BMJ Best Practice

Gout

Straight to the point of care

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Summary

Gout is characterized by acute onset of severe joint pain, with 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, colchicine, corticosteroids, or interleukin-1 inhibitors are used to treat acute disease.

Uric acid-lowering drugs (e.g., allopurinol, febuxostat, or probenecid) may be used 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.

[BMJ talk medicine podcast: gout] (https://soundcloud.com/bmjpodcasts/gout?in=bmjpodcasts/sets/bmj-best-practice-clinical)

THEORY

Epidemiology

Estimates of the prevalence and incidence of gout vary widely depending on the population studied and methods used. Globally reported prevalence ranges from <1% to 6.8%, and incidence ranges from 0.58 to 2.89 per 1000 person-years.[1] There are an estimated 41.2 million prevalent cases of gout worldwide, with 7.4 million incident cases per year. Incidence increased by 7.2%, and prevalence by 5.5%, between 1990 and 2017. The largest increases in prevalence were seen in the US, Canada and Oman.[2]

Gout is more prevalent in men than women, and increases with age for both groups.[2]

Prevalence varies geographically and racially, with the highest rates reported in Pacific countries, Australia and the US in 2017.[2] An estimated 9.3% to 13.9% of Maori men and 14.9% of Pacific island men suffer from severe gout.[3] [4]

The prevalence of gout among US adults in 2016 was 3.9% (9.2 million people), of which 5.2% were male and 2.7% were female.[5] The annual incidence of gout in the US in people over 50 years of age has been estimated at 1.6 per 1000 in men and 0.3 per 1000 in women.[6]

Data from primary care practices in the UK was used to estimate the prevalence (2.49%) and incidence (1.77 per 1000 person-years) of gout in 2012.[7] When compared with incidence and prevalence rates from 1997, an increase of 63.9% in prevalence, and 29.6% in incidence was seen.[7]

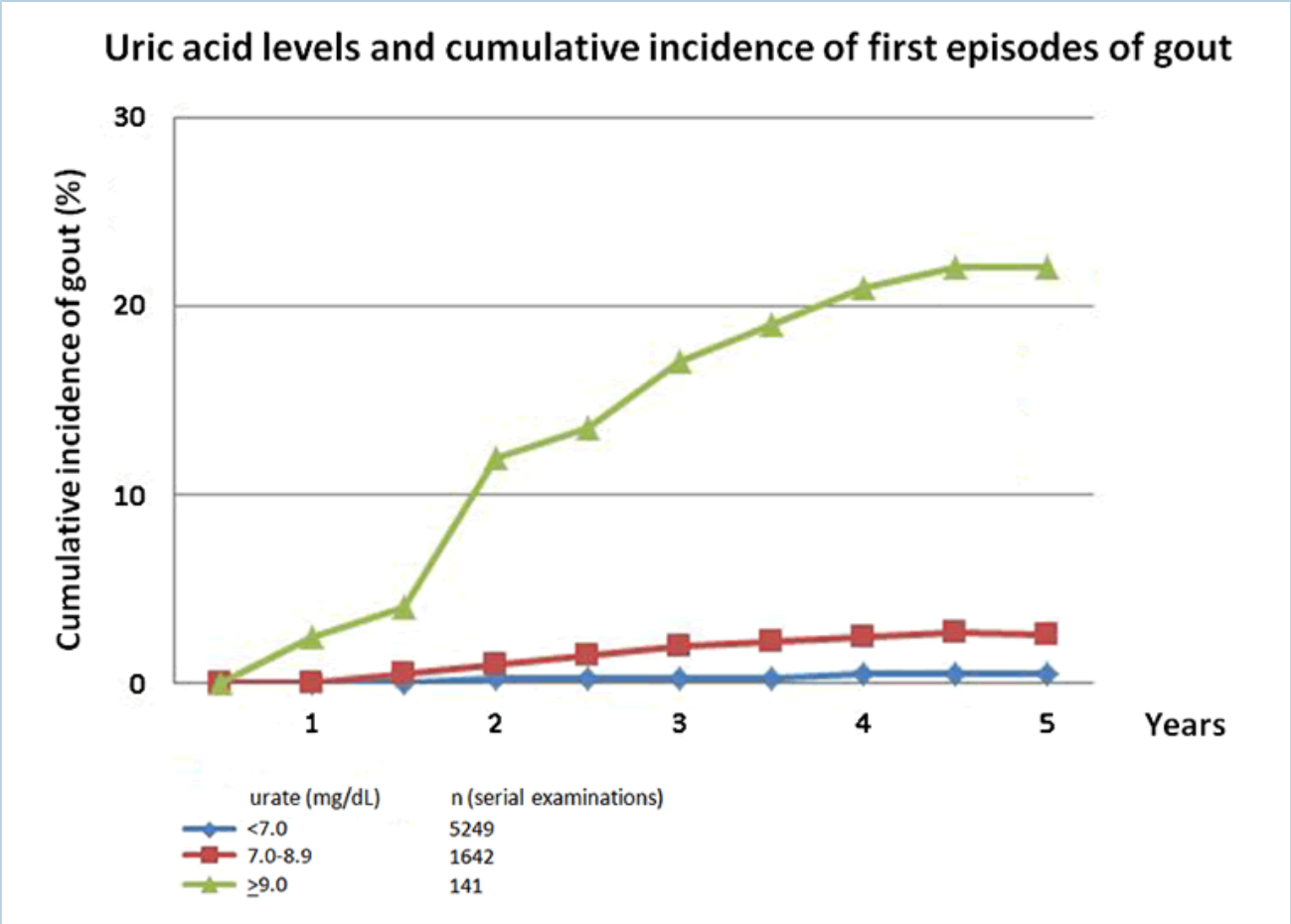
Gout is rare in premenopausal women.[8]

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.[9]



Uric acid levels and cumulative incidence of first episodes of gout

Adapted from Campion EW, Glynn RJ, DeLabry LO. Asymptomatic hyperuricemia. Risks and consequences in the Normative Aging Study. Am J Med. 1987;82:421-426

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.[10] Aspirin, cyclosporine, tacrolimus, or pyrazinamide can raise serum uric acid level by increasing uric acid reabsorption.[11] [12] Diuretics can increase urate levels and are associated with an increased risk of gout.[13] [14]

Risk factors for hyperuricemia may eventually lead to gout, and include dietary factors such as consumption of seafood, meat, and alcohol, especially beer.[14] [15] [16] Obesity, insulin resistance, and hypertension have also been implicated.[13] [17] [18]

High cell turnover, such as from hematologic cancer and chemotherapy, and specific genetic enzymatic abnormalities, constitute endogenous sources of purine and urate production.[10]

Pathophysiology

Humans and some other higher primates develop gout spontaneously. Humans no longer express the gene for the enzyme uricase, which, in animals, degrades uric acid to the more soluble compound allantoin. This, coupled with a high rate of renal reabsorption of urate, results in hyperuricemia and gout.[19] [20] [21] [22] 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 risk for gout.[9] Drugs that reduce urate levels decrease the risk of recurrent attacks.[23]

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.[24]

Urate crystals in the joint interact with undifferentiated phagocytes and trigger an acute inflammatory response by inducing tumor necrosis factor (TNF)-alpha and activating signal pathways and endothelial cells.[25] 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.[10] [26] 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.[27] [28]

In addition there is evidence that urate crystals activate NALP3 inflammasome (a key regulator of IL-1beta secretion), which plays a role in the gout inflammatory reaction.[29]

Urate crystals can induce chondrocytes to produce metalloproteinase and nitric oxide, and chronic inflammation, leading to synovitis, cartilage loss, bone damage by inhibiting osteoblasts, and bone erosions.[30] [31]

Genetic mutations that potentially predispose people to hyperuricemia and gout have been identified.[32] [33] [34] [35] [36] However, further study is required to determine their clinical significance.

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.[10]

Case history

Case history #1

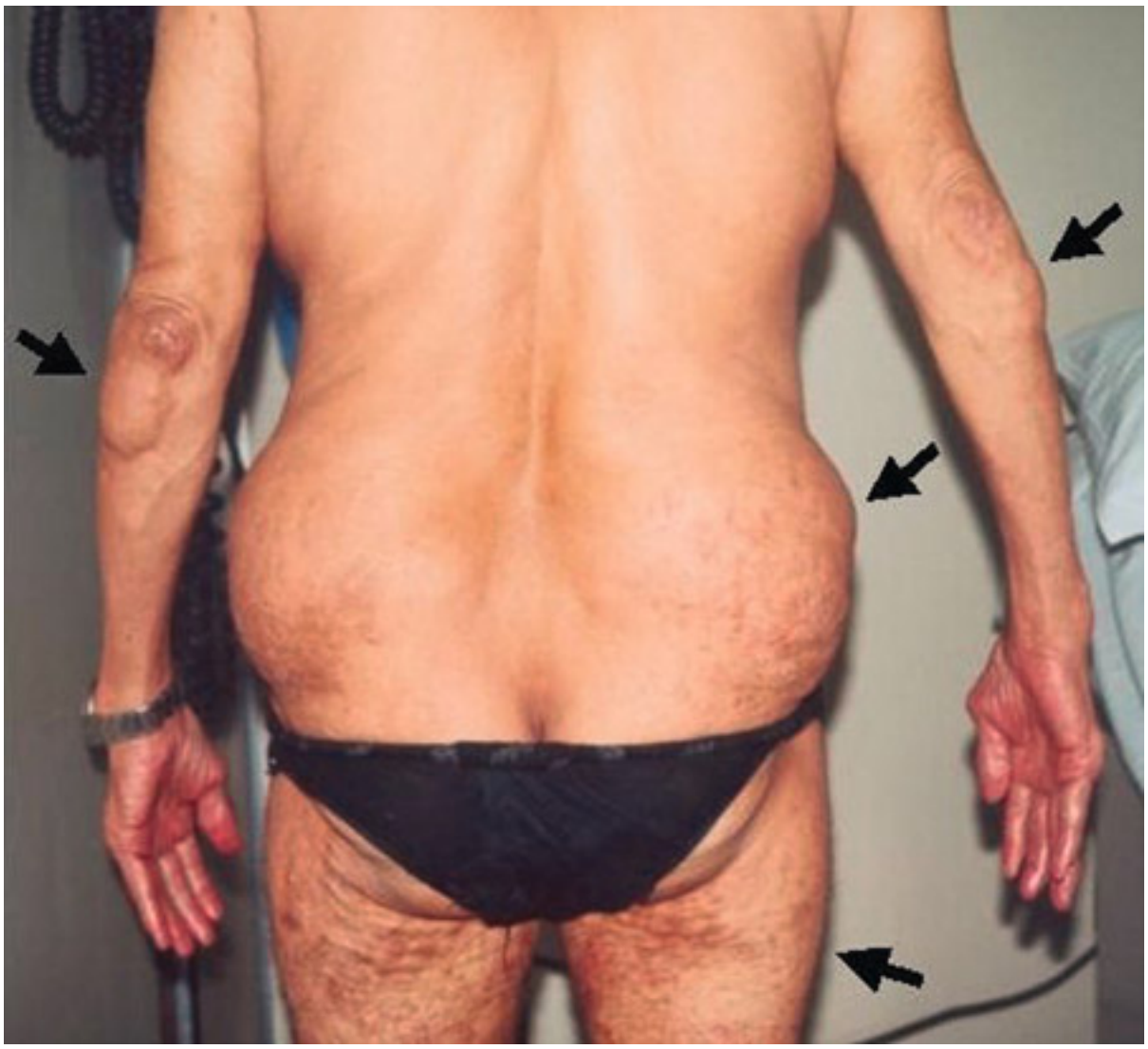
A 54-year-old man complains of severe pain and swelling in his right first toe that developed overnight. He is limping because of the pain and states that this is the most severe pain he has ever had ("even covering my foot with the bed sheet hurts"). He has had no previous episodes. His only medication 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

