

Treatment Options for Acute Gout

Brian W. Coburn; and Ted R. Mikuls, MD, MSPH

Careful consideration of comorbidities and contraindications are important when determining the appropriate treatment of patients with gout.

Gout is an extremely painful arthritis initiated by innate immune responses to monosodium urate crystals that accumulate in affected joints and surrounding tissues. As a result, gout is characterized by painful arthritis flares followed by intervening periods of disease quiescence. Over time, gout can lead to chronic pain, disability, and tophi. Nearly 10% of those aged > 65 years report having gout. The overall prevalence in the U.S. population approaches 4%.¹

Gout treatment has 2 overarching goals: alleviating the pain and inflammation caused by acute gout attacks and long-term management that is focused on lowering serum urate (sUA) levels to reduce the risk of future attacks. Alleviating the pain and inflammation of an acute attack is often complicated by patient characteristics, namely, other chronic health conditions that frequently accompany gout, such as diabetes mellitus (DM), chronic kidney disease (CKD), hypertension, and cardiovascular disease (CVD).

Patients with gout tend to be older and have multiple comorbidities that require the use of many medications.² Because the VA patient population tends to be older, acute gout and attendant complications of treatment are an important consideration for

VA health care providers (HCPs).

Recently, the American College of Rheumatology (ACR) released management recommendations for gout, including those for the treatment of acute gout.³ The ACR recommends 3 first-line therapies, but limited guidance is provided for deciding among therapies. This article briefly reviews the relevant ACR recommendations and details important comorbidity and concomitant medication considerations in the treatment of acute gout.

ACUTE GOUT CHARACTERISTICS

Acute gout attacks are characterized by a rapid onset and escalation with joint pain typically peaking within 24 hours of attack onset. An acute attack often begins to remit after 5 to 12 days without intervention, but complete resolution may take longer in some patients.⁴ In one study, at 24 hours after attack onset, 16% of patients on placebo had > 50% reduction in pain compared with 70% that had no recovery at all.⁵ By 48 hours, one-third of patients on placebo achieved a 50% reduction in pain.⁶ Acute gout attacks are most commonly monoarticular, although 10% to 40% can involve ≥ 2 joints.⁷ The first metatarsophalangeal (MTP) joint is the initial site of involvement in about 50% of cases and

is eventually observed in the majority of patients with gout (Figure 1).⁷ Other commonly affected joints include the midfoot, ankle, knee, wrist, elbow, and fingers. Most patients still reach peak pain within 24 hours with pain remitting predictably over 1 to 2 weeks. Chronic or variable intensity pain is more common among those with long-standing disease, polyarticular gout, or tophi.

TREATMENT RECOMMENDATIONS

Therapy for acute gout attacks aims to reduce pain and promote a full, early resolution. The ACR recommends pharmacologic therapy as first-line treatment with adjunctive topical ice and rest as needed.³ Typically, monotherapy is appropriate if the individual is experiencing mild-to-moderate pain affecting ≤ 2 joints of any size. Severe pain or attacks affecting multiple joints may benefit from initial combination therapy. Three first-line therapies are available: nonsteroidal anti-inflammatory drugs (NSAIDs) or cyclooxygenase-2 (COX-2) inhibitors, colchicine, or systemic glucocorticoids (Figure 2).

Few studies compare the efficacy of first-line therapeutic categories. There are no clinical trials directly comparing colchicine with NSAIDs or colchicine with glucocorticoids. No difference in mean reduction of pain and no differences in adverse events (AEs) were shown in a trial

Dr. Mikuls is a staff rheumatologist and research scientist at the VA Nebraska Western-Iowa Health Care System. **Mr. Coburn** is a MD-PhD student and Dr. Mikuls is the Umbach Professor of Rheumatology at the University of Nebraska Medical Center, all in Omaha.

Figure 1. Gout Involving the First Metatarsophalangeal Joint

The first metatarsophalangeal joint is the most common site for acute gout attacks, known as podagra.

that compared glucocorticoids with NSAIDs.⁸ Thus, without further study, treatment choices made by HCPs are often guided by factors other than the existence of robust evidence.

