Gout

The right clinical information, right where it's needed
# Table of Contents

## Summary

## Basics

- Definition
- Epidemiology
- Etiology
- Pathophysiology

## Prevention

- Primary prevention
- Secondary prevention

## Diagnosis

- Case history
- Step-by-step diagnostic approach
- Risk factors
- History & examination factors
- Diagnostic tests
- Differential diagnosis
- Diagnostic criteria

## Treatment

- Step-by-step treatment approach
- Treatment details overview
- Treatment options
- Emerging

## Follow up

- Recommendations
- Complications
- Prognosis

## Guidelines

- Diagnostic guidelines
- Treatment guidelines

## Online resources

## Evidence scores

## References

## Images

## Disclaimer
**Summary**

- Acute onset of severe joint pain.
- Swelling, effusion, warmth, erythema and/or tenderness of the involved joint(s).
- Arthrocentesis with synovial fluid analysis shows strongly negative birefringent needle-shaped crystals under polarized light.
- Nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, or corticosteroids are used to treat acute disease.
- Allopurinol, febuxostat, probenecid, or lesinurad may be used as uric acid-lowering drugs when long-term prevention of crystal deposition is indicated.
- Complications include joint destruction, kidney disease, and urolithiasis.
Definition

Gout is a syndrome characterized by: hyperuricemia and deposition of urate crystals causing attacks of acute inflammatory arthritis; tophi around the joints and possible joint destruction; renal glomerular, tubular, and interstitial disease; and uric acid urolithiasis. The disease most commonly affects the first toe (podagra), foot, ankle, knee, fingers, wrist, and elbow; however, it can affect any joint.

Epidemiology

The annual incidence of gout in the US in people over 50 years of age is 1.6 per 1000 in men and 0.3 per 1000 in women. The annual incidence of gout in men increases from 1 per 1000 under 45 years of age, to 1.8 per 1000 at 55 to 64 years of age. Gout is more common in men and is rare in premenopausal women. The prevalence in the western world is about 1%, with a male to female ratio of 7:1 to 9:1. The prevalence varies geographically and racially. In New Zealanders with a European background, the prevalence is 3.6%. In the Maoris population, it is as high as 6.4%. The incidence of gout that is not associated with diuretic use has doubled over the past 20 years. This trend may be related to lifestyle changes and increased obesity.

Etiology

There is a causal relationship between hyperuricemia (high urate level) and gout. Urate is a metabolite of purines and the ionized form of uric acid (a weak acid at a physiologic pH); hence, uric acid exists mostly as urate. Hyperuricemia does not always lead to gout, but the incidence of gout increases with urate level. The annual incidence of gout in men is 0.4% for a urate level of 7 to 7.9 mg/dL, 0.8% for 8 to 8.9 mg/dL, 4.3% for 9 to 9.9 mg/dL, and 7% for levels >10 mg/dL.
Hyperuricemia is due to renal underexcretion of urate in 90% of cases and to overproduction in 10%, although there is often an overlap of both.[9]

Risk factors for hyperuricemia may eventually lead to gout and include dietary factors such as consumption of seafood, meat, and alcohol, especially beer.[2] Another source of purines and urate is endogenous production due to high cell turnover, such as from hematologic cancer and chemotherapy. A small proportion of overproducers have a specific genetic enzymatic abnormality. Drugs such as diuretics can increase urate levels. Other risk factors for gout include obesity, insulin resistance, and hypertension.[10] [11]

Pathophysiology

Humans and some other higher primates develop gout spontaneously. Humans no longer express the gene for the enzyme uricase, which degrades uric acid to the more soluble compound allantoin in animals. This, coupled with a high rate of renal reabsorption of urate, results in hyperuricemia and gout.[12] [13] [14] [15]

Uric acid exists as urate at a physiologic pH. High urate levels result in supersaturation and crystal formation, leading to gout. Urate levels directly correlate with the risk of the disease. Drugs that reduce urate levels decrease the risk of recurrent attacks.[16]
The solubility of urate in the joints depends on temperature, pH, nonaggregated proteoglycans, and other factors. Gout more commonly affects the first metatarsophalangeal joint (cool part of the body) and osteoarthritic joints.[17]

Urate crystals in the joint interact with undifferentiated phagocytes and trigger an acute inflammatory response by inducing TNF-alpha and activating signal pathways and endothelial cells.[18] TNF-alpha, interleukin (IL)-8, and other chemokines lead to neutrophil adhesion to endothelium, influx, and amplification, resulting in neutrophilic synovitis.

Colchicine works by intercepting the neutrophil-endothelial interaction.[9] [19] IL-8 accounts for 90% of the chemotactic activity of neutrophils in response to uric acid crystals; hence, inhibiting IL-8 may have therapeutic implications.[20] [21] In addition there is an evidence that urate crystals activate NALP3 inflammasome that induces the secretion of IL-1beta, which plays a role in the gout inflammatory reaction.[22] This pathway has been the target of new therapeutic interventions in gout that inhibit the IL-1beta response.[23] [24] [25] [26]

Spontaneous resolution of gout attack results from clearance of urate crystals by differentiated phagocytes, coating of the crystals with proteins, neutrophilic apoptosis, and inactivation of inflammatory mediators.[9] Urate crystals can induce chronic inflammation, leading to synovitis, cartilage loss, and bone erosions. They may also induce chondrocytes to produce metalloproteinase and nitric oxide, which results in cartilage loss, and may cause bone damage by inhibiting osteoblasts.[27] [28]
Primary prevention

There are no prospective studies or evidence regarding effective intervention for primary prevention of gout or hyperuricemia.\[29\]

Secondary prevention

Hyperuricemia does not always lead to gout, but the incidence of gout increases with urate level.\[8\] Patients with hyperuricemia and gout should avoid risk factors that may precipitate gout such as excessive alcohol consumption, diuretic use, and weight gain, which will help reduce uric acid level and hence gout flares.\[101\] Patients with lymphoproliferative disorders requiring chemotherapy are given intravenous hydration and allopurinol to prevent hyperuricemia and complications such as acute renal failure due to uric acid nephropathy.\[102\]
Case history

**Case history #1**

A 54-year-old man complains of severe pain and swelling in his right first toe that developed overnight. He is limping because of the pain and states that this is the most severe pain he has ever had ("even covering my foot with the bed sheet hurts"). He has had no previous episodes. His only medication is hydrochlorothiazide for hypertension. He drinks 2 to 3 beers a day. On examination, he is obese. There is swelling, erythema, warmth, and tenderness of the right first toe. There is also tenderness and warmth with mild swelling over the mid foot.

**Case history #2**

An 85-year-old man presents with several days of swelling and severe pain in both hands limiting his ability to use his walker. He has a history of gout but has not experienced these symptoms before. On examination, he has a temperature of 100.1 °F (37.8 °C). There is diffuse warmth, mild erythema, and pitting edema over the dorsum of both hands. There is tenderness and limited hand grip bilaterally. There are multiple nodules around several of the proximal interphalangeal and distal interphalangeal joints, and effusion and tenderness in his left olecranon bursa with palpable nodules.

**Other presentations**

Gout may also present as acute bursitis, especially in the olecranon and prepatellar bursae.

[Fig-1]

Chronic tophaceous gout may cause inflammatory destructive polyarthritis.

