

# 2012 American College of Rheumatology Guidelines for Management of Gout. Part 2: Therapy and Antiinflammatory Prophylaxis of Acute Gouty Arthritis

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## Introduction

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

for the management and antiinflammatory prophylaxis of acute attacks of gouty arthritis complement our article on

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## Significance & Innovations

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

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

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

Urate-lowering therapy (ULT) is a cornerstone in the management of gout (1) and, when effective in lowering serum urate, is associated with a decreased risk of acute gouty attacks (6). However, during the initial phase of ULT, there is an early increase in acute gout attacks, which has been hypothesized due to remodeling of articular urate crystal deposits as a result of rapid and substantial lowering of ambient urate concentrations (7). Acute gout attacks attributable to the initiation of ULT may contribute to nonadherence in long-term gout treatment, as reported in recent studies (8).

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

Prior gout recommendations and guidelines, at the independent (i.e., non-pharmaceutical industry sponsored) national or multinational rheumatology society level, have

fees, speaking fees, and/or honoraria (less than \$10,000 each) from Novartis, Takeda, and Ardea, has received research funding from Fonterra, and holds a patent from Fonterra for milk products for gout. Dr. Niyyar has received honoraria (less than \$10,000) from the American Society of Nephrology. Dr. Kerr has served as a study investigator (more than \$10,000 each) for Savient and Nuon. Dr. Edwards has received consultant fees, speaking fees, and/or honoraria (less than \$10,000 each) from Savient, Takeda, Ardea, and Regeneron, and (more than \$10,000) from Novartis, and has given expert testimony for Novartis. Dr. Mandell has received consultant fees, speaking fees, and/or honoraria (less than \$10,000 each) from Savient, Novartis, and Pfizer. Dr. Schumacher has received consultant fees (less than \$10,000 each) from Pfizer, Regeneron, West-Ward, and Ardea, and (more than \$10,000) from Novartis. Dr. Terkeltaub has received consultant fees (less than \$10,000 each) from Takeda, Savient, Ardea, BioCryst, URL, Regeneron, Pfizer, Metabolex, Nuon, Chugai, EnzymeRx, Ajanta, Anadys, Celgene, Isis, and Prescription Solutions, and (more than \$10,000) from Novartis, has received grant support from the VA San Diego Healthcare System and the NIH, and has served as a paid investment consultant for Leerink Swann, Medacorp, and Guidepoint.

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

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

So that the voting panel could focus on gout treatment decisions, a number of key assumptions were made, as described in part 1 of the guidelines (1). Importantly, each proposed recommendation assumed that correct diagnoses of gout and acute gouty arthritis attacks had been made for the voting scenario in question. For treatment purposes, it was also assumed that treating clinicians were competent, and considered underlying medical comorbidities (including diabetes mellitus, gastrointestinal disease, hypertension, and hepatic, cardiac, and renal disease) and potential drug toxicities and drug–drug interactions when making both treatment choices and dosing decisions on chosen pharmacologic interventions. The RAND/University of California at Los Angeles (UCLA) methodology used here emphasizes the level of evidence, safety, and quality of therapy, and excludes analyses of societal cost of health care. As such, the ACR gout guidelines are designed to reflect best practice, supported either by level of evidence or consensus-based decision making. These guidelines cannot substitute for individualized direct assessment of the patient, coupled with clinical decision making by a competent health care practitioner. The motivation, financial circumstances, and preferences of the gout patient also need to be considered in clinical practice, and it is incumbent on the treating clinician to weigh the issues not addressed by this methodology, such as treatment costs, when making management decisions. Last, the guidelines for gout management presented herein were not designed to determine eligibility for health care cost coverage by third party payors.