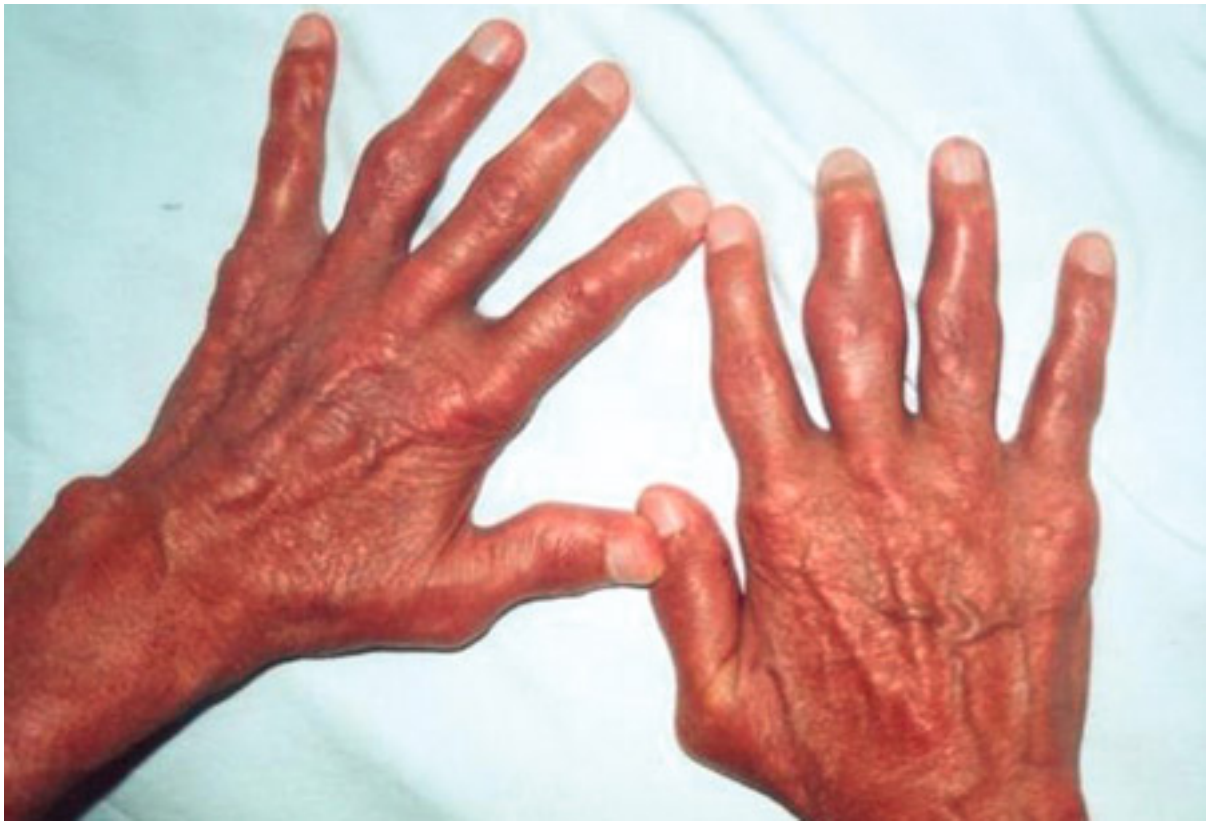
An 85-year-old man presents with several days of swelling and severe pain in both hands limiting his ability to use his walker. He has a history of gout but has not experienced these symptoms before. On examination, he has a temperature of 100.1°F (37.8°C). There is diffuse warmth, mild erythema, and 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. Chronic tophaceous gout may cause inflammatory destructive polyarthritis. This usually occurs in people with a long-standing history of attacks (mean 10 years) and with higher uric acid levels.



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



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

Approach

Gout is clinically suspected in patients with typical history and examination findings.

A clinical diagnosis can be made with a good degree of certainty in patients with a reliable history of recurrent acute monoarthritis of the first metatarsophalangeal joint (podagra).[53] Rapid onset of severe pain, redness or swelling of joints other than the first metatarsophalangeal (e.g., midfoot, ankle, knee, hand, wrist, elbow) may also indicate a diagnosis of gout.[53]

Diagnosis is confirmed by arthrocentesis showing monosodium urate crystals.[53]

Alternatively, diagnosis may be based upon fulfillment of ≥6 of the following criteria from the American College of Rheumatology (ACR):[54]

- 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.

In 2015 the ACR published new classification criteria; however, these criteria are intended to identify people who may be eligible for entry into a clinical study and they are not intended to be used to diagnose gout.[55] [56]

History

Gout is more common in men and rare in premenopausal women.[2] [3] [5] [8] [37] 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.[53] [57] Symptoms often develop overnight.[53]

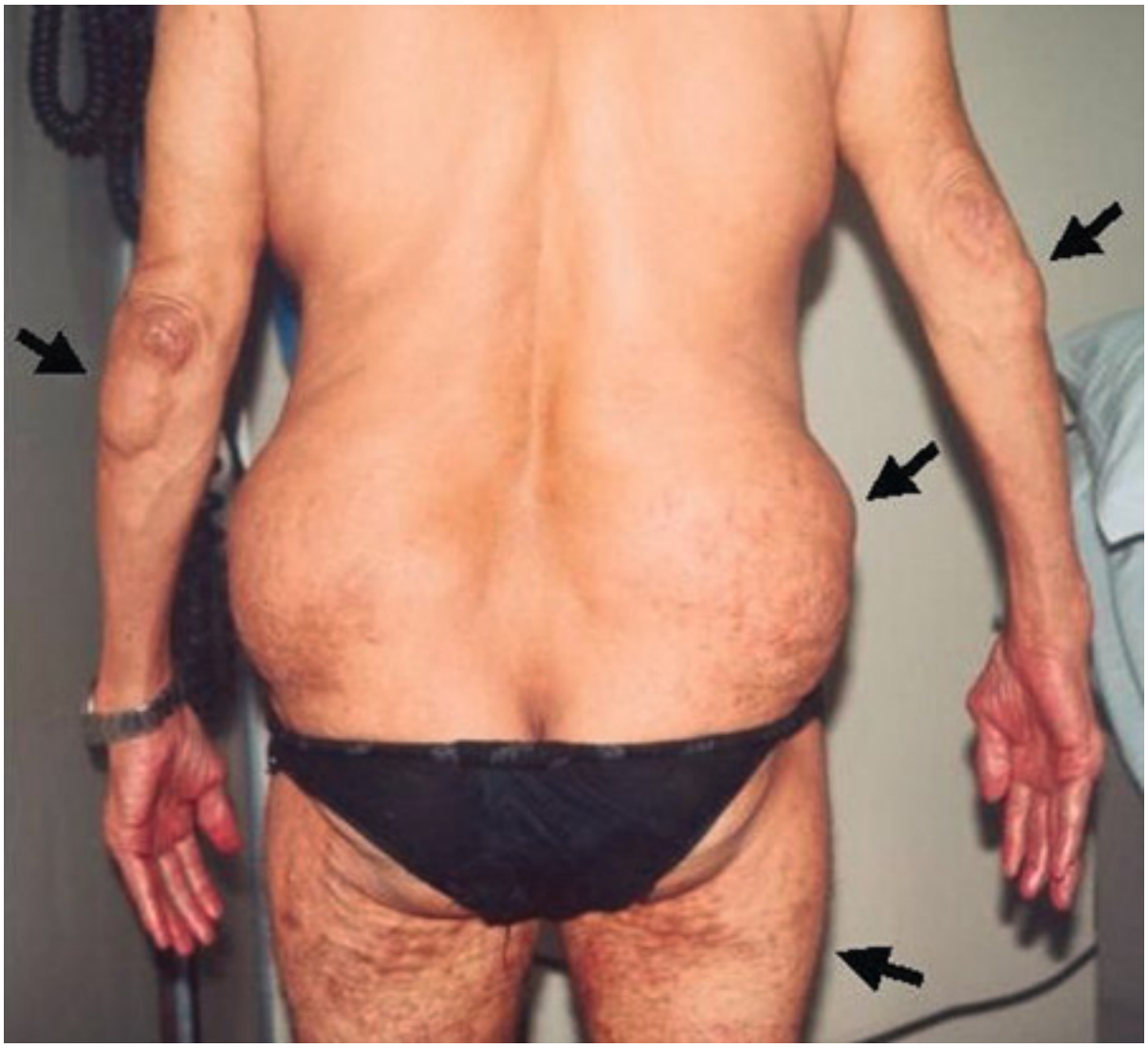
The disease may be oligoarticular (<4 joints involved) or, to a lesser degree, polyarticular (e.g., in older people, where it may be associated with marked edema and swelling of the hands and feet). The most commonly affected joints are the first metatarsophalangeal, tarsometatarsal, ankle, and knee joints, but almost any other joint may be affected.[57]

