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2020 American College of Rheumatology Guideline for the Management of Gout

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ABSTRACT

Objective: To provide guidance for the management of gout including indications for and optimal use of urate-lowering therapy (ULT), treatment of gout flares, and lifestyle and other medication recommendations.

Methods: Fifty-seven patient intervention comparator outcome (PICO) questions were developed. This was followed by a systematic literature review including network meta-analyses with rating of the available evidence according to GRADE methodology, and patient input. A group consensus process was used to compose the final recommendations and grade their strength as strong or conditional.

Results: Forty-two recommendations (including 16 strong recommendations) were generated. Strong recommendations included initiation of urate-lowering therapy (ULT) for all patients with tophaceous gout, radiographic damage due to gout, or frequent gout flares; allopurinol as the preferred first-line ULT, including in those with moderate-to-severe chronic kidney disease (CKD≥3); using a low starting dose of allopurinol (≤100 mg/day, and lower in CKD) or febuxostat (≤40 mg/day); a treat-to-target management strategy with ULT dose titration guided by serial serum urate (SU) measurements with a SU target of <6 mg/dL. When initiating ULT, concomitant anti-inflammatory prophylaxis therapy was strongly recommended for a duration of at least 3-6 months. For management of gout flares, colchicine, NSAIDs, or glucocorticoids (oral, intra-articular, or intramuscular) were strongly recommended.

Discussion: This guideline provides direction for clinicians and patients making decisions on the management of gout, using GRADE methodology and informed by a consensus process based on evidence from the current literature and patient preferences.

SIGNIFICANCE & INNOVATION

- For patients with indications for urate-lowering therapy (ULT), we strongly recommended the use of a treat-to-target strategy that is supported by randomized clinical trial data and patient preferences.
- We strongly recommend allopurinol as first-line ULT, including for those with moderate-to-severe chronic kidney disease (CKD≥3).
- We strongly recommend using anti-inflammatory prophylaxis when starting ULT for at least 3-6 months rather than <3 months.
- We conducted network meta-analyses (NMA) to support decision-making regarding use of ULT and anti-inflammatory agents, with GRADE methodology for summarizing supporting evidence.

INTRODUCTION

Gout is the most common form of inflammatory arthritis, affecting 9.2 million adults (3.9%) in the United States (1). While the etiology of gout is well-understood and there are effective and inexpensive medications to treat gout, gaps in quality of care persist (2-4). The 2012 American College of Rheumatology (ACR) (5, 6) and other international specialty society guidelines recommend treat-to-target strategies with use of urate-lowering therapy (ULT) (7-10). Despite these recommendations, over the past 2 decades there has been no increase in ULT utilization. Adherence to ULT remains poor (2, 11), the lowest among 7 common chronic medical conditions (12). Complicating these efforts, the prior 2012 ACR guidelines have been criticized due to low quality of evidence supporting treat-to-target recommendations (13, 14).

Since the 2012 ACR gout guidelines (5, 6), several clinical trials have been conducted that provide additional evidence regarding the management of patients with gout, leading the ACR Guidelines Subcommittee to determine that new guidelines were warranted.

METHODS

This guideline follows the ACR guideline development process (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines) using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to rate the certainty of evidence and develop recommendations (15-17), with an emphasis on developing actionable guidelines. ACR policy guided management of conflicts of interest and disclosures (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines/Gout). Supplementary Appendix 1 presents a detailed description of the methods.

Briefly, the Core Team, Expert Panel, and Voting Panel (consisting of rheumatologists, a general internist, a nephrologist, a physician assistant and a patient representative) generated 57 Patient-Intervention-Comparator-Outcome (PICO) questions to address: Indications for ULT (5 questions), approaches to initiating ULT (7 questions), ongoing ULT management (18 questions), gout flares (10 questions), and lifestyle and other medication strategies in patients with gout (9 questions) and in individuals with asymptomatic hyperuricemia (8 questions). PICO questions were posted on the ACR website for public comment (October 30-November 30, 2018).

An in-person Patient Panel of 8 male patients with gout, moderated by one of the voting panel members (JS), reviewed the evidence report (along with a summary and interpretation by the moderator) and provided patient perspectives and preferences.

The Core Team pre-specified outcomes as critical or important for each PICO for the systematic literature review. Outcomes varied across PICO topic (see Supplementary Appendix 2 for detail). Gout flare, SU (and tophus for PICO 1) were specified as critical outcomes for all PICOs specific to ULT. Pain was identified as critical for PICOs specific to gout

flare. Gout flare was specified as the only critical outcome for management of lifestyle factors. All other outcomes were specified as important. Without standardized definitions for gout flare as an outcome (18), flare definitions varied by duration of follow-up in the various studies. Based on Patient Panel input, we specified that longer term outcomes (e.g., 24-month) would be critical, while shorter durations (e.g., ≤ 12-month) were considered important; it was recognized that very short time-points (e.g., <6-months) may reflect the expected flares during ULT initiation.

We conducted systematic literature reviews (including 2 network meta-analyses [NMA]) to address each PICO question. The first NMA evaluated the impact of starting ULT vs. no ULT and the relative impact of the various ULT agents (see Supplementary Appendix 3 for detail). The second NMA evaluated anti-inflammatory agents in gout flare management (see Supplementary Appendix 4 for detail). To accomplish this second NMA, we grouped similar agents into nodes (e.g., acetic acid derivatives, profens, COX-2 agents, corticosteroids, IL-1 inhibitors).

The lowest level of evidence for the outcomes deemed critical to patients determined the certainty of evidence for each PICO (15). For PICOS specific to ULT, on the basis of input from the patient panel, prior focus group work citing the importance of SU, gout flare and tophi to patients (19) and prior guidance from the GRADE working group (20) we made the following decisions. Where there was moderate or high certainty of evidence demonstrating improvement in any one of these 3 outcomes, we deemed this sufficient evidence to support a strong recommendation. The certainty of evidence from the other two outcomes were then designated as important but not critical to support the recommendation. The certainty of the evidence for each recommendation is presented in Tables 1-8, and the certainty of evidence for each outcome within each PICO is in the full evidence report (see Supplementary Appendix 5).