## Materials and methods

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

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

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

**Systematic review.** PubMed and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched to find all articles on gout with the help of an experienced librarian. PubMed is a database of medical literature from the 1950s to the present. CENTRAL includes references from PubMed, Embase, and the Cochrane Review Groups’ specialized registers of controlled trials and hand search results. We used search terminology (hedge) based on the Cochrane Highly Sensitive Search Strategy for identifying

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

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

**Case scenarios.** Through an interactive, iterative process, the CEP developed unique case scenarios of acute gouty attacks with varied treatment options, and the type of attack by severity, duration, and extent of the attack. The objective was to represent a broad spectrum of attacks that a clinician might see in a busy practice. For the case scenarios, the severity of acute gout differed based on self-reported worst pain on a 0–10 visual analog scale (VAS) (19,20). Pain  $\leq 4$  was considered mild, 5–6 was considered moderate, and  $\geq 7$  was considered severe (19,20). Case scenarios also varied by duration of the acute gout attack; we divided this into early (<12 hours), well established (12–36 hours), and late (>36 hours). Case scenarios also varied in the number of active joints involved: 1 or a few small joints, 1 or 2 large joints (ankle, knee, wrist, elbow, hip, or shoulder), and polyarticular involve-

ment (defined as either acute arthritis involving 3 separate large joints, or acute arthritis of 4 or more joints, with arthritis involving more than 1 "region" of joints). Joint regions were defined as: forefoot (metatarsal joints and toes), midfoot (tarsal joints), ankle/hindfoot, knee, hip, fingers, wrist, elbow, shoulder, or other (Figure 1). The management strategies presented were developed for case scenarios involving gouty arthritis, but the intent was that acute bursal inflammation due to gout (e.g., in the prepatellar or olecranon bursa) and small joint involvement would have comparable recommendations for overall management strategies.

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

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

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

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

Severity of Acute Gouty Arthritis Attack	
Intensity of attack based on self-reported pain (0-10 visual analog scale)	
Mild	≤ 4
Moderate	5-6
Severe	≥ 7

Duration of the gouty arthritis attack since onset	
Early	< 12 Hours after attack onset
Well-Established	12 to 36 Hours after attack onset
Late	> 36 Hours after attack onset

Extent of acute gouty arthritis attack	
Based on number of active joints	
One or a few small joints	
1 or 2 large* joints	
* defined as: ankle, knee, wrist, elbow, hip, shoulder	
Polyarticular	
• 4 or more joints, with arthritis involving more than 1 region <sup>§</sup>	
§ Regions defined as: forefoot (metatarsophalangeal joints, toes), midfoot (tarsal joints), ankle/hindfoot, knee, hip, fingers, wrist, elbow, shoulder, other	
• Acute gout attack involving 3 separate large joints is considered as a form of polyarticular gout for this scheme of management	

**Figure 1.** Case scenarios for defining acute gouty arthritis attack features. These case scenarios were generated by the core expert panel, and therapeutic decision-making options for these scenarios were voted on by the task force panel.

ceived potential COI during the guideline development process, and for an additional 12 months afterward.