Physical examination

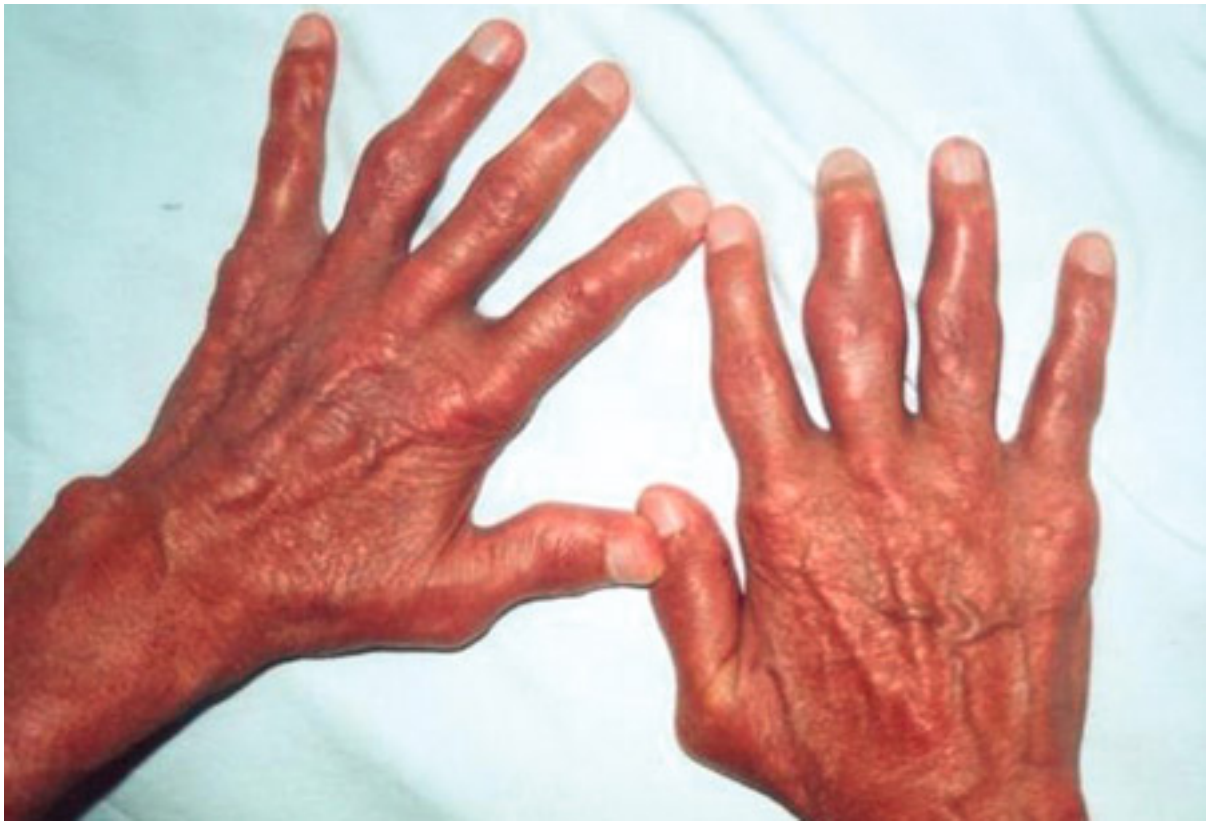
Involved joints are warm, red, and swollen.[53] Usually, there is considerable tenderness and limited range of movement due to pain.

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.[53] [57] Tophi may also be evident over the dorsal aspects of hands and feet, and in the helix of the ears.



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



Chronic tophaceous gout showing nodules in periarticular structures and arthritis

Investigations

The following tests may be considered in people with symptoms typical of gout.

Arthrocentesis with synovial fluid analysis

- Provides definitive diagnosis.[53] [58]
- The synovial fluid white blood cell count usually exceeds 2000/mm³, and the cells are mostly polymorphonuclear neutrophils 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.[59]
- In the UK, a serum urate level 6 mg/dL or more confirms a diagnosis of gout. If the serum urate level is below 6 mg/dL during a gout flare, and gout is suspected, the test should be repeated at least two weeks after the flare has settled.[53]

Ultrasound

- Ultrasound is more sensitive than radiographs in detecting erosions, tophi, and the gout-specific double contour sign (linear urate deposits over hyaline cartilage). Ultrasound findings, including tophi and erosion beside a double contour sign, have a sensitivity of 65% and specificity approaching 90%.[60] [61]

- Ultrasound is recommended for patients in the UK if joint aspiration can't be performed, or if the diagnosis of gout is uncertain.[53]

Dual energy computed tomography (DECT)

- Could be helpful in the diagnosis of gout when it is in question, or for patients with contraindications for, or who refuse to have joint aspiration.[53] [62] [63] [64]
- Evidence suggests that DECT is valid and reliable, more sensitive than radiographs and computed tomography, and at least comparable to ultrasound for the diagnosis of gout.[65] [66] [67]
- One meta-analysis concluded that DECT has a high diagnostic accuracy in established gout, but low sensitivity for recent-onset gout.[64] [68]

Radiography

- Radiographs are of limited diagnostic utility.[52] In late/severe gout, radiographic changes may help to differentiate between chronic gout and other joint conditions.[69]
- X-ray findings suggestive of gout include soft-tissue opacifications with densities between soft tissue and bone, articular and periarticular bone erosions, and osteophytes at the margins of opacifications or erosions.[70] The hands are an optimal place to look for gouty erosions.

History and exam

Key diagnostic factors

men ages >40 years (common)

- Gout is more common in men; incidence increases with age.[2] [3] [5] [6] [15]

use of gout-inducing medication (common)

- Use of drugs including aspirin, cyclosporine, tacrolimus, or pyrazinamide increase urate reabsorption.[11] [12]

consumption of meat, seafood, or alcohol (common)

- Meta-analyses of prospective cohort and cross sectional studies report that increased serum urate levels or gout correlate with red meat, seafood, and alcohol intake.[14] [16]
- One 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 1.51 (95% CI 1.17 to 1.95) and 1.41 (95% CI 1.07 to 1.86), respectively.[15]

history 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.[10]

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. Symptoms often develop overnight.[53]

joint stiffness (common)

- Joint stiffness in the morning 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.[57]

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.[57]

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.[57]
- May also be evident over dorsal aspects of hands and feet, and in the helix of the ears.

Other diagnostic factors

erythema and warmth (common)

- May be subtle at times, requiring careful examination.

family history of gout (uncommon)

- Family history of gout may increase risk of hyperuricemia and gout.[50] [51]

Risk factors

Strong

older age

- Annual incidence of gout increases with age.[2] [15]

male sex

- More common in men.[2] [3] [5] [6]

menopausal status

- Gout is rare in premenopausal women.[8]

consumption of meat, seafood, alcohol

- Meta-analyses of prospective cohort and cross-sectional studies report that increased serum urate levels or gout correlate with red meat, seafood, and alcohol intake.[14] [16]

- One 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 1.51 (95% CI 1.17 to 1.95) and 1.41 (95% CI 1.07 to 1.86), respectively.[15]

use of diuretics

- Thiazide and loop diuretics are associated with an increased risk of gout and of gout flares.[37]
- One meta-analysis of cohort studies concluded that diuretic use more than doubles the risk of developing gout compared with no diuretic use.[13]

use of cyclosporine or tacrolimus

- Lead to increased tubular reabsorption of urate as well as decreased glomerular filtration and interstitial nephropathy.[11] [12]

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.[10]

genetic susceptibility

- Some urate overproducers have specific genetic defects, such as hypoxanthine-guanine phosphoribosyl transferase (HPRT) deficiency, 5-phosphoribosyl-l-pyrophosphate (PRPP) synthetase hyperactivity, and glucose-6-phosphate dehydrogenase (G6PD) deficiency.[32] [33] [34]
- The most complete form of HPRT deficiency is associated with Lesch-Nyhan syndrome (premature gout and learning disabilities in children).[38] The partial deficit of the enzyme is associated with gout and hyperuricemia without neurologic manifestations.

high cell turnover rate

- Conditions that lead to high endogenous purine metabolism include hematologic malignancies, myeloproliferative disorders, psoriasis, and chemotherapy-induced cell death.[10]

Weak

obesity

- Increases the risk of gout.[17] [18]
- One meta-analysis of cohort studies reported that people with a body mass index of ≥30 are more than twice as likely to develop gout as people without this risk factor.[13]

adiposity and insulin resistance

- Associated with hyperuricemia.[17] [18] [39] [40] [41]
- Weight loss is associated with lower urate level and risk of gout, and reduced serum urate in those with gout.[42] [43] [44]

exogenous insulin

- Exogenous pharmacologic insulin can reduce the renal excretion of urate.[45] [46]

hypertension

- An independent risk factor for gout.[17] [37]
- Renal urate excretion is inappropriately low relative to glomerular filtration rate.[47] This may reflect early nephrocalcinosis in hypertensive patients. Gout, in turn, may be associated with a higher incidence of hypertension and cardiovascular morbidity.[48]
- One meta-analysis of cohort studies concluded that people with hypertension have more than double the risk of developing gout (relative risk 2.11) compared with normotensive individuals.[13]

renal insufficiency

- Has been found to be associated with higher risk of incident gout or gout flares.[37]

diabetes mellitus

- Epidemiologic studies suggest that patients with diabetes mellitus are at a higher risk of incident gout and/or gout flares.[37] However, a subsequent meta-analysis of observational studies concluded that diabetes mellitus may be a protective factor for the risk of gout.[49]

hyperlipidemia

- Hypertriglyceridemia and hypercholesterolemia are associated with a higher risk of incident gout and/or gout flares in epidemiologic studies.[37] However, confounding factors may have influenced findings.

family history of gout

- Risk of hyperuricemia and gout may be higher in people with a family history of gout.[50] [51]

Tests

1st test to order

Test	Result
arthrocentesis with synovial fluid analysis • Provides definitive diagnosis.[53] [58] Excludes septic arthritis and differentiates gout from pseudogout (calcium pyrophosphate deposition disease). • The synovial fluid WBC count usually exceeds 2000/mm³, and the cells are mostly polymorphonuclear neutrophils (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. • At times, poor transportation conditions or a long lag time between obtaining the synovial fluid and examining the specimen make it difficult to identify the crystals. • An expert, such as a rheumatologist or experienced technician, should examine the synovial fluid. • If the analysis fails to show monosodium urate crystals or other etiology for the acute inflammatory arthritis, repeating arthrocentesis during future attacks should be considered. •	**WBC count above 2000/mm³ (mean, 20,000/mm³); strongly negative birefringent needle-shaped crystals under polarized light**