[Fig-2]

This usually occurs in people with a long-standing history of attacks (mean 10 years) and with higher uric acid levels.

**Step-by-step diagnostic approach**

Gout is clinically suspected in patients with typical history and examination findings. Diagnosis is confirmed by arthrocentesis showing monosodium urate crystals. Alternatively, diagnosis may be based upon fulfillment of ≥6 of the following criteria from the American College of Rheumatology (ACR):[41]

- More than one attack of acute arthritis
- Maximum inflammation developed within 1 day
- Monoarthritis attack, redness observed over joints
- First metatarsophalangeal joint painful or swollen
- Unilateral first metatarsophalangeal joint attack
- Unilateral tarsal joint attack
• Tophus (confirmed or suspected)
• Hyperuricemia
• Asymmetric swelling within a joint on x-ray film
• Subcortical cyst without erosions on x-ray film
• Joint culture negative for organism during attack.

However, the diagnosis can be made clinically with a good degree of certainty without the presence of crystals and without fulfilling the points suggested by the ACR criteria. For example, cases with a reliable history of recurrent acute monoarthritis of the first metatarsophalangeal joint (podagra).

In 2015 the ACR published new classification criteria; however, these criteria are intended for identifying people who may be eligible for entry into a clinical study and they are not intended to be used to diagnose gout.[42] [43]

History
Gout is more common in men and rare in premenopausal women. A history of previous attacks that are self-limiting (7 to 14 days) supports the diagnosis. Medications, dietary habits, and family history should be assessed.

The most common presentation is acute monoarticular arthritis characterized by sudden-onset severe pain and swelling. However, the disease may also be oligoarticular (<4 joints involved) or, to a lesser degree, polyarticular. The most commonly affected joints are the first metatarsophalangeal, tarsometatarsal, ankle, and knee joints, but almost any other joint may be affected.

In older people, the disease may be polyarticular and associated with marked edema and swelling of the hands and feet.

Physical examination
Involved joints are warm, red, and swollen. Usually, there is considerable tenderness and limited range of movement due to pain.

All joints should be examined, as others may be affected in a more subtle fashion.

Hard subcutaneous nodules (tophi) over the extensor surface of the joint, especially over the elbows, knees, and Achilles tendons, may be present.

[Fig-1]

Tophi may also be evident over the dorsal aspects of hands and feet, and in the helix of the ears.

[Fig-2]

Diagnostic tests
Arthrocentesis with synovial fluid analysis provides definitive diagnosis. The synovial fluid WBC count usually exceeds 2000/mm^3, and the cells are mostly PMNs type. Monosodium urate crystals (intracellular and/or extracellular needle-shaped crystals strongly negative for birefringence under polarized light) confirm the diagnosis. Synovial fluid analysis should be considered in most patients, but the diagnosis can often be made clinically.
Serum uric acid level may be low, normal, or high during an acute gout attack. This test becomes more reliable when done at least 2 weeks after the attack resolves.

Radiographs are not useful for diagnosis, but may differentiate between chronic gout and other joint conditions.[44] Ultrasound is more sensitive than radiographs in detecting erosions, tophi, and the gout-specific double contour sign (linear urate deposits over hyaline cartilage). Ultrasound and dual-energy computed tomography may be helpful, but the potential benefit of imaging over clinical diagnosis requires further study.[45]

[VIDEO: Aspiration and injection of the knee: animated demonstration ]

[VIDEO: Aspiration and injection of the shoulder: animated demonstration ]

Risk factors

**Strong**

**older age**

- Incidence increases with age, peaking in men between 40 and 60 years and in women between 50 and 70 years.[2]

**male gender**

- More common in men.[3]

**menopausal status**

- Gout is especially rare in premenopausal women.[3] [29]

**consumption of meat, seafood, alcohol**

- A prospective 12-year follow-up of 47,150 men reported a higher risk of gout among those in the highest versus lowest quintiles of seafood and meat consumption, relative risks (RRs) 1.51 (95% CI 1.17 to 1.95) and 1.41 (95% CI 1.07 to 1.86), respectively.
- Dairy consumption is associated with a lower risk, RR 0.56 (95% CI 0.42 to 0.74) comparing the highest quintiles with the lowest quintile.[2]
- Consumption of alcohol, especially beer and liquor, is associated with a higher risk.[29] An additional daily serving of beer is associated with an RR of 1.49 (95% CI 1.32 to 1.70) and liquor with an RR of 1.15 (95% CI 1.04 to 1.28). An additional daily serving of wine is not associated with increased risk, RR 1.04 (95% CI 0.88 to 1.22).[30]

**use of diuretics**

- Thiazide and loop diuretics are associated with an increased risk of gout and of gout flares.[29]

**use of cyclosporine or tacrolimus**

- Lead to increased tubular reabsorption of urate as well as decreased glomerular filtration and interstitial nephropathy.

**use of pyrazinamide**

- Increases urate reabsorption.
use of aspirin

- Doses of ≤325 mg elevate urate levels, while higher doses have uricosuric effects and lead to lower urate levels.[9]

genetic susceptibility

- Some urate overproducers have specific genetic defects, such as hypoxanthine-guanine phosphoribosyl transferase (HPRT) deficiency, 5-phosphoribosyl-1-pyrophosphate (PRPP) synthetase hyperactivity, and glucose-6-phosphate dehydrogenase (G6PD) deficiency.
- The most complete form of HPRT deficiency is associated with Lesch-Nyhan syndrome (premature gout and mental retardation in children). The partial deficit of the enzyme is associated with gout and hyperuricemia without neurologic manifestations.
- Both PRPP synthetase hyperactivity and HPRT deficiency are X-linked, while G6PD deficiency is autosomal recessive. G6PD deficiency is associated with von Gierke's disease, a type-1 glycogen storage disease.[31]

high cell turnover state

- Conditions that lead to high endogenous purine metabolism include hematologic malignancies, myeloproliferative disorders, psoriasis, and chemotherapy-induced cell death.

Weak adiposity and insulin resistance

- Associated with hyperuricemia.[11] [32] [33] [34]
- Small open-label studies show that weight loss is associated with lower urate level and risk of gout.[35] [36]
- Exogenous insulin can reduce the renal excretion of urate.[37] Also, insulin can enhance renal urate reabsorption.[38]

hypertension

- An independent risk factor for gout.[10] [29] Renal urate excretion is inappropriately low relative to glomerular filtration rate.[39] This may reflect early nephrocalcinosis in hypertensive patients. Gout, in turn, may be associated with a higher incidence of hypertension and cardiovascular morbidity.[40]

renal insufficiency

- Has been found to be associated with higher risk of incident gout or gout flares.[29]

diabetes mellitus

- Has been found to be associated with a higher risk of incident gout and/or gout flares in epidemiological studies.[29] However, there are many confounding factors that may have influenced the findings. Variations in case definition, and the use of study populations from particular geographic locations, should be kept in mind.

hyperlipidemia

- Hypertriglyceridemia and hypercholesterolemia have been found to be associated with a higher risk of incident gout and/or gout flares in epidemiological studies.[29] However, there are many confounding factors that may have influenced the findings. Variations in case definition, and the use of study populations from particular geographic locations, should be kept in mind.
History & examination factors

