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

DINESH KHANNA,1 JOHN D. FITZGERALD,2 PUJA P. KHANNA,1 SANGMEE BAE,2 MANJIT K. SINGH,3 TUHINA NEOGI,4 MICHAEL H. PILLINGER,5 JOAN MERILL,6 SUSAN LEE,7 SHRADDHA PRakash,2 MARIAN KALDAS,2 MANEESH GOGIA,2 FERNANDO PEREZ-RUIZ,8 WILL TAYLOR,9 FRÉDÉRIC LIOTÉ,10 HYON CHOI,4 JASVINDER A. SINGH,11 NICOLA DALBETH,12 SANFORD KAPLAN,13 VANDANA NIYYAR,14 DANIELLE JONES,14 STEVEN A. YAROWS,15 BLAKE ROESSLER,1 GAIL KERR,16 CHARLES KING,17 GERALD LEVY,18 DANIEL E. FURST,2 N. LAWRENCE EDWARDS,19 BRIAN MANDELL,20 H. RALPH SCHUMACHER,21 MARK ROBBINS,22 NEIL WENGER,2 and ROBERT TERKELTAUB7

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.

Drs. Dinesh Khanna, FitzGerald, and Puja P. Khanna contributed equally to this work.

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Address correspondence to Robert Terkeltaub, MD, VA Healthcare System/University of California, San Diego, 111K, 3350 La Jolla Village Drive, San Diego, CA 92161. E-mail: rterkeltaub@ucsd.edu.

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health-related quality of life are now better appreciated in many gout patients, particularly those with multiple comorbidities 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 nonpharmacologic and pharmacologic recommendations for effective treatments in gout with an acceptable risk/benefit ratio. Our assignment was to focus on 4 specific domains in gout management. Two of these domains are addressed herein, i.e., urate-lowering therapy (ULT) and chronic gouty arthritis with tophaceous disease detected on physical examination (designated by the ACR with the terminology “chronic tophaceous gouty arthropathy” [CTGA] and specifically represented in the fundamental case scenarios 7–9 described herein). The remaining 2 domains (analgescic 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-

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**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 events.
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 is contraindicated.
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/(ISSN)2151-4658).
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, azathioprine, 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 payer 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; JDF, 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 basis ranging from 1–9 on a Likert scale using the Delphi process, followed by a face-to-face group discussion and then revoting of the same scenarios. 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 studies, or standard of care.

**Systematic review.** PubMed and the Cochrane Central Register of Controlled Trials from the 1950s to the present were searched to find articles on gout with the help of an experienced librarian. We used a search strategy based on the Cochrane Highly Sensitive Search Strategy for identifying randomized trials. The search was expanded to include articles discussing research designs such as cohort, case–control, and cross-sectional studies. Limits included English language and the exclusion of “animal only” studies. The exact terms, process, and results of the search are summarized in Supplemental Figure 4 (available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658).

**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-
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 (probencid and off-label use as uricosuric therapy) of fenofibrate and losartan, but did not include sulfipyrazone or benz bromarone. 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 2. 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-
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; CKD = chronic kidney disease; CrCl = creatinine clearance.
The TFP provided guidance for referral to a specialist, with caution to avoid appearing self-serving. Although limited by the absence of outcomes data on potential benefits of referral, the TFP recommended that gout case scenarios including any of the following should be among those where referral to a specialist is considered (evidence C for all): 1) unclear etiology of hyperuricemia; 2) refractory signs or symptoms of gout; 3) difficulty in reaching the target urate level, particularly with renal impairment and a trial of XOI treatment; and 4) multiple and/or serious adverse events from pharmacologic ULT.

**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 vote suggested the particular benefits of thiazide diuretics for blood pressure control and outcomes in many patients with hypertension.