Other tests to consider

Test	Result
serum uric acid level • Gout can develop with levels lower than the upper limit of normal values.[59] • Should be obtained around 2 weeks after the attack resolves, as it may be falsely low or normal during the attack.[59] • In the UK, a serum urate level 6 mg/dL or more confirms a diagnosis of gout. If the serum urate level is below 6 mg/dL during a gout flare, and gout is suspected, the test should be repeated at least two weeks after the flare has settled.[53]	**above 7 mg/dL in men; above 6 mg/dL in women**
ultrasound • Ultrasound-detected erosions are most commonly found in the first metatarsophalangeal joint and the metacarpophalangeal joints.[77] • Ultrasound findings, including tophi and erosion beside a double contour sign, have a sensitivity of 65% and specificity approaching 90%.[60] [61] • Ultrasound is recommended for patients in the UK if joint aspiration can't be performed, or if the diagnosis of gout is uncertain.[53]	**erosions, tophi, double contour line**
dual energy computed tomography (DECT) • Could be helpful in the diagnosis of gout when it is in question, or for patients with contraindications for, or who refuse to have joint aspiration.[53] [62] [63] [64] Evidence suggests that DECT is valid and reliable, more sensitive than radiographs and CT, and at least comparable to ultrasound for the diagnosis of gout.[65] [66] [67]	**erosions, tophi, double contour line**
x-ray of affected joint • Radiographs are of limited diagnostic utility.[52] In late/severe gout, radiographic changes may help to differentiate between chronic gout and other joint conditions.[69] • X-ray findings suggestive of gout include soft-tissue opacifications with densities between soft tissue and bone, articular and periarticular bone erosions, and osteophytes at the margins of opacifications or erosions.[70] • The hands are an optimal place to look for gouty erosions.	**periarticular erosions (may have an overhanging edge or punched-out appearance)**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Pseudogout (calcium pyrophosphate deposition disease)	• Presentation may be identical to that of gout.[57] • Pseudogout 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.[53] [57] • 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.
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 rheumatoid factor (RF) in 70% to 78% of cases; however, 30% of patients with gout have a positive RF.[78] • Anti-cyclic citrullinated peptide (anti-CCP) has high specificity, but low sensitivity, for RA. It may be useful in the early detection of patients who will have severe RA.[79]

Condition	Differentiating signs / symptoms	Differentiating tests
		• Synovial fluid is inflammatory (WBC count >2000/mm³), 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 and acro-osteolysis, ankylosis, spur formation, and spondylitis.[80]

Criteria

American College of Rheumatology preliminary criteria for the classification of the acute arthritis of primary gout[54]

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[55] [56]

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.[55] [56]

- 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] (http://goutclassificationcalculator.auckland.ac.nz)

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), corticosteroids, or colchicine are recommended first-line treatments for patients experiencing a gout flare.[53] [82] [83] The treatment course is generally 7 to 14 days. However, NSAIDs should be given for the shortest period possible, at the lowest effective dose.

The choice between treatments should be guided by patient preference, and potential risks and contraindications (e.g., renal impairment in the case of NSAIDs).[53] [82]

Initiation of treatment with urate-lowering drugs (e.g., xanthine oxidase inhibitors such as allopurinol and febuxostat; uricosuric agents such as probenecid or pegloticase) is not typically recommended in patients experiencing their first gout flare.[82] [84]

NSAIDs

- NSAIDs halt the inflammatory cascade of acute gout if they are started early, and are first-line therapy if no contraindications exist. They are also used to suppress gouty attacks when maintenance therapy with uric acid-lowering drugs is started.[82]
- It is common to use indomethacin, although there is no evidence to suggest that it is more effective than other NSAIDs.[85] One Cochrane review reported, with moderate certainty, that NSAIDs and selective cyclo-oxygenase-2 (COX-2) inhibitors have similar efficacy for pain, swelling, treatment success, and quality of life in patients with gout.[86] The review found no difference between groups for function, but this result was based on low-certainty evidence. Higher withdrawal rates due to adverse events (mainly gastrointestinal) were seen with nonselective NSAIDs.[86] An additional systematic review concluded that although COX-2 inhibitors are equally as effective as nonselective NSAIDs for pain relief in patients with gout, COX-2 inhibitors may be more beneficial overall.[87]
- Choice of NSAID should be guided by patient preference.[82]
- In patients at high risk of gastrointestinal complications, a proton-pump inhibitor or misoprostol should be co-prescribed. Proton-pump inhibitors should be considered for all patients who are taking an NSAID.[53] COX-2 inhibitors may be safer than traditional NSAIDs in patients with a history of gastrointestinal bleeding or comorbidities.

Corticosteroids

- Corticosteroids can be given either as an intra-articular injection for monoarticular acute gout or parenterally for oligoarticular or polyarticular acute gout.[82]
- In the UK, off label use of intra-articular or intramuscular injections of corticosteroids are only considered if NSAIDs and colchicine are contraindicated.[53]
- Corticosteroids are probably more effective than colchicine for acute gout, although there are no head-to-head trials.[88] Corticosteroids are associated with potentially serious adverse effects.
- One Cochrane review reported moderate certainty evidence that corticosteroids had similar efficacy for pain, inflammation, function, and treatment success when compared with NSAIDs for patients with gout.[86]

Colchicine

- Minimal effective dose should be used because of the narrow benefit to risk index.[82] The conclusion of one Cochrane review, based on low-quality evidence, suggests that low-dose colchicine may be effective for the treatment of gout compared with placebo, and may have similar efficacy compared with NSAIDs.[89]
- Common adverse effects are diarrhea, nausea, and vomiting.[90] In rare cases, colchicine treatment has been associated with an increased risk for fetal chromosomal aberrations.[91]

Interleukin-(IL)-1 inhibitors

- Anakinra and canakinumab are second-line therapies. They are conditionally recommended over no therapy (beyond supportive/analgesic treatment) for patients experiencing a gout flare who are refractory to, are intolerant of, or have contraindications to other anti-inflammatory therapies.[53] [82]

Anakinra

- Anakinra, a recombinant IL-1 receptor antagonist, has been found to be noninferior to usual treatment (patient choice of either colchicine, naproxen, or prednisone) for the management of acute gout flare.[92] In patients for whom a NSAID and colchicine was ineffective or contraindicated, treatment with either anakinra or the corticosteroid triamcinolone reduced patient-assessed gout flare pain to a similar extent within 72 hours.[93] Anakinra is off-label for the treatment of gout in the US and Europe.

Canakinumab

- An IL-1-beta inhibitor monoclonal antibody. Pooled results from two randomized, double-blind trials indicate that patients who received 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; P <0.0001), and a 56% reduction in risk of new flares over a 24-week period (hazard ratio [HR] 0.44; P ≤0.0001).[94]
- The US Food and Drug Administration (FDA) panel rejected the approval of canakinumab for the treatment of gout due to the potential risk of infection, hypertriglyceridemia, and elevated uric acid levels.[95]
- Canakinumab is approved by the European Medicines Agency for the symptomatic treatment of adult patients with frequent gouty arthritis attacks (at least three 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.

Long-term management: dietary modifications

The long-term management of gout includes dietary modifications and weight loss (if indicated).[15] [17] [53] Limiting the intake of alcohol, purine, and high-fructose corn syrup, in conjunction with weight loss, are conditionally recommended lifestyle changes for people with gout.[82] [96] [97] Nonetheless, there is a paucity of high-quality evidence to support or refute the use of lifestyle modifications, or dietary supplements for improving outcomes in people with chronic gout.[98] [99]

Initiating urate-lowering drugs

Initiation of treatment with urate-lowering drugs (e.g., xanthine oxidase inhibitors such as allopurinol and febuxostat; uricosuric agents such as probenecid or pegloticase) is recommended for patients with gout with any of the following:[53] [82]

- ≥1 subcutaneous tophi
- Evidence of radiographic damage (any modality) attributable to gout
- Frequent gout flares (defined as ≥2 annually).

Urate-lowering drugs may also be used to treat patients:[53] [82]

- Who have experienced at least one previous gout flare but have infrequent flares (<2/year)
- Who are experiencing their first flare and have comorbid moderate-to-severe chronic kidney disease (stage ≥3), serum urate concentration >9 mg/ dL, or urolithiasis
- Who receive diuretic therapy
- Who have chronic gouty arthritis.

Patients experiencing their first gout flare, and those with asymptomatic hyperuricemia, should not be treated with urate-lowering drugs.[53] [82]

In the US, treatment can be initiated during a gout flare.[82] [Evidence C] There is evidence to suggest that starting urate-lowering therapy during a flare does not significantly extend flare duration or severity.[100] [101] Furthermore, symptoms related to the current flare may motivate patients to take urate-lowering therapy (ULT). However, in the UK, it is recommended that ULT is started at least 2 to 4 weeks after a gout flare has settled, unless the patient is experiencing frequent flares, in which case ULT can be started during a flare.[53]

The decision to initiate urate-lowering treatment should be based on patient preference.[82]

Urate-lowering drugs are typically prescribed to target serum uric acid levels <6 mg/dL, to prevent supersaturation and crystal formation.[53] [82] In the UK, a lower target serum urate level below 5 mg/dL should be considered for patients who:[53]

- Have tophi or chronic gouty arthritis
- Continue to have frequent flares despite having a serum urate level below 6 mg/dL.