Key diagnostic factors

men aged between 40 and 60 years (common)
- Incidence increases with age, peaking in men between 40 and 60 years of age.[2] [3]

use of gout-inducing medication (common)
- Use of drugs including aspirin, cyclosporine, tacrolimus, or pyrazinamide increase urate reabsorption.

consumption of meat, seafood, or alcohol (common)
- A prospective 12-year follow-up of 47,150 men reported a higher risk of gout among those in the highest versus lowest quintiles of seafood and meat consumption, relative risks (RRs) 1.51 (95% CI 1.17 to 1.95) and 1.41 (95% CI 1.07 to 1.86), respectively.[2] Consumption of alcohol, especially beer and liquor, is associated with a higher risk. An additional daily serving of beer is associated with an RR of 1.49 (95% CI 1.32 to 1.70) and liquor with an RR of 1.15 (95% CI 1.04 to 1.28).[30]

hx of medical condition with high cell turnover rate (common)
- Conditions that lead to high endogenous purine metabolism include hematologic malignancies, myeloproliferative disorders, psoriasis, and chemotherapy-induced cell death.

rapid-onset severe pain (common)
- Patients with an acute attack can often pinpoint the onset to the hour. They may describe the pain as the most severe they have ever experienced.

joint stiffness (common)
- Morning stiffness is prominent and reflects the underlying inflammatory mechanism. Function may be limited because of pain and stiffness.

foot joint distribution (common)
- Most commonly involved are joints in the feet, especially the first metatarsophalangeal, tarsometatarsal, and ankle joints.

few affected joints (common)
- Pattern is usually monoarticular or oligoarticular (<4 joints). Can be polyarticular, affecting multiple joints in the hands and feet, especially in older people.

swelling and joint effusion (common)
- Reflect the inflammatory nature of the disease.

tenderness (common)
- Prominent diffuse joint tenderness usually exists.

tophi (common)
- May be present over extensor surface joints, especially the elbows, knees, and Achilles tendons.
- May also be evident over dorsal aspects of hands and feet, and in helix of the ears.
Other diagnostic factors

**erythema and warmth (common)**

- May be subtle at times, requiring careful examination.

**family history of gout (uncommon)**

- Presence of family members with gout at a fairly young age may suggest a genetic defect in a specific enzyme.

Diagnostic tests

**1st test to order**

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>arthrocentesis with synovial fluid analysis</td>
<td>WBC count above 2000/mm$^3$ (mean, 20,000/mm$^3$); strongly negative birefringent needle-shaped crystals under polarized light</td>
</tr>
<tr>
<td><strong>Other tests to consider</strong></td>
<td></td>
</tr>
<tr>
<td>uric acid level</td>
<td>above 7 mg/dL in men; above 6 mg/dL in women</td>
</tr>
<tr>
<td>x-ray of affected joint</td>
<td>periarticular erosions (may have an overhanging edge or punched-out appearance)</td>
</tr>
</tbody>
</table>
### Ultrasound

- Ultrasound-detected erosions are most commonly found in the first metatarsophalangeal joint and the metacarpophalangeal joints.[50]

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>ultrasound</td>
<td>erosions, tophi, double contour line</td>
</tr>
</tbody>
</table>

### Differential diagnosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
</table>
| Pseudogout (calcium pyrophosphate deposition disease) | • Presentation may be identical to that of gout.  
• Is less common in people younger than 50 years of age.  
• Is more likely to affect wrist and knee joints. | • Chondrocalcinosis (radiographic calcification of cartilage in certain joints) is usually present.  
• Ultrasound may help to differentiate calcium pyrophosphate deposition disease (CPPD) from gout. Calcium pyrophosphate deposits are found deeper in the cartilage and are less homogenous (lumpy-bumpy) than the superficial double contour sign seen in gout.  
• The definitive diagnosis is finding calcium pyrophosphate crystals in the synovial fluid. These are rhomboid-shaped, weakly positively birefringent crystals. |
| Septic arthritis                               | • Presentation may be identical to that of gout.  
• Occurs in both sexes and at any age.  
• Risk factors for infection, such as intravenous drug use and immunocompromise, may be present. | • Synovial fluid microscopy and culture may be Gram positive and show growth.  
• Blood cultures may grow the causal bacteria.  
• Coexistence of crystals and infection in the joint is not uncommon. |
| Trauma                                         | • A positive history is present.  
• Usually, there are fewer inflammatory signs, such as erythema or warmth, on joint examination than with gout. | • Synovial fluid is usually bloody and has no monosodium urate crystals. |
<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
</table>
| Rheumatoid arthritis (RA) | • Chronic tophaceous and polyarticular gout may present like RA, and tophi can be misdiagnosed as rheumatoid nodules.  
  • History of intermittent, acute, self-limited attacks of arthritis and podagra suggests gout.  
  • RA and gout appear to be negatively correlated, as very few cases of coexistence have been reported. | • Associated with positive RF in 70% to 78% of cases; however, 30% of patients with gout have a positive RF.[51]  
  • Anticyclic citrullinated peptide (anti-CCP) is a new diagnostic test for RA. It has a high specificity, but a low sensitivity and it may be useful in the early detection of patients who will have severe RA.[52]  
  • Synovial fluid is inflammatory (WBC count >2000/mm^3), but no monosodium urate crystals are found. |
| Reactive arthritis         | • Recent infection with appropriate organism.  
  • Oligoarthritis present.  
  • Commonly affects weight-bearing joints.  
  • May have tendon insertion inflammation and dactylitis (whole digit inflammation).  
  • Conjunctivitis, urethritis, and stomatitis may be present. | • X-rays may show soft-tissue swelling.                                                                                                                                                                                                                                            |
| Psoriatic arthritis        | • Patients usually have a history of psoriasis.  
  • Asymmetrical joint distribution.  
  • Commonly affects the distal interphalangeal joints.  
  • Presence of dactylitis. | • Typical radiographic findings include joint erosions, joint space narrowing, bony proliferation including periarticular and shaft periostitis, osteolysis including "pencil in cup" deformity andacro-osteolysis, ankylosis, spur formation, and spondylitis.[53] |

**Diagnostic criteria**

**American College of Rheumatology preliminary criteria for the classification of the acute arthritis of primary gout[41]**

Diagnosis is satisfied by:

1. Characteristic monosodium urate crystals in joint fluid, or

2. Characteristic monosodium urate crystals from tophus, or

3. Fulfillment of ≥6 of the following criteria:
• More than one attack of acute arthritis
• Maximum inflammation developed within 1 day
• Monoarthritis attack, redness observed over joints
• First metatarsophalangeal joint painful or swollen
• Unilateral first metatarsophalangeal joint attack
• Unilateral tarsal joint attack
• Tophus (confirmed or suspected)
• Hyperuricemia
• Asymmetric swelling within a joint on x-ray film
• Subcortical cyst without erosions on x-ray film
• Joint culture negative for organism during attack.