We additionally report the results, using the more conservative rating of the evidence using the lowest level of evidence for any of the critical outcomes. Applying these more conservative rules, the summary certainty of evidence fell (in comparison to the reported results) for some of the ULT recommendation statements, which would result in a lower strength of recommendation for 2 recommendations, (PICO 2, ULT indication for patients with erosions and PICO 27, switching to pegloticase for ULT failure). The details are available in the evidence report.

Medication costs (not part of the systematic literature review) reported as Average Wholesale Pricing as sourced from Lexicomp® on August 23, 2019, were provided to the Voting Panel as cost of treatment was included as part of the evaluation of risks and benefits of treatment medications (see Supplementary Appendix 6).

PICO questions were drafted into recommendation statements and were sent to the Voting Panel with the evidence report prior to Round 1 voting. At a face-to-face meeting, the Voting Panel again reviewed draft recommendations, a summary of the voting from Round 1, the evidence report, and summary of Patient Panel statements. (One patient from the Patient Panel (JES) and the Patient Panel moderator (JS) attended the Voting Panel and were available to answer

questions about the Patient Panel statements.) To become a recommendation (for or against) in this guideline, at least 70% consensus of the Voting Panel was required.

The strength of each recommendation was rated as **strong** or **conditional**. **Strong** recommendations reflect decisions supported by moderate or high certainty of evidence where the benefits consistently outweigh the risks, and, with only rare exceptions, an informed patient and their provider would be expected to reach the same decision. **Conditional** recommendations reflect scenarios for which the benefits and risks may be more closely balanced and/or only low certainty of evidence or no data are available.

Recommendations in this guideline apply to patients with gout, with the exception of a single recommendation regarding the use of urate-lowering therapy in individuals with asymptomatic hyperuricemia defined as an individual with serum urate >=6.8mg/dL with no prior gout flares or subcutaneous tophi. Patients with evidence of MSU deposition on advanced imaging may still be considered asymptomatic so long as they have not had a prior gout flare or subcutaneous tophi.

These guidelines do not directly address the impact of gout or hyperuricemia on other comorbidities, such as cardiovascular disease (CVD), hypertension, urolithiasis, or chronic kidney disease (CKD). As we developed these guidelines for use by providers practicing in the U.S., we considered pharmacologic therapies available in the U.S. with select exceptions. Although lesinurad was withdrawn from the U.S. market by the manufacturer during the course of guideline development, it remains FDA-approved, and we therefore considered the data in relation to relevant PICOs. To facilitate the two NMAs, we also considered medications not available in the U.S. to permit comparisons with other available medications in the network analysis.

RESULTS/RECOMMENDATIONS

Indications for Pharmacologic Urate-Lowering Therapy (Table 1, Figure 1 – Supplementary Appendix 7)

We strongly recommend initiating urate-lowering therapy for gout patients with any of the following characteristics:

- One or more subcutaneous tophi.
- Evidence of radiographic damage (any modality) attributable to gout.
- Frequent gout flares, defined as two or more annually.

From the ULT NMA (see Supplementary Appendix 3) and randomized clinical trials (RCTs) of pegloticase (21-23) and lesinurad (24), there was high certainty of evidence regarding the efficacy of ULT in reducing flare frequency (23-26), tophi (21, 23), and SU (23-26). While many Patient Panel participants reported that they were initially hesitant to start ULT, after experiencing improved control of inflammatory symptoms and tophi, they became strong advocates for its earlier institution.

For patients who have previously experienced more than one flare but have infrequent flares (<2/year), we conditionally recommend initiating ULT.

For patients with less frequent flares and no tophi, the potential clinical benefit of ULT would be lower than the ULT benefit for patients with more burdensome gout. In a single study (moderate certainty of evidence), patients with ≤2 previous flares (and no more than 1 gout flare in the preceding year) randomized to febuxostat (vs. placebo) were less likely to experience a subsequent flare (30% vs. 41%, p <0.05) (27).

Specific characteristics for patients with infrequent flares (e.g., SU >9 mg/dL, CKD, CVD) that might influence the risk-benefit assessment were considered, but due to insufficient data for these subgroups, the Voting Panel did not find that these conditions warranted stronger ULT recommendations specific to these subgroups.

For patients with gout experiencing their first gout flare, we conditionally recommend against initiating ULT, with the following exceptions in whom we conditionally recommend initiating ULT: patients with comorbid moderate-to-severe chronic kidney disease (CKD ≥3), SU >9 mg/dL, or urolithiasis.

While conditionally recommending against ULT initiation following the first gout flare in an "uncomplicated" gout patient, the Voting Panel considered Patient Panel input recognizing that there may be patients who would prefer (or benefit from) ULT, underscoring the need for shared decision-making. As noted above, data from the RCT in patients with ≤2 previous flares (and no more than 1 gout flare in the preceding year) supported the benefit of ULT on reduction of SU and gout flare risk (27). For patients with moderate-to-severe CKD (e.g., stage 3 or worse), there is a higher likelihood for gout progression and development of clinical tophi (28-30). Furthermore, treatment options for gout flare are limited in this population, and there may be added benefit of using ULT to prevent progression of renal disease (31). Similarly, patients with markedly elevated SU (> 9 mg/dL) are more likely to experience gout progression (26, 32). For patients with a history of urolithiasis, allopurinol and febuxostat provide benefit, as both medications lower 24-hour urinary uric acid excretion more than placebo (33). Among patients with calcium oxalate stones and hyperuricosuria, allopurinol (300 mg/day) is superior to placebo in reducing the three-year incidence of stone-related events (34).

For individuals with asymptomatic hyperuricemia, we conditionally recommend against initiating ULT.

For patients with asymptomatic hyperuricemia, RCTs (designed to study CVD outcomes) demonstrated significant reduction in incident gout flares over 3 years. However, the development of incident gout was low for both ULT and placebo arms (<1% vs. 5%) (35, 36). In other words, 24 patients would need to be treated with ULT for 3 years to prevent a single (incident) gout flare. From observational studies, among patients with asymptomatic hyperuricemia with SU >9mg/dL, only 20% went on to develop gout within 5 years (32). The Voting Panel felt that, on average, for the majority

of patients with asymptomatic hyperuricemia (including those with comorbid CKD, CVD, urolithiasis, or hypertension), the benefits of ULT would not outweigh potential treatment costs or risks for the large number of patients unlikely to progress to gout. This is also the case for patients with asymptomatic hyperuricemia with MSU crystal deposition as noted on imaging tests such as ultrasound or DECT.

