

Diagnosis and Management of Acute Gout

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Risk factors for the development of acute gout include hyperuricemia, increased age, and a family history of gout. Consumption of alcohol and purine-rich foods and medications such as thiazide diuretics, loop diuretics, and cyclosporine contribute to the development of hyperuricemia. Hypertension, diabetes, obesity, and chronic renal failure are often associated with gout. When gout is suspected, aspiration of the affected joint should be performed to confirm the presence of intracellular negatively birefringent needle-shaped crystals by compensated polarized light microscopy. However, in some situations this is not practical. The most recent European League Against Rheumatism report proposes ten key recommendations for the diagnosis of gout:¹ (1) The rapid onset of severe pain and swelling (especially with overlying erythema) within 6 to 12 hours is highly suggestive of crystal inflammation. However, this is not specific for gout. (2) Classic podagra, involvement of the first metatarsophalangeal joint, has a high sensitivity and specificity, but is not definitive without crystal identification. (3) Definitive diagnosis is made by demonstration of monosodium urate (MSU) crystals in synovial fluid or tophus. (4) Synovial fluid from undiagnosed inflammatory arthritis should be routinely examined for the presence of monosodium urate crystals. (5) Identification of MSU crystals may be possible in intercritical periods (between attacks). (6) If septic arthritis is suspected, gram stain and culture of synovial fluid should be performed even if MSU crystals are present. (7) Serum uric acid levels alone cannot confirm or exclude gout, as patients with hyperuricemia may not develop gout, and uric acid may be normal during acute attacks. (8) In selected patients (those with a personal or family history of onset of gout before age 25, or patients with renal calculi), determination of renal uric acid excretion is useful for evaluation and management. (9) Radiographs are not helpful in confirming the diagnosis of early or acute gout, although they may be useful for differential diagnosis and may show characteristic changes in chronic gout. (10) Risk factors for gout and associated comorbidities should be assessed, includ-

ing features of the metabolic syndrome (obesity, hyperglycemia, hyperlipidemia, and hypertension).

The differential diagnosis for symptoms suggesting an acute gout attack includes acute pseudogout, septic arthritis, inflammatory arthritis, cellulitis, and trauma. Because these diagnoses may have similar presentations, it is important to establish a correct diagnosis, as the treatment implications are significant. For example, pseudogout, caused by calcium pyrophosphate crystals, should not be treated with urate-lowering therapy; and septic arthritis demands immediate attention with antibiotics and joint drainage.

A definitive diagnosis of acute gout is made by detection of monosodium urate crystals in the synovial fluid of an inflamed joint.

MEDICAL TREATMENT FOR ACUTE GOUT

Colchicine

Colchicine has been used both in the acute setting and in the management of chronic gout. It exerts anti-inflammatory effects through several mechanisms. Colchicine binds to tubulin causing anti-proliferative effects by arresting cell growth. It also inhibits phagocytic and cytokine secretory functions of leukocytes. Chemotactic responses of neutrophils to leukotriene B₄, IL-8, and other cytokines are disrupted. At high concentrations, colchicine has recently been shown to inhibit urate crystal-induced activation of NALP3 inflammasome.² This protein complex cleaves caspase-1 which

then activates interleukin 1- β , a pro-inflammatory cytokine felt to be central in the pathogenesis of gout.

The optimal dosing of colchicine for treatment of acute gout remains controversial. In the only published randomized, placebo-controlled study of colchicine therapy, patients in the treatment group received oral colchicine 1 mg then 0.5 mg every 2 hours until a complete response or until side effects developed.³ Of the 22 patients in the treatment group, 73% achieved greater than a 50% reduction in pain within 48 hours. However, gastrointestinal toxicity (diarrhea and/or vomiting) developed in 55% of the patients before the reduction in pain was achieved, and all patients experienced these adverse side effects at some point during the study. A randomized, controlled multicenter trial, presented in abstract form, compared high-dose colchicine (1.2 mg, then 0.6 mg hourly for six hours) versus low-dose colchicine (1.2 mg, then 0.6 mg in one hour) and showed equivalent efficacy and less gastrointestinal toxicity with the lower dose regimen.⁴ Recently, the European League Against Rheumatism issued consensus guidelines in favor of lower doses of colchicine to avoid unacceptable side effects while maintaining efficacy.⁵ They recommend a maximum of three tablets of 0.5 mg in the first 24 hours.