American College of Rheumatology/European League Against Rheumatism (ACR-EULAR) gout classification criteria[42] [43]

In 2015 the ACR published new classification criteria; however, these criteria are intended for identifying people who may be eligible for entry into a clinical study and they are not intended to be used to diagnose gout.[42] [43]

• The sensitivity of the 2015 classification criteria is 92%, and the specificity is 89%.
• The criteria include clinical, imaging, and laboratory-based features.
• The maximum possible score in the final criteria is 23 and a threshold score of 8 classifies an individual as having gout.
• A unique aspect of these classification criteria is that there are 2 categories that elicit negative scores. Specifically, if the synovial fluid is negative for monosodium urate, 2 points are subtracted from the total score. Similarly, if the serum urate level is <4 mg/dL (<0.24 mmol/L), 4 points are subtracted from the total score.
• Associated Web-based calculators are available. [ACR-EULAR gout classification criteria calculator]

[VIDEO: ACR-EULAR Gout Classification Criteria Calculator ]
Step-by-step treatment approach

The short-term treatment goal for acute gout is rapid resolution of pain and preservation of function. Long-term goals are to prevent recurrent attacks and chronic joint destruction. The earlier treatment is initiated, the better the clinical response.

Short-term management

Nonsteroidal anti-inflammatory drugs (NSAIDs) are first-line therapy for an acute attack if no contraindications exist. It is common to use indomethacin, although there is no evidence that it is more efficacious than other NSAIDs and it is associated with more adverse effects.

An alternative to NSAIDs is colchicine. Evidence To avoid adverse effects, particularly diarrhea, the total daily dose should not exceed 3 mg. One study showed that 1.2 mg of colchicine, followed by 0.6 mg after 1 hour was better tolerated and as effective as taking total of 4.8 mg over 6 hours.[58] The effect though was modest, with only approximately one third of patients reaching 50% reduction in pain within 72 hours.

Corticosteroids are a possible alternative if both NSAIDs and colchicine are contraindicated (for instance, in patients with renal insufficiency). They can be given either as an intra-articular injection for monoarticular acute gout or parenterally for oligoarticular or polyarticular acute gout. Potential serious side effects of corticosteroids should be considered. Corticosteroids are probably more effective than colchicine for acute gout, although there are no head-to-head comparison trials of these two types of drug.[59] Evidence A randomized double-blinded controlled trial showed that oral prednisone and indomethacin were comparable in efficacy and adverse reactions when used for the treatment for acute gout in patients presenting to the emergency room.[60] Oral prednisone could be considered as a first-line treatment for acute gout, as it is effective and associated with few adverse events, especially when used for a short period of time.[60]

Long-term management

The long-term management for gout includes dietary modifications and weight loss (if indicated).[2] Nonetheless, there is a paucity of high-quality evidence to either support or refute the use of lifestyle modifications for improving outcomes in people with chronic gout.[61]

Prophylactic drug therapy is indicated by presence of the following factors:

- Recurrent attacks (>2-3 per year)
- Tophaceous gout
- Radiographic changes and chronic destructive joint disease
- Urate nephrolithiasis
- Patient preference because of severe and debilitating polyarticular attacks.

Allopurinol reduces the production of uric acid. It should be started 2 weeks after the last exacerbation at a low dose of 100 mg/day. The dose should be increased over several weeks to months until the uric acid level is <6 mg/dL. A retrospective case-controlled study suggested an increased risk of hypersensitivity to allopurinol when used at a dose >1.5 mg per mL of GFR.[62] This was reflected in the 2012 American
College of Rheumatology guidelines for gout management, which recommend an initial dose of 100 mg/day, and lower starting dose in those with renal insufficiency.[63] It is safe to titrate until the goals of therapy have been reached, as long as it is tolerated and there is no evidence of adverse reaction. There is a suggestion that allopurinol use might be associated with a modest decrease in the risk of death in subjects with hyperuricemia.[64]

The American College of Physicians have not included a recommendation to lower serum uric acid levels below 6 mg/dL in their 2016 guidelines on the management of acute and recurrent gout.[65] This is based on the lack of long-term clinical trial data. While there are no long-term clinical trial data concerning the long-term benefits and harms of this approach, there is evidence from population data about the long-term safety of uric acid lowering drugs, especially allopurinol, which the FDA approved in 1966. The saturation threshold for urate is 6.8 mg/dL, although uric acid levels fluctuate significantly as does the saturation threshold, which is lower in synovial fluid/joints. The standard practice of lowering serum uric acid levels to <6 mg/dL aims to buffer against those fluctuations.

In populations where HLA-B*5801 positive subjects are at high risk for severe allopurinol hypersensitivity reaction (e.g., Koreans with renal insufficiency, Han Chinese descent, and Thai descent), HLA-B*5801 screening should be considered.[63] A large retrospective study conducted in Taiwan estimated the annual incidence of hypersensitivity reaction in new users of allopurinol at 4.68 per 1000, with mortality of 0.39 per 1000.[66] The risk of hypersensitivity was statistically significant among patients with renal or cardiovascular disease who were prescribed allopurinol for asymptomatic hyperuricemia.

Febuxostat is a nonpurine selective xanthine oxidase inhibitor that reduces the production of uric acid. The goal is to reduce uric acid level to <6 mg/dL to prevent supersaturation and crystal formation.[67] The commonly reported adverse effects are elevated LFTs, headache, hypertension, diarrhea, and arthralgia/stiffness.[68] [69] Two phase III clinical trials showed that febuxostat was more effective than allopurinol in reducing the uric acid level.[70] [71] An open extension trial for subjects up to 40 months from these 2 trials showed that a greater percentage of subjects on febuxostat compared with subjects on allopurinol maintained this benefit.[72] However, caution is needed in interpreting the results of these studies. They all compared febuxostat to a maximum of 300 mg/day of allopurinol. Recommendations and standard practices for rheumatologists are to titrate the dose of allopurinol until the target of uric acid <6 mg/dL is reached, with a maximum dose of 800 mg/day. Concluding that febuxostat is more effective or superior to allopurinol is inappropriate given the relatively low dose of allopurinol. The UK National Institute for Health and Care Excellence (NICE) has recommended that febuxostat be considered as an option for the management of chronic hyperuricemia in gout only for people who are intolerant of allopurinol, or for whom allopurinol is contraindicated.[67] Preliminary results from a safety clinical trial show an increased risk of heart-related death with febuxostat compared to allopurinol. The Food and Drug Administration are evaluating this safety issue and will release an update once completed.[73]

If the patient cannot tolerate allopurinol, probenecid (a uricosuric agent) should be considered. Uricosuric agents increase renal excretion of uric acid and are contraindicated in known over-producers of uric acid. A 24-hour urine collection for uric acid should be obtained first. If it exceeds 800 mg per 24 hours, probenecid is contraindicated as it increases the risk of urate nephrolithiasis. Probenecid is not effective in patients with renal insufficiency, but it could be even considered as a first-line option in patients with gout and normal renal function.

