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2012 American College of Rheumatology Guidelines for Management of Gout Part I: Systematic Non-pharmacologic and Pharmacologic Therapeutic Approaches to Hyperuricemia

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AUTHOR CONTRIBUTIONS

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Addendum

Therapies that were approved after the original literature review are not included in these recommendations.

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INTRODUCTION

Gout is a disorder that manifests as a spectrum of clinical and pathologic features built on a foundation of an excess body burden of uric acid, manifested in part by hyperuricemia, which is variably defined as serum urate 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 sites, mediates most of the clinical and pathologic features of gout. Typically, the disease first presents as arthritis that is acute and episodic, but can become recurrent in the majority of individuals. Gout also can manifest as chronic arthritis of one or more joints (1;2). Tophi, mainly in articular, periarticular, bursal, bone, auricular, and cutaneous tissues are a pathognomonic feature of gout, and are detectable by physical exam, and/or by imaging approaches and pathology examination (3;4;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 self-reported prevalence in the USA recently estimated at 3.9% of adults (~8.3 million people)(6). Prevalence of gout has risen in many countries (e.g., New Zealand), and especially in the USA over the last few decades, mediated by factors such as increased prevalence of co-morbidities that promote hyperuricemia, including hypertension, obesity, metabolic syndrome, type 2 diabetes, and chronic kidney disease (CKD)(7–10). Other factors in the rising prevalence of gout include certain dietary trends and widespread prescription of thiazide and loop diuretics for cardiovascular diseases (11). Many gout patients, including the growing subset of affected elderly, have complex co-morbidities and medication profiles that complicate overall management (12). Long-term morbidity and impairment of health-related quality of life are now better appreciated in many gout patients, particularly those with multiple co-morbidities and/or chronic gouty arthritis (13;14). Despite advanced understanding of the molecular bases of hyperuricemia and gouty inflammation, and the extensive practice experience of many providers, substantial quality of care gaps exist in gout management (15). Moreover, significant shortfalls in patient education and adherence have been identified in gout (16).

On behalf of the American College of Rheumatology (ACR), we were charged with developing systematic non-pharmacologic and pharmacologic recommendations for effective treatments in gout with acceptable risk-benefit ratio. Our assignment was to focus on four specific domains in gout management. Two of these domains are addressed herein, (i) Urate-lowering therapy (ULT), and (ii) chronic gouty arthritis with tophaceous disease detected on physical examination (designated by the ACR with the terminology “chronic tophaceous gouty arthropathy” (abbreviated CTGA), and specifically represented in the

fundamental case scenarios 7–9 described herein). Domains iii-iv (analgesic and anti-inflammatory management of acute gouty arthritis, and pharmacologic anti-inflammatory prophylaxis of attacks of gouty arthritis, respectively) are addressed in a separate manuscript (Part II of the guidelines)(17).

There are multiple lines of epidemiologic and experimental evidence that hyperuricemia, via effects of excess soluble urate, may play a role in some human renal, cardiovascular, and metabolic co-morbidities 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 Research and Development/University of California at Los Angeles (RAND/UCLA) Appropriateness Method (19) to generate recommendations, and engaged a diverse, international panel of experts. Creating novel classification of gout as a disease, new gout diagnostic criteria, or definition of treatment outcomes were 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, 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 (NICE) single technology appraisal (STA) process has been applied to ULT in gout using febuxostat (25). New guidelines were requested by the ACR, as 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 (DECT)(28;29), are being investigated for impact on gout diagnosis, and 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 examine 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 Methodology (19) (Table 1). Individual results of this work are designated as “recommendations” rather than guidelines, in order to reflect the non-prescriptive nature of decision-making evaluated by experts, and based on available evidence at the time. The recommendations cannot substitute for individualized, 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 (eg, with anticoagulants, azathioprine, amoxicillin), and effects of co-morbidities such as diabetes, 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.