Recommendations for Choice of Initial Urate-Lowering Therapy in Patients with Gout (Table 2, Figure 2 – Supplementary Appendix 7)

For patients starting ULT, we strongly recommend:

- Allopurinol over all other urate-lowering therapies as the preferred first-line agent for all patients, including those with moderate-to-severe CKD (CKD ≥3).
- Either allopurinol or febuxostat over probenecid for patients with moderate-to-severe CKD (CKD ≥3).
- Against pegloticase as a first-line therapy.
- Starting with low dose allopurinol ≤100 mg/day (and lower in patients with CKD≥3), febuxostat ≤40 mg/day or probenecid* 500 mg once to twice daily with subsequent dose titration over starting at a higher dose (*recommendation for use of low dose probenecid is a **conditional** recommendation).
- Administering concomitant anti-inflammatory prophylaxis therapy (e.g., colchicine, NSAIDs, prednisone/prednisolone) over no anti-inflammatory prophylaxis therapy.
- Continuing concomitant anti-inflammatory prophylaxis therapy for 3-6 months rather than <3 months, with ongoing evaluation and continued prophylaxis as needed if the patient continues to experience gout flares.

The Voting Panel strongly recommended allopurinol as the preferred first-line agent given its efficacy when dosed appropriately (often required doses >300mg/d (37) up to a maximum FDA approved dose of 800mg/d (38), tolerability, safety, and lower cost. Using a lower starting dose mitigates safety issues specific to allopurinol hypersensitivity syndrome (AHS) (39, 40). The Voting Panel indicated that an optimal trial of oral medication would be appropriate prior to pegloticase due to cost differences and potential adverse effects of the latter medication.

A lower starting dose of any ULT reduces the risk of flare associated with initiation (41). The Patient Panel voiced a strong preference for safer ULT prescribing regimens through lower starting doses with subsequent dose escalation, even if such regimen required more blood draws and provider visits, over alternate regimens (e.g., starting higher doses) that might incur more risk. Even lower starting allopurinol doses (e.g., ≤50 mg/day) should be considered in patients with CKD. While higher starting dose and CKD are associated with risk of AHS (39), patients with CKD may still require dose titration above 300 mg/day to achieve SU target (42, 43). A population pharmacokinetic–pharmacodynamics study found that larger body size and diuretic use indicated the need for higher allopurinol doses to achieve greater urate

reduction. Worse renal function only had a modest negative impact on urate reduction (44). Other studies have demonstrated that allopurinol dose escalation can be done safely in this population (40, 45).

There is moderate certainty of evidence to support the strong recommendations to use anti-inflammatory prophylaxis therapy when initiating ULT based on 8 RCTs (41, 46-52) and 2 observational studies (53, 54). Continuation of prophylaxis for at least 3-6 months after ULT initiation was recommended because shorter durations were associated with flares upon cessation of prophylaxis (55, 56). After cessation, monitoring for flare activity and continuation of anti-inflammatory treatment as needed if the patient continues to experience flares was recommended.

Timing of ULT initiation

When the decision is made that ULT is indicated while the patient is experiencing a gout flare, we conditionally recommend starting ULT during the gout flare over starting ULT after the gout flare has resolved.

Starting ULT during a flare has conceptual benefits including the time-efficiency offered by initiating therapy during the concurrent flare visit rather than risk the patient not returning for ULT initiation. Furthermore, input from Patient Panel emphasized that patients are likely to be highly motivated to take ULT by symptoms related to the current flare. On the other hand, concerns about starting ULT during a flare include potential extension or worsening of a flare, as well as the possibility of information overload for patients that may lead to conflating flare management and long-term ULT. Two small RCTs (57, 58) and an observational study (59) support the hypothesis that starting ULT during a flare does not significantly extend flare duration or severity. Input from the Patient Panel, citing their own ability to simultaneously process information related to flare treatment and ULT initiation together, with their preference to start on a treatment path sooner to prevent future flares, influenced the final recommendation. As with all conditional recommendations, there may be patient factors or preferences that would reasonably support the alternative of delaying ULT initiation until the flare has resolved.

For all patients on ULT (Table 3, Figure 2 – Supplementary Appendix 7), we strongly recommend:

- A treat-to-target management strategy that includes ULT dose titration and subsequent dosing guided by serial serum urate (SU) measurements to achieve a target SU, rather than a fixed-dose ULT strategy.
- Achieving and maintaining a SU target of <6 mg/dL over use of no target.

We recommend using a treat-to-target management strategy to optimize patient outcomes by achieving and maintaining a SU target of <6 mg/dL over a fixed-dose strategy. There is moderate- and high-quality evidence supporting these 2 recommendation. In a RCT from the United Kingdom (43), patients randomized to a nurse-led, treat-to-target protocol demonstrated greater ULT adherence, lower SU concentrations, reduction in tophi and a lower proportion with frequent (≥2) gout flares at 24-months, compared with patients randomized to general practitioner led usual care (an

approach more often characterized by a fixed-dose strategy when ULT is administered). Two separate pharmacist-led interventions in the U.S., both incorporating treat-to-target strategies, were superior to usual care in terms of treatment adherence, SU outcomes, and higher allopurinol dosing (60, 61). Additional studies provide support for ULT dose escalation to achieve target SU levels, including dose titration of allopurinol in patients with CKD (40, 43). While a specific dose titration schedule is left to provider and patient to individualize based on patient comorbidities and preferences, ULT titration should occur over a reasonable timeframe (e.g., weeks-to-months, not years) to prevent "treatment inertia" (62). In contrast to the 2012 ACR gout guidelines, due to lack of supporting evidence for additional specific thresholds, we do not define further thresholds for patients warranting more intensive ULT.

For all patients on ULT, we conditionally recommend delivery of an augmented protocol of ULT dose management by non-physician providers to optimize the treat-to-target strategy that includes patient education, shared decision-making, and treat-to-target protocol.