One double blind randomized controlled trial demonstrated that more intensive serum urate lowering does not improve bone erosion scores in patients with erosive gout at 2 years.[102]

Pharmacologic anti-inflammatory prophylaxis (e.g., NSAIDs, low-dose colchicine, low dose oral steroid) is recommended for all gout patients during the initiation and titration of a urate-lowering drug.[53] [82] [85] In the UK, colchicine is preferred form of prophylaxis; off-label use of low dose NSAIDs or oral corticosteroid should only be considered if colchicine is contraindicated, not tolerated or ineffective.[53] Anti-inflammatory prophylaxis should be continued for at least 3 to 6 months after reaching the target level of uric acid.[82]

Patients with a confirmed diagnosis of gout who require urate-lowering drugs should continue urate-lowering therapy indefinitely (unless there is a serious adverse effect).[53] [82] Adherence rates should be monitored carefully.[103]

Relapse of gout is common after discontinuation of urate-lowering drug treatment.[104]

Xanthine oxidase inhibitors

Allopurinol is the preferred first-line urate-lowering agent for all patients with gout, including those with moderate-to-severe chronic kidney disease (stage ≥3).[82] [105]

In the UK, allopurinol is recommended as joint first line treatment with febuxostat, however, for patients with major cardiovascular disease (e.g., previous myocardial infarction, stroke, or unstable angina) allopurinol should be offered as first line treatment.[53]

Allopurinol can be started at a low dose (e.g., ≤100 mg/day and lower in patients with chronic kidney disease [stage ≥3]) during a gout flare, or once the flare has abated, depending on patient preference.[82]

The allopurinol dose should be increased over several weeks to months, with a serum urate target <6 mg/dL.[82] Evidence from one randomized controlled trial indicates that, in addition to reducing monosodium urate crystal burden, long-term allopurinol can slow the progression of bone erosion using a treat-to-serum urate target (<6 mg/dL) strategy.[106]

In the UK, if the target serum urate level is not reached or first line treatment with allopurinol is not tolerated, switching to a second line treatment with febuxostat should be considered, taking into account any comorbidities or preferences.[53]

Allopurinol hypersensitivity

- Allopurinol should be initiated at lower doses in patients with renal insufficiency because of the risk of allopurinol hypersensitivity.[82] Gradual allopurinol dose escalation, in conjunction with kidney and liver function monitoring, may be considered in patients with kidney impairment.[107]
- Prospective cohort studies suggest that allopurinol therapy is associated with a reduced incidence of renal disease.[108] [109]
- In populations where HLA-B*5801-positive people 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 may be considered.[82] One 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.[110] The risk of hypersensitivity was statistically significant among patients with renal or cardiovascular disease who were prescribed allopurinol for asymptomatic hyperuricemia.[110] A subsequent Taiwanese cohort study found that allopurinol is associated with a 5.5-fold increased risk of cutaneous adverse reactions compared with febuxostat.[111]

Febuxostat

- Febuxostat is a nonpurine selective xanthine oxidase inhibitor that reduces the production of uric acid.
- The FDA recommends that febuxostat should only be prescribed for patients who:[112]
    - Have failed treatment with or cannot tolerate allopurinol, and
    - Have been counseled regarding the cardiovascular risk.
- The American College of Rheumatology guidelines recommend that patients with gout who are taking febuxostat, and have a history of cardiovascular disease or a new cardiovascular event, should switch to another urate-lowering therapy, if available.[82]
- The UK Medicines and Healthcare products Regulatory Agency recommends that patients with preexisting major cardiovascular disease (e.g., myocardial infarction, stroke, or unstable angina) should avoid treatment with febuxostat unless no other therapy options are available.[113]
- Febuxostat is recommended as joint first line treatment with allopurinol in the UK, once the patient's comorbidities and preferences are noted.[53] If the target serum urate level is not reached or first

line treatment with febuxostat is not tolerated, switching to a second line treatment with allopurinol should be considered, taking into account any comorbidities or preferences.[53]

- In randomized controlled trials of patients with hyperuricemia or gout, febuxostat reduced serum urate level more effectively than allopurinol.[114] [115] Open label-data suggest that this benefit is maintained for up to 40 months.[116] In these studies, however, allopurinol was administered at doses less than the maximum approved dose for this indication. A subsequent double blind noninferiority trial demonstrated comparative efficacy for febuxostat and allopurinol in controlling flares when given at standard doses at 72 weeks.[117]
- Commonly reported adverse effects of febuxostat therapy include elevated liver function tests, headache, hypertension, diarrhea, and arthralgia/stiffness.[118] [119]
- Cardiovascular death and all-cause mortality were significantly more common among patients taking febuxostat than those taking allopurinol (4.3% vs. 3.2%, HR 1.34 [95% CI 1.03 to 1.73]; 7.8% vs. 6.4%, HR 1.22 [95% CI 1.01 to 1.47], respectively) in a multicenter noninferiority trial of patients with gout and cardiovascular disease.[120] Febuxostat was noninferior to allopurinol with respect to a composite primary outcome of cardiovascular events. Conversely, evidence from subsequent systematic reviews suggest that there is no significant association with high blood pressure, all cause mortality, myocardial infarction, or stroke for either febuxostat or allopurinol, and no significant difference between the two treatments for the composite outcome of major adverse cardiovascular events (including cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and unstable angina with urgent coronary revascularization) among adult patients with hyperuricemia and/or gout.[121] [122] [123]

Uricosuric agents

If the patient cannot tolerate allopurinol or febuxostat, starting probenecid at a low dose may be considered.[82] [124]

Uricosuric agents increase renal excretion of uric acid. They are contraindicated in known over-producers of uric acid.

A 24-hour urine collection for uric acid should be obtained before prescribing probenecid. If uric acid excretion exceeds 800 mg in 24 hours, probenecid is contraindicated, as it increases the risk of urate nephrolithiasis.

Probenecid is not effective in patients with renal insufficiency. Allopurinol or febuxostat are recommended for patients with moderate-to-severe chronic kidney disease (stage ≥3).[82]

Pegloticase

Intravenous pegloticase (a pegylated recombinant mammalian uricase) is an option for patients with gout who fail to achieve a uric acid level of <6 mg/dL, and who continue to have frequent gout flares (≥2 flares/year), or have nonresolving subcutaneous tophi, with conventional urate-lowering agents.[82] [125] [126]

Pegloticase is associated with anaphylaxis and serious hypersensitivity reactions. Only administer this drug in a specialized care setting under a clinician who is experienced in managing infusion reactions and anaphylaxis. Monitor serum uric acid levels prior to each infusion. Discontinue pegloticase if serum uric acid level increases to >6 mg/dL, particularly if two consecutive levels are >6 mg/dL; patients who have lost therapeutic response are at an increased risk of developing infusion reactions or anaphylaxis. Other urate-lowering drugs should not be taken concomitantly as they affect serum uric acid levels. Premedicate

patients with an antihistamine and corticosteroid prior to administration. Monitor patients closely during and after infusion.

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute		(summary)
acute gout		
	1st	nonsteroidal anti-inflammatory drug
	1st	corticosteroid
	1st	colchicine
	2nd	interleukin (IL) -1 inhibitor

Ongoing		(summary)
recurrent gout: 2-3 weeks post acute episode		
	1st	allopurinol
	plus	suppressive therapy
	2nd	febuxostat
	plus	suppressive therapy
	3rd	probenecid
	plus	suppressive therapy
	4th	pegloticase
	plus	suppressive therapy

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute

acute gout

1st **nonsteroidal anti-inflammatory drug**

Primary options

» naproxen: 500 mg orally twice daily

OR

» ibuprofen: 400-800 mg orally three to four times daily

OR

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

OR

» meloxicam: 7.5 to 15 mg orally once daily

OR

» indomethacin: 25-50 mg orally three times daily

OR

» celecoxib: 100-200 mg orally twice daily

» Nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or colchicine are recommended first-line treatments for patients experiencing a gout flare.[53] [82] [83] The choice between treatments should be guided by patient preference and potential risks and contraindications (e.g., renal impairment in the case of NSAIDs).[53] [82]

» NSAIDs halt the inflammatory cascade if they are started early. Also used to suppress gouty attacks when maintenance therapy with urate-lowering drugs is started.[82]

» It is common to use indomethacin, although there is no evidence to suggest that it is more effective than other NSAIDs.[85]

Acute

» One Cochrane review reported, with moderate certainty, that NSAIDs and selective cyclo-oxygenase-2 (COX-2) inhibitors have similar efficacy for pain, swelling, treatment success, and quality of life in patients with gout.[86] The review found no difference between groups for function, but this result was based on low-certainty evidence. Higher withdrawal rates due to adverse events (mainly gastrointestinal) were seen with nonselective NSAIDs.[86] An additional systematic review concluded that although COX-2 inhibitors are equally as effective as nonselective NSAIDs for pain relief in patients with gout, COX-2 inhibitors may be more beneficial overall.[87]

» Choice of NSAID should be guided by patient preference.[82]

» In patients at high risk of gastrointestinal complications, a proton-pump inhibitor or misoprostol should be co-prescribed.

» Proton-pump inhibitors should be considered for all patients who are taking an NSAID.[53]

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

» Treatment course is generally 7 to 14 days. However, NSAIDs should be given for the shortest period possible, at the lowest effective dose.

1st **corticosteroid**

Primary options

» prednisone: 1 mg/kg orally given as a single dose
This regimen may be adequate if started within 24 hours of attack.

OR

» 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

OR

» 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-

Acute

articularly as a single dose; consult specialist for guidance on parenteral dose

OR

» 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

» Corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), or colchicine are recommended first-line treatments for patients experiencing a gout flare.[53] [82] [83]

» The choice between treatments should be guided by patient preference and potential risks and contraindications (e.g., renal impairment in the case of NSAIDs).[82]

» Corticosteroids can be given either as an intra-articular injection for monoarticular acute gout or parenterally for oligoarticular or polyarticular acute gout.[82] Parenteral dose depends on the severity of the presentation; switch to oral dosing after 1-2 days and then taper oral dose as usual.

» In the UK, off-label use of intra-articular or intramuscular injections of corticosteroids are only considered if NSAIDs and colchicine are contraindicated.[53]

» Corticosteroids are probably more effective than colchicine for acute gout, although there are no head-to-head trials.[88]

» Corticosteroids are associated with potentially serious adverse effects.

» One Cochrane review reported moderate-certainty evidence that corticosteroids had similar efficacy for pain, inflammation, function, and treatment success when compared with NSAIDs for patients with gout.[86]

» Should be avoided if septic arthritis has not been excluded.

»

1st **colchicine**

Primary options

» colchicine: 1.2 mg orally initially, followed by 0.6 mg orally after 1 hour, maximum 1.8 mg total dose

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» Colchicine, nonsteroidal anti-inflammatory drugs (NSAIDs), or corticosteroids are recommended first-line treatments for patients experiencing a gout flare.[53] [82] [83]

» The choice between treatments should be guided by patient preference and potential risks and contraindications (e.g., renal impairment in the case of NSAIDs).[82]

» Minimal effective dose of colchicine should be used because of the narrow benefit to risk index.[82] The conclusion of one Cochrane review, based on low-quality evidence, suggests that low-dose colchicine may be effective for the treatment of gout compared with placebo, and may have similar efficacy compared with NSAIDs.[89]

» Common adverse effects are diarrhea, nausea, and vomiting.[90] In rare cases, colchicine treatment has been associated with an increased risk for fetal chromosomal aberrations.[91]

» Give until relief, nausea/vomiting, diarrhea, or maximum dose reached; diarrhea likely will precede pain relief; wait 3 days between courses.