METHODS

Project design and development of recommendations and grading of evidence

The overall design of the project is schematized in Supplemental Figure 1. 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 (Supplemental Figure 2). Pharmacologic approaches, and diet, lifestyle and non-pharmacologic measures (e.g., weight loss, exercise) were addressed within each domain. The CEP leaders communicated with an international panel of gout experts, and the PIs, 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 domain leaders and PIs to refine case scenarios. Though 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 given to the TFP in conjunction with clinical scenarios representing a broad scope of disease, with multiple questions of interest, and alternative options, for each case scenario.

By ACR mandate, the TFP had a majority of members without perceived potential conflict of interest (COI), and had diverse experience and expertise, as described in detail in Supplemental Figure 2. The TFP included 7 rheumatologists (one of whom is a Chair of Internal Medicine, and one an Internal Medicine Residency Training Program Director), 2 primary care physicians, a nephrologist, and a patient representative. There were 2 rounds of ratings, the first anonymously 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 to 9 on a Likert scale using Delphi process, followed by a face-to-face group discussion and then re-voting 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 on the Likert Scale was considered ***Uncertain***= risk-benefit ratio is uncertain. A vote of 7–9 on the Likert Scale was rated as ***Appropriate***= benefits clearly outweigh the risks. Samples of votes taken and results are provided in Supplemental Figure 3. 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 1/3 of the votes graded (“inappropriate”) for the scenario. The final rating was done anonymously in a 2-day face-to-face meeting, facilitated by an experienced moderator (Neil Wenger). During the face-to-face TFP meeting, some case scenarios were clarified for content or verbiage, and re-voted 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., more than one) 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 Cochrane Central Register of Controlled Trials (CENTRAL) from the 1950s to the present were searched to find articles on gout with help of an experienced librarian (Rikke Ogawa). 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.

Clinical Case Descriptions

The TFP evaluated scenarios with a broad spectrum of clinical gout, similar to what a clinician might see in a busy practice, and divided into mild, moderate, and severe disease activity in each of three distinct "treatment groups" (Figure 1A–B). In generating these nine 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 medication regimen. Conversely, severe disease activity level was intended to represent patients with disease activity equal or greater 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 not only that the diagnosis of gout was correct, and that there was some clinical evidence of gout disease activity. This included intermittent symptoms of variable frequency, specifically presented to the TFP as episodes of acute gouty arthritis of at least moderate to severe pain intensity (17). Clinical evidence of gout disease activity, presented to the TFP, also included one or more tophi detected by physical exam, or alternatively, chronic symptomatic arthritis (ie, "chronic arthropathy" or "synovitis") due to gout, with or without confirmed joint damage (e.g., deformity, erosion due to gout on imaging study). Hyperuricemia was defined here as serum urate >6.8 mg/dL (2). We determined all aspects of case scenario definitions by a structured iterative process, using regular electronic 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; uricosuric agents were defined to include agents available in the USA (probenecid, and off-label use (as uricosuric therapy) of fenofibrate and losartan), but did not include sulfinpyrazone or benzbromarone. Other agents and modalities were self-explanatory. Evaluation by the TFP of effectiveness of a given therapeutic option assumed that patients in 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 (Supplemental Material Discussion). 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 the supplemental materials. Based on the policies of the ACR, which are aligned with those of many medical societies, no more than

49% of project participants could have COI at any given time. It was required that the project PI (John FitzGerald) 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 non-pharmacologic and pharmacologic management approach intended to be applicable to all patients with gout, which is summarized in Figure 3. This was based on the assumption that the diagnosis of gout was correct before initiation of management. The approach highlighted patient education on the disease and treatments and their objectives, and initiation of diet and lifestyle recommendations. The TFP also recommended elimination of prescription medication that were non-essential for the optimal management of co-morbidities (eg, hypertension, CHF, hyperlipidemia, or major organ transplant) in an individual patient, where such medication elevated serum urate levels; with prime examples being thiazide and loop diuretics, niacin, and calcineurin inhibitors (Evidence C). Though 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 co-morbidity 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, and thereby could merit laboratory investigations such as urinalysis, renal ultrasound, a complete hemogram, or urine uric acid quantification as indicated. In this context, the TFP specifically recommended screening for uric acid overproduction (by urine uric acid evaluation for uric acid overproduction), in patient subsets with gout clinical disease onset before age 25 (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. Though 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 amongst those where referral to a specialist is considered (Evidence C for all): (i) Unclear etiology of hyperuricemia; (ii) Refractory signs or symptoms of gout; (iii) Difficulty in reaching the target serum urate level, particularly with renal impairment and a trial of XOI treatment; (iv) 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 thorough physical exam 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, suggest 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 non-pharmacologic ULT measures in gout

