Management of Gout

Background
Gout is a painful inflammatory arthritis caused by precipitation of monosodium urate crystals. It is a condition that more commonly affects middle age and older adults. The management of gout includes treating acute attacks, urate-lowering therapy, and preventing recurrence of acute attacks. This document reviews the latest treatments of gout.

Management of Acute Gout
Acute gout attack is characterized by sudden onset of severe debilitating pain with progressive worsening over the first 24 hours. Most attacks usually resolve within three to ten days. Generally joint rest for a few days helps resolve attacks and icing the affected site may reduce pain.

Fast-acting NSAIDs are generally the drugs of choice for the treatment of acute gout when there are no contraindications. However, their use is limited in patients with renal insufficiency, risk factors for gastrointestinal (GI) bleeding, or comorbidities such as heart failure. The risk of side effects such as dyspepsia, hyperkalemia, and azotemia increase with advanced age.

In patients without renal insufficiency, GI bleeding risk, or other problematic comorbidities, NSAIDs should be started within 12 to 24 hours of acute attack for maximum benefit. Start NSAIDs at the highest dose for two to three days, then decrease over approximately two weeks. Continue NSAIDs for at least 48 hours after resolution of symptoms.

Avoid NSAIDs in patients with creatinine clearance (CrCl) <50 mL/min, peptic ulcers, hepatic dysfunction, congestive heart failure, and those on anticoagulation therapy. In general, an NSAID with a shorter half-life is preferred (e.g., ibuprofen, diclofenac, etc). Close monitoring of creatinine, blood pressure, and electrolytes periodically is also recommended.

In patients with increased risk of peptic ulcers, bleeds or perforations, coadministration of gastroprotective agents such as proton pump inhibitors (omeprazoles, etc) may reduce the risk of gastrointestinal bleeding associated with NSAID use.

Head-to-head studies have shown similar benefits in gout management amongst different NSAID agents. Some of the NSAIDs most commonly used for acute gout and their dosages include indomethacin (Indocin) 50 mg three to four times daily for three days, then 50 mg twice daily for four to seven days, naproxen (Naprosyn) 750 mg to 1000 mg daily in divided doses for three days, then 500 mg to 750 mg daily in divided doses for four to seven days, and sulindac (Clinoril) 300 mg to 400 mg daily in divided doses for seven to ten days. Indomethacin should be avoided in the elderly patient due to the potential for adverse CNS effects in this age group.

COX-2 inhibitors, or cyclooxygenase-2 inhibitors, appear to be comparably effective to traditional NSAIDs for acute gout. However, they are more costly and have been associated with increased cardiovascular risk as with other NSAIDs. The same contraindications and precaution associated with traditional NSAIDs apply to the COX-2 inhibitors.

Corticosteroids have established efficacy in the treatment of acute gout. Some rheumatologists now recommend corticosteroids over NSAIDs as the preferred choice for treatment of acute gout. Corticosteroids are especially useful in patients who cannot tolerate NSAIDs (e.g., moderate-to-severe chronic kidney disease, history of GI bleeds, etc). Corticosteroids can be given orally, intravenously, intramuscularly, intra-articularly, or indirectly via adrenocorticotropic hormone (ACTH).

One of the safest options is intra-articular corticosteroids (e.g., methylprednisolone acetate 5 mg to 25 mg per joint, triamcinolone 10 mg per knee joint or triamcinolone 8 mg in smaller joints, or betamethasone 3 mg to 6 mg) especially if only one joint or when larger joints are involved.
patient with multiple smaller joints affected, oral, intramuscular, or intravenous corticosteroids are a more practical approach.\textsuperscript{1} If oral treatment is preferred, consider a short course of daily prednisone 20 mg to 60 mg or prednisolone 35 mg or equivalent until symptoms resolve, generally within five to seven days.\textsuperscript{9,11,12} Although corticosteroid doses are traditionally tapered over seven to 14 days to prevent potential rebound, more recent data suggest that rebound is not an issue when corticosteroids are used for short-term (five to seven days).\textsuperscript{9,11,13} Single-dose intramuscular betamethasone 7 mg or triamcinolone acetonide 60 mg and IV methylprednisolone 125 mg have also been found to be effective.\textsuperscript{1}