2nd **interleukin (IL) -1 inhibitor**

Primary options

» anakinra: consult specialist for guidance on dose

OR

» canakinumab: consult specialist for guidance on dose

» Anakinra and canakinumab are second-line therapies. They are conditionally recommended over no therapy (beyond supportive/analgesic treatment) for patients experiencing a gout flare who are refractory to, are intolerant of, or have contraindications to other anti-inflammatory therapies.[53] [82]

» Anakinra, a recombinant IL-1 receptor antagonist, has been found to be noninferior to usual treatment (patient choice of either colchicine, naproxen, or prednisone) for the management of acute gout flare.[92] In patients for whom a nonsteroidal anti-inflammatory drug (NSAID) and colchicine was ineffective or contraindicated, treatment with either anakinra or the corticosteroid triamcinolone reduced patient-

Acute

assessed gout flare pain to a similar extent within 72 hours.[93] Anakinra is off-label for the treatment of gout in the US and Europe.

» Canakinumab is an IL-1-beta inhibitor monoclonal antibody. Pooled results from two randomized, double-blind trials indicate that patients who received 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; P <0.0001), and a 56% reduction in risk of new flares over a 24-week period (hazard ratio 0.44; P ≤0.0001).[94]

» The US Food and Drug Administration panel rejected the approval of canakinumab for the treatment of gout due to the potential risk of infection, hypertriglyceridemia, and elevated uric acid levels.[95]

» Canakinumab is approved by the European Medicines Agency for the symptomatic treatment of adult patients with frequent gouty arthritis attacks (at least three 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.

Ongoing

recurrent gout: 2-3 weeks post acute episode

1st **allopurinol**

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

» Initiation of treatment with urate-lowering drugs (e.g., xanthine oxidase inhibitors such as allopurinol and febuxostat; uricosuric agents such as probenecid or pegloticase) is recommended for patients with gout with ≥1 subcutaneous tophi, evidence of radiographic damage (any modality) attributable to gout, or frequent gout flares (defined as ≥2 annually).[53] [82]

» Urate-lowering drugs may also be used to treat: patients who have experienced at least one previous gout flare but have infrequent flares (<2/year); patients experiencing their first flare who have comorbid moderate-to-severe chronic kidney disease (stage ≥3), serum urate concentration >9 mg/dL, or urolithiasis; patients who receive diuretic therapy; and patients who have chronic gouty arthritis.[53] [82]

» Patients experiencing their first gout flare, and those with asymptomatic hyperuricemia, should not be treated with urate-lowering drugs.[53] [82]

» In the US, treatment can be initiated during a gout flare.[82] [Evidence C] There is evidence to suggest that starting urate-lowering therapy during a flare does not significantly extend flare duration or severity.[100] [101] Furthermore, symptoms related to the current flare may motivate patients to take urate-lowering therapy (ULT). The decision to initiate ULT should be based on patient preference.[82] However, in the UK, it is recommended that ULT is started at least 2 to 4 weeks after a gout flare has settled, unless the patient is experiencing frequent flares, in which case ULT can be started during a flare.[53]

» Urate-lowering drugs are typically prescribed to target serum uric acid levels <6 mg/dL, to prevent supersaturation and crystal formation.[53] [82] In the UK, a lower target serum urate level below 5 mg/dL should be

Ongoing

considered for patients who have tophi or chronic gouty arthritis, or who continue to have frequent flares despite having a serum urate level below 6 mg/dL.[53]

» One double blind randomized controlled trial demonstrated that more intensive serum urate lowering does not improve bone erosion scores in patients with erosive gout at 2 years.[102]

» Allopurinol is the preferred first-line urate-lowering agent for all patients with gout, including those with moderate-to-severe chronic kidney disease (stage ≥3).[82] [105]

» In the UK, allopurinol is recommended as joint first line treatment with febuxostat, however, for patients with major cardiovascular disease (e.g., previous myocardial infarction, stroke, or unstable angina) allopurinol should be offered as first line treatment.[53]

» It can be started at a low dose (≤100 mg/day and lower in patients with chronic kidney disease [stage ≥3]) during a gout flare, or once the flare has abated depending on patient preference.[82]

» The dose should be increased over several weeks to months until the uric acid level is <6 mg/dL.[82]

» Evidence from one randomized controlled trial indicates that, in addition to reducing monosodium urate crystal burden, long-term allopurinol can slow the progression of bone erosion using a treat-to-serum urate target (<6 mg/dL) strategy.[106]

» In the UK, if the target serum urate level is not reached or first line treatment with allopurinol is not tolerated, switching to a second line treatment with febuxostat should be considered, taking into account any comorbidities or preferences.[53]

» Allopurinol should be initiated at lower doses in patients with renal insufficiency because of the risk of allopurinol hypersensitivity.[82] Gradual allopurinol dose escalation, in conjunction with kidney and liver function monitoring, may be considered in patients with kidney impairment.[107]

» Prospective cohort studies suggest that allopurinol therapy is associated with a reduced incidence of renal disease.[108] [109]

» In populations where HLA-B*5801-positive people are at high risk for severe allopurinol

Ongoing

hypersensitivity reaction (e.g., Koreans with renal insufficiency, Han Chinese descent, and Thai descent), HLA-B*5801 screening may be considered.[82] One 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.[110] The risk of hypersensitivity was statistically significant among patients with renal or cardiovascular disease who were prescribed allopurinol for asymptomatic hyperuricemia.[110] A subsequent Taiwanese cohort study found that allopurinol is associated with a 5.5-fold increased risk of cutaneous adverse reactions compared with febuxostat.[111]

plus **suppressive therapy**

Treatment recommended for ALL patients in selected patient group

Primary options

» naproxen: 250 mg orally twice daily

OR

» ibuprofen: 400 mg orally three times daily

OR

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

OR

» meloxicam: 7.5 to 15 mg orally once daily

OR

» indomethacin: 25 mg orally three times daily

OR

» celecoxib: 100-200 mg orally once daily

OR

» colchicine: 0.6 mg orally once daily

Secondary options

» prednisone: 7.5 to 10 mg orally once daily initially, adjust to lowest dose that prevents gout flares

Ongoing

» Suppressive (prophylactic) therapy such as nonsteroidal anti-inflammatory drugs (NSAIDs), low-dose colchicine, or low dose oral corticosteroid should be considered during initiation and tapering of a urate-lowering agent.[53] [82] [85]

» The therapy should be continued for at least 3 to 6 months after reaching the target level of serum uric acid.[82]

» Prednisone may be considered if both NSAIDs and colchicine are contraindicated, at the lowest dose to prevent gout flares.[53]

2nd **febuxostat**

Primary options

» febuxostat: 40-80 mg orally once daily

» Febuxostat is a nonpurine selective xanthine oxidase inhibitor that reduces the production of uric acid.

» The US Food and Drug Administration recommends that febuxostat should only be prescribed for patients who have failed treatment with, or cannot tolerate, allopurinol and who have been counseled regarding the cardiovascular risk.[112]

» American College of Rheumatology guidelines recommend that patients with gout who are taking febuxostat, and have a history of cardiovascular disease or a new cardiovascular event, should switch to another urate-lowering therapy, if available.[82]

» The Medicines and Healthcare Products Regulatory Agency in the UK recommends that patients with pre-existing major cardiovascular disease (e.g., myocardial infarction, stroke, or unstable angina) should avoid treatment with febuxostat unless no other therapy options are available.[113]

» Febuxostat is recommended as joint first line treatment with allopurinol in the UK, once the patients comorbidities and preferences are noted.[53] If the target serum urate level is not reached or first line treatment with febuxostat is not tolerated, switching to a second line treatment with allopurinol should be considered, taking into account any comorbidities or preferences.[53]

» In randomized controlled trials of patients with hyperuricemia or gout, febuxostat

Ongoing

reduced serum urate level more effectively than allopurinol.[114] [115] Open-label data suggest that this benefit is maintained for up to 40 months.[116] In these studies, however, allopurinol was administered at doses less than the maximum approved dose for this indication. A subsequent double blind noninferiority trial demonstrated comparative efficacy for febuxostat and allopurinol in controlling flares when given at standard doses at 72 weeks.[117]

» Commonly reported adverse effects of febuxostat therapy include elevated liver function tests, headache, hypertension, diarrhea, and arthralgia/stiffness.[118] [119]

» Cardiovascular death and all-cause mortality were significantly more common among patients taking febuxostat than those taking allopurinol (4.3% vs. 3.2%, hazard ratio [HR] 1.34 [95% CI 1.03 to 1.73]; 7.8% vs. 6.4%, HR 1.22 [95% CI 1.01 to 1.47], respectively) in a multicenter noninferiority trial of patients with gout and cardiovascular disease.[120] Febuxostat was noninferior to allopurinol with respect to a composite primary outcome of cardiovascular events.

» Conversely, evidence from subsequent systematic reviews suggest that there is no significant association with high blood pressure, all cause mortality, myocardial infarction, or stroke for either febuxostat or allopurinol, and no significant difference between the two treatments for the composite outcome of major adverse cardiovascular events (including cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and unstable angina with urgent coronary revascularization) among adult patients with hyperuricemia and/or gout.[121] [122] [123]

» Febuxostat should not be started during an acute attack, as it might prolong the attack or precipitate more attacks.[127]

» Goal is to reduce uric acid level <6 mg/dL to prevent supersaturation and crystal formation.

» Adjust dose according to serum urate target level of 6 mg/dL.

plus **suppressive therapy**

Treatment recommended for ALL patients in selected patient group

Primary options

» naproxen: 250 mg orally twice daily

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OR

» ibuprofen: 400 mg orally three times daily

OR

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

OR

» meloxicam: 7.5 to 15 mg orally once daily

OR

» indomethacin: 25 mg orally three times daily

OR

» celecoxib: 100-200 mg orally once daily

OR

» colchicine: 0.6 mg orally once daily

Secondary options

» prednisone: 7.5 to 10 mg orally once daily initially, adjust to lowest dose that prevents gout flares

» Suppressive (prophylactic) therapy such as nonsteroidal anti-inflammatory drugs (NSAIDs), low-dose colchicine, or low dose oral corticosteroid should be considered during initiation and tapering of a urate-lowering agent.[53] [82] [85]

» The therapy should be continued for at least 3 to 6 months after reaching the target level of serum uric acid.[82]

» Prednisone may be considered if both NSAIDs and colchicine are contraindicated, at the lowest dose to prevent gout flares.[53]

3rd **probenecid**

Primary options

» probenecid: 250-1000 mg orally twice daily

» If the patient cannot tolerate allopurinol or febuxostat, starting probenecid at a low dose may be considered.[82] [124]

MANAGEMENT

Ongoing

» Probenecid increases the renal excretion of uric acid. It is contraindicated in known over-producers of uric acid.