The TFP recommended certain diet and lifestyle measures for the vast majority of patients with gout (Evidence B-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, 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 (34,35), and obesity, metabolic syndrome, diabetes, hyperlipidemia, and hypertension.

Dietary recommendations were grouped into 3 simple qualitative categories, termed “limit”, “avoid”, or “encourage” (Figure 4). This approach, with rare exceptions (36,37), 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 time frame. The evidence sources were epidemiologic studies of hyperuricemia and incident gout, including long-term prospective analyses and internet-based case-crossover studies. The TFP recommended that gout patients limit their consumption of purine-rich meat and seafood (Evidence B) as well as high fructose corn syrup sweetened soft drinks and energy drinks (Evidence C), and encouraged the consumption of low-fat or non-fat dairy products (Evidence B) (38)(Figure 4). The TFP also 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)(39). 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 ~10–18% decrease in serum urate (38). In further discussion by the TFP, again without a specific vote, the TFP viewed this degree of serum urate-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 I and II of the 2012 ACR Guidelines for gout, the recommendations assumed a lack of contra-indications, intolerance, serious adverse events, or drug-drug interactions for given agents. The TFP recommended gout with CKD stage 2–5, or end stage renal disease (ESRD), 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, or usage of individual agents in the presence of a given degree of either renal impairment, or other co-morbidities such as hepatic impairment.

TFP recommendations for pharmacologic ULT, presented graphically in Figure 3, included recommendation of xanthine oxidase inhibitor (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 contra-indication or intolerance to at least one 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/min.

The TFP recommended that pharmacologic ULT could be started during an acute gout attack, providing that effective anti-inflammatory 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 target, at a minimum, of < 6 mg/dL in all gout case scenarios (Evidence A). Moreover, the TFP recommended that the target serum urate 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-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 3A. Importantly, the TFP recommended that the starting dose of allopurinol be no greater than 100 mg per day (Evidence B)(40), consistent with prior 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 (40), 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 daily or less failed to achieve the serum urate target of <6 mg/dL (26,41), or < 5 mg/dL (42,43), in more than half of 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 (43,44). Importantly, in doing so, the TFP also recommended that the maintenance dose 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 (45,46). The estimated incidence of AHS is ~1:1000 in the USA 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 (47). Concurrent thiazide use and renal impairment have been implicated as risk factors for AHS (48–50). A widely employed risk management strategy has been a non-evidence-based algorithm for allopurinol maintenance dosing, calibrated to renal impairment (51)(Evidence C); 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 (40) further buttressed 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).

The TFP also weighed the rapidly emerging area of pharmacogenetics to screen for AHS (47,52,53), and recommended that, prior to initiation of allopurinol, HLA-B*5801 testing should be considered in selected patients sub-populations at 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 (54–56). Such high-risk individuals were recommended to be prescribed an alternative to allopurinol if HLA-B*5801 positive (Evidence A). The TFP recommended the HLA-B*5801 screening to be done by the rapid, widely available, PCR-based approach (Evidence A), which, in only ~10% of tests, requires more cumbersome, follow-up 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 Caucasians, with HLA-B*5801 prevalence ~2%, had a substantially lower HLA-B*5801 hazard ratio and negative predictive value of the test than in the aforementioned Asian sub-populations (47,53,57).

