

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

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.

The American College of Rheumatology is an independent, professional, medical and scientific society which does not guarantee, warrant, or endorse any commercial product or service.

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

Supported by a research grant from the American College of Rheumatology and by the National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH (grant K24-AR-063120).

¹Dinesh Khanna, MD, MSc, Puja P. Khanna, MD, MPH, Blake Roessler, MD: University of Michigan, Ann Arbor; ²John D. Fitzgerald, MD, Sangmee Bae, MD, Shraddha Prakash, MD, Marian Kaldas, MD, Maneesh Gogia, MD, Daniel E. Furst, MD, Neil Wenger, MD: University of California, Los Angeles; ³Manjit K. Singh, MD: Rochester General Health System, Rochester, New York; ⁴Tuhina Neogi, MD, PhD, FRCPC, Hyon Choi, MD, DrPH: Boston University Medical Center, Boston, Massachusetts; ⁵Michael H. Pillinger, MD: VA Medical Center and New York University School of Medicine, New York; ⁶Joan Merrill, MD: Oklahoma Medical Research Foundation, Oklahoma City; ⁷Susan Lee, MD, Robert Terkeltaub, MD: VA Healthcare System and University of California, San Diego; ⁸Fernando Perez-Ruiz, MD, PhD: Hospital Universitario Cruces, Vizcaya, Spain; ⁹Will

Taylor, PhD, MBChB: University of Otago, Wellington, New Zealand; ¹⁰Frédéric Lioté, MD, PhD: Université Paris Diderot, Sorbonne Paris Cité, and Hôpital Lariboisière, Paris, France; ¹¹Jasvinder A. Singh, MBBS, MPH: VA Medical Center and University of Alabama, Birmingham; ¹²Nicola Dalbeth, MD, FRACP: University of Auckland, Auckland, New Zealand; ¹³Sanford Kaplan, DDS: Oral and Maxillofacial Surgery, Beverly Hills, California; ¹⁴Vandana Niyyar, MD, Danielle Jones, MD, FACP: Emory University, Atlanta, Georgia; ¹⁵Steven A. Yarows, MD, FACP, FASH: IHA University of Michigan Health System, Chelsea; ¹⁶Gail Kerr, MD, FRCP(Edin): Veterans Affairs Medical Center, Washington, DC; ¹⁷Charles King, MD: North Mississippi Medical Center, Tupelo; ¹⁸Gerald Levy, MD, MBA: Southern California Permanente Medical Group, Downey; ¹⁹N. Lawrence Edwards, MD: University of Florida, Gainesville; ²⁰Brian Mandell, MD, PhD: Cleveland Clinic, Cleveland, Ohio; ²¹H. Ralph Schumacher, MD: VA Medical Center and University of Pennsylvania, Philadelphia; ²²Mark Robbins, MD, MPH: Harvard Vanguard Medical Associates/Atrius Health, Somerville, Massachusetts.

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.

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. Lioté 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,

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.

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

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. Niyar 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 Leerink Swann, Medacorp, and Guidepoint.

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.

Submitted for publication January 9, 2012; accepted in revised form June 15, 2012.

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 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 (analgesic and antiinflammatory management of acute gouty arthritis and pharmacologic antiinflammatory prophylaxis of attacks of gouty arthritis) are addressed in part 2 of the guidelines as a separate article (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 aug-

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](http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658)).

mented 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-

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 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](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](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](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](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](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-

GOUT CASE SCENARIOS			
Symptoms	Tophus or Tophi detected on Physical Exam	Frequency	CASE SCENARIO NUMBER
Intermittent symptoms	NO	Infrequent Symptoms (≤ 1 attack/yr)	1
	NO	Frequent Symptoms (2-6 attacks/yr)	2
	NO	Very Frequent Symptoms (> 7 attacks/yr)	3
Intermittent symptoms	YES	Infrequent Symptoms (≤ 1 attack/yr)	4
	YES	Frequent Symptoms (2-6 attacks/yr)	5
	YES	Very Frequent Symptoms (> 7 attacks/yr)	6

A

Case scenarios for Chronic Tophaceous Gouty Arthropathy

Disease Severity	Characteristics	CASE SCENARIO NUMBER
Mild	<ul style="list-style-type: none"> •Simple chronic tophaceous gouty arthropathy •Affecting 1 joint •Stable disease 	7
Moderate	<ul style="list-style-type: none"> •Simple chronic tophaceous gouty arthropathy •Affecting 2-4 joints •Stable disease 	8
Severe	<ul style="list-style-type: none"> •Chronic tophaceous gouty arthropathy of >4 joints OR •≥ 1 unstable, complicated, severe articular tophus or tophi 	9