Lesinurad, a uricosuric agent that inhibits uric acid transporters (URAT1 and OAT4) in the proximal tubule of the kidney, may be considered as an adjunctive therapy to allopurinol or febuxostat in patients who have not achieved target serum uric acid levels with a xanthine oxidase inhibitor alone. It is approved by
the Food and Drug Administration (FDA) for use in combination with allopurinol or febuxostat only. In two phase III trials (CLEAR 1 and CLEAR 2), a combination of lesinurad and allopurinol modestly increased the proportion of people achieving serum uric acid <6 mg/dL at 6 months compared with allopurinol alone.[74] [75] Lesinurad was associated with ≥1.5 increase in serum creatinine and elevation in liver function tests. In addition, lesinurad (at a higher dose than approved) in combination with febuxostat has been found to be more effective in reducing the uric acid level to below 5 mg/dL than febuxostat alone (76.1% vs 46.8% p<0.001), while lesinurad (at the approved dose) combined with febuxostat was not associated with a statistically significant difference.[76]

Combined treatment with allopurinol and benz bromarone, a potent uricosuric agent, appears to be effective in nonresponders to allopurinol who have moderate or severe renal insufficiency.[77] It may also be more effective than probenecid.[78] Benz bromarone was never approved in the US following reports of serious hepatotoxicity, and it has been withdrawn in many countries. Overall, there is a dearth of good-quality evidence regarding the safety and efficacy of uricosuric agents.

Intravenous pegloticase (a pegylated recombinant mammalian uricase) is an option for patients with refractory tophaceous gout that is not responsive to treatment with other available conventional uric acid-lowering agents.[79] [3A]Evidence

Urate-lowering agents should not be started until at least 2 weeks after the resolution of acute gout, as such agents may increase the risk of recurrence or prolongation of the attacks by rapidly decreasing the serum urate level. NSAIDs or low-dose colchicine should be considered as prophylaxis during the initiation and titration of a urate-lowering agent. They should be continued for 3 to 12 months after reaching the target level of uric acid. Once patients with gout start on urate-lowering agents, they need to take them permanently unless there is a serious adverse reaction; provided that the diagnosis of gout is accurate.

[VIDEO: Aspiration and injection of the knee: animated demonstration ]

[VIDEO: Aspiration and injection of the shoulder: animated demonstration ]

### Treatment details overview

Consult your local pharmaceutical database for comprehensive drug information including contraindications, drug interactions, and alternative dosing. (see Disclaimer)

<table>
<thead>
<tr>
<th>Acute</th>
<th>(summary)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient group</td>
<td>Tx line</td>
</tr>
<tr>
<td>acute gout</td>
<td>1st</td>
</tr>
<tr>
<td></td>
<td>2nd</td>
</tr>
<tr>
<td></td>
<td>3rd</td>
</tr>
<tr>
<td>Patient group</td>
<td>Tx line</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>recurrent gout: 2 to 3 weeks post</td>
<td>1st</td>
</tr>
<tr>
<td>acute episode</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Treatment options

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Tx line</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>acute gout</td>
<td>1st</td>
<td>nonsteroidal anti-inflammatory drug (NSAID)</td>
</tr>
</tbody>
</table>

» Halt the inflammatory cascade if they are started early. Also used to suppress gouty attacks when maintenance therapy with uric acid-lowering drugs is started.

» There is no evidence that indomethacin is superior to other NSAIDs. Two noninferiority studies showed indomethacin was as efficacious as etoricoxib and was associated with more adverse effects.[81] [82]

» Should be used with preventive measures, such as proton-pump inhibitors or misoprostol, in patients at high risk of GI complications.

» COX-2 inhibitors may be safer than traditional NSAIDs in patients with a history of GI bleeding or comorbidities.

**Primary options**

» naproxen: 500 mg orally twice daily for 10-14 days

OR

**Primary options**

» ibuprofen: 400-800 mg orally three to four times daily for 10-14 days

OR

**Primary options**

» diclofenac potassium: 50 mg orally (immediate-release) three times daily for 10-14 days

OR

**Primary options**

» meloxicam: 7.5 to 15 mg orally once daily for 10-14 days

OR

**Primary options**
Acute

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Tx line</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>» indomethacin: 25-50 mg orally three times daily for 10-14 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Primary options</td>
</tr>
<tr>
<td></td>
<td></td>
<td>» celecoxib: 100-200 mg orally twice daily for 10-14 days</td>
</tr>
<tr>
<td>2nd</td>
<td>colchicine</td>
<td>Used when nonsteroidal anti-inflammatory drugs (NSAIDs) and COX-2 inhibitors are contraindicated because of a history of GI bleeding or comorbidities.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>» Minimal effective dose should be used because of the narrow benefit to risk index. Common adverse effects are diarrhea, nausea, and vomiting.1[C]Evidence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>» Intravenous use should be avoided because of increased toxicity.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>» Give until relief, nausea/vomiting, diarrhea, or maximum dose reached; diarrhea likely will precede pain relief; wait 3 days between courses.</td>
</tr>
<tr>
<td>3rd</td>
<td>corticosteroid</td>
<td>A possible alternative if both nonsteroidal anti-inflammatory drugs (NSAIDs) and colchicine are contraindicated (for instance, in patients with renal insufficiency). Probably more effective than colchicine for acute gout, although there are no head-to-head comparison trials of these two types of drug.[59] 2[B]Evidence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>» A randomized controlled trial showed that oral prednisone and indomethacin were comparable in efficacy and adverse reactions when used for the treatment for acute gout in patients presenting to the emergency room.[60]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>» Used as an intra-articular injection for monoarticular gout and orally for oligoarticular and polyarticular gout.</td>
</tr>
</tbody>
</table>
### Acute

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Tx line</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>[VIDEO: Aspiration and injection of the knee: animated demonstration ]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[VIDEO: Aspiration and injection of the shoulder: animated demonstration ]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>» Potential serious side effects of corticosteroids should be considered. Should be avoided if septic arthritis has not been excluded.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Primary options</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>» prednisone: 1 mg/kg orally given as a single dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>This regimen may be adequate if started within 24 hours of attack.</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td><strong>Primary options</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>» prednisone: 20-40 mg orally once daily initially, decrease by 5-10 mg/day decrements every 3 days until discontinuation; or 30 mg orally once daily for 5 days</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td><strong>Primary options</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>» methylprednisolone acetate: small joint: 4-10 mg intra-articularly as a single dose; medium joint: 10-40 mg intra-articularly as a single dose; large joint: 20-80 mg intra-articularly as a single dose</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td><strong>Primary options</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>» triamcinolone acetonide: small joint: 2.5 to 10 mg intra-articularly as a single dose; larger joint: 5-40 mg intra-articularly as a single dose</td>
</tr>
</tbody>
</table>

### Ongoing

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Tx line</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>recurrent gout: 2 to 3 weeks post acute episode</td>
<td>1st</td>
<td>xanthine oxidase inhibitor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>» Allopurinol and febuxostat reduce the production of uric acid. Goal is to reduce</td>
</tr>
</tbody>
</table>
### Ongoing

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Tx line</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>uric acid level below 6 mg/dL to prevent supersaturation and crystal formation.</td>
</tr>
</tbody>
</table>

- They should not be started during an acute attack as they might prolong the attack or precipitate more attacks. Adjust dose according to serum urate target level of 6 mg/dL.

- The starting dose for allopurinol should be low to reduce the risk of hypersensitivity, a condition characterized by eosinophilia, dermatitis, hepatitis, and renal failure, and associated with 20% mortality. In cases of hypersensitivity reaction where allopurinol is necessary and the only treatment option, allopurinol desensitization under close monitoring should be considered.

- In populations where HLA-B*5801 positive subjects are at high risk for severe allopurinol hypersensitivity reaction (e.g., Koreans with renal insufficiency, Han Chinese descent, and Thai descent), HLA-B*5801 screening should be considered.