Based on recent nurse- (43) and pharmacist-led (60, 61) interventions, the Voting Panel supported the benefit of an augmented delivery-of-care using patient education and shared decision-making through implementation of a treat-to-target protocol over usual care. However, the panel recognized that these resources may not be available in all healthcare settings, and that the key is for the treating provider (which could be the treating physician) to educate the patient and implement a treat-to-target protocol.

Duration of ULT

We conditionally recommend continuing ULT indefinitely over stopping ULT.

For patients in clinical remission on ULT (e.g., no flares for >=1 year and no tophi (63)), the Voting Panel considered ULT cessation or tapering. In a single case series where ULT was withheld in patients in clinical remission with years of well-controlled SU prior to cessation, only 13% (27/211) patients whose SU remained <7 mg/dL off ULT had no flares during a 5-year follow-up period. Furthermore, patients with higher SU concentrations after withholding therapy flared more frequently with greater likelihood of flares associated with higher SU levels (37). The Patient Panel voiced concerns about a return or worsening of gout symptoms, tophi, or joint damage with ULT cessation. If therapy is well-tolerated and not burdensome, they expressed a preference to continue treatment.

Recommendations for patients on specific ULT medications (Table 4, Figure 3 – Supplementary Appendix 7)

Allopurinol

- **We conditionally recommend testing HLA-B*5801 prior to starting allopurinol for patients of Southeast Asian descent (e.g., Han Chinese, Korean, Thai) and African-American patients over not testing HLA-B*5801.**

- **We <u>conditionally recommend against</u> universal testing for HLA-B*5801 prior to starting allopurinol in patients of other ethnic or racial background over testing HLA-B*5801.**
- **As noted above, we <u>strongly recommend</u> starting allopurinol in daily doses <u><</u>100 mg (and lower in patients with CKD) over starting at a higher dose.**

The HLA-B*5801 allele is associated with a markedly elevated risk for AHS (64, 65). The prevalence of HLA B*5801 is highest among persons of Han Chinese, Korean, and Thai descent (7.4%) (66), lower among African-Americans (3.8%), and even lower among Caucasians and Hispanics (0.7% each) (66). Testing for this allele among Asians and African-American patients was reported to be cost-effective (incremental cost-effectiveness ratios [ICERs] <$109,000/quality-adjusted life-years) (67). Asian and African-American patients on allopurinol both have increased a 3-fold risk of AHS compared to Caucasian patients on allopurinol (68).

For patients with a prior allergic response to allopurinol who cannot be treated with other oral ULT, we <u>conditionally recommend</u> allopurinol desensitization, though the level of evidence supporting this recommendation was very low (69, 70). The Voting Panel recognized that desensitization protocols (69, 70) are not commonly used, with limited experience among the majority of currently practicing rheumatologists.

<u>Febuxostat</u>

We <u>conditionally recommend</u> that patients on febuxostat with a history of CVD or a new CVD-related event to switch to an alternative oral ULT agent if available and consistent with other recommendations in this guideline.

At the Voting Panel meeting, there was much discussion about the data, Patient Panel input, and interest to provide recommendations consistent with the FDA Black Box Warning for febuxostat (71). The Voting Panel considered data from the CARES RCT (72) and 2 observational studies (73, 74). In the FDA-mandated CARES trial of febuxostat versus allopurinol (72), there was no difference between the two arms in the primary composite CVD endpoint. Febuxostat, however, was associated with a higher risk of CVD-related death and all-cause mortality (driven by CVD deaths) compared with allopurinol, but there was no association with the other three secondary CVD outcomes (nonfatal myocardial infarction, nonfatal stroke, or urgent revascularization for unstable angina). Interpretation of these results is complicated by a high dropout rate with a majority of deaths occurring after ULT discontinuation (72). Moreover, the lack of an untreated control group means the absolute CVD risk related to febuxostat is unknown. A large observational study (recruitment not selected for CVD) did not find an increased risk of CVD or all-cause mortality associated with febuxostat initiation compared with allopurinol using methods to address confounding by indication (73). Another study using a managed care database reported lower risk of any major CVD event among febuxostat initiators than allopurinol initiators, though confounding by indication may not have been adequately addressed (74). The Patient Panel representative stated members would be willing to accept "some" incremental CVD risk as long as the treatment

adequately controlled their gout. Thus, as for many such decisions with conditional recommendations, providers and patients should engage in shared decision-making when considering febuxostat in patients at high risk for CVD.

Uricosurics

For patients considered for, or on uricosuric treatment, we conditionally recommend against checking urinary uric acid over checking urinary uric acid.

For patients on uricosuric treatment, we conditionally recommend against alkalinizing the urine.

A single observational study demonstrated that higher levels of 24-hour urinary uric acid levels and higher levels undissociated urinary uric acid were associated with urolithiasis (75). However, the Voting Panel indicated that the challenges with 24-hour urine collection or nomogram-based testing, which can both be affected by diet, negate the utility of such testing in light of a very low level of evidence.

We found no evidence to support a recommendation of checking urinary uric acid while on uricosuric treatment, or for alkalinizing the urine. The Voting Panel supported standard best practice that patients with known renal calculi or moderate-to-severe CKD (CKD≥3) should not be treated with uricosurics. For patients treated with uricosurics, patients should be counseled about adequate hydration, but need not be prescribed alkalinizing agents given lack of evidence for efficacy.

As use of uricosurics remains infrequent, we did not formally vote on indications for uricosuric medications. However, we concur with the 2012 guidelines that add-on therapy to partially responsive XOI treatment can result in improved SU control (24, 25, 76).

When to Consider Changing ULT Strategy (Table 5, Figure 2 – Supplementary Appendix 7)

For patients on their first xanthine oxidase inhibitor (XOI), who have persistent SU >6 mg/dl despite maximum-tolerated or FDA-indicated XOI dose and have continued frequent gout flares (≥2 flares/year) OR non-resolving subcutaneous tophi, we conditionally recommend switching to a second XOI over adding a uricosuric agent.

Several lesinurad studies demonstrate the benefit of adding a uricosuric medication to XOI treatment (25, 76). However, we found no studies directly addressing the choice in the above PICO resulting in the conditional recommendation for switching to a second XOI after first XOI failure.

For patients with gout for whom XOI, uricosurics, and other interventions have failed to achieve SU target, and who continue to have frequent gout flares (≥2 flares/year) OR non-resolving subcutaneous tophi, we strongly recommend switching to pegloticase over continuing current ULT.