Recommendations specific to primary uricosuric urate-lowering monotherapy

Under conditions where uricosuric monotherapy was employed as a primary ULT modality (Table 3B), probenecid was recommended by the TFP as the first choice amongst uricosuric drugs currently available in the USA (Evidence B). The TFP recommended that a history of urolithiasis contraindicates first line use of a potent uricosuric for ULT (Evidence C), given that probenecid (and benzbromarone, which is unavailable in the USA) were associated with ~10–11% risk of urolithiasis (58,59). 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 indicative of uric acid overproduction contra-indicates 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 (58). The TFP did recommend that when initiating uricosuric ULT, patients should also be instructed to increase fluid intake and consider urine alkalinization (e.g., with potassium citrate) (Evidence C for all)(58), 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 has not yet been met and under circumstances where gout remained symptomatic (i.e., where there were one or more continuing clinical signs and symptoms of gout, such as recent acute gout attacks, tophi, and chronic gouty arthritis) (Figure 5, Table 4). In doing so, the TFP, in limited voting scenarios, first considered the potential role of imaging in 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 non-tophaceous 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 indication 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 (60). Conversely, the "double contour" sign was not universally detectable (i.e., absent in ~40% in an ultrasound survey of multiple joints) in patients with early gout not in ULT, in a recent study (61).

For all 9 case scenarios when the serum urate target has not been met, the TFP recommended upwards dose titration of one XOI (allopurinol or febuxostat), to the respective maximum appropriate dose for the individual patient (Evidence A) (Figure 5, 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 USA, 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, probenecid, and use of other agents with clinically significant uricosuric effects, such as fenofibrate and losartan, were recommended by the TFP as therapeutically useful in a comprehensive ULT program in refractory disease (Evidence B). Specifically, the TFP recommended a combination oral ULT approach (one XOI agent: allopurinol or febuxostat; and one uricosuric: probenecid, fenofibrate, or losartan as currently available agents in the USA) as an option when the serum urate target has not been met, across the 9 case scenarios (Evidence B) (Figure 5, Table 4) (62–64).

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 therapy options (Figure 5, Table 4) (Evidence A). In 2 large placebo-controlled RCTs, pegloticase 8 mg every 2 weeks was effective in reducing SUA< 6 mg/dL in 42% of patients on vs. 0% in placebo group at 6 months (27). In addition, 45% of patients on pegloticase 8 mg q 2 weeks had complete resolution of one or more tophi vs. 8% in the placebo group with significant improvement in the chronic arthropathy and health-related quality of life. Importantly, the TFP did not recommend pegloticase as first line ULT for any case scenarios. The TFP also did not achieve a 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 exam, has been achieved.

DISCUSSION

We present the first ACR evidence-and consensus-based pharmacologic and non-pharmacologic 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) and assembled at the level of national and multinational rheumatology societies in the last decade by EULAR, and by the BSR, did not comprehensively evaluate newer evidence and therapies, including febuxostat and pegloticase (21,24). The ACR-sponsored work presented here in Part I 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. Based on the existing evidence in gout patients, 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. 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 modification for gout, especially for direct intervention studies.

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 co-morbidities 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 use of high-resolution ultrasound and DECT that may inform disease classification and prognosis in gout, and, as more outcomes data emerge on ULT-induced alterations in imaging findings of gout (65).

Specific TFP recommendations on indications for pharmacologic ULT initiation were accompanied by novel TFP recommendations that either allopurinol or febuxostat are appropriate as the first line of pharmacologic ULT, though the issue of allopurinol non-titration in comparison clinical trial designs for these agents was recognized. Probenecid was recommended as an alternative first line therapy, if at least one XOI drug was contra-indicated or not tolerated, but probenecid monotherapy was not recommended as a first line approach in those with a creatinine clearance less than 50. 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 was an exclusion criterion in some studies (42,64)). Reservations also included multiple drug interactions, the ~10% urolithiasis risk, and complexity of risk management in dose escalation of probenecid ULT as 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 gout patients to achieve, at a minimum, a serum urate below 6 mg/dL. In those with greater disease severity and urate burden, such as those with tophi detected on physical exam, and with CTGA, the TFP recommended that serum urate 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 also made the novel recommendation that rapid, PCR-based HLA-B*5801 screening should be considered as a risk management component in sub-populations where both 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, such as Koreans with stage 3 (or worse) CKD, and all those of Han Chinese and Thai descent. It is anticipated additional high-risk sub-populations for AHS will be identified in future studies. Third, the TFP recommended steady upwards titration of allopurinol, 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 (51), 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 (44,66).