Treatment with NSAIDs or COX-2 inhibitors should be initiated at the approved dose and continued until the gout attack has completely resolved. In one study, 73% of patients had pain reduction of $\geq 50\%$ when taking NSAIDs relative to only 27% of patients on placebo.⁸ All available NSAIDs are considered effective, but only 3 NSAIDs are specifically approved for treatment of acute gout (naproxen, indomethacin, and sulindac). There is no evidence supporting one NSAID as being more effective than another; evidence fails to show a meaningful difference.⁸ Limited evidence indicates that selective COX-2 inhibitors, including celecoxib, have similar efficacy as nonselective NSAIDs but may have fewer AEs, driven in part by fewer gastrointestinal (GI) events (6% vs 16% for GI events).⁸

Colchicine has long been used as prophylaxis for acute gout attacks and has been endorsed for the

treatment of acute attacks. Recent evidence suggests that colchicine initially dosed at 1.2 mg followed by a single 0.6-mg dose 1 hour later is as effective with fewer AEs compared with a traditional regimen of 1.2 mg followed by 0.6 mg every hour for up to 6 hours.⁵ About 40% of patients have 50% pain reduction within 24 hours and a 40% absolute risk reduction in AEs on this low-dose regimen. The efficacy of colchicine relative to other therapies is poorly defined, especially for patients presenting longer after attack onset. The ACR guidelines recommend colchicine only if treatment is initiated within 36 hours of attack onset, but this is based solely on expert consensus. Likewise, the above trial for low-dose colchicine did not provide information about dosing beyond the first 6 hours, leaving little guidance for follow-up treatment of residual pain beyond the 32 hours reported.⁵ Traditionally, one 0.6-mg dose is provided every 12 to 24 hours.³

Systemic glucocorticoids are also commonly used in treating acute gout.⁹ There was a small pain reduction benefit for prednisolone,

but the difference was not clinically significant in one clinical trial comparing oral prednisolone 30 mg daily for 5 days vs a combination of indomethacin for 5 days and an initial intramuscular injection of diclofenac 75 mg.¹⁰ The prednisolone group also had fewer patients with AEs, including abdominal pain (0% vs 30%) and GI bleeding (0% vs 11%). The lower incidence of short-term AEs may be a primary benefit of systemic glucocorticoids.¹¹

Intra-articular glucocorticoids are not suggested first-line therapies but are commonly used by rheumatologists.⁹ In an uncontrolled study conducted by Fernández and colleagues, intra-articular glucocorticoid injections helped to quickly resolve 20 out of 20 crystal-proven gout attacks.¹² However, no randomized controlled trials have examined this approach. Although seemingly efficacious, other considerations are important for this modality. Intra-articular glucocorticoids may not be preferred for polyarticular attacks or attacks in difficult-to-aspirate joints. Additionally, intra-articular glucocorticoids have been anecdotally associated with rebound attacks (ie, attacks that occur shortly after resolution without other interventions). However, the Fernández study had no such attacks occur among participants.¹² Finally, septic arthritis must be ruled out as in any case of acute onset monoarticular arthritis.

Biologic agents targeting interleukin-1 (IL-1) are not currently approved for gout, although there is burgeoning data suggesting that this strategy may have substantial merit.¹³ Additionally, there is limited evidence that adrenocorticotropic hormone (ACTH) may provide rapid pain relief when other available therapies are ineffective or

contraindicated. However, ACTH studies have not provided robust trial designs, and drug costs remain substantial, thus limiting the widespread use of ACTH in acute gout.^{14,15} Anti-IL-1 agents and ACTH may both be considered as second-line options if first-line therapies are contraindicated or fail. Careful consideration should be given to AE profiles, patient preferences, and cost.

COMORBIDITIES

Acute gout care, especially in the context of comorbidities, has been identified as a critical treatment concern by an international panel of rheumatologists as part of the 3e (Evidence, Expertise, Exchange) Initiative.¹⁶ However, regular clinical trial exclusion criteria have limited data necessary to guide treatment when comorbidities are present. Therefore, studies of acute gout treatment in the context of disease comorbidity represents a major unmet need in understanding and optimizing gout care.