B

Figure 1. Fundamental case scenarios evaluated by the task force panel (TFP). The TFP evaluated a broad spectrum of severity of gout, with presenting clinical information comparable to that encountered in practice. Scenarios were formulated iteratively by the core expert panel, as described in the text, and were not intended to serve as disease classification criteria. All case scenarios assumed that the diagnosis of gout was correct, and that there was some evidence of gout disease activity. Three distinct “treatment groups” for these recommendations, each with 3 case scenarios designed to succinctly represent clinically-based decision making and totaling 9 in all, are shown. The treatment group with intermittent attacks of acute gouty arthritis of at least moderate to severe pain intensity (case scenarios 1–3; **A**). Gout associated with clinically apparent high body urate burden was evaluated in case scenarios where there were ≥ 1 tophi on physical examination, and either **A**, intermittently symptomatic acute gouty arthritis (case scenarios 4–6), or **B**, chronic joint symptoms due to synovitis attributable to gout or articular tophus or tophi in case scenarios 7–9 (the domain termed chronic tophaceous gouty arthropathy [CTGA]). Severity of case scenarios in the CTGA domain was distinguished by extent and characteristics of the tophi and chronic arthropathy, with variable inflammatory and deforming features detected on physical examination (see Figure 2).

ication regimen. Conversely, the severe disease activity level was intended to represent patients with disease activity greater than or equal to that of the “average” subject studied in a clinical trial. The case scenarios were not intended to serve as classification criteria. To allow the TFP to focus on management decisions, each case scenario had the assumption that the diagnosis of gout was correct. In addition, it was assumed that there was some clinical evidence of gout disease activity. This included intermittent symptoms of variable frequency, specifically pre-

sented to the TFP as episodes of acute gouty arthritis of at least moderate to severe pain intensity (17). Other clinical evidence of gout disease activity, presented to the TFP in specific case scenarios, was tophi detected by physical examination, or alternatively, chronic symptomatic arthritis (i.e., “chronic arthropathy” or “synovitis”) due to gout, with or without confirmed joint damage (e.g., deformity, erosion due to gout on an imaging study) (Figure 2). Hyperuricemia was defined here as a serum urate level >6.8 mg/dl (2). We determined all aspects of case scenario definitions by a structured iterative process, using regular e-mail and teleconferences at least once per month. Multiple revisions to the proposed parameters were carried out, until accepted by the CEP domain leaders.

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 sulfapyrazone 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](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](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-