The TFP recommended uricosuric therapy as a valuable component of comprehensive urate-lowering strategies. Specific, novel TFP recommendations on appropriateness of use of combination XOI and uricosuric ULT as a second line approach in refractory disease across the case scenarios studied here reinforce BSR recommendations on such combination therapy (24). Significantly, for combination with a XOI drug, the TFP recommended not simply probenecid, but also, as alternatives, other medications with less marked uricosuric effects (fenofibrate, 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 with XOI therapy to decrease the risk of uricosuric induced urolithiasis, while increasing the velocity of size reduction of body urate stores and tophi (62).

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 I 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 serum urate target, would be more informative than past trials (26,41,67). Another issue was variability in endpoints and outcomes 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 on 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 NICE concluded that febuxostat should be recommended for ULT in gout only in patients with contra-indications or intolerance to allopurinol (25). Conversely, PCR-based HLA-B*5801 pharmacogenetic 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 (47,52,53). Last, third line ULT with pegloticase is an expensive biologic therapy approach for gout, and additional biologics 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 anti-inflammatory prophylaxis of gouty arthritis presented in a separate manuscript (Part II of the guidelines)(17), will require updating as new evidence emerges for appropriate evaluation, 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key points

- Patient education on diet, lifestyle, treatment objectives, and management of comorbidities, are recommended core therapeutic measures 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 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 dose of allopurinol should be no greater than 100 mg per day, and less than that in moderate to severe chronic kidney disease (CKD), followed by gradual upwards titration of the maintenance dose, which can exceed 300 mg daily even in patients with CKD
- Prior to initiation of allopurinol, rapid, PCR-based HLA-B*5801 screening should be considered as a risk management component in sub-populations where both 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 (eg, Koreans with stage 3 or worse CKD, and all those of Han Chinese and Thai descent)
- Combination oral ULT, with one XOI agent and one 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 therapy options

Figure 1A

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***

Figure 1B

Case scenarios for Chronic Tophaceous Gouty Arthropathy (CTGA, see accompanying Figure 2)

Disease Severity	Characteristics	CASE SCENARIO NUMBER
Mild	•Simple chronic tophaceous gouty arthropathy •Affecting 1 joint •Stable disease	***7***
Moderate	•Simple chronic tophaceous gouty arthropathy •Affecting 2-4 joints •Stable disease	***8***
Severe	•Chronic tophaceous gouty arthropathy of >4 joints OR • ≥1 unstable, complicated, severe articular tophus or tophi	***9***

Figure 1. Fundamental Case Scenarios Evaluated by the 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 CEP, 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 presented in panels A-B. The

"treatment group" with intermittent attacks of acute gout, but no tophi detected on physical examination, was sub-divided based on increasing yearly frequency of episodes of acute gouty arthritis of at least moderate to severe pain intensity (**Case Scenarios 1–3**)(panel A). Gout associated with clinically apparent high body urate burden was evaluated in case scenarios where there were one or more tophi on physical exam, and either intermittently symptomatic acute gouty arthritis (**Case Scenarios 4–6**)(panel A), or in panel 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 accompanying Figure 2).