For patients with gout for whom XOI, uricosurics, and other interventions have failed to achieve SU target, but who have infrequent gout flares (<2 flares/year) AND no tophi, we strongly recommend against switching to pegloticase over continuing current ULT.

In clinical trials, patients with were 3 or more self-reported gout flares during the previous 18 months; 1 or more tophi; and gouty arthropathy, defined clinically or radiographically as joint damage due to gout were randomly assigned to pegloticase treatment. Patients additionally had contraindication to treatment with allopurinol or history of failure to normalize UA despite 3 or more months of treatment with the maximum medically appropriate allopurinol dose (determined by the treating physician). For these patients with frequent gout flare or non-resolving subcutaneous tophi, clinical trials demonstrate improved serum urate, low frequency of flares (77), reduction in tophi (21), and improved quality of life (22) for patients receiving pegloticase. However, these outcomes come at high cost, twice monthly infusions and potential for serious allergic reactions. For patients with infrequent gout flares and no tophi, we would expect a similar benefit in serum urate reduction. Because, patients with only infrequent flares, the magnitude of benefit would be substantially smaller than in patients with frequent flares) and there would be no benefit in reduction of tophi when no tophi are present. The harms and costs of administering pegloticase would likely be similar in patients with mild versus severe disease, resulting in limited benefit and appreciable harm along with very high costs, leading the panel to conclude that the costs and harms clearly outweigh the benefits. This along with strong patient panel statements that they would not want to get twice-monthly infusions to prevent infrequent gout flares resulted in strong recommendation against using pegloticase for patients with mild disease.

The above scenarios represent extremes of gout clinical severity resulting in strong "for" and "against" recommendations. The Voting Panel considered intermediary scenarios, but given the potential variability, the panel opted simply to defer to provider judgment, balanced with patient preferences, regarding the optimal treatment strategy for individuals not described above. To clarify, as outlined above, there is a strong recommendation to follow a treat-to-target management strategy for all patients on ULT. However, the recommendation for treat-to-target strategy is not absolute and not meant to be pursued at "any cost". Even strong recommendations require sound clinical judgment to balance of potential clinical benefits and harms (including costs) of medical decisions (78)s.

Gout Flare Management (Table 6, Figure 4 – Supplementary Appendix 7)

For patients experiencing a gout flare, we strongly recommend using colchicine, NSAIDs, or glucocorticoids (oral, intra-articular or intramuscular) as appropriate first-line therapy for gout flares over IL-1 inhibitors or ACTH.

When colchicine is the chosen agent, we strongly recommend low-dose colchicine over high-dose colchicine given similar efficacy and a lower risk of adverse effects.

For patients experiencing a gout flare, we conditionally recommend using topical ice as an adjuvant treatment over no adjuvant treatment.

For patients experiencing a gout flare for whom the above anti-inflammatory therapies are either poorly tolerated or contraindicated, we conditionally recommend using IL-1 inhibition over no therapy (beyond supportive/analgesic treatment).

For patients who are unable to take oral medications, we strongly recommend glucocorticoids (intramuscular, intravenous or intra-articular) over IL-1 inhibitors or ACTH.

The Voting Panel's recommendation of colchicine, NSAIDs, or glucocorticoids as preferred first-line therapies was based on substantial trial data demonstrating efficacy, relative low cost (vs. IL-1 inhibitors and ACTH), and tolerability of these agents in flare management, particularly when dosed early after symptom onset. Appropriate dosing and duration should be guided by severity of the flare. For colchicine specifically, the FDA-approved dosing should be followed, (1.2mg immediately followed by 0.6mg an hour later, with ongoing anti-inflammatory therapy until the flare resolves). Based on similar efficacy between agents demonstrated in the NMA (79-88), the Voting Panel did not further prioritize between the first-line agents, noting that treatment selection should be driven by patient factors (e.g., comorbidity, access, past experience) as part of shared decision-making. Likewise, parenteral glucocorticoids were favored over alternative agents when oral dosing is not possible. In patients experiencing inadequate response to an initial agent, the Voting Panel cited insufficient evidence to make specific recommendations regarding subsequent anti-inflammatory agents to use. If a patient is unable to tolerate or has contra-indications to any of the other conventional alternatives, the Voting Panel conditionally recommended the use of IL-1 inhibitors (84, 88-90), recognizing concerns over patient access due to cost. Noting limited supporting data (91), the Voting Panel recommended the use of topical ice as an adjuvant therapy for flares.

Underscoring the importance of optimal flare management, the Patient Panel emphasized its preference for early intervention given the challenges of engaging a provider in timely manner, including an at-home "medication-in-pocket" strategy for patients who are able to identify the early signs of flare onset. In the absence of "rapid" access to an effective oral medication, the Patient Panel also indicated its preference for an injectable therapy in appropriate circumstances to achieve pain relief as quickly as possible.

***Management of Lifestyle Factors* (Table 7, Figure 5 – Supplementary Appendix 7)**

For patients with gout, regardless of disease activity, we conditionally recommend:

- Limiting alcohol intake
- Limiting purine intake

- Limiting high-fructose corn syrup
- Using a weight loss program for those patients who are overweight/obese (no specific program endorsed)

For patients with gout, regardless of disease activity, we <u>conditionally recommend against</u>

- Adding vitamin C supplementation

The Voting Panel discussed data demonstrating the important genetic contributions to the development and severity of hyperuricemia and gout (92, 93). The Voting Panel informally recommend that providers be mindful when soliciting dietary habits from patients and ensuring that discussions regarding dietary recommendations are not misinterpreted as "patient-blaming" as patients frequently feel stigmatized when discussing gout with their providers (94). Dietary modifications likely yield only small changes in SU, but dietary factors may serve as triggers for flares, and patients frequently seek advice on dietary management.

<u>Alcohol</u>

SU level among patients who limited or abstained from alcohol was 1.6 mg/dL lower compared with patients who did not do so (95, 96). From a recent diet and genetics meta-analysis that was noted above (92), the impact of diet or individual food items on SU was small. As an example, a unit of beer raised SU by 0.16 mg/dL. The effects of a healthy diet, Mediterranean diet or DASH diet were even smaller (92).