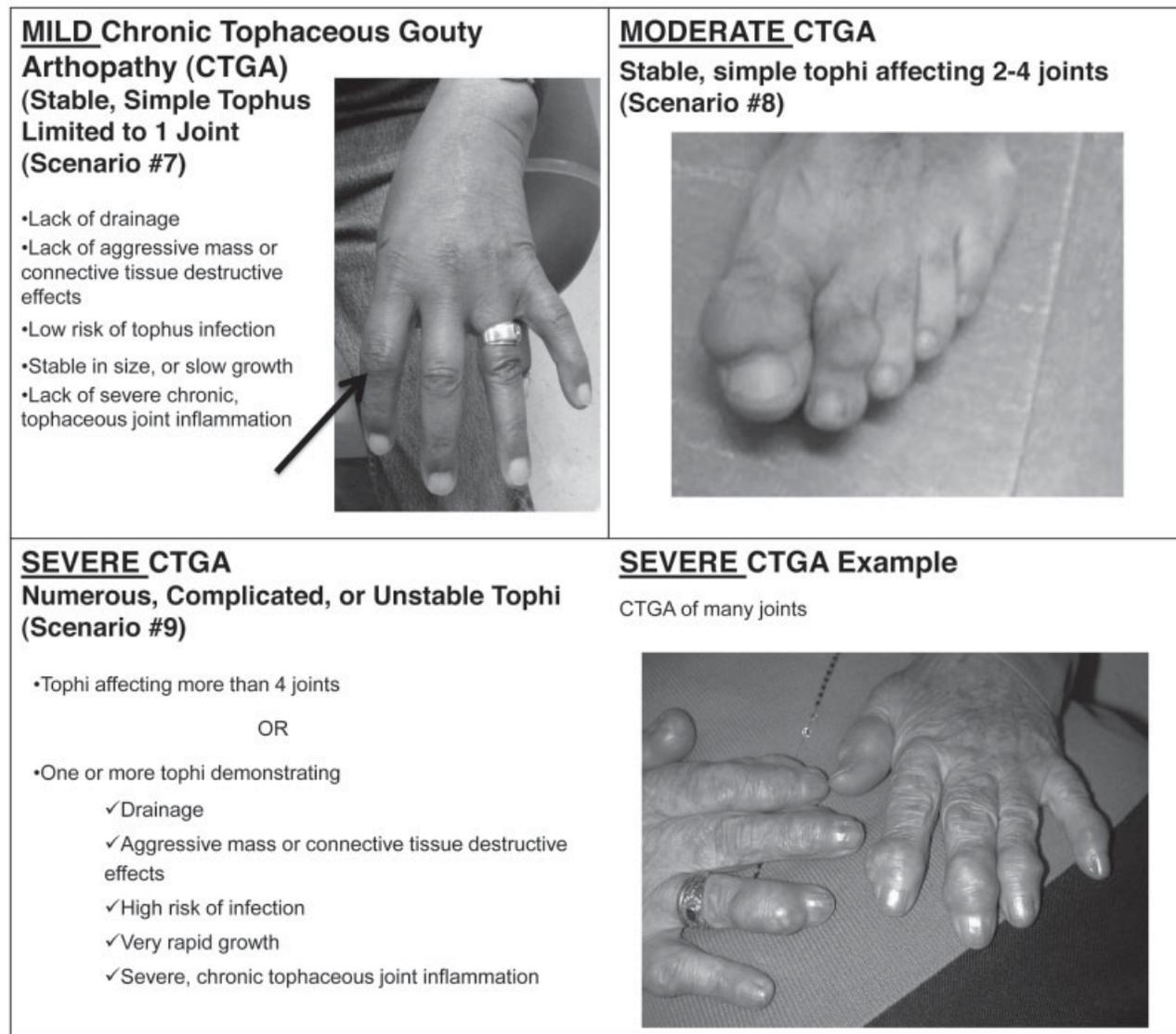
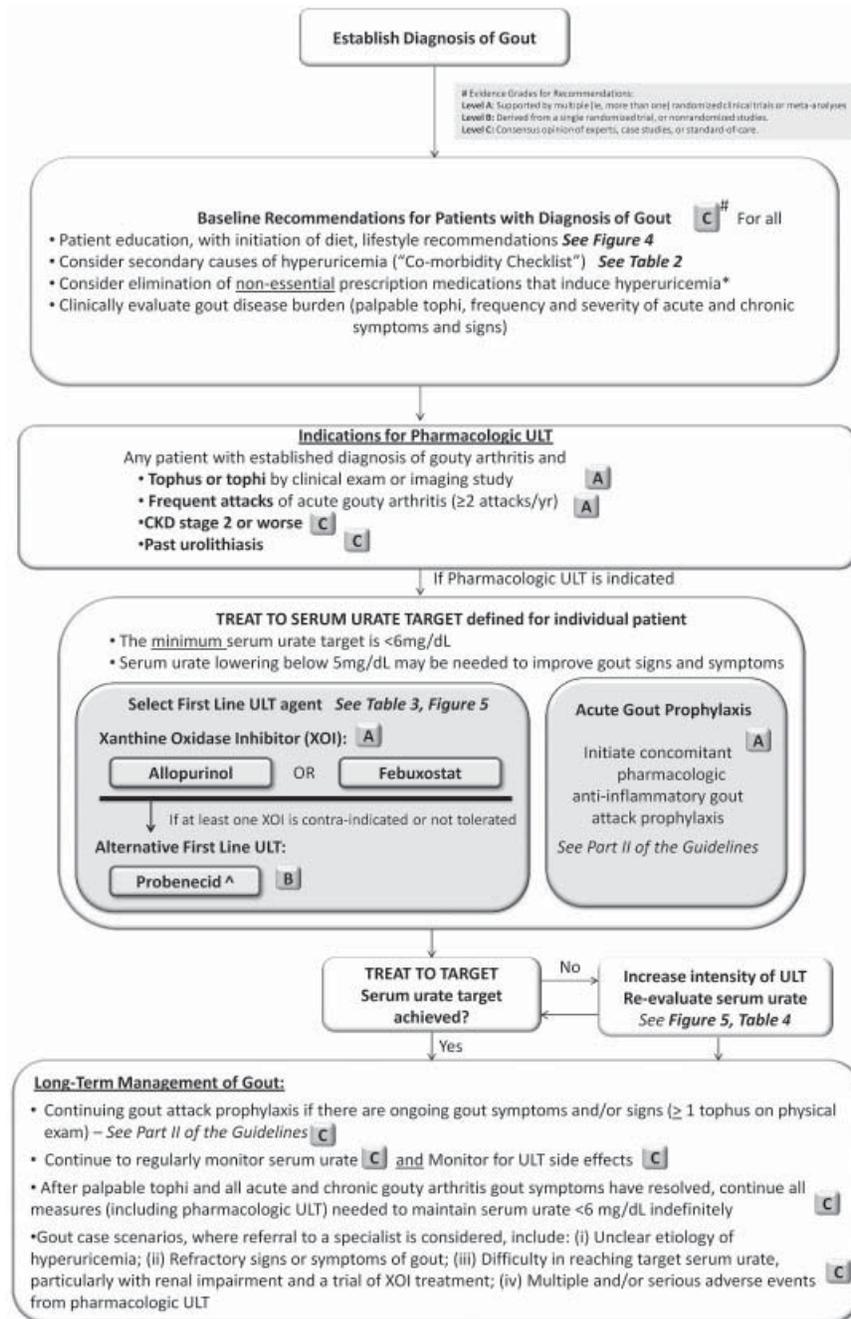


Figure 2. Detailed pictorial representations of chronic arthropathy in chronic tophaceous gouty arthropathy (CTGA) case scenarios presented to the task force panel (TFP). A core element of our approach was to present the TFP and the readership with specifically detailed summaries of the CTGA case scenarios (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.