## Results

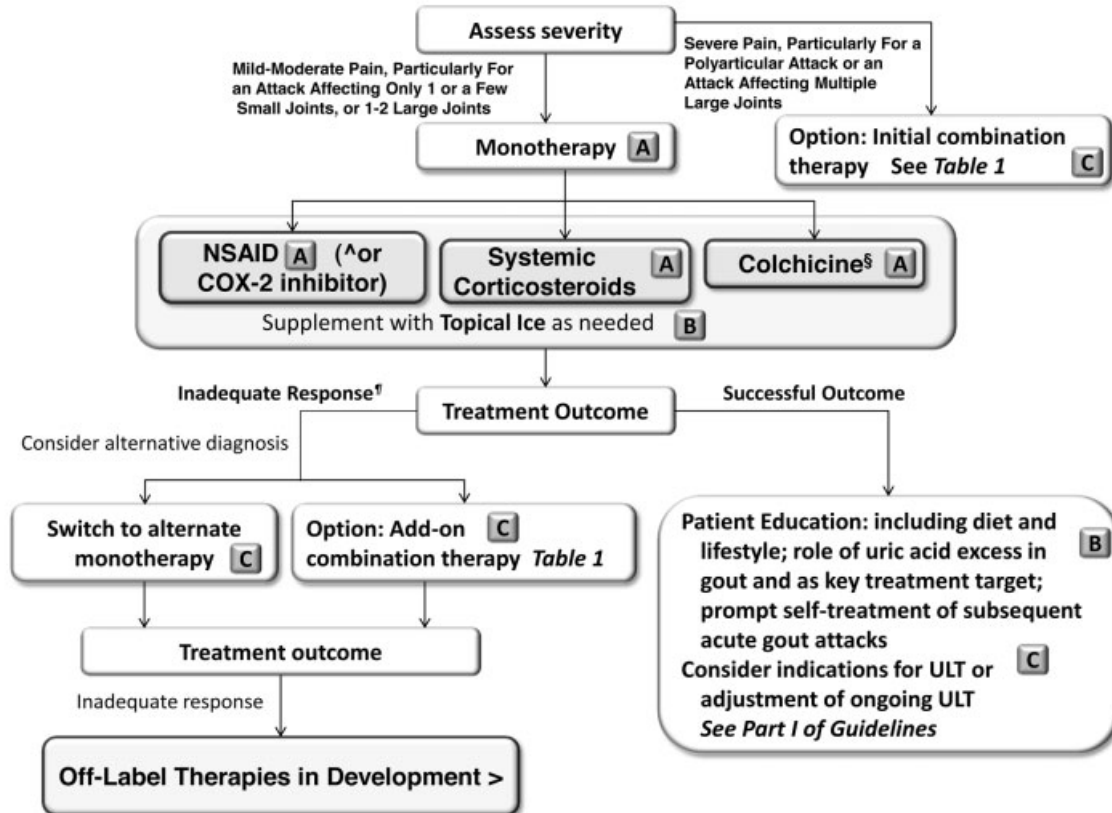
**General principles for treatment of the acute attack of gouty arthritis (“acute gout” management).** Figure 2 summarizes the overall recommendations on treatment of an acute gouty arthritis attack. The TFP recommended that an acute gouty arthritis attack should be treated with pharmacologic therapy (evidence C), and that treatment should be preferentially initiated within 24 hours of onset of an acute gout attack (evidence C). The latter recommendation was based on consensus that early treatment leads to better patient-reported outcomes. The TFP also recommended continuing established pharmacologic ULT without interruption during an acute attack of gout (evidence C), i.e., do not stop ULT therapy during an acute attack. The TFP also recommended patient education, not simply on dietary and other triggers of acute gout attacks, but also providing the patients with instruction so that they can initiate treatment upon signs and symptoms of an acute gout attack, without the need to consult their health care practitioner for each attack (evidence B) (24). Moreover, fundamental patient education includes discussion that gout is caused by body excess of uric acid, and that only effective ULT is potentially “curative” (evidence B) (24).

**Initial pharmacologic treatment of the acute attack of gouty arthritis.** The TFP recommended that the choice of pharmacologic agent should be based upon severity of pain and the number of joints involved (Figure 2). For attacks of mild/moderate gout severity (≤6 of 10 on a 0–10 pain VAS) particularly those involving 1 or a few small joints or 1 or 2 large joints, the TFP recommended that initiating monotherapy was appropriate, with recommended options being oral nonsteroidal antiinflammatory drugs (NSAIDs), systemic corticosteroids, or oral colchicine (evidence A for all therapeutic categories) (25–28) (Figure 2). The TFP also voted that combination therapy was an appropriate option to consider when the acute gout attack was characterized by severe pain, particularly in an acute polyarticular gout attack or an attack involving 1–2 large joints (evidence C) (Figure 2). The TFP did not rank one therapeutic class over another. Therefore, it is at the discretion of the prescribing physicians to choose the most appropriate monotherapy based on the patient’s preference, prior response to pharmacologic therapy for an acute gout attack, and associated comorbidities. Recommendations for appropriate combination therapy options are highlighted in Table 1 and discussed below. The TFP did not vote on case scenarios for specific renal or hepatic function impairment–adjusted dosing and individual contraindications or drug–drug interactions with pharmacologic therapies (29–31).

## Management of an Acute Gout Attack

### General Principles:

- Acute gouty arthritis attacks should be treated with pharmacologic therapy **C** #
- To provide optimal care, pharmacologic treatment should be initiated within 24 hours of acute gout attack onset **C**
- Ongoing pharmacologic ULT should not be interrupted during an acute gout attack **C**



### # 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.

§ Colchicine was recommended as an appropriate option for acute gout if started within 36 hours of symptom onset.

^ Selective COX-2 inhibition with agents available outside the USA such as etoricoxib (Evidence A) was recommended as an option in patients with GI contra-indications or intolerance to NSAIDs, but selective COX-2 inhibition shares many adverse events with NSAID therapy. COX-2 inhibition therapy with celecoxib (Evidence B) requires high doses and has unclear risk-benefit ratio at this time.