Overdose or chronic administration of colchicine may result in side effects including granulocytopenia, aplastic anemia, and reversible myopathic and neuropathic toxicity.⁶ Patients with abnormal renal function are at increased risk for developing neuromuscular toxicity by accumulation of toxic plasma levels of colchicine. This condition typically presents with proximal muscle weakness and elevated CPK, which can mimic polymyositis. Symptoms of colchicine myopathy resolve within three to four weeks after discontinuing the medication. Colchicine is contraindicated in patients on hemodialysis and should be used

Table 1. Half-Life of Various NSAIDs.¹²

Short Half-Life (<6 hours)	Long Half-Life (>6 hours)
Ibuprofen (2 hours)	Nabumetone (24 hours)
Diclofenac (1-2 hours)	Naproxen (14 hours)
Indomethacin (2.5 hours)	Etodolac (7 hours)
Ketoprofen (2 hours)	Sulindac (13 hours)

Table 2. Recommended Corticosteroid Dose Based on Joint Size.¹⁷

Joint	Intra-articular corticosteroid dose
Knee	40 mg triamcinolone
Ankle	30 mg triamcinolone
Wrist	30 mg triamcinolone
Elbow	30 mg triamcinolone
Metacarpophalangeal joints	10 mg triamcinolone
Proximal interphalangeal joints	10 mg triamcinolone

with caution in patients with renal insufficiency or hepatobiliary dysfunction.⁷ Drug interactions have been reported with cyclosporine, statins, and macrolides.

The FDA recently withdrew its approval for the use of intravenous colchicine.² The most common side effect associated with IV colchicine is local extravasation of the drug which can lead to painful inflammation and necrosis of surrounding tissue.^{8,9} Increased risk of systemic side effects such as renal and hepatic toxicity, bone marrow suppression, and congestive heart failure have also been reported with IV colchicine.⁸ Fifty reports of adverse events, including 23 deaths, were submitted to the FDA through June 2007.¹⁰ Three of these deaths were attributed to an IV colchicine compounding error.

Non-steroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs are commonly used for treatment of acute gout. The anti-inflammatory effects of these medications occur mainly through inhibition of the cyclo-oxygenase enzyme which prevents the transformation of arachidonic acid to prostaglandins, particularly prostaglandin E₂. Other NSAID mechanisms include inhibition of lipooxygenase with reduced generation of leukotriene B₄ and inhibition of neutrophil activation and aggregation.¹¹

Early administration and appropriate dosage of NSAIDs are more important in achieving a therapeutic response than the particular NSAID used. However, NSAIDs with short half-lives (less than six hours) reach steady-state levels more quickly than NSAIDs with long half-lives (more than six hours) and may be preferred in managing acute gout. (Table 1)

Regardless of which NSAID is administered, large initial doses are recommended (indomethacin 150-200 mg/day, naproxen 1000 mg/day, diclofenac 150 mg/day). Duration of treatment is generally 4-8 days which minimizes potential adverse side effects. Patients should be treated until symptoms resolve and then gradually tapered.

Traditional NSAIDs inhibit both COX-1 and COX-2, with their main anti-inflammatory effects being via inhibition of COX-2 and most adverse effects by inhibition of COX-1.¹³ While both selective and non-selective NSAIDs inhibit COX-2 equally, the selective COX-2 inhibitors spare inhibition of COX-1 therefore reducing gastrointestinal toxicity. Etoricoxib, a selective COX-2 inhibitor, was shown to be as efficacious as indomethacin for treatment of acute gout with fewer gastrointestinal side effects.¹⁴ This medication is not FDA-approved for use in the United States because of potential cardiovascular side effects. Celecoxib is the only approved selective COX-2 inhibitor available in the US; however, no trials of its use in gout have been published.

The FDA recently withdrew its approval for the use of intravenous colchicine

Relative contraindications to the use of NSAIDs include severe heart failure, peptic ulcer disease, gastrointestinal hemorrhage, aspirin-induced or NSAID-induced asthma and renal impairment. There is an increased risk of bleeding when NSAIDs are used concomitantly with warfarin.

CORTICOSTEROIDS **Systemic corticosteroids**

Systemic corticosteroids may be used for treating acute gout when NSAIDs and colchicine are contraindicated. Corticosteroids exert their anti-inflammatory effect by inhibition of pro-inflammatory cytokines (IL-1, IL-6, IL-8, and TNF- α) and upregulation of genes for lipocortin and vasocortin, which have anti-inflammatory effects by inhibiting phospholipase A₂.

A Cochrane review evaluated the efficacy and safety of systemic corticosteroids for the treatment of acute gout.¹⁵ Only three

studies involving a total of 74 patients were found that met the search criteria. In the first study, intramuscular (IM) injections of triamcinolone were compared to oral indomethacin. Intramuscular triamcinolone was compared to IM injections of ACTH in the second study. Oral prednisolone was compared to IM diclofenac combined with oral indomethacin in the third study. The results of these three studies show no clinically relevant differences between systemic corticosteroids and comparator drugs. No significant adverse side effects attributable to corticosteroids were found. This review concluded that systemic steroids are a safe and effective treatment for acute gout, but more studies are needed.