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 discontin-

uation 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-



Examples of serum urate-elevating drugs that might be non-essential in a given patient, and potentially replaced by alternative agents that do not elevate serum urate:

- Niacin for management of hyperlipidemia
- Thiazide and loop diuretics for hypertension. However, in discussion, and without a specific vote, the TFP recognized the value of thiazide treatment in many patients with hypertension, and cautioned against imprudent cessation of thiazide treatment to lessen hyperuricemia at the cost of worsened control of blood pressure in difficult to control hypertension.
- Calcineurin inhibition with cyclosporine or tacrolimus, if it is not essential for immune suppression
- Probenecid is not recommended as a first line or alternative first line ULT agent if the CrCl is <50 (Evidence C)

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.

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

<p>Appropriate to consider in the clinical evaluation, and if clinically indicated, to evaluate (evidence C for all)*</p> <p>Obesity, dietary factors</p> <p>Excessive alcohol intake</p> <p>Metabolic syndrome, type 2 diabetes mellitus</p> <p>Hypertension†</p> <p>Hyperlipidemia, modifiable risk factors for coronary artery disease or stroke</p> <p>Serum urate-elevating medications†</p> <p>History of urolithiasis</p> <p>Chronic kidney, glomerular, or interstitial renal disease (e.g., analgesic nephropathy, polycystic kidney disease)</p> <p>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)</p> <p>Lead intoxication</p>
--

* 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.

duction (by urine uric acid evaluation) in patient subsets with gout clinical disease onset before age 25 years (evidence C) or a history of urolithiasis (evidence C).

The TFP provided guidance for referral to a specialist, with caution to avoid appearing self-serving. Although limited by the absence of outcomes data on potential benefits of referral, 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 serum urate level, particularly with renal impairment and a trial of XO1 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 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 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.

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 urolithiasis 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 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#:

Evidence Grades for Recommendations:
Level A: Supported by multiple (ie, more than one) 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.

- **Weight loss for obese patients, to achieve BMI that promotes general health**
- **Healthy overall diet [^]**
- **Exercise (Achieve physical fitness)**
- **Smoking cessation**
- **Stay well hydrated**

Avoid	Limit	Encourage ^{>}
<ul style="list-style-type: none"> • Organ meats high in purine content (eg, sweetbreads, liver, kidney) B 	<p>Serving Sizes of:</p> <ul style="list-style-type: none"> • Beef, Lamb, Pork • Seafood with high purine content (eg, sardines, shellfish) B 	<ul style="list-style-type: none"> • Low-fat or non-fat dairy products B
<ul style="list-style-type: none"> • High fructose corn syrup-sweetened sodas, other beverages, or foods C 	<ul style="list-style-type: none"> • Servings of naturally sweet fruit juices • Table sugar, and sweetened beverages and desserts • Table salt, including in sauces and gravies C 	<ul style="list-style-type: none"> • Vegetables C
<ul style="list-style-type: none"> • 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 B • Any alcohol use in gout during periods of frequent gout attacks, or advanced gout under poor control C 	<ul style="list-style-type: none"> • Alcohol (particularly beer, but also wine and spirits) in all gout patients B 	

[^]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.

The TFP recommended gout with CKD stage 2–5 or end-stage renal disease as an appropriate indication, by itself, for pharmacologic ULT (evidence C) in patients with prior gout attacks and current hyperuricemia. In pharmacologic ULT, certain treatment choices (e.g., probenecid) and drug dosing decisions (e.g., allopurinol) are impacted by the creatinine clearance. The TFP, without a direct vote, discussed and recognized the clinical value of accurate measurement of creatinine clearance, not simply the serum creatinine, in ascertaining the degree of renal impairment. However, the scope of the project did allow for detailed prescriptive recommendations regarding specific ULT drug doses, usage of individual agents in the presence of a given degree of either renal impairment, or other comorbidities such as hepatic impairment.