When steroids are used, especially for prolonged periods of time, patients should be monitored for hyperglycemia, hypertension, electrolyte shifts, infections, mood, and mental problems.\textsuperscript{2,9}

Corticotropin (adrenocorticotropic hormone, ACTH) 40 units administered intramuscularly can also be given to stimulate corticosteroid production by patient’s own adrenal gland.\textsuperscript{4} In addition to inducing corticosteroid production by the adrenal glands, corticotropin activates the melanocortin type 3 receptor, which interferes with the acute inflammatory response of gout.\textsuperscript{2} However, corticotropin is not a preferred agent due to its relatively short duration of action, which increases the possibility of rebound flare-ups and treatment failure. Repeat injections are often required to eliminate symptoms of acute gout attack.\textsuperscript{9,14} To be effective, corticotropin requires an unsuppressed adrenal axis and should not be administered to patients who have recently received systemic steroids.\textsuperscript{14}

**Colchicine** has been used for the treatment of gout for centuries. However, it has fallen out of favor as a drug of choice for acute gout due to its narrow therapeutic index and poor tolerability.\textsuperscript{4,8} About 80% of patients cannot tolerate the frequent GI side effects (e.g., nausea, vomiting, diarrhea).\textsuperscript{4} It is a poor choice for patients with renal impairment, hepatic impairment, or arrhythmias, since these conditions can enhance the risk of colchicine’s toxicity.\textsuperscript{1}

In the past, colchicine was generally dosed at 0.6 mg taken orally every hour until relief or side-effects occur or until a maximum dosage of 6 mg is reached. However, this regimen has been shown to be too rigorous for some patients, especially the elderly, and can result in adverse events rates of 50% to 80%.\textsuperscript{9} Alternative regimens such as loading the patient with 1 mg orally followed by 0.5 mg or 0.6 mg every two to six hours up to a maximum of 2.5 mg in 24 hours and 6 mg over four days or 0.5 mg to 1 mg three times daily have been proposed.\textsuperscript{4,7,9} The latest thinking is that taking more than three 0.6 mg tablets for acute gout is not more effective and it increases adverse effects.\textsuperscript{34} The recommended dosage for the brand Colcrys (U.S.) is 1.2 mg loading dose at the first sign of a gout flare followed by 0.6 mg one hour later. The maximum dose is 1.8 mg over a one hour period.\textsuperscript{26} Adjust Colcrys dose and dosing frequency according to the patient’s age, renal function, hepatic function, and usage of interacting drugs.\textsuperscript{26}

Colchicine can also be used prophylactically at low doses (0.6 mg orally once or twice daily) to avoid rebound flare-ups in people treated with corticosteroids or corticotropin, and to prevent recurrent attacks when urate lowering therapy is initiated. As with acute dosing, prophylactic colchicine doses should be adjusted depending on the patient’s renal or hepatic function, tolerability, and presence of interacting drugs. Intravenous colchicine is not recommended as it has been associated with serious toxicities, including deaths.\textsuperscript{1,8,15} Currently, there are no approved IV colchicines available in the U.S. or Canada and the FDA has ordered companies to stop making unapproved IV colchicines.\textsuperscript{15}

**Management of Chronic Gout**

The goal of long-term gout management is to lower serum uric acid levels to approximately 6 mg/dL (360 umol/L) or less.\textsuperscript{4,6} In some cases, <5 mg/dL (300 umol/L) is needed for resolution of tophi.\textsuperscript{2} Urate-lowering therapy is the main focus of chronic gout management. The decision to begin urate-lowering therapy depends on the baseline serum uric acid levels, an individual’s risk for recurrent gout attacks, and/or damage by tophi (deposits of monosodium urate stones).\textsuperscript{1} Uric acid levels >9 mg/dL (540 umol/L) pose a higher risk for recurrent gouty arthritis.\textsuperscript{4} In general, urate-lowering therapy should be considered in uncomplicated gout if a second attack or further attacks of gout occur within one year.\textsuperscript{1} Therapy should be considered in patients...
with visible gouty tophi, renal insufficiency, and those who need to continue to take diuretics.¹