† Inadequate response is defined as

< 20% improvement in pain score within 24 hours or  
< 50% at ≥ 24 hours

> Off-label use of biologic IL-1 inhibitor treatment has been investigated for acute gout when non-biologic therapeutic categories are ineffective or contra-indicated, but this approach is not approved for gout by medical regulatory agencies at the time this is written.

**Figure 2.** Overview of management of an acute gout attack. This algorithm summarizes the recommendations by the task force panel on the overall approach to management of an acute attack of gouty arthritis, with further details, as expanded in other figures and tables, referenced in the figure and discussed in the text. ULT = urate-lowering therapy; NSAID = nonsteroidal antiinflammatory drug; COX-2 = cyclooxygenase 2; GI = gastrointestinal; IL-1 = interleukin-1.

**Table 1. Task force panel (TFP) recommendations for combination therapy approach to acute gouty arthritis**

Initial combination therapy is an appropriate option for an acute, severe gout attack, particularly with involvement of multiple large joints or polyarticular arthritis (evidence C)

Acceptable combination therapy approaches include the initial simultaneous use of full doses (or, where appropriate, prophylaxis doses) of either: 1) colchicine and nonsteroidal antiinflammatory drugs (NSAIDs), 2) oral corticosteroids and colchicine, or 3) intra-articular steroids with all other modalities (evidence C)

For patients not responding adequately to initial pharmacologic monotherapy, adding a second appropriate agent is an acceptable option (evidence C)\*

The TFP was not asked to vote on use of NSAIDs and systemic corticosteroids in combination, given core expert panel concerns about synergistic gastrointestinal tract toxicity

\* Assumes that the initial diagnosis of acute gout was correct, and that the lack of adequate response of acute gout was to an appropriate first-line therapy option.

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

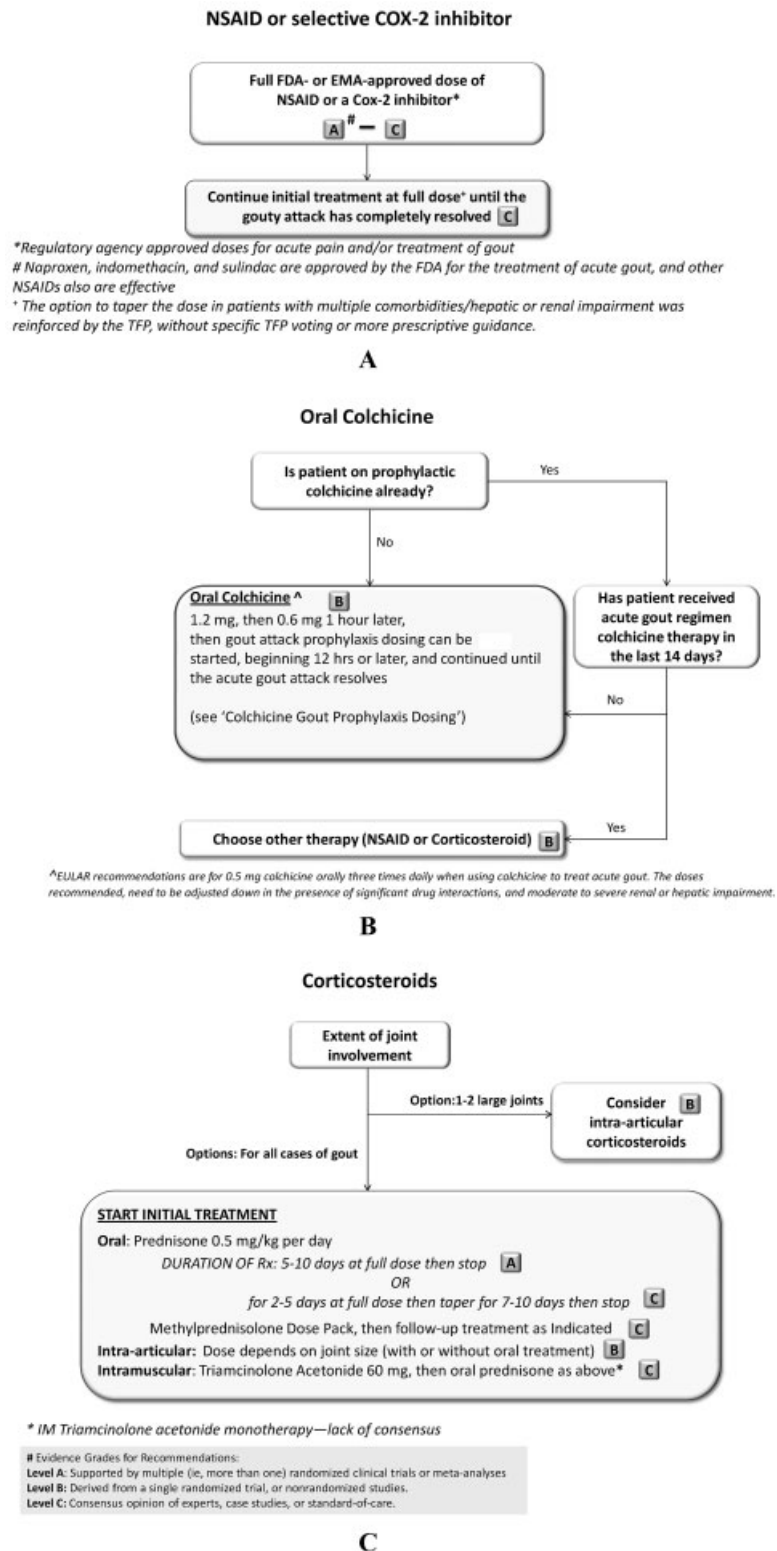
The TFP did not reach a consensus to preferentially recommend any one specific NSAID as first-line treatment. The TFP did recommend continuing the initial NSAID inhibitor treatment regimen at the full dose (if appropriate) until the acute gouty attack completely resolved (evidence C). The option to taper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