Chronic Kidney Disease

Chronic kidney disease is common in gout; 20% of patients with gout have an estimated glomerular filtration rate (eGFR) of < 30 mL/min.² Thus, CKD is an important consideration when deciding the best treatment for acute gout. The ACR recommendations do not provide specific guidance on NSAID use in CKD but suggest the potential option of tapering the dose as pain begins to resolve. There is mixed evidence that NSAIDs accelerate CKD progression with the best evidence for high-dose NSAID use.¹⁷ When prescribing the concomitant use of NSAIDs with other medications affecting kidney function, HCPs should consider CKD.

For colchicine, current labeling and evidence indicate that no dose adjustments are needed for stage 3

or better CKD (eGFR \geq 60 mL/min) even among the elderly.^{18,19} Although labeling indicates that a single unadjusted dose (0.6 mg) can be given once every 2 weeks for those with severe CKD (eGFR < 30 mL/min) or for those who are on dialysis, alternative therapies should be considered, as AEs increase with decreasing renal function.¹⁹ Colchicine should not be used in those with eGFR < 10 mL/min.²⁰ All patients who have CKD and are treated with colchicine should be informed of the AEs and closely observed for signs of toxicity, including blood dyscrasias, neuromyopathy, emesis, or diarrhea.

Considering the potential complications for NSAIDs and colchicine, patients with CKD may be good candidates for glucocorticoid therapy, administered either systemically or as an intra-articular injection. Alternatively, second-line agents such as ACTH or IL-1 inhibition may be considered in such patients.

Hypertension

Hypertension is one of the most common comorbidities among patients with gout. It is important for HCP consideration when deciding treatment. Poorly controlled hypertension is a contraindication for both NSAIDs and systemic glucocorticoids. Patients with hypertension in the absence of significant renal impairment may be good candidates for colchicine.

Diabetes and Hyperlipidemia

Glucocorticoids should be avoided if possible in the setting of inadequately controlled type 2 DM (T2DM) or hyperlipidemia. Glucocorticoids exacerbate insulin resistance and stimulate glucose secretion from the liver. This can create substantial and sometimes dangerous fluctuations in circulating glucose concentrations. Additionally, glucocorticoids may increase serum

triglycerides and low-density lipoprotein levels. Thus, patients with T2DM or hyperlipidemia may be good candidates for alternative treatments, such as colchicine or NSAIDs.

Cardiovascular Disease

Cardiovascular disease risk has been shown to increase with the use of COX-2 inhibitors. This risk may be present for all NSAIDs. Current FDA labeling suggests limiting NSAID and COX-2 inhibitor use in patients with a history of myocardial infarction (MI), congestive heart failure, or stroke. Given the potential impact on cardiovascular risk factors, including hypertension, T2DM, and hyperlipidemia, glucocorticoids may not be ideal for patients with known CVD or those at high risk.