- Febuxostat is a nonpurine selective xanthine oxidase inhibitor. The UK National Institute for Health and Care Excellence (NICE) has recommended that febuxostat be considered as an option for the management of chronic hyperuricemia in gout only for people who are intolerant to allopurinol, or for whom allopurinol is contraindicated. Preliminary results from a safety clinical trial show an increased risk of heart-related death with febuxostat compared to allopurinol. The Food and Drug Administration are evaluating this safety issue and will release an update once completed.

### Primary options

- **allopurinol**: 100 mg orally once daily initially, increase by 100 mg/day increments every week according to serum urate level, maximum 800 mg/day; a lower starting dose may be required in patients with renal impairment

### Secondary options

- **febuxostat**: 40-80 mg orally once daily

### suppressive therapy

- Suppressive (prophylactic) therapy such as nonsteroidal anti-inflammatory drugs (NSAIDs)
or low-dose colchicine should be considered during initiation and tapering of a urate-lowering agent. They should be continued for 3 to 12 months after reaching the target level of serum uric acid.

» Prednisone may be considered if both NSAIDs and colchicine are contraindicated, at the lowest dose to prevent gout flares.

**Primary options**

» **naproxen**: 250-500 mg orally twice daily

OR

**Primary options**

» **ibuprofen**: 400-800 mg orally three times daily

OR

**Primary options**

» **diclofenac potassium**: 50 mg orally (immediate-release) two to three times daily

OR

**Primary options**

» **meloxicam**: 7.5 to 15 mg orally once daily

OR

**Primary options**

» **indomethacin**: 25-50 mg orally three times daily

OR

**Primary options**

» **celecoxib**: 100-200 mg orally once to twice daily

OR

**Primary options**

» **colchicine**: 0.6 mg orally once daily
<table>
<thead>
<tr>
<th>Patient group</th>
<th>Tx line</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td><strong>adjunct</strong> lesinurad</td>
<td></td>
</tr>
<tr>
<td></td>
<td>» A uricosuric agent that inhibits the uric acid transporters (URAT1 and OAT4) in the proximal tubule of the kidney.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>» Approved by the Food and Drug Administration (FDA) to be used in combination with allopurinol or febuxostat only.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>» May be considered as an adjunctive therapy to allopurinol or febuxostat in patients who have not achieved target serum uric acid levels with a xanthine oxidase inhibitor alone.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>» In two phase III trials, a combination of lesinurad and allopurinol increased modestly the proportion of people achieving serum uric acid &lt;6 mg/dL at 6 months compared with allopurinol alone. Lesinurad was associated with ≥1.5 increase in serum creatinine and elevation in liver function tests.[74] [75]</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Primary options</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>» lesinurad: 200 mg orally once daily</td>
<td></td>
</tr>
<tr>
<td>2nd probenecid</td>
<td><strong>Primary options</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>» probenecid: 250-1000 mg orally twice daily plus suppressive therapy</td>
<td></td>
</tr>
</tbody>
</table>
## Gout
### Treatment

<table>
<thead>
<tr>
<th>Ongoing Patient group</th>
<th>Tx line</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>» Suppressive (prophylactic) therapy such as nonsteroidal anti-inflammatory drugs (NSAIDs) or low-dose colchicine should be considered during initiation and tapering of a urate-lowering agent. They should be continued for 3 to 12 months after reaching the target level of serum uric acid.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>» Prednisone may be considered if both NSAIDs and colchicine are contraindicated, at the lowest dose to prevent gout flares.</td>
</tr>
</tbody>
</table>

**Primary options**

- **naproxen**: 250-500 mg orally twice daily

**OR**

**Primary options**

- **ibuprofen**: 400-800 mg orally three times daily

**OR**

**Primary options**

- **diclofenac potassium**: 50 mg orally (immediate-release) two to three times daily

**OR**

**Primary options**

- **meloxicam**: 7.5 to 15 mg orally once daily

**OR**

**Primary options**

- **indomethacin**: 25-50 mg orally three times daily

**OR**

**Primary options**

- **celecoxib**: 100-200 mg orally once to twice daily

**OR**

**Primary options**

- **colchicine**: 0.6 mg orally once daily

**OR**

**Secondary options**
**Treatment**

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Tx line</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td>» prednisone: 7.5 to 10 mg orally once daily initially, adjust to lowest dose that prevents gout flares</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3rd intravenous pegloticase</td>
</tr>
<tr>
<td></td>
<td></td>
<td>» Intravenous pegloticase (a pegylated recombinant mammalian uricase) may be an option for patients with refractory tophaceous gout that is not responsive to treatment with other available conventional uric acid-lowering agents. [79]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>» Gout flares may occur during initial treatment, and infusion reactions may be problematic. Anaphylaxis has occurred.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>» Serum uric acid levels should be monitored 24 to 72 hours before infusions and consideration given to stopping treatment if levels increase to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed. Other urate-lowering drugs should not be given concomitantly as this may make such changes harder to detect.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>» Premedication with antihistamines and corticosteroids should be given.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Primary options</td>
</tr>
<tr>
<td></td>
<td></td>
<td>» pegloticase: 8 mg intravenously every 2 weeks</td>
</tr>
<tr>
<td></td>
<td>plus</td>
<td>suppressive therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>» Suppressive (prophylactic) therapy such as nonsteroidal anti-inflammatory drugs (NSAIDs) or low-dose colchicine should be considered during initiation and tapering of a urate-lowering agent. They should be continued for 3 to 12 months after reaching the target level of serum uric acid.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>» Prednisone may be considered if both NSAIDs and colchicine are contraindicated, at the lowest dose to prevent gout flares.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Primary options</td>
</tr>
<tr>
<td></td>
<td></td>
<td>» naproxen: 250-500 mg orally twice daily</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Primary options</td>
</tr>
<tr>
<td></td>
<td></td>
<td>» ibuprofen: 400-800 mg orally three times daily</td>
</tr>
<tr>
<td>Ongoing</td>
<td>Tx line</td>
<td>Treatment</td>
</tr>
<tr>
<td>---------</td>
<td>---------</td>
<td>-----------</td>
</tr>
<tr>
<td>Patient group</td>
<td></td>
<td>Primary options</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Primary options</td>
</tr>
<tr>
<td></td>
<td>» diclofenac potassium: 50 mg orally (immediate-release) two to three times daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Primary options</td>
</tr>
<tr>
<td></td>
<td>» meloxicam: 7.5 to 15 mg orally once daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Primary options</td>
</tr>
<tr>
<td></td>
<td>» indomethacin: 25-50 mg orally three times daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Primary options</td>
</tr>
<tr>
<td></td>
<td>» celecoxib: 100-200 mg orally once to twice daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Primary options</td>
</tr>
<tr>
<td></td>
<td>» colchicine: 0.6 mg orally once daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Secondary options</td>
</tr>
<tr>
<td></td>
<td>» prednisone: 7.5 to 10 mg orally once daily initially, adjust to lowest dose that prevents gout flares</td>
<td></td>
</tr>
</tbody>
</table>
Gout Treatment

Emerging

Oxypurinol

This agent is a xanthine oxidase inhibitor that may be a substitute for allopurinol in patients with minor hypersensitivity to that drug. It is available in the US on compassionate use-only basis.