Urate-lowering therapy should not be initiated during an acute attack due to risk of rebound or flares of acute gout attack. It is recommended to initiate urate-lowering therapy within one to two weeks after the acute attack has subsided.¹

**Xanthine oxidase inhibitor**, such as allopurinol (Zyloprim, Alloprin [Canada]), is the agent of choice to lower serum uric acid. Allopurinol blocks xanthine oxidase and thereby reduces the generation of uric acid. Allopurinol is effective in both underexcreters (those with 24 hour urine uric acid <800 mg on a regular diet or 600 mg in 24 hours on a purine-restricted diet) and overproducers (those with 24 hour urine uric acid >800 mg).²,¹⁴

**Allopurinol** is generally dosed from 100 mg to 800 mg/day with 300 mg/day being the most commonly prescribed dose.¹⁸,⁹ (Doses greater than 300 mg/day are given in divided doses, two or three times daily.)²⁸ In patients with normal renal function, the dose depends on disease severity. The minimum effective dose is 100 to 200 mg daily. The average daily dose is 200 to 300 mg for mild gout, 400 to 600 mg for moderate gout, and for severe gout, 700 to 800 mg.²⁸,²⁹ Experts recommend starting with 100 mg per day, then increasing by 100 mg per day once every one to four weeks until target serum uric acid is achieved. For patients with renal insufficiency, the starting dose is 50 to 100 mg per day. Serum uric acid should be measured monthly and the dosage increased monthly until the target serum uric acid level is achieved.⁹

Per current product labeling, patients with CrCl 10 to 20 mL/min should receive no more than 200 mg daily. Patients with CrCl less than 10 mL/min should not receive >100 mg daily. Patients with CrCl <3 mL/min should lengthen the interval between doses.²⁸,²⁹

Experts suggest that allopurinol is generally under-dosed in clinical practice with 300 mg/day being the most commonly prescribed dose.¹,⁸ The reasons for underutilization of allopurinol are concerns of its adverse effects (GI intolerance, rash, rare but frequently fatal hypersensitivity syndrome), conservative renal dosage adjustment, and inadequate published randomized controlled trials of efficacy and safety of allopurinol over 300 mg/day.⁸,¹⁶ The conservative allopurinol renal adjustment has been disputed.¹⁷,¹⁸

Side effects of allopurinol include rash, GI disturbances, and headache. Rarely, potentially fatal hypersensitivity reactions can occur, more commonly in patients with renal insufficiency and those who are taking a diuretic.⁴

To prevent an acute attack as a result of starting allopurinol, prophylactic colchicine 0.6 mg once or twice daily or a low-dose NSAID (e.g., indomethacin 25 mg twice daily or naproxen 250 mg twice daily) can be used if there are no limitations.¹⁹ Colchicine dosage should be adjusted depending on patient renal and hepatic function, tolerability, and presence of interacting drugs. Prophylactic treatment is best started two to three weeks prior to starting allopurinol or other uric acid-lowering agent and continued for up to six months.² The British guidelines recommend limiting the duration of NSAID use to six weeks.¹ A general approach is to continue prophylactic treatment until serum uric acid is within normal range. Prophylactic treatment is not recommended unless the patient is taking a uric acid lowering agent. Corticosteroids are not ideal for gout exacerbation related to allopurinol use since the potential for adverse effects increases with prolonged use of corticosteroids. Allopurinol should not be discontinued during treatment of acute attacks.⁹