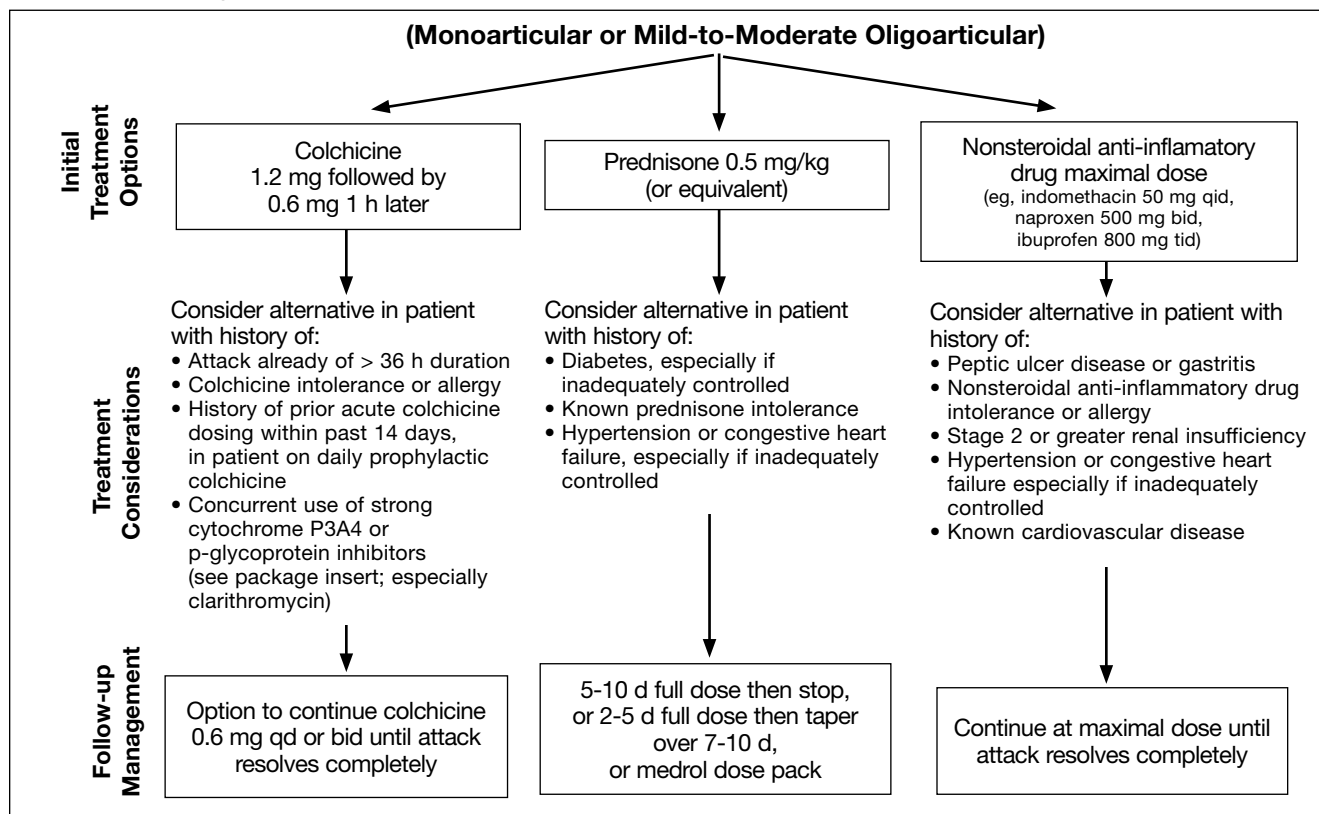
Recent evidence has shown that colchicine use is associated with a lower risk of MI among patients with gout.²¹ These results, in addition to a proposed dual role of IL-1 in both gout and CVD, suggest that either colchicine or IL-1 inhibitors may be rational agents in the treatment of acute gout in the context of CVD.²²

Hepatic Impairment and GI Bleeding

Patients with cirrhosis should avoid NSAID use due to the potential increased bleeding risk from underlying coagulopathy. Additionally, colchicine clearance may be reduced in patients with severe liver impairment, mandating close surveillance when this agent is used. If hepatic impairment is mild to moderate, judicious use of any of the first-line therapies may be appropriate.

Patients with GI bleeding or a history of peptic ulcer disease should avoid NSAID use because of increased bleeding risk. If an NSAID is used, proton pump inhibitors decrease the risk of NSAID-associated mucosal damage.

Figure 2. Management of Acute Gout Attack^a



American College of Rheumatology (ACR) guidelines recommend 3 first-line treatments for acute gout attacks. Proper consideration of comorbidities helps optimize treatment.

^aIf inadequate response (< 50% pain decrease at 24 hours), switch agent or consider adding an additional agent; for severe gout attacks (eg, polyarticular), combination therapy may be considered. Adapted with permission from an unpublished figure created by Michael Pillinger, MD.

DRUG INTERACTIONS

Colchicine is metabolized by the cytochrome P450 3A4 enzyme (CYP3A4) and is a substrate for P-glycoprotein (P-gp). Therefore, concomitant use of colchicine with potent inhibitors of CYP3A4 or P-gp should be avoided when possible. These agents include macrolide antibiotics (clarithromycin), calcium channel blockers (verapamil and diltiazem), and cyclosporine (commonly used in transplant patients who are at high risk for gout). New evidence-based dosing recommendations indicate that no dose reduction is required with azithromycin.²³

Nonsteroidal anti-inflammatory drugs are contraindicated with the concomitant use of angiotensin-converting enzyme (ACE) inhibitors and/or diuretics. Prostaglandin production is decreased while using NSAIDs, resulting in increased constriction of afferent renal arterioles and decreased glomerular filtration pressure. This physiologic effect of NSAIDs can be exacerbated when used in combination with ACE inhibitors or diuretics, both of which can also reduce glomerular filtration pressures. Combination therapy with either ACE inhibitors or diuretics increases the risk for NSAID-mediated acute kidney injury.