Rilonacept

A phase II double-blind trial of gout flare prophylaxis during initiation of urate-lowering therapy randomized 83 patients to subcutaneous rilonacept (a soluble IL-1 receptor-Fc fusion protein) or placebo.[84] At 12 weeks, there were significantly fewer patients with one or more gout flare in the rilonacept group than in the placebo group (15% vs. 45%, respectively). The results were replicated in a phase III, randomized, double-blind, placebo-controlled trial of rilonacept. The mean number of gout flares per patient over the 16 week study period was significantly lower in both rilonacept arms relative to placebo (0.29 for rilonacept 80 mg; 0.21 for rilonacept 160 mg; 1.06 for placebo). There were no safety signals during a four week extension of this trial.[85] The study was limited by comparing rilonacept with placebo rather than standard care, such as colchicine or nonsteroidal anti-inflammatory drugs (NSAIDs).[86] A double-blind randomized study of treatment of acute gout attacks in 255 patients showed that adding rilonacept to indomethacin was no more effective than indomethacin alone.[24] The study included a third arm of high-dose rilonacept that was associated with less pain reduction compared with the other 2 arms, but the study did not plan this analysis.

Canakinumab

A fully humanized anti-interleukin-1 beta monoclonal antibody. In an 8-week, single-blind, double-dummy, dose-ranging study, patients with acute gout who did not respond or had contraindications to NSAIDs and/or colchicine were randomized to receive a single subcutaneous dose of canakinumab (various doses; n = 143) or an intramuscular dose of triamcinolone (n = 57). While canakinumab was associated with numerically less pain (100-mm visual analog score), only the highest dose was statistically superior to triamcinolone at 24, 48, and 72 hours. Canakinumab also prevented recurrent flares and did not appear to increase the risk of serious adverse effects.[26] However, an oral corticosteroid or intra-articular injection may have been a more appropriate comparator. In a different analysis of the same study, treatment with canakinumab was associated with significantly reduced tenderness and swelling at 72 hours compared with triamcinolone. Improvements in the SF-36 physical health scores were observed at 7 days post-dose in both treatment groups, but increases in scores were highest for canakinumab.[87] A 24-week double-blind study compared different doses of canakinumab with colchicine for the prevention of gout flares during initiation of treatment with allopurinol.[88] Patients taking canakinumab were significantly less likely to experience gout flares than those taking colchicine. The colchicine dose was lower than that used in the UK or US. Two 12-week, randomized, double-blind studies with double-blind 12-week extensions compared canakinumab with triamcinolone in patients with gouty arthritis not suitable for NSAIDs and/or colchicine (beta-RELIEVED and beta-RELIEVED-II).[89] Pooled results of the studies showed that patients who took a single dose of canakinumab during an acute flare experienced rapid and effective pain relief compared with patients receiving triamcinolone (mean 72-hour visual analog scale pain score of 25.0 mm vs. 35.7 mm, respectively; difference, -10.7 mm; p<0.0001), and a 56% reduction in risk of new flares over the 24-week period (HR: 0.44; p<0.0001). In June 2011, a Food and Drug Administration (FDA) panel rejected canakinumab as a treatment for gout because of the potential risk of infection, hypertriglyceridemia, and elevated uric acid levels. [FDA Arthritis Advisory Committee: FDA briefing document on supplemental canakinumab] In the UK, the National Institute of Health and Care Excellence (NICE) has stated that it was unable to recommend the use in the National Health Service (NHS) of canakinumab for treating gouty arthritis attacks and reducing the frequency of subsequent attacks because no evidence submission was received from the manufacturer.[90] It has been approved by the European Medicines Agency (EMA) for the symptomatic treatment of adult patients with frequent gouty arthritis attacks (at least 3 attacks in the previous 12 months) in whom NSAIDs and colchicine are contraindicated, are not tolerated, or do not provide an adequate response, and in whom repeated courses of corticosteroids are not appropriate.

Arhalofenate

This PDF of the BMJ Best Practice topic is based on the web version that was last updated: Nov 24, 2017. BMJ Best Practice topics are regularly updated and the most recent version of the topics can be found on bestpractice.bmj.com. Use of this content is subject to our disclaimer. © BMJ Publishing Group Ltd 2018. All rights reserved.
A novel anti-inflammatory and a uricosuric agent that inhibits URAT1 and has anti-inflammatory features based on mice data, inhibiting the release of interleukin-1 beta and other inflammatory mediators. A phase IIIB study randomized 248 subjects to receive one of two different doses of arhalofenate; allopurinol; allopurinol plus colchicine; or placebo. The primary outcome was gout flare prevention at 12 weeks. The higher dose of arhalofenate decreased gout flares by 46%, which was statistically significant only in comparison with allopurinol alone or placebo, and not in comparison with the allopurinol plus colchicine arm. The mean decrease in serum uric acid level was disappointing, only 12.5% ±16 (mean ± SD) with the lower dose of arhalofenate and 16.5% ± 15 with the higher dose of arhalofenate, while the decrease was 24.9 ± 19.7 with allopurinol plus colchicine and 28.8% ± 20.3 in the allopurinol group. The study design did not follow typical clinical practice, in having an arm initiating allopurinol 300 mg/day as opposed to 100 mg/day, and without a suppressive therapy (such as colchicine), which was used in only one arm of the comparison group.[91]

**Purine nucleoside phosphorylase inhibitor (BCX4208)**

In a double-blind, placebo-controlled study, BCX4208 significantly reduced serum uric acid over a 3-week period (-2.7 mg/dL, -3.3 mg/dL, and -3.4 mg/dL in the 40 mg/day, 80 mg/day, and 120 mg/day dose groups, respectively, compared with -0.4 mg/dL for placebo).[92] Approximately one third of patients receiving BCX4208 achieved serum uric acid <6 mg/dL, irrespective of dose. No subject in the placebo group achieved serum uric acid <6 mg/dL. The drug produced moderate reductions in lymphocyte subsets, but was well tolerated.
# Recommendations

## Monitoring

Patients should be monitored for recurrent attacks, the development of tophi, and radiographic changes.

In patients taking uric acid-lowering agents, follow-up uric acid levels every 1 to 3 months initially, then every 6 months (target level <6 mg/dL).

Patients should be monitored for adverse effects of nonsteroidal anti-inflammatory drugs and colchicine, especially if they are used for prolonged periods. For nonsteroidal anti-inflammatory drugs, colchicine, and allopurinol, CBC, renal function tests, and LFTs should be obtained every 3 to 6 months.

When initiating allopurinol, patients should be closely monitored for hypersensitivity syndrome (eosinophilia, dermatitis, and multisystem failure).

Long-term colchicine use may be associated with neuromyopathy. Probenecid may increase the risk of nephrolithiasis.

Most of the above medications, and specifically allopurinol, have multiple drug interactions that may require adjustments to medication dosages.

## Patient instructions

Foods that have a high purine content (i.e., alcohol, seafood, and offal) are associated with higher risk of elevated uric acid and gout.[2]

Reducing intake of alcohol, especially beer, lowers the risk of gout.[30]

Reducing seafood and meat intake helps to a lesser degree.

Reducing the intake of vegetables high in purines (i.e., asparagus, spinach, and mushrooms) does not seem to affect uric acid levels.

Dairy products reduce the risk of gout.