One randomized, controlled trial published after the Cochrane review tested the equivalence of prednisolone and naproxen for treatment of monoarticular gout.¹⁶ One-hundred and twenty primary care patients with confirmed gout were randomly assigned to receive either prednisolone (35 mg daily) or naproxen (500 mg twice daily) for five days. The primary outcome was pain. After 90 hours, the reduction in pain score was similar for both groups. Adverse effects were also comparable between both groups. This study suggests that corticosteroids are as effective and as safe as NSAIDs in the acute setting.

Corticosteroids should be used with caution in patients with poorly controlled diabetes mellitus, hypertension, congestive heart failure, advanced coronary artery disease or severe infection. When using prednisone most practitioners start at a dose of 20-40 mg per day and gradually taper and discontinue the drug over 10-14 days.

Intraarticular corticosteroids

Intraarticular corticosteroids have a role in the treatment of mono- or oligoarticular gout.¹¹ The absence of joint infection should be confirmed before injection of corticosteroid. The dose of steroid varies based on the size of the joint involved. (Table 2) Some potential (but rare) side effects of intra-articular corticosteroids include skin atrophy and septic arthritis. Systemic absorption does occur, but the clinical impact of this effect is mild and short-lived.

ACTH

Synthetic adrenocorticotropic hormone (ACTH) is another steroid preparation that has been useful in the acute set-

ting; however, it is not universally available.¹⁸ It is administered by intramuscular or intravenous injection of 40-80 IU. ACTH induces glucocorticoid release from the adrenal cortex.¹¹ Drawbacks include rebound attacks, mild hypokalemia, worsening of glycemic control, and fluid retention. Other features that render this a less attractive option are cost, inconvenience of parenteral administration, and dependence on the sensitivity of the adrenal cortex.¹¹

Anakinra

The inhibition of IL-1 has been investigated as a novel therapeutic option for the treatment of acute gout. Monosodium urate crystals activate toll-like receptors and the NALP3 "inflammasome complex" to release IL-1b from monocytes and synovial mononuclear cells. So, et al conducted a pilot study in which 10 patients with gout who were unable to tolerate conventional anti-inflammatory medication were given anakinra, an IL-1 inhibitor, daily at a dose of 100 mg subcutaneously for three days.¹⁹ All 10 patients had a rapid response and no adverse side effects were noted. While these preliminary data are promising, these findings need to be confirmed in a larger, controlled study.

COMMON PITFALLS IN THE MANAGEMENT OF ACUTE GOUT

Patients taking uric acid lowering agents (allopurinol, febuxostat, or probenecid) should continue these medications during an acute attack. There are no data to suggest that a flare is exacerbated by continuing anti-hyperuricemics. An acute attack may, however, be precipitated during initiation or dose adjustment of urate lowering therapy if the patient is not also taking a prophylactic medication (colchicine or NSAIDs). This occurs as a result of fluctuations in serum uric acid levels that may trigger an acute attack.

In one study, a retrospective chart review was performed to assess the treatment of acute gout in hospitalized patients.²⁰ Only 25% of patients diagnosed with acute gout had arthrocentesis performed for crystal analysis, despite this being the gold standard. Combination anti-inflammatory agents (prednisone with colchicine, NSAIDs with colchicine, and steroid with NSAIDs) were used in over 50% of patients. There is a paucity of evidence to support such treatment, and this practice increases the risk of combined side effects.

Over 80% of patients given colchicine or NSAIDs had renal failure. Renal failure increases the time needed for clearance of colchicine, thereby increasing the risk of toxic side effects. NSAIDs should be avoided in patients in this setting given their potential for further renal toxicity.

Other pitfalls in management include delays in treatment, insufficient doses of medications, and premature termination of treatment. An appropriate dose of anti-inflammatory medication (NSAIDs, colchicine, or corticosteroids) should be given at the first onset of symptoms. Treatment should be continued until symptoms have resolved and then tapered for at least 2-3 days until all signs of inflammation are absent.⁷

SUMMARY

A definitive diagnosis of acute gout is made by detection of monosodium urate crystals in the synovial fluid of an inflamed joint. However, when this is not feasible a clinical diagnosis can sometimes be made with reasonable accuracy. The mainstays of acute gout management are colchicine, NSAIDs, and systemic or intra-articular corticosteroids. NSAIDs are preferable to colchicine because of their more favorable side effect profile. Successful treatment occurs with the prompt initiation of high dose short half-life NSAIDs. Since many patients with gout have comorbidities that preclude the use of NSAIDs or colchicine, systemic corticosteroids are commonly used to treat acute gouty arthritis. Intra-articular injections are appropriate in the setting of mono- or oligoarticular involvement. Adequate duration of anti-inflammatory therapy and careful patient education are essential elements of successful therapy for acute gout. Evaluation and management of hyperuricemia should be undertaken when all symptoms of acute gout are resolved and the patient is stable on daily prophylaxis with NSAIDs or colchicine.

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Discussion of off-label use of medication: anakinra

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