**Colchicine.** The TFP recommended oral colchicine as one of the appropriate primary modality options to treat acute gout, but only for gout attacks where the onset was no greater than 36 hours prior to treatment initiation (evidence C) (Figure 3B). The TFP recommended that acute gout can be treated with a loading dose of 1.2 mg of colchicine followed by 0.6 mg 1 hour later (evidence B) (10), and this regimen can then be followed by gout attack prophylaxis dosing 0.6 mg once or twice daily (unless dose adjustment is required) 12 hours later, until the gout attack resolves (evidence C) (26). For countries where 1.0 mg or 0.5 mg rather than 0.6 mg tablets of colchicine are available, the TFP recommended, as appropriate, 1.0 mg colchicine as the loading dose, followed by 0.5 mg 1 hour later, and then followed, as needed, after 12 hours, by continued colchicine (up to 0.5 mg 3 times daily) until the acute attack resolves (evidence C). In doing so, the TFP rationale was informed by pharmacokinetics of the low-dose colchicine regimen, where the exposure to the drug in plasma becomes markedly reduced ~12 hours after administration in healthy volunteers (26). The TFP also evaluated prior EULAR recommendations on a colchicine dosing regimen for acute gout (0.5 mg 3 times daily) and the BSR-recommended maximum dosage for acute gout of 2 mg colchicine per day (10,12).

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

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

Where intraarticular joint injection is impractical (e.g., polyarticular joint involvement, patient preference, or injection of the involved joint site is not in the scope of the provider's usual practice), the TFP recommended oral cor-