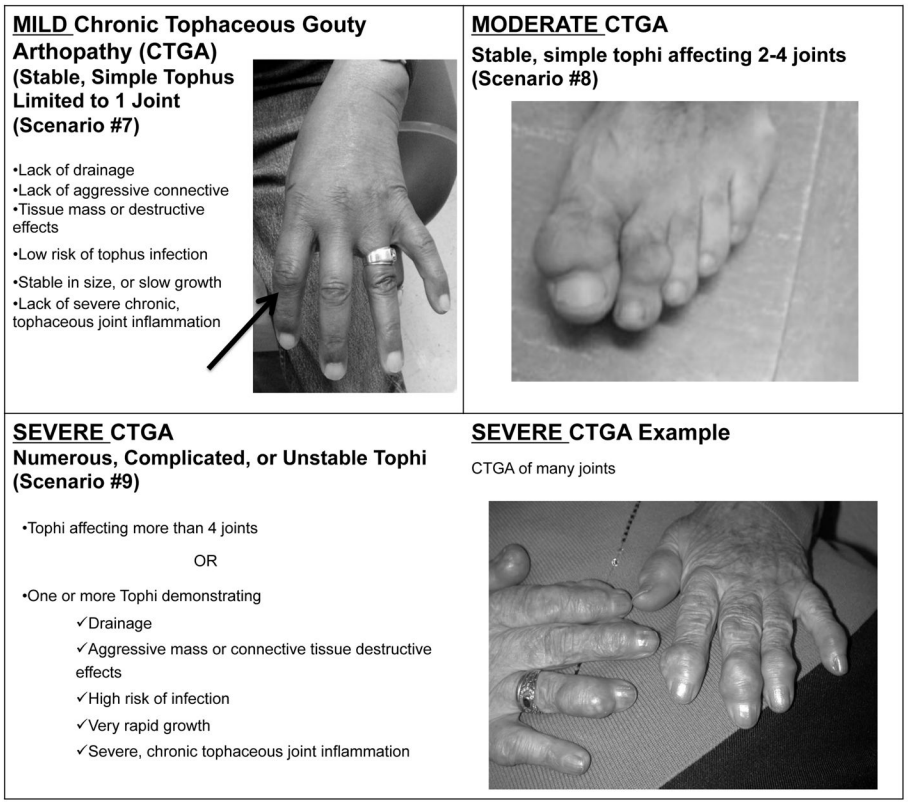

Figure 2. Detailed pictorial representations of chronic arthropathy in CTGA case scenarios presented to the TFP

A core element of our approach was to present the TFP, and the readership of the ultimate publication, with specifically detailed summaries of the CTGA case scenarios (numbers 7–9 in Figure 1), 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, and the other two by Dr. Fernando Perez-Ruiz.

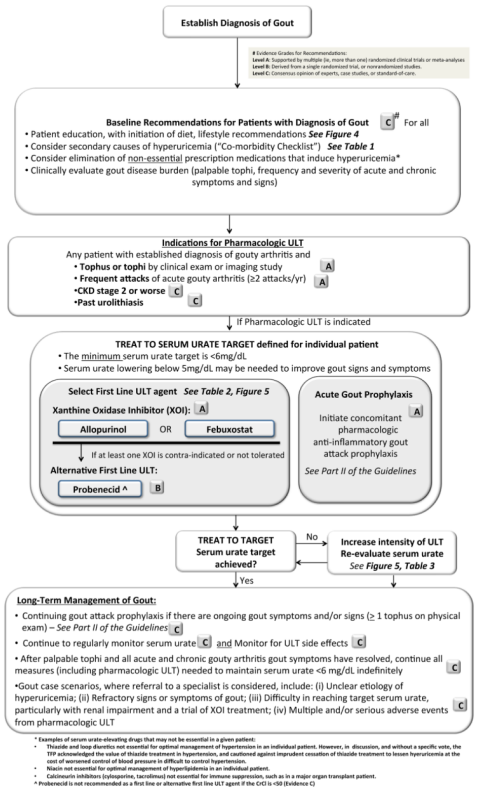

Figure 3. Baseline recommendations and overall strategic plan for patients with gout

This algorithm summarizes overall treatment strategies and flow of management decisions for gout. Certain elements, including non-pharmacologic and pharmacologic measures, the approach to refractory disease, and treatment and anti-inflammatory prophylaxis of acute gout attacks, are developed further in Tables 2–4 and Figures 4–5, and in Part II of the guidelines, as respectively referenced in the figure. Evidence Grades (A-C, as indicated) are summarized for each TFP recommendation, and the text discusses, in detail, each aspect of clinical decision making.