In a case-crossover study, consuming >1-2 alcoholic beverage servings in the prior 24 hours was associated with 40% higher risk of gout flare than periods without alcohol consumption, with a dose-response relationship (97). A small cohort study demonstrated that despite ULT, heavy drinkers (30 or more units of alcohol a week) were more likely to continue having gout flares compared with those who do did not drink heavily (95).

<u>Low Purine Diet</u>

From the same case-crossover study above, there was a dose-response relationship between increasing purine intake and risk of gout flare (98). However, a small RCT (n=29, all on ULT and SU at target at the start of trial) using an educational intervention focused on low purine intake did not result in lower SU concentrations compared with usual diet, despite significant improvements in patient dietary knowledge (99).

<u>High-Fructose Corn Syrup</u>

Ingestion of 1 g of fructose/kg of body weight increases SU by 1 to 2 mg/dL within 2 hours of ingestion (100). In the National Health and Nutrition Examination Survey (NHANES) artificially sweetened carbonated beverage consumption was associated with higher SU levels (101). In the Nurses' Health Study, greater consumption of high-fructose corn syrup

was associated with higher risk of incident gout (102). However, there were no data focused on patients with existing gout.

Weight Loss

The Voting Panel considered the impact of weight loss and specific dietary programs (including Dietary Approaches to Stop Hypertension [DASH] diet (103)). Due to small sample sizes, studies on patients without gout (or not defined) and risk of bias assessments, the certainty of the evidence was rated as very low for both SU and flares. Several studies and a systematic literature review (104) addressed weight loss approaches either directly (96, 105) or indirectly (e.g., bariatric surgery (106, 107) or dietary advice (108)). In a small (n=11) cohort of obese patients, a mean weight loss of 5 kg resulted in a mean SU lowering of 1.1 mg/dL (96). In a large cohort study, obesity was associated with a higher risk of incident gout, but not recurrent gout flares (105). However, changes in body mass index (BMI) over time were associated with the risk of recurrent gout flare. An increase in BMI of >5% was associated with a 60% higher odds of recurrent flare, and a decrease in BMI decrease of >5% was associated with a 40% lower odds of recurrent flare compared with those without weight change (-3.5% $\leq$ BMI $\leq$ 3.5%) (105).

A small study of 12 patients undergoing bariatric surgery (mean 34.3 kg weight loss over 12 months) demonstrated a mean SU reduction of 2.0 mg/dL (106). Likewise, gout patients losing weight through bariatric surgery or diet experienced reduced flare frequency (108), although patients undergoing bariatric surgery may actually have a transient increase in flares risk during the first post-operative month (106).

Other Dietary Recommendations

The Voting Panel reviewed the data for cherries/cherry extract and dairy protein. The certainty of evidence drawn mainly from observational studies was low or very low precluding specific recommendations on these topics.

The Panel reached consensus that data on vitamin C was insufficient to support continued recommendation for its use in patients with gout. Two small RCTs (n=29, n=40) found clinically insignificant changes in SU concentrations for patients with gout taking vitamin C (99, 109).

Management of Concurrent Medications (Table 8, Figure 5 – Supplementary Appendix 7)

For patients with gout, regardless of disease activity, we conditionally recommend:

- Switching hydrochlorothiazide to an alternate anti-hypertensive when feasible.
- Choosing losartan preferentially as an anti-hypertensive agent when feasible.

For patients with gout, regardless of disease activity, we conditionally recommend against

- Stopping low-dose aspirin (for patients taking this medication for appropriate indications).
- Adding or switching cholesterol-lowering agents to fenofibrate.

Medications noted above are known to have effects on SU (110). The Voting Panel made recommendations specific to hydrochlorothiazide and losartan (111) in clinical scenarios where such changes are feasible. Switching, stopping, or adding a medication should only be considered when the potential SU/gout benefits exceed the potential risks or harms of the medication change.

Recognizing that there are few practical alternatives to low-dose aspirin, the Voting Panel specifically recommended against its cessation as a means of SU reduction when a patient is on it for an appropriate indication. Likewise, the Voting Panel specifically recommended against adding or switching cholesterol-lowering agents (e.g., statins, bile acid sequestrants, nicotinic acid agents, etc.) to fenofibrate despite its urate-lowering effects (112), as the risks, including side effects of the medication, were felt to outweigh potential benefits. Although likely to render only modest urate-lowering effects, the risk associated with switching from an angiotensin-converting-enzyme inhibitor to losartan seems to be sufficiently low in most patients to merit this change when feasible.

DISCUSSION

This guideline reinforces many of the prior 2012 ACR gout guideline recommendations with updated literature and GRADE methodology, including incorporation of patient preferences and consideration of costs. The Voting Panel endorsed 42 recommendations overall, including 16 strong recommendations focused on ULT management [indications (n=3), initiation (n=6), titration and treat-to-target approach (n=2), approaches following ULT failure (n=2)]; and flare management (n=3).

Data from newer randomized control trials comparing treat-to-target protocols vs. usual care (43, 61) provide the basis for the strong recommendation to use a treat-to-target strategy with ULT that includes a plan to achieve and maintain a SU target of <6 mg/dL to optimize patient outcomes. Findings from the evidence report resonated with the Patient Panel who concurred that their own SU levels correlated with related symptoms and changes in tophi. Patients on our panel articulated that SU assessments reinforced the importance of treatment adherence.

These guidelines reinforce the strategy of starting with low-dose ULT and titrating up to achieve SU target. This strategy mitigates the risk of treatment-related adverse effects (e.g., hypersensitivity) as well as flare risk accompanying ULT initiation (39, 41). Lacking data on optimal titration regimens, the Voting Panel indicated that titration should be individualized, based on available provider resources (e.g., staff for augmented delivery-of-care), patient preferences, the timing of ambulatory encounters, and anti-inflammatory treatments. As described above, ULT titration should occur over weeks-to-months, not years. The 2012 ACR gout guideline recommended titration every 2-5 weeks (5). As noted in

the ACR Gout Quality Measures manuscript, SU should be checked after each dose titration (113). To limit the risk of ULT-related flares, these guidelines reinforce prior recommendations to use concurrent anti-inflammatory prophylaxis for 3-6 months duration, a shorter duration than advocated for in prior recommendations, but one that should be extended in the setting of frequent ongoing flares.