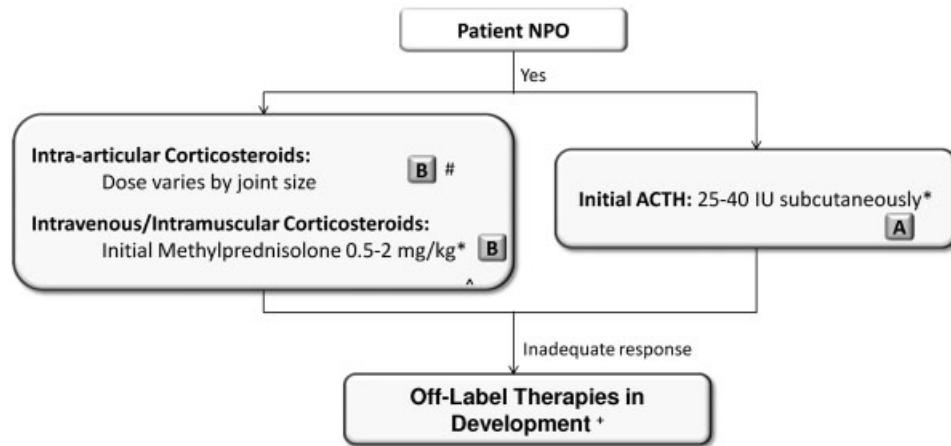


**Figure 3.** Recommendations for the individual pharmacologic monotherapy options for an acute gouty arthritis attack. The figure is separated into distinct parts that schematize use of the first-line therapy options (A, nonsteroidal antiinflammatory drugs [NSAIDs], B, colchicine, and C, corticosteroids), and specific recommendations by the task force panel (TFP). COX-2 = cyclooxygenase 2; FDA = Food and Drug Administration; EMA = European Medical Agency; EULAR = European League Against Rheumatism; IM = intramuscular.

ticosteroids, prednisone, or prednisolone at a starting dosage of at least 0.5 mg/kg per day for 5–10 days, followed by discontinuation (evidence A) (28,43), or alternately, 2–5

days at the full dose, followed by tapering for 7–10 days, and then discontinuation (evidence C). Acknowledging current prevalence of usage, the TFP recommended, as an





\* Can be repeated. Subsequent dose will be determined based on initial response.

\*Lack of consensus: IM Triamcinolone acetonide monotherapy, and IM Ketorolac NSAID therapy.

\* Off-label biologic IL-1 inhibitor treatment, such as with anakinra, has not been approved by medical regulatory agencies for gout at the time this is written, and has unclear risk-benefit ratio.

# 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.

**Figure 4.** Acute gouty arthritis attack management in the nothing by mouth (NPO) patient. The figure schematizes options for management of acute gout in the patient unable to take oral antiinflammatory medications, and specific recommendations by the task force panel on decision making in this setting. ACTH = adrenocorticotropic hormone; IL-1 = interleukin-1; IM = intramuscular; NSAID = nonsteroidal antiinflammatory drug.

appropriate option according to provider and patient preference, the use of an oral methylprednisolone dose pack for initial treatment of an acute attack of gout (evidence C).

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

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

given CEP concerns about synergistic gastrointestinal tract toxicity of that drug combination.

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

For the scenario of a patient with an acute attack of gouty arthritis not responding adequately to initial pharmacologic monotherapy, the TFP advised, without a specific vote, that alternative diagnoses to gout should be considered (Figure 2 and Table 1). For patients not responding to initial therapy, the TFP also recommended switching to another monotherapy recommended above (evidence C) or adding a second recommended agent (evidence C). Use of a biologic interleukin-1 (IL-1) inhibitor (anakinra 100 mg subcutaneously daily for 3 consecutive

days; evidence B) (44,45) or canakinumab 150 mg subcutaneously (46,47) as an option for severe attacks of acute gouty arthritis refractory to other agents was graded as evidence A in the systematic review. Given a lack of randomized studies for anakinra (44,45) and the unclear risk/benefit ratio and lack of FDA approval for canakinumab (46,47) at the time this was written, the authors, independent of TFP discussion, assessed the role of IL-1 inhibitor therapy in acute gout as uncertain.

#### Case scenarios for the nothing by mouth (NPO) patient.

Acute gout attacks are common in the in-hospital setting, where patients may be NPO due to different surgical and medical conditions. In such a scenario, the TFP recommended intraarticular injection of corticosteroids for involvement of 1 or 2 joints (with the dose depending on the size of the joint; evidence B) (42) (Figure 4). The TFP also recommended, as appropriate options, intravenous or intramuscular methylprednisolone at an initial dose at 0.5–2.0 mg/kg (evidence B) (48).