**Febuxostat** (Uloric), a selective xanthine oxidase inhibitor, was approved in the U.S. in 2009 and in Canada in 2010. Febuxostat lowers serum uric acid levels by inhibiting both the oxidized and reduced forms of xanthine oxidase. Febuxostat does not have a purine-like core structure, which has been implicated in some of the sensitivity reactions seen with allopurinol.⁸,¹⁹ The recommended dosage of febuxostat is 40 mg to 80 mg daily in the U.S. and 80 mg daily in Canada.²⁰,³⁰ No dosage adjustment is needed for patients with mild to moderate renal or hepatic impairment. In comparative trials, the efficacy of febuxostat 40 mg daily appears to be comparable to allopurinol 300 mg daily, and febuxostat 80 mg daily appears to be more effective than allopurinol 300 mg daily in reducing uric acid levels to goal <6 mg/dL (360 umol/L). It should be noted that these studies only used allopurinol doses up to 300 mg daily.⁸,¹⁹ Although febuxostat is a more selective xanthine oxidase inhibitor than allopurinol, it is unclear if this will offer more effective control of gout flares. Febuxostat is significantly more costly than allopurinol.⁹
Consider febuxostat in patients with allopurinol drug hypersensitivity, intolerance, or treatment failure.5 8

**Uricosurics,** such as probenecid (Benemid, Benuryl [Canada] and sulfinpyrazone (Apo-
sulfinpyrazone [Canada only]), increase uric acid excretion. Uricosuric agents should only be used in younger patients (<60 years old) that are underexcreters of uric acid, who do not have history of kidney stones, and who do not require aspirin or diuretic therapy.2,8 Low-dose aspirin (75 mg/day to 150 mg/day) does not appear to have significant effect on serum uric acid level, while aspirin in higher doses (600 mg/day to 2400 mg/day) can reduce the effectiveness of uricosuric agents. High-dose aspirin should be avoided.1 Side effects include GI disturbances, rash, and kidney stone formation. Per U.S. product labeling, the usual initial dose of probenecid is 250 mg twice daily for one week followed by 500 mg twice daily thereafter.14,31 Some patients may require further titration up to a maximum of 2 grams daily given in divided doses, two or three times a day.51 Per Canadian product labelling, the initial dose is 250 mg twice daily for one week, then increase to 500 mg twice daily. If symptoms persist, in nongeriatric patients dose can be increased every four weeks in 500 mg increments. The maintenance dose is 1000 mg to 3000 mg daily in divided doses (two or three times per day).33 The usual sulfinpyrazone (Canada only) dose is 200 mg to 400 mg per day (given in divided doses, two to three times daily).32 The dosage can be increased to 800 mg per day if necessary or lowered to as low as 200 mg per day if blood urate level is controlled.32 Both drugs should be titrated to a serum uric acid level of 6 mg/dL (360 umol/L) or less.9

**Krystexxa (pegloticase),** a PEGylated uric acid specific enzyme (urate oxidase), is the latest FDA approved agent for the management of refractory gout. It works by catalyzing the oxidation of uric acid to allantoin, which is an inert and water soluble purine metabolite that can be easily excreted renally. In clinical trials, pegloticase 8 mg administered intravenously every two weeks was shown to lower serum uric acid level and significantly improve or reverse the course of severe, crippling, and debilitating refractory gout.21 After six months of therapy, 45% of patients achieved complete resolution of tophi.

Pegloticase should only be administered under the supervision of a healthcare professional due to the risk of infusion reactions and anaphylaxis. Patients should be premedicated with antihistamines and corticosteroids prior to infusion and should be closely monitored. Since the risk of anaphylaxis and infusion reactions is higher in patients who have lost therapeutic response, patients’ serum uric acid levels should be monitored prior to infusions and discontinuation of treatment should be considered if uric acid level increases to above 6 mg/dL (360 umol/L), particularly when two consecutive levels above 6 mg/dL (360 umol/L) are observed.21

In the first few months of therapy, up to 80% of patients treated with pegloticase experience gout flare, but it tapers off with continued therapy in responders.8 Discontinuation of pegloticase is not necessary if gout flare occurs; however, gout flare prophylaxis with NSAIDs or colchicine is recommended for at least the first six months of treatment unless there are contraindications. Side effects of pegloticase include gout flares, infusion reaction, nausea, contusion or ecchymosis, nasopharyngitis, constipation, chest pain, anaphylaxis, and vomiting. Use with caution in patients with congestive heart failure as heart failure exacerbations have been reported in clinical trials.21 Pegloticase is contraindicated in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency due to the risk of hemolysis and methemoglobinemia. Screening patients at higher risk for G6PD deficiency (e.g., patients of African or Mediterranean ancestry) is recommended prior to initiation of pegloticase therapy. Reserve pegloticase for patients who are not responsive to appropriately dosed oral urate-lowering therapies. Although uricase oxidase (e.g., rasburicase [Elitek, Fasturttec, Canada]) has been used to treat chemotherapy-induced hyperuricemia for years, the safety and efficacy of pegloticase in the treatment of chemotherapy-induced hyperuricemia is unknown.