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

The TFP recommended 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 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 <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

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

<p>Allopurinol</p> <p>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)</p> <p>Gradually titrate maintenance dose upward every 2–5 weeks to appropriate maximum dose in order to treat to chosen SUA target (evidence C)</p> <p>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)</p> <p>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; evidence A)</p> <p>Uricosuric therapy</p> <p>Probenecid is the first choice among uricosuric agents for ULT monotherapy (evidence B)</p> <p>In gout patients with a creatinine clearance <50 ml/minute, probenecid is not recommended as first-line ULT monotherapy (evidence C)</p> <p>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 (evidence B)</p> <p>History of urolithiasis contraindicates first-line uricosuric urate-lowering monotherapy (evidence C)</p> <p>Urinary uric acid should be measured before initiation of uricosuric ULT (evidence C)</p> <p>Elevated urine uric acid indicative of uric acid overproduction contraindicates uricosuric ULT (evidence C)</p> <p>Continue to monitor urinary uric acid during uricosuric ULT (evidence C)</p> <p>Consider urine alkalization (e.g., with potassium citrate) with monitoring of urine pH, in addition to increased fluid intake, as a risk management strategy for urolithiasis (evidence C)</p>
<p>* ULT = urate-lowering therapy; CKD = chronic kidney disease; SUA = serum uric acid.</p>

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).

PHARMACOLOGIC ULT ESCALATION: MEASURE	CASE SCENARIOS 1-9								
	← No tophi on exam →			← ≥ 1 Tophus on exam →					
	← Intermittent Symptoms →			← CTGA →					
	1	2	3	4	5	6	7	8	9
SINGLE AGENT XO _I titrated to maximum appropriate dose (Alternative if XO _I contra-indicated or not tolerated : Probenecid)	± [§]	+	+	+	+	+	+	+	+
↓ Serum urate target not achieved, continuing disease activity									
Add URICOSURIC* to XO _I with both agents titrated to maximum appropriate dose	± [§]	+	+	+	+	+	+	+	+
↓ Serum urate target not achieved, continuing disease activity									
PEGLOTICASE	-	-	+	-	± [¶]	+	+	+	+

Case Scenarios 1-3: Progressively mild, moderate, and severe frequency of intermittent acute gout 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 gout 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 XO_I 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 XO_I inhibitor therapy can include probenecid, or off-label use of losartan or fenofibrate.

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; XO_I = 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*

Attempt upward dose titration of 1 XO_I 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 XO_I (evidence C)†
 Effective therapeutic options include addition of a uricosuric agent (e.g., probenecid, fenofibrate, or losartan) to an XO_I 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; XO_I = 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 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 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 XOI agent was not tolerated or did not achieve the serum urate target, substitution of another XOI 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 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. Probenecid was recommended as an alternative first-line therapy if at least 1 XO1 drug was contraindicated or not tolerated, but probenecid monotherapy was not recommended as a first-line approach in those with a creatinine clearance less than 50 ml/minute. In discussion, TFP res-

ervations 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.

The TFP recommended uricosuric therapy as a valuable component of comprehensive urate-lowering strategies. Specific novel TFP recommendations on appropriateness of use of combination XO1 and uricosuric ULT 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 XO1 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 XO1 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.

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.

ACKNOWLEDGMENTS

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 librarian.

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.

Study conception and design. Dinesh Khanna, Fitzgerald, Puja P. Khanna, Bae, Neogi, Pillinger, Merrill, 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, Merrill, Lee, Prakash, Kaldas, Lioté, Choi, Kaplan, Niyyar, Jones, Yarows, Roessler, Kerr, King, Levy, Furst, Mandell, Schumacher, Robbins, Wenger, Terkeltaub.

REFERENCES

1. Neogi T. Clinical practice: gout. *N Engl J Med* 2011;364:443–52.
2. Terkeltaub R. Update on gout: new therapeutic strategies and options. *Nat Rev Rheumatol* 2010;6:30–8.
3. Dalbeth N, Aati O, Gao A, House M, Liu Q, Horne A, et al. Assessment of tophus size: a comparison between physical measurement methods and dual-energy computed tomography scanning. *J Clin Rheumatol* 2012;18:23–7.
4. Dalbeth N, Clark B, Gregory K, Gamble G, Sheehan T, Doyle A, et al. Mechanisms of bone erosion in gout: a quantitative analysis using plain radiography and computed tomography. *Ann Rheum Dis* 2009;68:1290–5.