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

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

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

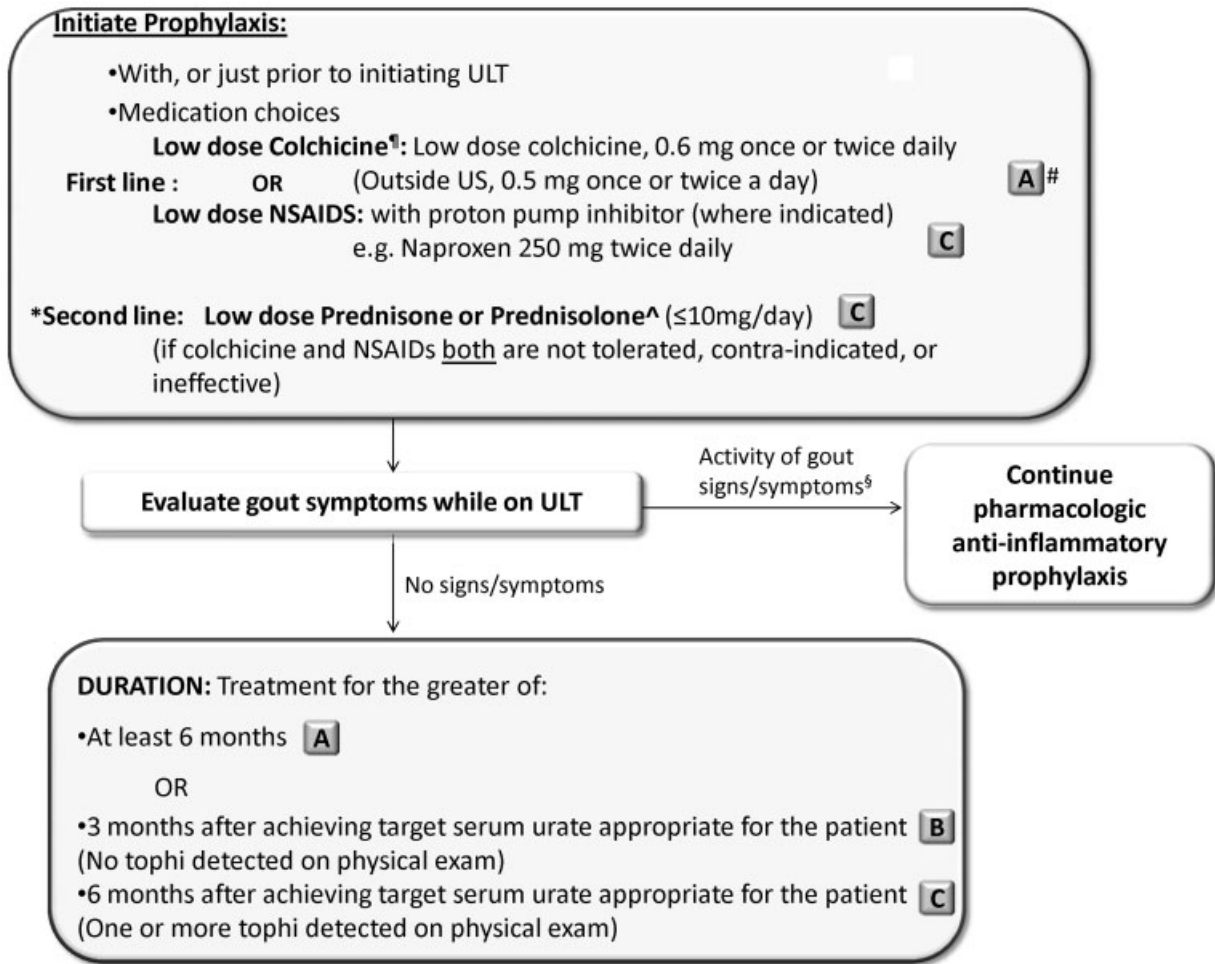
#### Recommendations for pharmacologic antiinflammatory prophylaxis of attacks of acute gout

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

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

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

**Duration of antiinflammatory prophylaxis of acute gout attacks.** The TFP recommended to continue pharmacologic gout attack prophylaxis if there is any clinical evidence of continuing gout disease activity (such as 1 or



<sup>^</sup>Without specific task force panel (TFP) vote, the TFP advised that this measure requires particular, continued attention to risk-benefit ratio

<sup>§</sup> Examples include: acute gouty arthritis in the past 3 months, presence of palpable tophus or tophi, chronic tophaceous gouty arthropathy (with chronic synovitis) in the past 3 months

<sup>\*</sup>Lack of consensus: Prednisone/prednisolone at doses above 10 mg/day.