Expect Krystexxa to cost more than $20,000/year, compared to under $100/year (U.S.) for allopurinol and under $2000/year (U.S.) for Uloric.

**Emerging Therapies**

Preliminary data on biologic therapies such as anakinra (Kinerei) and rilonacept (Arcalyt, U.S. Copyright © 2010 by Therapeutic Research Center
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only), both anti IL-1 agents; etanercept (Enbrel) and infliximab (Remicade), both TNF-alpha inhibitors; and canakinumab (Ilaris) (anti IL-1 beta agent) have shown them to be useful in the treatment of acute refractory gout.\(^{22-24}\) Use of these emerging therapies may be considered in patients with refractory gout. However, referral to a rheumatologist is recommended in these cases.

Several investigational agents for gout management being studied include apremilast (phosphodiesterase 4 and TNF-alpha inhibitor), uricase-PEG 20 (urate oxidase), RDEA594 (uricosuric), and BCX-4208 (purine nucleoside phosphorylase inhibitor).\(^{22}\)

**Other Preventive Measures**

In patients with recurrent gout attacks, offending drugs (e.g., thiazide diuretics, niacin, levodopa, cyclosporine, ethambutol, pyrazinamide, aspirin, etc) should be removed if applicable.\(^{9,25}\) In addition, patients should be counseled about lifestyle changes that may help reduce the incidence of gout attack.\(^{1,6,9}\)

Limiting alcohol intake is recommended. Chronic alcohol intake and binge drinking should be avoided. Beer contains high purine content and has the highest risk for inducing gout attack. Moderate wine drinking does not increase the risk of gout. However, the quantity of alcohol, regardless of type consumed, strongly correlates with gout.\(^{1,9}\)

Complete dietary purine restriction is rarely necessary, and it’s been shown that a diet totally restricted in purines lowers the mean serum uric acid level by only about 1 mg/dL.\(^{1}\) However, limiting high purine foods (e.g., red meat) and limiting high protein content in diet is recommended.\(^{1}\) Liver, kidney, shellfish, and yeast extracts should be avoided.\(^{1}\) In obese patients, a modified diet to help achieve ideal body weight should be considered. However, patients should be warned to stay away from high-protein, low-carbohydrate diets (e.g., Atkins diet, etc). Encourage patients to drink lots of water, especially those with history of kidney stones.\(^{1}\)

**Conclusion**

There are a number of medications (e.g., NSAIDs, colchicine, corticosteroids) used for the management of acute gout attacks. When selecting a drug, a patient’s comorbid conditions and chronic medications should be taken into consideration.

To prevent future gout attacks, allopurinol or uricosuric agents can be used to lower serum uric acid level. In patients who are intolerant or have failed allopurinol and uricosuric agents, febuxostat can be considered [Evidence level C, consensus].\(^{6,27}\)

In refractory gout that is resistant to conventional treatments, pegloticase can be considered.

**Levels of Evidence**

In accordance with the trend towards Evidence-Based Medicine, we are citing the **LEVEL OF EVIDENCE** for the statements we publish.

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<td>A</td>
<td>High-quality randomized controlled trial (RCT) High-quality meta-analysis (quantitative systematic review)</td>
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<tr>
<td>B</td>
<td>Nonrandomized clinical trial Nonquantitative systematic review Lower quality RCT Clinical cohort study Case-control study Historical control Epidemiologic study</td>
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<td>C</td>
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**Project Leader in preparation of this Detail-Document: Wan-Chih Tom, Pharm.D.**

**References**


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