5. Desai MA, Peterson JJ, Garner HW, Kransdorf MJ. Clinical utility of dual-energy CT for evaluation of tophaceous gout. *Radiographics* 2011;31:1365–75.
6. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007–2008. *Arthritis Rheum* 2011;63:3136–41.
7. Bhole V, de Vera M, Rahman MM, Krishnan E, Choi H. Epidemiology of gout in women: fifty-two-year followup of a prospective cohort. *Arthritis Rheum* 2010;62:1069–76.
8. Pillinger MH, Goldfarb DS, Keenan RT. Gout and its comorbidities. *Bull NYU Hosp Jt Dis* 2010;68:199–203.
9. Brook RA, Forsythe A, Smeeding JE, Lawrence EN. Chronic gout: epidemiology, disease progression, treatment and disease burden. *Curr Med Res Opin* 2010;26:2813–21.
10. Roddy E, Doherty M. Epidemiology of gout. *Arthritis Res Ther* 2010;12:223.
11. McAdams DeMarco MA, Maynard JW, Baer AN, Gelber AC, Young JH, Alonso A, et al. Diuretic use, increased serum urate levels, and risk of incident gout in a population-based study of adults with hypertension: the Atherosclerosis Risk in Communities cohort study. *Arthritis Rheum* 2012;64:121–9.
12. Choi HK. A prescription for lifestyle change in patients with hyperuricemia and gout. *Curr Opin Rheumatol* 2010;22:165–72.
13. Becker MA, Schumacher HR, Benjamin KL, Gorevic P, Greenwald M, Fessel J, et al. Quality of life and disability in patients with treatment-failure gout. *J Rheumatol* 2009;36:1041–8.
14. Khanna PP, Khanna D. Health-related quality of life and outcome measures in gout. In: Terkeltaub R, editor. *Gout and other crystal arthropathies*. 1st ed. Philadelphia: Elsevier; 2011. p. 217–25.
15. Singh JA, Hodges JS, Toscano JP, Asch SM. Quality of care for gout in the US needs improvement. *Arthritis Rheum* 2007;57:822–9.
16. Harrold LR, Andrade SE, Briesacher BA, Raebel MA, Fouayzi H, Yood RA, et al. Adherence with urate-lowering therapies for the treatment of gout. *Arthritis Res Ther* 2009;11:R46.
17. Khanna D, Khanna PP, FitzGerald JD, Singh MK, Bae S, Neogi T, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 2: therapy and antiinflammatory prophylaxis of acute gouty arthritis. *Arthritis Care Res (Hoboken)* 2012;64:1447–61.
18. Neogi T, George J, Rekhraj S, Struthers AD, Choi H, Terkeltaub RA. Are either or both hyperuricemia and xanthine oxidase directly toxic to the vasculature? A critical appraisal [review]. *Arthritis Rheum* 2012;64:327–38.
19. Brook R. The RAND/UCLA Appropriateness Method. In: McCormick KA, Moore SR, Siegel RA, editors. *Methodology perspectives: AHCPR no. 95-009*. Rockville (MD): Public Health Service; 1994. p. 59–70.
20. Zhang W, Doherty M, Pascual E, Bardin T, Barskova V, Conaghan P, et al. EULAR evidence based recommendations for gout. Part I: diagnosis. Report of a task force of the Standing Committee for International Clinical Studies Including Therapeutics (ESCSIT). *Ann Rheum Dis* 2006;65:1301–11.
21. Zhang W, Doherty M, Bardin T, Pascual E, Barskova V, Conaghan P, et al. EULAR evidence based recommendations for gout. Part II: management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCSIT). *Ann Rheum Dis* 2006;65:1312–24.
22. Romeijnders AC, Gorter KJ. Summary of the Dutch College of General Practitioners' "gout" standard. *Ned Tijdschr Geneesk* 2002;146:309–13. In Dutch.
23. Yamanaka H. Revised version of guideline for the management of hyperuricemia and gout. *Nihon Rinsho* 2008;66:643–6. In Japanese.
24. Jordan KM, Cameron JS, Snaith M, Zhang W, Doherty M, Seckl J, et al. British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of gout. *Rheumatology (Oxford)* 2007;46:1372–4.
25. Stevenson M, Pandor A. Febuxostat for the management of hyperuricaemia in patients with gout: a NICE single technology appraisal. *Pharmacoeconomics* 2011;29:133–40.
26. Becker MA, Schumacher HR, Espinoza LR, Wells AF, MacDonald P, Lloyd E, et al. The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: the CONFIRMS trial. *Arthritis Res Ther* 2010;12:R63.
27. Sundy JS, Baraf HS, Yood RA, Edwards NL, Gutierrez-Urena SR, Treadwell EL, et al. Efficacy and tolerability of pegloticase for the treatment of chronic gout in patients refractory to conventional treatment: two randomized controlled trials. *JAMA* 2011;306:711–20.
28. Choi HK, Al-Arfaj AM, Eftekhari A, Munk PL, Shojania K, Reid G, et al. Dual energy computed tomography in tophaceous gout. *Ann Rheum Dis* 2009;68:1609–12.
29. Dalbeth N, Schauer C, MacDonald P, Perez-Ruiz F, Schumacher HR, Hamburger S, et al. Methods of tophus assessment in clinical trials of chronic gout: a systematic literature review and pictorial reference guide. *Ann Rheum Dis* 2011;70:597–604.
30. Shekelle PG, Woolf SH, Eccles M, Grimshaw J. Clinical guidelines: developing guidelines. *BMJ* 1999;318:593–6.
31. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). Developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. *Circulation* 2005;112:e154–235.
32. Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2012;64:625–39.
33. Grossman JM, Gordon R, Ranganath VK, Deal C, Caplan L, Chen W, et al. American College of Rheumatology 2010 recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. *Arthritis Care Res (Hoboken)* 2010;62:1515–26.
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 ahead of print.
35. Krishnan E, Baker JF, Furst DE, Schumacher HR. Gout and the risk of acute myocardial infarction. *Arthritis Rheum* 2006;54:2688–96.
36. Krishnan E, Svendsen K, Neaton JD, Grandits G, Kuller LH. Long-term cardiovascular mortality among middle-aged men with gout. *Arch Intern Med* 2008;168:1104–10.
37. Dalbeth N, Ames R, Gamble GD, Horne A, Wong S, Kuhn-Sherlock B, et al. Effects of skim milk powder enriched with glycomacropeptide and G600 milk fat extract on frequency of gout flares: a proof-of-concept randomised controlled trial. *Ann Rheum Dis* 2012;71:929–34.
38. Desein PH, Shipton EA, Stanwix AE, Joffe BI, Ramokgadi J. Beneficial effects of weight loss associated with moderate calorie/carbohydrate restriction, and increased proportional intake of protein and unsaturated fat on serum urate and lipoprotein levels in gout: a pilot study. *Ann Rheum Dis* 2000;59:539–43.
39. Choi HK, Atkinson K, Karlson EW, Willett W, Curhan G. Purine-rich foods, dairy and protein intake, and the risk of gout in men. *N Engl J Med* 2004;350:1093–103.
40. Choi HK, Atkinson K, Karlson EW, Willett W, Curhan G. Alcohol intake and risk of incident gout in men: a prospective study. *Lancet* 2004;363:1277–81.
41. Choi HK, Willett W, Curhan G. Fructose-rich beverages and the risk of gout in women. *JAMA* 2010;304:2270–8.
42. Choi HK, Curhan G. Soft drinks, fructose consumption, and