» A 24-hour urine collection for uric acid should be obtained before prescribing probenecid.

» If uric acid excretion exceeds 800 mg in 24 hours, probenecid is contraindicated, as it increases the risk of urate nephrolithiasis.

» Probenecid is not effective in patients with renal insufficiency.

plus **suppressive therapy**

Treatment recommended for ALL patients in selected patient group

Primary options

» naproxen: 250 mg orally twice daily

OR

» ibuprofen: 400 mg orally three times daily

OR

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

OR

» meloxicam: 7.5 to 15 mg orally once daily

OR

» indomethacin: 25 mg orally three times daily

OR

» celecoxib: 100-200 mg orally once daily

OR

» colchicine: 0.6 mg orally once daily

Secondary options

» prednisone: 7.5 to 10 mg orally once daily initially, adjust to lowest dose that prevents gout flares

» Suppressive (prophylactic) therapy such as nonsteroidal anti-inflammatory drugs

Ongoing

(NSAIDs), low-dose colchicine, or low dose oral corticosteroid should be considered during initiation and tapering of a urate-lowering agent.[53] [82] [85]

» The therapy should be continued for 3 to 6 months after reaching the target level of serum uric acid.[82]

» Prednisone may be considered if both NSAIDs and colchicine are contraindicated, at the lowest dose to prevent gout flares.[53]

4th **pegloticase**

Primary options

» pegloticase: 8 mg intravenously every 2 weeks

» Intravenous pegloticase (a pegylated recombinant mammalian uricase) is an option for patients with gout who fail to achieve a uric acid level of <6 mg/dL, and who continue to have frequent gout flares (≥2 flares/year) or have nonresolving subcutaneous tophi with conventional urate-lowering agents.[82] [125] [126]

» Gout flares may occur during initial treatment.

» Pegloticase is associated with anaphylaxis and serious hypersensitivity reactions. Only administer this drug in a specialized care setting under a clinician who is experienced in managing infusion reactions and anaphylaxis. Monitor serum uric acid levels prior to each infusion. Discontinue pegloticase if serum uric acid level increases to >6 mg/dL, particularly if two consecutive levels are >6 mg/dL; patients who have lost therapeutic response are at an increased risk of developing infusion reactions or anaphylaxis. Other urate-lowering drugs should not be taken concomitantly as they affect serum uric acid levels. Premedicate patients with an antihistamine and corticosteroid prior to administration. Monitor patients closely during and after infusion.

plus **suppressive therapy**

Treatment recommended for ALL patients in selected patient group

Primary options

» naproxen: 250 mg orally twice daily

OR

MANAGEMENT

Ongoing

» ibuprofen: 400 mg orally three times daily

OR

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

OR

» meloxicam: 7.5 to 15 mg orally once daily

OR

» indomethacin: 25 mg orally three times daily

OR

» celecoxib: 100-200 mg orally once daily

OR

» colchicine: 0.6 mg orally once daily

Secondary options

» prednisone: 7.5 to 10 mg orally once daily initially, adjust to lowest dose that prevents gout flares

» Suppressive (prophylactic) therapy such as nonsteroidal anti-inflammatory drugs (NSAIDs), low-dose colchicine, or a low-dose corticosteroid should be considered during initiation and tapering of a urate-lowering agent.[53] [82] [85]

» The therapy should be continued for 3 to 6 months after reaching the target level of serum uric acid.[82]

» Prednisone may be considered if both NSAIDs and colchicine are contraindicated, at the lowest dose to prevent gout flares.[53]

Emerging

Arhalofenate

Arhalofenate, a novel anti-inflammatory and uricosuric agent that inhibits the anion exchanger URAT1. In a 12-week phase 2B study, arhalofenate decreased gout flares significantly compared with allopurinol.[128] However, some elements of study design deviated from routine clinical practice, such as initiating allopurinol at a higher dose than usual. Results from a small open-label phase 2 study suggest that the combination of arhalofenate and febuxostat reduces serum uric acid level to a greater extent than either drug alone.[129] The combination appeared to be safe and well tolerated.

Pegloticase plus methotrexate

Pegloticase has also been granted approval by the US Food and Drug Administration for the treatment of chronic gout in adults refractory to conventional therapy, in combination with methotrexate. The approval is based on one open-label trial which demonstrated that combination treatment of pegloticase plus methotrexate increased the proportion of patients who maintained therapeutic response at 6 months compared with pegloticase alone.[130]

Primary prevention

Lifestyle advice on diet, weight loss, or exercise may be recommended for patients with asymptomatic hyperuricemia.[52] There is an absence of evidence supporting the use of urate-lowering therapy in these patients.[52]

Secondary prevention

Hyperuricemia does not always lead to gout, but the incidence of gout increases with urate level.[9]

Patients with hyperuricemia and gout should avoid risk factors that may precipitate gout, such as excessive alcohol consumption, diuretic use, and weight gain.[142]

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.[138]

Patient discussions

Patients should be made aware of the signs, symptoms and causes of gout. They should also be advised of any risk factors they have for gout, for example:[53]

- Genetics
- Excess body weight or obesity
- Medicine they may be taking
- Comorbidities such as kidney disease or hypertension.

Patients should understand that gout is a lifelong condition, and that disease progression will occur without long term urate lowering treatment to eliminate urate crystals and prevent flares, shrink tophi and prevent long term joint damage.[53]

Patients should be advised that foods with a high purine content (i.e., alcohol, seafood, and offal) are associated with higher risk for elevated uric acid and gout.[15]

Reducing intake of alcohol, especially beer, lowers the risk of gout.[141]

Reducing seafood and meat intake helps to a lesser degree.

Reducing fructose and concentrated sweets might help to reduce uric acid and the risk for gout attacks.

Dairy products reduce the risk of gout.[14] [37]

FOLLOW UP

Monitoring

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 to 12 months (target level <6 mg/dL). In the UK, annual monitoring of serum urate level is recommended for patients with gout who are continuing urate-lowering therapy after reaching their target serum urate level.[53]

Patients should be monitored for adverse effects of nonsteroidal anti-inflammatory drugs (NSAIDs) and colchicine, especially if they are used for prolonged periods. For NSAIDs, colchicine, and allopurinol, complete blood count, renal function tests, and liver function tests should be obtained every 3 to 6 months.

When initiating allopurinol, patients should be closely monitored for drug-induced hypersensitivity syndrome (fever, eosinophilia, widespread rash, facial edema, and multisystem failure).[140]

Long-term colchicine use may be associated with neuromyopathy. Probenecid may increase the risk of nephrolithiasis.[57]

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

Complications

Complications	Timeframe	Likelihood
acute uric acid nephropathy	**short term**	**low**
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.[138]		
chronic kidney disease	**long term**	**low**
Evidence suggests an association between gout and chronic kidney disease (CKD). A retrospective cohort study found that people with gout were at higher risk of developing CKD stage 3 than a matched control group (adjusted hazard ratio 1.78, 95% CI 1.70 to 1.85).[139]		
nephrolithiasis	**variable**	**medium**
Prevalence of uric acid calculi in patients with gout is 10% to 20%.[136] Prevalence increases with uric acid level.[137]		

Prognosis

Gout attacks are painful and debilitating, but self-limiting. In patients who have not been treated 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.[132]

In untreated gout:[133]

- About 2% of patients develop severe debilitating arthritis (typically 20 years after the first attack)
- Tophi occur in about 50% after 10 years, and 72% after 20 years.

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 effects.

Data from a general population cohort study suggest that allopurinol initiation modestly reduces risk of death in patients with hyperuricemia and patients with gout.[134] Another study found no difference in mortality in people with incident gout who were treated with allopurinol compared with matched controls, based on propensity scores.[135]

Prospective cohort studies suggest that allopurinol therapy is associated with a reduced incidence of renal disease.[108] [109]

Diagnostic guidelines

International

ACR appropriateness criteria: chronic extremity joint pain – suspected inflammatory arthritis (https://www.acr.org/Clinical-Resources/Clinical-Tools-and-Reference/Appropriateness-Criteria) [63]

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

2018 updated European League Against Rheumatism evidence-based recommendations for the diagnosis of gout (https://www.eular.org/recommendations_management.cfm) [81]

Published by: European League Against Rheumatism **Last published:** 2019

Gout: diagnosis and management (https://www.nice.org.uk/guidance/ng219) [53]

Published by: National Institute for Health and Care Excellence (UK) **Last published:** 2022

Treatment guidelines

International

Guideline for the management of gout (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines) [82]

Published by: American College of Rheumatology **Last published:** 2020

EULAR evidence-based recommendations for the management of gout (https://www.eular.org/recommendations_management.cfm) [131]

Published by: European League Against Rheumatism **Last published:** 2017

Gout: diagnosis and management#(https://www.nice.org.uk/guidance/ng219) [53]

Published by: National Institute for Health and Care Excellence (UK) **Last published:** 2022

The British Society for Rheumatology guideline for the management of gout (https://www.rheumatology.org.uk/practice-quality/guidelines) [124]

Published by: British Society for Rheumatology **Last published:** 2017

Online resources

1. BMJ talk medicine podcast: gout (https://soundcloud.com/bmjpodcasts/gout?in=bmjpodcasts/sets/bmj-best-practice-clinical) *(external link)*

2. ACR-EULAR gout classification criteria calculator (http://goutclassificationcalculator.auckland.ac.nz) *(external link)*

EVIDENCE TABLES

Evidence tables

What are the effects of urate-lowering therapy (ULT)# during a gout flare compared with ULT after a gout flare has resolved in people diagnosed with gout?[82]

This table is a summary of the analysis reported in a guideline (underpinned by a systematic review) that focuses on the above important clinical question.

View the full source guideline (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines/Gout)

Evidence C *	Confidence in the evidence is very low or low where GRADE has been performed and there may be no difference in effectiveness between the intervention and comparison for key outcomes. However, this is uncertain and new evidence could change this in the future.