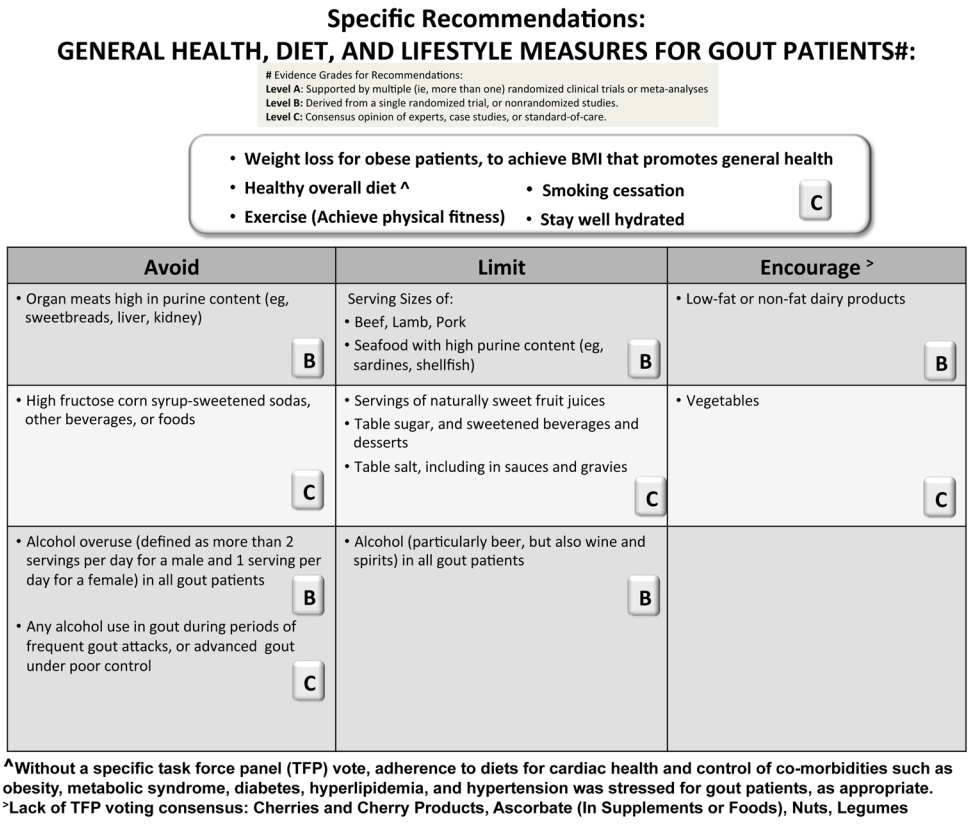

Figure 4. Specific TFP recommendations on general health, diet, lifestyle measures for gout patients

The figure presents the TFP recommendations on non-pharmacologic measures for gout patients, 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 “limit”, “avoid”, or “encourage”, reflecting 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 “lack of consensus” also are cited.

Case Scenario-Specific Escalation of Pharmacologic ULT in Gout, Including for Refractory Disease (see accompanying Table 3)

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 XOI titrated to maximum appropriate dose (Alternative if XOI contra-indicated or not tolerated : Probenecid)	±§	+	+	+	+	+	+	+	+
⬇ *Serum urate target not achieved, continuing disease activity*									
Add **URICOSURIC* to XOI** with both agents titrated to maximum appropriate dose	±§	+	+	+	+	+	+	+	+
⬇ *Serum urate target not achieved, , continuing disease activity*									
PEGLOTICASE	–	–	+	–	±¶	+	+	+	+

Progressively mild, moderate, and severe frequency of intermittent acute gout symptoms are evaluated for case scenarios numbered 1-3, and 4-6, and progressive severity of CTGA (mild, moderate, and severe) evaluated in case scenarios numbered 7-9 (as described in Figure 1 A-B).