**Table 2. Specific recommendation of a comorbidity checklist for gout patients**

<table>
<thead>
<tr>
<th>Category</th>
<th>Evidence Grade</th>
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<tbody>
<tr>
<td>Appropriate to consider in the clinical evaluation, and if clinically indicated, to evaluate (evidence C for all)*</td>
<td>Level A = supported by multiple (i.e., &gt;1) randomized clinical trials or meta-analyses; level B = derived from a single randomized trial or nonrandomized studies; level C = consensus opinion of experts, case studies, or standard of care.</td>
</tr>
<tr>
<td>Obesity, dietary factors</td>
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<tr>
<td>Excessive alcohol intake</td>
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<tr>
<td>Metabolic syndrome, type 2 diabetes mellitus</td>
<td></td>
</tr>
<tr>
<td>Hypertension†</td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia, modifiable risk factors for coronary artery disease or stroke</td>
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</tr>
<tr>
<td>Serum urate–elevating medications†</td>
<td></td>
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<tr>
<td>History of urolithiasis</td>
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<tr>
<td>Chronic kidney, glomerular, or interstitial renal disease</td>
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<tr>
<td>(e.g., analgesic nephropathy, polycystic kidney disease)</td>
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<tr>
<td>In selected cases, potential genetic or acquired cause of uric acid overproduction (e.g., inborn error of purine metabolism or psoriasis, myeloproliferative, or lymphoproliferative disease, respectively)</td>
<td></td>
</tr>
<tr>
<td>Lead intoxication</td>
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</table>

* Evidence grades for recommendations: level A = supported by multiple (i.e., >1) randomized clinical trials or meta-analyses; level B = derived from a single randomized trial or nonrandomized studies; level C = consensus opinion of experts, case studies, or standard of care.  
† The task force panel, without a specific vote, recognized the particular benefits of thiazide diuretics for blood pressure control and outcomes in many patients with 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 risk factors associated with dietary vegetable intake (43,45). However, there was no specific TFP vote on the question of avoidance of excess purine intake 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 nonpharmacologic ULT measures in gout.** The TFP recommended certain diet and lifestyle measures for the majority of patients with gout (evidence B and C for individual measures) (Figure 4). 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.

**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.
Specific Recommendations:
GENERAL HEALTH, DIET, AND LIFESTYLE MEASURES FOR GOUT PATIENTS#

<table>
<thead>
<tr>
<th>Avoid</th>
<th>Limit</th>
<th>Encourage</th>
</tr>
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<tbody>
<tr>
<td>• Organ meats high in purine content (e.g., sweetbreads, liver, kidney)</td>
<td>• Serving Sizes of:</td>
<td>• Low-fat or non-fat dairy products</td>
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<tr>
<td></td>
<td>• Beef, Lamb, Pork</td>
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<tr>
<td></td>
<td>• Seafood with high purine content (e.g., sardines, shellfish)</td>
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<tr>
<td>• High fructose corn syrup-sweetened sodas, other beverages, or foods</td>
<td>• Servings of naturally sweet fruit juices</td>
<td>• Vegetables</td>
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<td></td>
<td>• Table sugar, and sweetened beverages and desserts</td>
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<td></td>
<td>• Table salt, including in sauces and gravies</td>
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<tr>
<td>• Alcohol overuse (defined as more than 2 servings per day for a male and 1 serving per day for a female) in all gout patients</td>
<td>• Alcohol (particularly beer, but also wine and spirits) in all gout patients</td>
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<tr>
<td>• Any alcohol use in gout during periods of frequent gout attacks, or advanced gout under poor control</td>
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*Without a specific task force panel (TFP) vote, adherence to diets for cardiac health and control of co-morbidities such as obesity, metabolic syndrome, diabetes, hyperlipidemia, and hypertension was stressed for gout patients, as appropriate.
* The TFP recommendation to “encourage” intake was not intended to advocate excesses in consumption of specific dietary items. There was a lack of TFP voting consensus on: Berries and Berry Products, Ascorbic acid (in Supplements or Foods), Nuts, Legumes. The TFP did not specifically vote on the question of limits on consumption of nutrient-rich vegetables and legumes.