## Complications

<table>
<thead>
<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>acute uric acid nephropathy</td>
<td>short term</td>
<td>low</td>
</tr>
</tbody>
</table>

Occurs most commonly in patients treated with cytotoxic agents, especially for lymphoproliferative disorders and large tumor burdens (tumor lysis syndrome).

Usually occurs with very high uric acid levels exceeding 20 mg/dL and urine uric acid/creatinine ratio exceeding 1.

Patients may develop acute and oliguric renal failure. This is usually prevented with hydration and prophylaxis with allopurinol.
Uric acid calculi constitute 10% of the renal stones in the US. Their prevalence in patients with gout is variable (10% to 42%) and increases with uric acid level.[100]

## Prognosis

Gout attacks are painful and debilitating, but self-limiting. In patients untreated with uric acid-lowering drugs, the risk of recurrence after the first attack is 62%, 78%, and 84% during the first, second, and third year, respectively.[96]

In untreated gout, about 2% of patients developed severe debilitating arthritis typically 20 years after the first attack.[97]

Among people with untreated gout, tophi occur in about 50% after 10 years and 72% after 20 years.[97]

Appropriate treatment can suppress gout attacks and their recurrence, and prevent long-term consequences of the disease. There are currently few available uric acid-lowering agents, which is problematic in cases of medication intolerance or ineffectiveness. In addition, treatments for acute and chronic gout have considerable risks and adverse events.

Gout and untreated hyperuricemia may be associated with renal insufficiency. In a veteran population with gout, rates of incident kidney disease were lower in men with controlled serum urate levels than in those with high serum urate (2% vs. 4% at year 1, 3% vs. 6% at year 2, and 5% vs. 9% at year 3, respectively).[98] High serum urate conferred a significant risk of kidney disease development (HR 1.43, 95% CI 1.20 to 1.70).

In a UK cohort study comprising individuals with a history of hyperuricemia, allopurinol use was associated with a lower risk of all-cause mortality compared with non-use (HR 0.89, 95% CI 0.80 to 0.99).[64] Risk reduction was more pronounced when the analysis was limited to those with gout (HR 0.81, 95% CI 0.70 to 0.92). Another study found no difference in mortality in subjects with incident gout who were treated with allopurinol compared with matched controls based on propensity scores.[99]
Diagnostic guidelines

**International**


**Published by:** American College of Physicians  
**Last published:** 2016


**Published by:** American College of Rheumatology Ad Hoc Committee on Clinical Guidelines  
**Last published:** 1996


**Published by:** European League Against Rheumatism  
**Last published:** 2011


**Published by:** Japanese Society of Gout and Nucleic Acid Metabolism  
**Last published:** 2011


**Published by:** European League Against Rheumatism  
**Last published:** 2006
## Treatment guidelines

### International

#### Management of acute and recurrent gout: a clinical practice guideline from the American College of Physicians

**Published by:** American College of Physicians  
**Last published:** 2016


**Published by:** American College of Rheumatology  
**Last published:** 2012


**Published by:** European League Against Rheumatism  
**Last published:** 2016


**Published by:** National Institute for Health and Care Excellence (UK)  
**Last published:** 2008


**Published by:** British Society for Rheumatology; British Health Professionals in Rheumatology  
**Last published:** 2007
Japanese guideline for the management of hyperuricemia and gout: second edition

Published by: Japanese Society of Gout and Nucleic Acid Metabolism  Last published: 2011
Online resources

1. **ACR-EULAR gout classification criteria calculator** *(external link)*

2. **FDA Arthritis Advisory Committee: FDA briefing document on supplemental canakinumab** *(external link)*
# Evidence scores

1. Reduction in pain: there is poor-quality evidence that colchicine may be more effective than placebo at reducing pain in people with gout.[58]

   **Evidence level C:** Poor quality observational (cohort) studies or methodologically flawed randomized controlled trials (RCTs) of <200 participants.

2. Symptom resolution: there is moderate-quality evidence that corticosteroids are as effective as nonsteroidal anti-inflammatory drugs (NSAIDs) at reducing symptoms in people with acute gout.

   **Evidence level B:** Randomized controlled trials (RCTs) of <200 participants, methodologically flawed RCTs of >200 participants, methodologically flawed systematic reviews (SRs) or good quality observational (cohort) studies.

3. Efficacy of pegloticase for refractory gout: there is good-quality evidence that intravenous pegloticase can reduce serum urate levels in patients with gout refractory to treatment with allopurinol and febuxostat.[79] [80]

   **Evidence level A:** Systematic reviews (SRs) or randomized controlled trials (RCTs) of >200 participants.
Key articles


References


References


<table>
<thead>
<tr>
<th>References</th>
</tr>
</thead>
</table>


Images

Figure 1: Chronic tophaceous gout showing nodules in the hands, elbows, legs, buttocks, and abdominal wall (arrows)

Adapted from BMJ Case Reports 2009 [doi:10.1136/bcr.03.2009.1668] Copyright © 2009 by the BMJ Group Ltd
Figure 2: Chronic tophaceous gout showing nodules in periarticular structures and arthritis

Adapted from BMJ Case Reports 2009 [doi:10.1136/bcr.03.2009.1668] Copyright © 2009 by the BMJ Group Ltd
Figure 3: Uric acid levels and cumulative incidence of first episodes of gout

Disclaimer

This content is meant for medical professionals. The BMJ Publishing Group Ltd (“BMJ Group”) tries to ensure that the information provided is accurate and up to date, but we do not warrant that it is. The BMJ Group does not advocate or endorse the use of any drug or therapy contained within nor does it diagnose patients. Medical professionals should use their own professional judgement in using this information and caring for their patients and the information herein should not be considered a substitute for that.

This information is not intended to cover all possible diagnosis methods, treatments, follow up, drugs and any contraindications or side effects. We strongly recommend that users independently verify specified diagnosis, treatments and follow up and ensure it is appropriate for your patient. This information is provided on an “as is” basis and to the fullest extent permitted by law the BMJ Group assumes no responsibility for any aspect of healthcare administered with the aid of this information or any other use of this information.

View our full Website Terms and Conditions.
Contributors:

// Authors:

**Fadi Badlissi, MD, MSc**
Assistant Professor
Harvard Medical School, Attending Physician, Director of the Musculoskeletal Medicine Unit, Department of Orthopedics & Division of Rheumatology, Beth Israel Deaconess Medical Center, Boston, MA
DISCLOSURES: FB declares that he has no competing interests.

// Peer Reviewers:

**H. Ralph Schumacher, Jr., MD**
Professor of Medicine
VA Medical Center, Philadelphia, PA
DISCLOSURES: HRS has been a consultant for a number of pharmaceutical companies that produce drugs that can be used for the treatment of gout. Some companies have supplied HRS with funding. HRS is an author of a number of references cited in this monograph.

**Ade Adebajo, MD**
Associate Director of Teaching and Honorary Senior Lecturer in Rheumatology
Academic Rheumatology Group, Faculty of Medicine, University of Sheffield, Sheffield, UK
DISCLOSURES: AA declares that he has no competing interests.

**Martin Underwood, MBBS**
Professor of Primary Care Research
Warwick Medical School, Coventry, UK
DISCLOSURES: MU declares that he has no competing interests.