Breaking from prior ACR and EULAR guidelines, this guideline does not specify SU thresholds beyond <6 mg/dL for patient subsets with more severe disease (e.g., those with tophi). This guideline is not intended to contradict or dispute prior recommendations. There is ample evidence that lower SU levels hasten the resolution of tophi (23, 114) and are associated with less frequent gout flares (26, 114), suggesting that lower SU thresholds may be preferable for patients with more burdensome gout. However, in contrast to a treatment strategy using SU target of <6 mg/dL as studied in clinical trials (43), there are no trial data to support lower specific thresholds for such patients.

In contrast to the 2012 ACR gout guideline (which did not consider treatment costs), this document firmly places allopurinol as the preferred first-line ULT for all patients, including those with CKD, due to respective cost of each medication and potential CVD safety concerns that have recently emerged with febuxostat (72).

Under GRADE methodology, recommendations in these guidelines are supported by higher quality studies than the 2012 ACR gout guideline. This resulted in a more focused, less proscriptive document. Where certainty of data is less than moderate or high, conditional recommendations made herein are meant to highlight decisions that would benefit from a shared patient-provider decision-making process. This would include areas such as dietary, lifestyle, or concomitant medications that might affect SU levels, and for which the Patient Panel requested guidance. The Voting Panel aimed to provide guidance without implying any “patient-blaming” for the manifestations of gout given its strong genetic determinants.

Indications for ULT are expanded from the 2012 ACR gout guideline, but consistent with the recent EULAR gout guideline update (10), to include individuals with evidence of radiographic damage attributable to gout (using any modality, regardless of subcutaneous tophi or flare frequency). This strong recommendation recognizes the various ways in which gout may present, and that joint damage is reflective of an active biologic process. Also added were conditional recommendations (which would warrant provider-patient shared medical decision-making discussion) for ULT use in patients with either infrequent flares (<2 flares/year) or a first flare with marked hyperuricemia (SU >9 mg/dL).

Similar to the 2012 ACR guideline, the Voting Panel advocated a “medication-in-pocket” strategy for gout flare management, which the Patient Panel reinforced as a preferred approach.

This updated guideline effort also identifies a number of areas that inform a research agenda for gout management. While data support an active treat-to-target strategy, a question remains as to what may be the optimal SU threshold for patients with more severe disease, in addition to questions about threshold values in specific populations of gout

patients. Gout has differential impact on patients by gender, race or by presence of other comorbidities. This guideline is limited in commenting on specific groups of gout patients as more study on specific patient cohorts to determine if differential recommendations would be needed. Additional studies are needed to determine the safety of prolonged and profound treatment-related hypouricemia (e.g. SU ≤3 mg/dL), an important knowledge gap given that epidemiologic studies have suggested an inverse association of SU with select neurodegenerative disorders (115). While there are associations between SU and other comorbid conditions such as hypertension, CVD and CKD (116)), the benefit (or risk) of ULT in the absence of gout has yet to be established (117).

Gout has been characterized as a "curable disease" (118). As data continue to emerge supporting best practices in management, implementation of these recommendations will ideally lead to improved quality of care for patients with gout.

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Table 1: Indications for pharmacological urate-lowering therapy (ULT)

Recommendation	PICO	Certainty of evidence
For patients with one or more subcutaneous tophi, we **strongly** recommend initiating ULT over no ULT.	1	High
For patients with radiographic damage (any modality) attributable to gout, we **strongly** recommend initiating ULT over no ULT.	2	Moderate
For patients with frequent gout flares (≥ 2/year), we **strongly** recommend initiating ULT over no ULT.	3	High
For patients who have previously experienced more than one flare but have infrequent flares (< 2/year), we **conditionally** recommend initiating ULT over no ULT.	4	Moderate
For patients experiencing their first flare, we **conditionally** recommend **against** initiating ULT over no ULT, with the following exceptions.	5	Moderate
For patients experiencing their first flare and CKD ≥ 3, SU > 9 mg/dL, or urolithiasis, then we **conditionally** recommend initiating ULT.	5	Very low
For patients with asymptomatic hyperuricemia, we **conditionally** recommend **against** initiating any pharmacologic urate-	57	High*

* There is randomized clinical trial data to support the benefit that ULT lowers the proportion of patients developing incident gout. . However, based on the attributable risk, 24 patients would need to be treated for 3 years to prevent a single (incident) gout flare leading to the recommendation **against** initiating ULT in this patient group.

lowering therapy (allopurinol, febuxostat, probenecid) over initiation of pharmacologic ULT.		

Legend: ULT = Urate Lowering Therapy, CKD = Chronic Kidney Disease, SU = serum urate, Asymptomatic Hyperuricemia = Serum urate > 6.8 mg/dL with no prior gout flares or subcutaneous tophi.

Table 2: Recommendations for Choice of Initial Urate-Lowering Therapy in Patients with Gout.

Recommendation	**PICO**	**Certainty of evidence**
For patients starting any ULT, we **strongly** recommend allopurinol over all other urate-lowering therapies as the preferred first-line agent for all patients, including in those with CKD ≥ 3. We **strongly** recommend a xanthine oxidase inhibitor over probenecid for those with CKD stage 3 or worse.	10	Moderate
For allopurinol and febuxostat, we **strongly** recommend starting at a low dose with subsequent dose titration to target over starting at a higher dose (e.g., ≤ 100 mg/d [and lower in patients with CKD] for allopurinol or ≤ 40 mg/d for febuxostat).	7	Moderate
For probenecid, we **conditionally** recommend **starting** at a low dose (500 mg once or twice daily) with dose titration over starting at a higher dose.		
We **strongly** recommend initiating concomitant anti-inflammatory prophylaxis therapy (e.g., colchicine, NSAIDs, prednisone/prednisolone) over no anti-inflammatory prophylaxis. The choice of specific anti-inflammatory prophylaxis should be based upon patient factors.	9	Moderate

We **strongly** recommend continuing prophylaxis for 3-6 months rather than <3 months, with ongoing evaluation and continued prophylaxis as needed if the patient continue to experience flares.	9	Moderate
When the decision is made that ULT is indicated while the patient is experiencing a gout flare, we **conditionally** recommend starting ULT during the gout flare over starting ULT after the gout flare has resolved.	6	Moderate
We **strongly** recommend **against** pegloticase as first-line therapy.	10	Moderate[†]

Table 3: Recommendations for All Patients On Urate Lowering Therapy.