§ 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,

Abbreviations: CKD, chronic kidney disease; ESRD, end stage renal disease; CTGA: Chronic Tophaceous Gouty Arthropathy.; ULT, urate-lowering therapy; XOI, xanthine oxidase inhibitor

Figure 5. Case scenario-specific escalation of pharmacologic ULT in gout, including approach to refractory disease

This figure, which accompanies Table 4, presents 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 (as numbered 1–9 above, and described in detail in Figure 1A–B) are considered. These recommendations specifically assume that for each case scenario: (i) The serum urate target needed to achieve improved gout signs and symptoms has not yet been achieved; (ii) Appropriate non-pharmacologic ULT measures have been applied; (iii) Appropriate treatment and anti-inflammatory prophylaxis are employed for attacks of acute gouty arthritis. Evidence Grades for individual TFP votes to recommend that are summarized here are presented in the text. The designation of ± for decision making in the figure indicates that the TFP recommended this measure only in clinical scenarios indicated by the symbol[§].

Table 1

KEY ASSUMPTIONS IN THE PROCESS APPLIED TO DEVELOP THE RECOMMENDATIONS:

1	Recommendations were developed using the RAND/UCLA 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, contra-indications, 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 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 Supplementary material for examples of voting scenarios).

Table 2

Specific Recommendation of a CO-MORBIDITY CHECKLIST for gout patients Appropriate to consider in the clinical workup, and if clinically indicated, to evaluate: (Evidence C[#] for all)

- Obesity, Dietary Factors
- Excessive Alcohol Intake
- Metabolic syndrome, Type 2 Diabetes Mellitus
- Hypertension
- Hyperlipidemia, Modifiable risk factors for CAD or stroke
- Serum urate-elevating medications
- History of urolithiasis
- CKD, glomerular or interstitial renal disease (eg, analgesic nephropathy, polycyctsic kidney disease)
- In selected cases, potential genetic or acquired cause of uric acid overproduction (eg, inborn error of purine metabolism, or psoriasis, myeloproliferative or lymphoproliferative disease, respectively)
- Lead intoxication

[#]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.

Table 3

Core recommendations in use of allopurinol and uricosuric ULT in gout

A. ALLOPURINOL:

- Starting dose 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)
- Gradually titrate maintenance dose upwards every 2–5 weeks to appropriate maximum dose, in order to treat to chosen SUA target (Evidence C)
- Dose can be raised above 300 mg daily, even with renal impairment, as long as this is accompanied by adequate patient education and monitoring for drug toxicity (eg, pruritis, rash, elevated hepatic transaminases) (Evidence B)
- Prior to initiation, consider HLA-B*5801 in selected patients, specifically in higher risk sub-populations for severe allopurinol hypersensitivity reaction (eg, Koreans with stage 3 or worse CKD; Han Chinese and Thai irrespective of renal function) (Evidence A)

B. URICOSURIC THERAPY:

- Probenecid is the first choice among uricosurics for ULT monotherapy (Evidence B)
- In gout patients with a creatinine clearance <50 ml/minute, probenecid is not recommended as first line ULT monotherapy (Evidence C)
- 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)
- History of urolithiasis contra-indicates first line uricosuric urate-lowering monotherapy (Evidence C)
- Urinary uric acid should be measured before initiation of uricosuric ULT (Evidence C)
- Elevated urine uric acid indicative of uric acid overproduction contra-indicates uricosuric ULT (Evidence C)
- Continue to monitor urinary uric acid during uricosuric ULT (Evidence C)
- Consider urine alkalinization (eg, with potassium citrate), with monitoring of urine pH, in addition to increased fluid intake, as a risk management strategy for urolithiasis (Evidence C)

Table 4

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

- Attempt upwards dose titration of one xanthine oxidase inhibitor (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 substitution be considered after initial failure of upward dose titration of one XOI (Evidence C)
- Effective therapeutic options include addition of a uricosuric agent (eg, 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

* 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 pegloticase serum urate lowering effect associated with increased risk of pegloticase infusion reactions