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 dosages, 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 effec-
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 C). The TFP weighed this measure as particularly useful to monitor adherence, given that poor adherence to ULT is a common problem in gout patients (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. TFP recommendations for use of allopurinol in gout are summarized in Table 3. Importantly, 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 partly 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 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 <6 mg/dl (26,46) or <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). 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 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>
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<td>SINGLE AGENT XOI titrated to maximum appropriate dose (Alternative if XOI contra-indicated or not tolerated: Probenecid)</td>
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<td>Add URICOSURIC* to XOI with both agents titrated to maximum appropriate dose</td>
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Case Scenarios 1-3: Progressively mild, moderate, and severe frequency of intermittent acute gouty symptoms (without tophi on physical exam) are evaluated for case scenarios numbered 1, 2, and 3, respectively. Case Scenarios 4-6: Progressively mild, moderate, and severe frequency of intermittent acute gouty symptoms (with one or more tophi detected on physical exam) are evaluated for case scenarios numbered 4, 5, and 6, respectively. Case Scenarios 7-9: Progressive severity of Chronic Tophaceous Gouty Arthropathy (CTGA), as anatomically mild, moderate, and severe chronic tophaceous arthritis, are evaluated in case scenarios numbered 7, 8, and 9, respectively.

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.

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.** Under conditions where uricosuric monotherapy was employed as a primary ULT modality (Table 3), probenecid was recommended by the TFP as the first choice among uricosuric drugs currently available in the US (evidence B). The TFP recommended that a history of urolithiasis contraindicates first-line use of a potent uricosuric agent for ULT (evidence C), given that probenecid (and benzbromarone, which is unavailable in the US) was associated with an ~9–11% risk of urolithiasis (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 alkalization (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 nonnontophaceous 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 detectable (i.e., absent in ~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 XOIs agent was not tolerated or did not achieve the serum urate target, substitution of another XOIs was an appropriate first-line option (evidence C).

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 XOIs 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 first work 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. Probencicid was recommended as an alternative first-line therapy if at least 1 XOI drug was contraindicated or not tolerated, but probencicid 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 disease control.

Dosing, efficacy, and safety of allopurinol were 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.

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The TFP recommended uricosuric therapy as a valuable component of comprehensive urate-lowering strategies. Specific novel TFP recommendations on appropriateness of use of combination XOIs and uricosuric ULTs as a second-line approach in refractory disease across the case scenarios studied here reinforce BSR recommendations on such
a combination therapy (24). Significantly, for combination
with an XOI drug, the TFP recommended not simply pro-
benecid, 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 stud-
ies will help understand how to optimize combinations of
uricosuric agents with XOI therapy to decrease the risk of
uricosuric-induced urolithiasis, while increasing the ve-
locity 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 recom-
mended pegloticase as a third-line agent in distinct case
scenarios of refractory disease with failure of appropri-
ately 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 qual-
ity 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 manage-
ment 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 allopuri-

The ACR guidelines for ULT in gout presented herein,
and for treatment and antinflammatory 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 cardio-
vascular disease outcomes. It is hoped that publication
of these guidelines, along with effective patient education
gout treatments and the objectives and safety issues of
management, will improve patient adherence, quality of
care, and outcomes in management of gout.

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

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Study conception and design. Dinesh Khanna, Fitzgerald, Puja P.
Khanna, Bae, Neogi, Pillinger, Merill, Lee, Prakash, Perez-Ruiz,
Choi, Jasvinder A. Singh, Dalbeth, Kaplan, Mandell, Schumacher,
Robbins, Wenger, Terkeltaub.

Acquisition of data. Dinesh Khanna, Fitzgerald, Puja P. Khanna,
Bae, Manjit K. Singh, Pillinger, Lee, Prakash, Gogia, Taylor, Choi,
Kaplan, Kerr, King, Edwards, Mandell, Wenger, Terkeltaub.

Analysis and interpretation of data. Dinesh Khanna, Fitzgerald,
Puja P. Khanna, Bae, Manjit K. Singh, Neogi, Merill, Lee, Prakash,
Kaldas, Li, Choi, Kaplan, Niyar, Jones, Yarows, Roessler, Kerr,
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