- the risk of gout in men: prospective cohort study. *BMJ* 2008; 36:309–12.
43. Singh JA, Reddy SG, Kundukulam J. Risk factors for gout and prevention: a systematic review of the literature. *Curr Opin Rheumatol* 2011;23:192–202.
 44. Zhang Y, Chen C, Choi H, Chaisson C, Hunter D, Niu J, et al. Purine-rich foods intake and recurrent gout attacks. *Ann Rheum Dis* 2012. E-pub ahead of print.
 45. Tsai YT, Liu JP, Tu YK, Lee MS, Chen PR, Hsu HC, et al. Relationship between dietary patterns and serum uric acid concentrations among ethnic Chinese adults in Taiwan. *Asia Pac J Clin Nutr* 2012;21:263–70.
 46. Zhang Y, Woods R, Chaisson CE, Neogi T, Niu J, McAlindon TE, et al. Alcohol consumption as a trigger of recurrent gout attacks. *Am J Med* 2006;119:800.e13–8.
 47. Stamp LK, Taylor WJ, Jones PB, Dockerty JL, Drake J, Frampton C, et al. Starting dose is a risk factor for allopurinol hypersensitivity syndrome: a proposed safe starting dose of allopurinol. *Arthritis Rheum* 2012;64:2529–36.
 48. Reinders MK, van Roon EN, Jansen TL, Delsing J, Griep EN, Hoekstra M, et al. Efficacy and tolerability of urate-lowering drugs in gout: a randomised controlled trial of benzbromarone versus probenecid after failure of allopurinol. *Ann Rheum Dis* 2009;68:51–6.
 49. Reinders MK, Haagsma C, Jansen TL, van Roon EN, Delsing J, van de Laar MA, et al. A randomised controlled trial on the efficacy and tolerability with dose escalation of allopurinol 300–600 mg/day versus benzbromarone 100–200 mg/day in patients with gout. *Ann Rheum Dis* 2009;68:892–7.
 50. Stamp LK, O'Donnell JL, Zhang M, James J, Frampton C, Barclay ML, et al. Using allopurinol above the dose based on creatinine clearance is effective and safe in patients with chronic gout, including those with renal impairment. *Arthritis Rheum* 2011;63:412–21.
 51. Lupton G, Odom R. Severe allopurinol hypersensitivity syndrome. *J Am Acad Dermatol* 1979;72:1361–8.
 52. Arellano F, Sacristan J. Allopurinol hypersensitivity syndrome: a review. *Ann Pharmacother* 1993;27:337–43.
 53. Zineh I, Mummaneni P, Lyndly J, Amur S, La Grenade LA, Chang SH, et al. Allopurinol pharmacogenetics: assessment of potential clinical usefulness. *Pharmacogenomics* 2011;12:1741–9.
 54. Hande KR. Evaluation of a thiazide-allopurinol drug interaction. *Am J Med Sci* 1986;292:213–6.
 55. Chao J, Terkeltaub R. A critical reappraisal of allopurinol dosing, safety, and efficacy for hyperuricemia in gout. *Curr Rheumatol Rep* 2009;11:135–40.
 56. Hande KR, Noone RM, Stone WJ. Severe allopurinol toxicity: description and guidelines for prevention in patients with renal insufficiency. *Am J Med* 1984;76:47–56.
 57. Somkrua R, Eickman EE, Saokaew S, Lohitnavy M, Chaiyakunapruk N. Association of HLA-B*5801 allele and allopurinol-induced Stevens Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. *BMC Med Genet* 2011;12:118.
 58. Lee MH, Stocker SL, Anderson J, Phillips EJ, Nolan D, Williams KM, et al. Initiating allopurinol therapy: do we need to know the patient's HLA status? *Intern Med J* 2011;42:411–6.
 59. Jung JW, Song WJ, Kim YS, Joo KW, Lee KW, Kim SH, et al. HLA-B58 can help the clinical decision on starting allopurinol in patients with chronic renal insufficiency. *Nephrol Dial Transplant* 2011;26:3567–72.
 60. Hung SI, Chung WH, Liou LB, Chu CC, Lin M, Huang HP, et al. HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. *Proc Natl Acad Sci USA* 2005;102:4134–9.
 61. Tassaneeyakul W, Jantararungtong T, Chen P, Lin PY, Tiamkao S, Khunarkornsiri U, et al. Strong association between HLA-B*5801 and allopurinol-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in a Thai population. *Pharmacogenet Genomics* 2009;19:704–9.
 62. Lonjou C, Borot N, Sekula P, Ledger N, Thomas L, Halevy S, et al, for the RegiSCAR Study Group. A European study of HLA-B in Stevens-Johnson syndrome and toxic epidermal necrolysis related to five high-risk drugs. *Pharmacogenet Genomics* 2008;18:99–107.
 63. Perez-Ruiz F, Hernandez-Baldizon S, Herrero-Beites AM, Gonzalez-Gay MA. Risk factors associated with renal lithiasis during uricosuric treatment of hyperuricemia in patients with gout. *Arthritis Care Res (Hoboken)* 2010;62:1299–305.
 64. Thompson GR, Duff IF, Robinson WD, Mikkelsen WM, Galindez H. Long term uricosuric therapy in gout. *Arthritis Rheum* 1962;5:384–96.
 65. Pineda C, Amezcua-Guerra LM, Solano C, Rodriguez-Henriquez P, Hernandez-Diaz C, Vargas A, et al. Joint and tendon subclinical involvement suggestive of gouty arthritis in asymptomatic hyperuricemia: an ultrasound controlled study. *Arthritis Res Ther* 2011;13:R4.
 66. Ottaviani S, Allard A, Bardin T, Richette P. An exploratory ultrasound study of early gout. *Clin Exp Rheumatol* 2011;29:816–21.
 67. Perez-Ruiz F, Calabozo M, Pijoan JI, Herrero-Beites AM, Ruibal A. Effect of urate-lowering therapy on the velocity of size reduction of tophi in chronic gout. *Arthritis Rheum* 2002; 47:356–60.
 68. Takahashi S, Moriwaki Y, Yamamoto T, Tsutsumi Z, Ka T, Fukuchi M. Effects of combination treatment using anti-hyperuricemic agents with fenofibrate and/or losartan on uric acid metabolism. *Ann Rheum Dis* 2003;62:572–5.
 69. Reinders MK, van Roon EN, Houtman PM, Brouwers JR, Jansen TL. Biochemical effectiveness of allopurinol and allopurinol-probenecid in previously benzbromarone-treated gout patients. *Clin Rheumatol* 2007;26:1459–65.
 70. Thiele RG, Schlesinger N. Ultrasonography shows disappearance of monosodium urate crystal deposition on hyaline cartilage after sustained normouricemia is achieved. *Rheumatol Int* 2010;30:495–503.
 71. Perez-Ruiz F, Hernando I, Villar I, Nolla JM. Correction of allopurinol dosing should be based on clearance of creatinine, but not plasma creatinine levels: another insight to allopurinol-related toxicity. *J Clin Rheumatol* 2005;11:129–33.
 72. Becker MA, Schumacher HR Jr, Wortmann RL, MacDonald PA, Eustace D, Palo WA, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. *N Engl J Med* 2005;353:2450–61.
 73. Schumacher HR Jr, Becker MA, Wortmann RL, MacDonald PA, Hunt B, Streit J, et al. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: a 28-week, phase III, randomized, double-blind, parallel-group trial. *Arthritis Rheum* 2008;59: 1540–8.