Additionally, NSAID use should be avoided in patients taking anticoagulants such as warfarin or heparin due to increased bleeding risk.

DIAGNOSIS

Diagnosis is a key component of proper treatment of acute gout. A gout diagnosis is usually made based on clinical signs and symptoms, including sudden onset of pain that peaks within 24 hours, past history of acute self-limited attacks of arthritis, first MTP involvement, and an elevated sUA. However, not all these factors must be present. In a study conducted by Janssens and colleagues, these

factors plus additional demographics had a sensitivity of 90% and specificity of 65% when compared with crystal diagnosis.²⁴ However, a normal sUA level does not exclude gout as a diagnosis due to the uricosuric effect of the inflammatory process.²⁵ In fact, one observational cohort recorded an average sUA decrease from baseline of 2 mg/dL during an acute gout attack.²⁶

Alternative diagnoses, including septic arthritis, should be considered, particularly in the context of treatment failure (< 50% reduction in pain) within the first 24 to 48 hours. A definitive diagnosis is made by identifying negatively birefringent crystals in the synovial fluid of the affected joint (using polarized microscopy) with negative cultures. In the absence of crystal confirmation, there is an emerging role for imaging in gout diagnosis, including the use of ultrasound and dual-energy computed tomography.²⁷

LONG-TERM TREATMENT CONSIDERATIONS

During treatment for acute gout attacks, urate-lowering therapy that was initiated before the attack should not be discontinued.²⁸ There is no evidence to suggest that current urate lowering has any AEs during attacks. However, removing treatment may increase sUA levels, precipitating attacks in other joints by “destabilizing” crystals still present. Current recommendations also state that urate-lowering therapy may be started during an attack despite traditionally being deferred until the attack has resolved.²⁸ In a randomized trial comparing a group starting allopurinol 300 mg during an attack vs a placebo group (with all patients receiving anti-inflammatory treatment for the acute attack), there was no difference in pain out-

comes.²⁹ Regardless of the chosen timing, lowering and maintaining sUA \leq 6.0 mg/dL is the primary method for minimizing long-term risk of gout attacks.²⁸

Health care providers should discuss with patients the likely need for indefinite urate-lowering therapy while noting that attacks related to therapy initiation are relatively common.³⁰ Current guidelines recommend starting urate-lowering therapy in low doses (\leq 100 mg/d for allopurinol) and titrating to achieve and maintain the target sUA level. Along with the judicious use of anti-inflammatory prophylaxis, this may minimize attacks related to therapy initiation.^{3,28} By lowering and maintaining sUA below the target level, monosodium urate crystals will dissolve, thereby eliminating the major inciting factor of acute attacks.

Other day-to-day triggers such as alcohol, meat or seafood consumption, and dehydration exist for some patients with gout. Patients should be informed of these inciting factors, as they could potentially be avoided, reducing the risk of future gout attacks. It is important to recognize, however, that dietary or behavioral interventions have generally yielded only modest sUA reductions. For the majority of patients, therefore, reduction and maintenance of sUA \leq 6.0 mg/dL requires pharmacologic intervention.

CONCLUSIONS

Gout attacks should be treated immediately with pharmacologic treatment when contraindications are absent. First-line treatment options include NSAIDs, colchicine, and systemic glucocorticoids. Use of these modalities can be complicated because of comorbidity and concomitant medication use that is

prevalent among patients with gout. Comorbidities commonly limiting treatment choice include hypertension (NSAIDs, glucocorticoids), CKD (NSAIDs, colchicine), CVD (NSAIDs, COX-2 inhibitors, glucocorticoids), T2DM (glucocorticoids), and liver disease (NSAIDs, colchicine). Careful consideration must be given to these comorbidities and contraindications as well as patient preferences. ●

Author disclosures

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