis.

In summary, these guidelines, the first from the ACR for the management and antiinflammatory prophylaxis of acute attacks of gouty arthritis, have been developed to provide recommendations to clinicians treating patients with gout. The ACR plans to update these guidelines to capture future treatments or advances in the
management and prophylaxis of acute gout, and as the risk/benefit ratios of emerging therapies are further investigated.

Addendum. Therapies that were approved after the original literature review, or diet and lifestyle measures studied after the original literature review, are not included in these recommendations.

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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.

Study conception and design.

Acquisition of data.

Analysis and interpretation of data.

REFERENCES


48. Wortmann RL, MacDonald PA, Hunt B, Jackson RL. Effect of prophylaxis on gout flares after the initiation of urate-lowering therapy: analysis of data from three phase III trials.