Recommendation	**PICO**	**Certainty of evidence**
For all patients on ULT, we **strongly** recommend a treat-to-target strategy of ULT dose management that includes dose titration and subsequent dosing guided by serial serum urate values to achieve a serum urate target over a fixed, standard dose ULT strategy.	13	Moderate
For all patients on ULT, we **strongly** recommend continuing ULT to achieve and maintain a serum urate target of <6mg/dL over no target.	14	High

[†] Moderate evidence in support of efficacy pegloticase, but due to cost, safety concerns, and favorable benefit to harm ratio other untried treatment options, the recommendation is against using pegloticase as first-line agent.

For all patients on ULT, we **conditionally** recommend delivery of an augmented protocol of ULT dose management by non-physician providers to optimize the treat-to-target strategy that includes patient education, shared decision-making, and treat-to-target protocol.	8	Moderate
We **conditionally** recommend continuing ULT indefinitely over stopping ULT.	19	Very Low

Table 4: Recommendations for patients on specific ULT medications

Recommendation	**PICO**	**Certainty of evidence**
Allopurinol		
We **conditionally** recommend testing HLA-B*5801 prior to starting allopurinol for patients of Southeast Asian descent (e.g., Han Chinese, Korean, Thai) and African-American patients who have a higher prevalence of HLA-B*5801.	12	Very low
We **conditionally** recommend **against** HLA-B*5801 testing in all others		
For patients with a prior allergic response to allopurinol who cannot be treated with other oral ULT, we **conditionally** recommend using allopurinol desensitization.	23	Very low
Febuxostat		

For patients with gout on febuxostat with a history of CVD or a new CV event, we **conditionally** recommend switching to an alternative ULT agent if available and consistent with other recommendations in this guideline.	22	Moderate
Uricosurics		
For patients considered for, or on uricosuric treatment, prior to starting any uricosuric treatment, we **conditionally** recommend **against** checking urinary uric acid over checking urinary uric acid.	28	Very Low
For patients on uricosuric treatment, we **conditionally** recommend **against** alkalinizing urine.	29	Very Low

Table 5: When to Consider Switching ULT Strategy.

Recommendation	**PICO**	**Certainty of evidence**
For patients with gout on their first XOI monotherapy at maximum tolerated or FDA indicated dose who are not at serum urate target and/or have continued frequent gout flares or non-resolving subcutaneous tophi, we **conditionally** recommend switching the first XOI to an alternate XOI agent over adding a uricosuric agent.	24	Very Low
For patients with gout where XOI, uricosurics and other interventions have failed to achieve serum urate target and who have frequent gout flares or non-resolving subcutaneous tophi, we **strongly** recommend switching to pegloticase over continuing current ULT.[‡]	27	Moderate

For patients with gout where XOI, uricosurics and other interventions have failed to achieve serum urate target and who have infrequent gout flares (<2 flares/year) and no tophi, we **strongly** recommend **against** switching to pegloticase over continuing current ULT.[‡]	27	Moderate

Table 6: Gout Flare Management

Recommendation	**PICO**	**Certainty of evidence**
For patients experiencing a gout flare**,** we **strongly** recommend using **oral** colchicine, NSAIDs, or glucocorticoids (oral, intra-articular or intramuscular) as appropriate first-line therapy for gout flares over IL-1 inhibitors or ACTH. (The choice of colchicine, NSAIDs, or glucocorticoids should be made based on patient factors and preferences) When colchicine is the chosen agent, we **strongly** recommend low-dose colchicine over high-dose colchicine given its similar	32	High[§]

[‡] There is moderate certainty of evidence about the efficacy of the benefits, harms and high certainty about the costs of pegloticase. For patients with high disease activity, the magnitude of potential benefits outweigh the harms and costs of the drug. For patients with minimal disease activity, the smaller potential benefits do not outweigh the harms and costs of the drug.

[§] High quality of evidence from NMA supporting canakinumab, which has superior pain score-mean reduction and day 2 joint tenderness-mean reduction. However, the voting panel raised concern that comparator was weak (triamcinolone 40 mg) and that cost issues significantly favor other agents.

efficacy and fewer adverse effects.		
For patients experiencing a gout flare for whom other anti-inflammatory therapies are poorly tolerated or contraindicated, we **conditionally** recommend using IL-1 inhibition over no therapy (beyond supportive / analgesic treatment).	33	Moderate
For patients who are NPO, we **strongly** recommend glucocorticoids (intramuscular, intravenous or intra-articular) over IL-1 inhibitors or ACTH.	32	High[§]
For patients experiencing a gout flare initiating anti-inflammatory treatment, we **conditionally** recommend using topical ice as an adjuvant treatment over no adjuvant treatment.	31	Low

Legend: NSAID = non-steroidal anti-inflammatory drugs, IL = interleukin, ACTH = Adrenocorticotropic hormone, NPO = nil per os

Table 7: Management of lifestyle factors

Recommendation	**PICO**	**Certainty of evidence**
For patients with gout, regardless of disease activity, we **conditionally** recommend limiting alcohol intake.	41	Low
For patients with gout, regardless of disease activity, we **conditionally** recommend limiting purine intake.	42	Low

For patients with gout, regardless of disease activity, we **conditionally** recommend limiting high-fructose corn syrup (HFCS).	43	Very Low
For overweight/obese patients with gout, regardless of disease activity, we **conditionally** recommend weight loss.	46	Very low
For patients with gout, regardless of disease activity, we **conditionally** recommend **against** adding vitamin C supplementation.	48	Low

Table 8: Management of Concurrent Medications

Recommendation	**PICO**	**Certainty of evidence**
For patients with gout, regardless of disease activity, we ***conditionally*** recommend ***switching*** hydrochlorothiazide to an alternate anti-hypertensive when feasible, and ***choosing*** losartan preferentially as an anti-hypertensive when feasible.	47	Very Low
We ***conditionally*** recommend ***against stopping*** low-dose aspirin (in those who are on this medication for appropriate indications).	47	Very Low
We ***conditionally*** recommend ***against adding or switching*** to fenofibrate.	47	Very Low