<sup>¶</sup> The TFP did not specifically address case scenarios involving renal impairment adjusted colchicine dosing for gout attack prophylaxis

#### # 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.

**Figure 5.** Pharmacologic antiinflammatory prophylaxis of gout attacks and its relationship to pharmacologic urate-lowering therapy (ULT). The figure provides an algorithm for use of antiinflammatory prophylaxis agents to prevent acute gout attacks. The schematic highlights specific recommendations by the TFP on decision making on the initiation, options, and duration of prophylaxis relative to pharmacologic ULT therapy, relative to achievement of the treatment objectives of ULT. NSAIDs = nonsteroidal antiinflammatory drugs.

more tophi detected on physical examination, recent acute gout attacks, or chronic gouty arthritis), and/or the serum urate target has not yet been achieved (1). Specifically, the TFP voted to continue the prophylaxis for the greater of:

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

level, where there has been resolution of tophi previously detected on physical examination (evidence C) (Figure 5).

### Discussion

Acute attacks of gout have a detrimental impact on the quality of life of the patient due to pain and dysfunction of affected joints, and acute gout can have a substantial economic and societal impact (58–60). Following a systematic review of the literature and use of a formal group assessment process, we provide the first ACR guidelines for the therapy and antiinflammatory prophylaxis of acute gout attacks.

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

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

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

With respect to antiinflammatory prophylaxis of acute gout attacks, low-dose colchicine or low-dose NSAIDs were recommended as acceptable first-line options by the TFP, with a higher evidence level for colchicine. The use of low-dose colchicine or an NSAID in gout attack prophylaxis is also recommended by EULAR (10). To date, in small clinical trials, low-dose daily oral colchicine was effective in preventing acute gout attacks (3,55), with supportive post hoc analyses in ULT trials (54). The efficacy of

low-dose NSAIDs for gout attack prophylaxis also was described in the febuxostat clinical trial program (54); however, prophylaxis was not the primary focus of the trials. Importantly, recent clinical trials of ULT agents have shown substantial rates of acute gout attacks in the first 6 months after the initiation of ULT, even when prophylaxis with colchicine 0.6 mg daily or low-dose NSAID therapy is administered (51–54). It is noteworthy that the TFP recommended prednisone or prednisolone  $\leq 10$  mg daily as a second-line option for acute gout prophylaxis, with the caveat that there is a lack of published robust data for the use of low-dose oral prednisone for gout prophylaxis. More investigation is needed to improve management for this clinical problem. Assessment of modulation of cardiovascular event risks by colchicine prophylaxis or by NSAIDs (66) in patients with gout would be particularly informative.

Limitations of the recommendations presented in this article include that only  $\sim 30\%$  were based on level A evidence, with approximately half based on level C evidence; this indicates the need for more studies in the aspects of gout management considered here. The process used here was limited by the current trial designs for assessment of acute gout therapies and prophylaxis of antiinflammatory pharmacologic agents in gout. For acute gout studies, most studies were on NSAIDs and involved an active comparator and noninferiority trial design. However, the majority of these studies failed to provide a noninferiority margin, which needs to be defined a priori to assess the validity of these trials. Although the majority of studies assessed pain as the primary outcome for the acute gout trials, there is a lack of a single uniform measure that precludes meta-analysis. Furthermore, there is a lack of consensus on what time period after initiation of therapy constitutes a primary response, since trials ranged from a few hours to 10 days. With the exception of recent analyses of biologic IL-1 inhibitors (56,57), there was a lack of robust clinical trials of gout attack prophylaxis using antiinflammatory pharmacologic agents. Also, the primary measure in these trials is the recurrence of self-reported acute gout attacks, an outcome that has not been validated using Outcome Measures in Rheumatology criteria (67). Efforts are underway to precisely define acute gout attack in gout clinical trials (68). Last, the RAND/UCLA methodology did not address important societal and patient preference issues on treatment costs and cost-effectiveness comparisons between medication choices for acute gout and pharmacologic prophylaxis of acute gout attacks. This is already a pressing question with respect to use of agents, including colchicine and COX-2 selective inhibitors, and would be expected to emerge as a larger issue if biologic IL-1 inhibitors, in late-stage clinical development after phase III studies at the time this was written, obtain regulatory approval for acute gout treatment and prophylaxis.

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

management and prophylaxis of acute gout, and as the risk/benefit ratios of emerging therapies are further investigated.

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

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## AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Terkeltaub had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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