Population: People with gout
Intervention: ULT during a gout flare
Comparison: ULT after a gout flare has resolved

Outcome	Effectiveness (BMJ rating)†	Confidence in evidence (GRADE)‡
Gout flares (follow up: 8 weeks, 12 weeks, and at mean 36 weeks; assessed with proportion of participants with at least one flare)	No statistically significant difference	Very Low
Gout flares (follow up: mean 30 days; assessed with proportion with flare in any joint)	No statistically significant difference	Low
Gout flares (follow up: mean 28 days; assessed with time from enrollment in study to resolution of acute gout attack [intention to treat])	No statistically significant difference	Low
Serum urate (follow up: mean 36 weeks; assessed with participants with serum urate <6mg/dL [approx >360 micromol/L])	No statistically significant difference	Very Low

Outcome	Effectiveness (BMJ rating)†	Confidence in evidence (GRADE)‡
Serum urate (follow up: mean 10 days; assessed with mean change in serum urate level, mg/dL)	Favors intervention	Moderate
Tophi (follow up: mean 36 weeks; assessed with proportion with tophi at follow up)	No statistically significant difference	Very Low
Pain (follow up: mean 10 days; assessed with visual analog scale or numerical rating score [range 0-10])	No statistically significant difference	Low
Serious adverse events: death; hypersensitivity reaction (follow up; mean 30 days; assessed with proportion with serious adverse event)	No statistically significant difference	Low

Recommendations as stated in the source guideline

When the decision is made that ULT is indicated while the patient is experiencing a gout flare, starting ULT during the gout flare over starting ULT after the gout flare has resolved is conditionally recommended. [b]

Note

[a] The guideline team assessed three studies related to this question; two of the studies (both small randomized controlled trials) explicitly mention evaluating allopurinol, but we were not able to confirm which specific ULT drug(s) were evaluated in the third (an observational study).

[b] The guideline team noted that since this is a conditional recommendation, there may be patient factors or preferences that support delaying ULT initiation until the flare has resolved.

* Evidence levels

The Evidence level is an internal rating applied by BMJ Best Practice. See the EBM Toolkit (https://bestpractice.bmj.com/info/evidence-tables/) for details.

Confidence in evidence

A - High or moderate to high

B - Moderate or low to moderate

C - Very low or low

† Effectiveness (BMJ rating)

Based on statistical significance, which demonstrates that the results are unlikely to be due to chance, but which does not necessarily translate to a clinical significance.

‡ Grade certainty ratings

High	The authors are very confident that the true effect is similar to the estimated effect.
Moderate	The authors are moderately confident that the true effect is likely to be close to the estimated effect.
Low	The authors have limited confidence in the effect estimate and the true effect may be substantially different.
Very Low	The authors have very little confidence in the effect estimate and the true effect is likely to be substantially different.

BMJ Best Practice EBM Toolkit: What is GRADE? (https://bestpractice.bmj.com/info/toolkit/learn-ebm/what-is-grade/)

Key articles

- National Institute for Health and Care Excellence. Gout: diagnosis and management. June 2022. [internet publication]. Full text (https://www.nice.org.uk/guidance/ng219)
- FitzGerald JD, Dalbeth N, Mikuls T, et al. 2020 American College of Rheumatology guideline for the management of gout. Arthritis Care Res (Hoboken). 2020 Jun;72(6):744-60. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/32391934?tool=bestpractice.bmj.com)
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Images

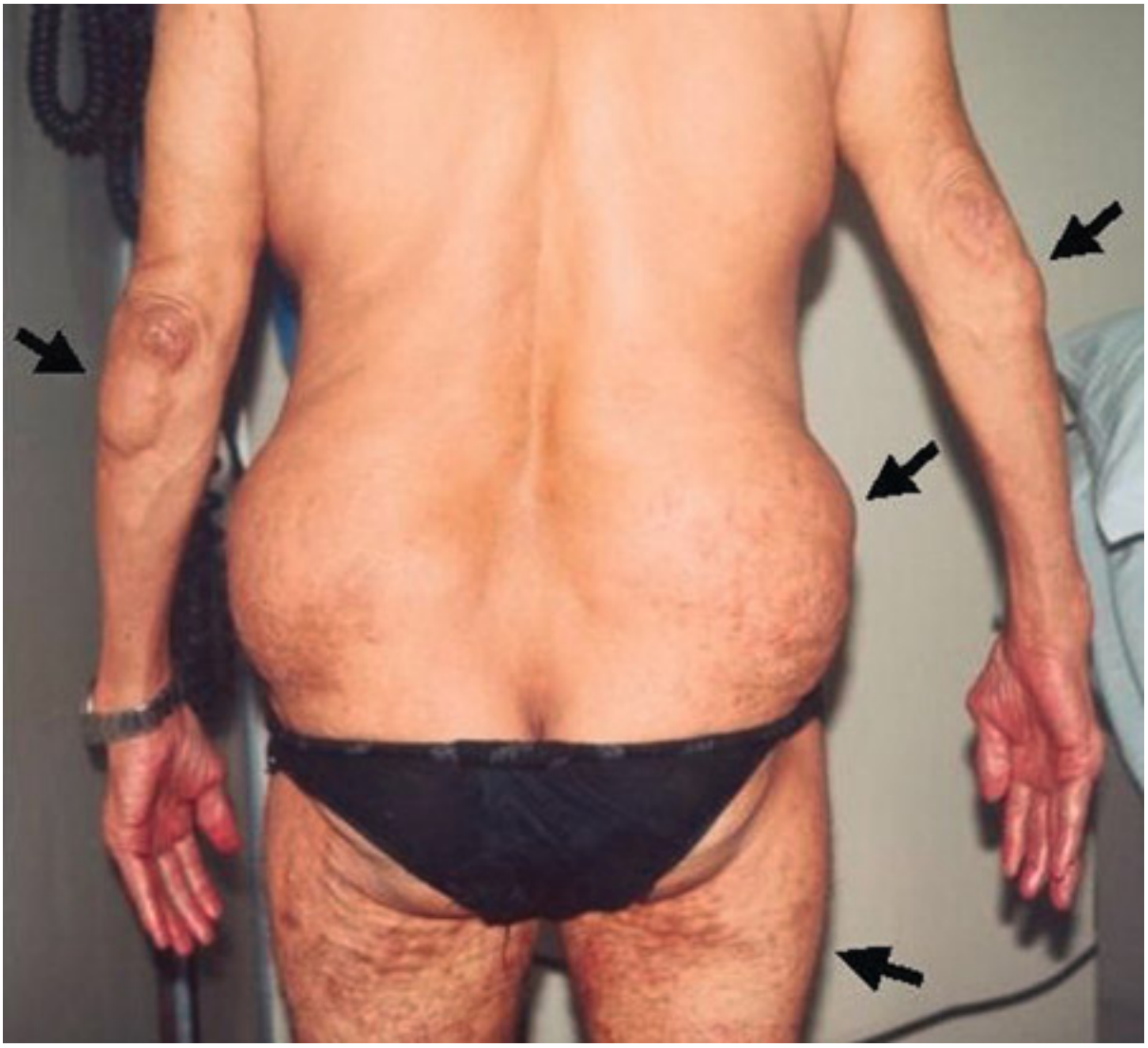

Figure 1: Chronic tophaceous gout showing nodules in the hands, elbows, legs, buttocks, and abdominal wall (arrows)

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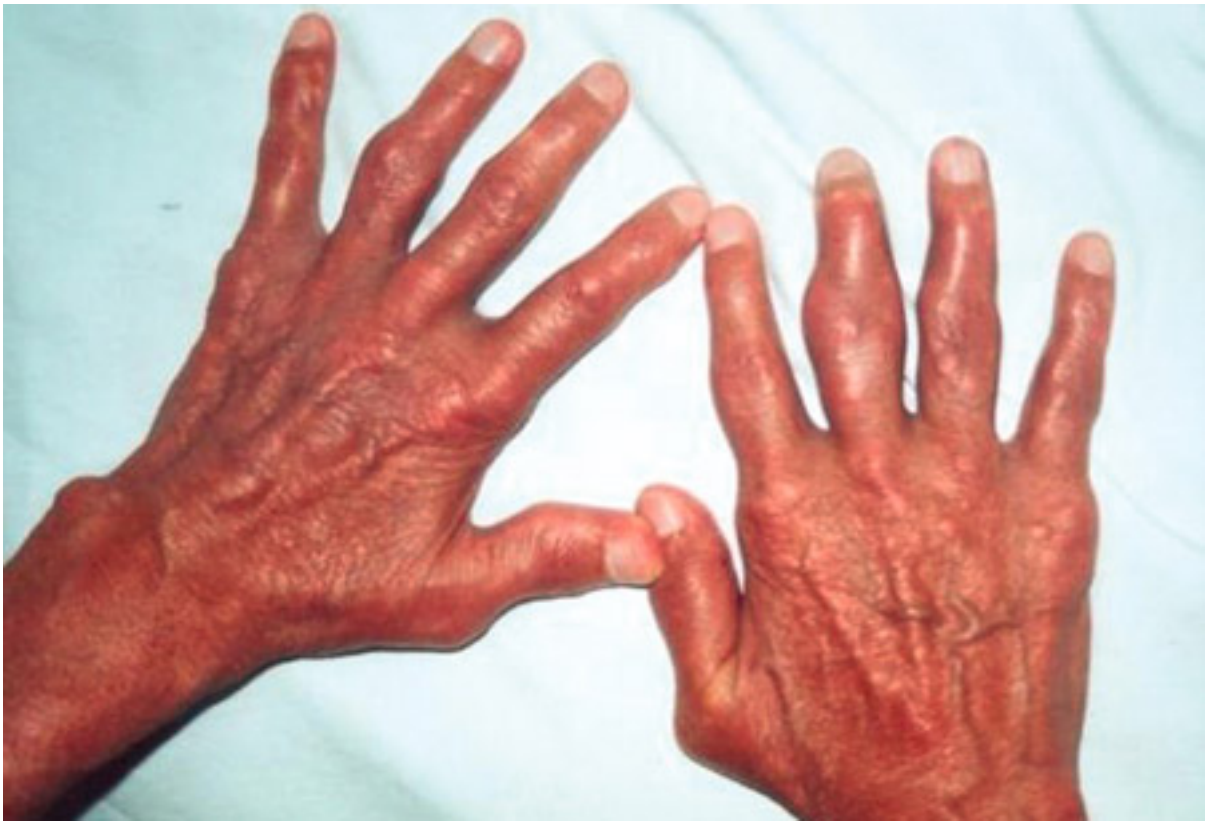

Figure 2: Chronic tophaceous gout showing nodules in periarticular structures and arthritis

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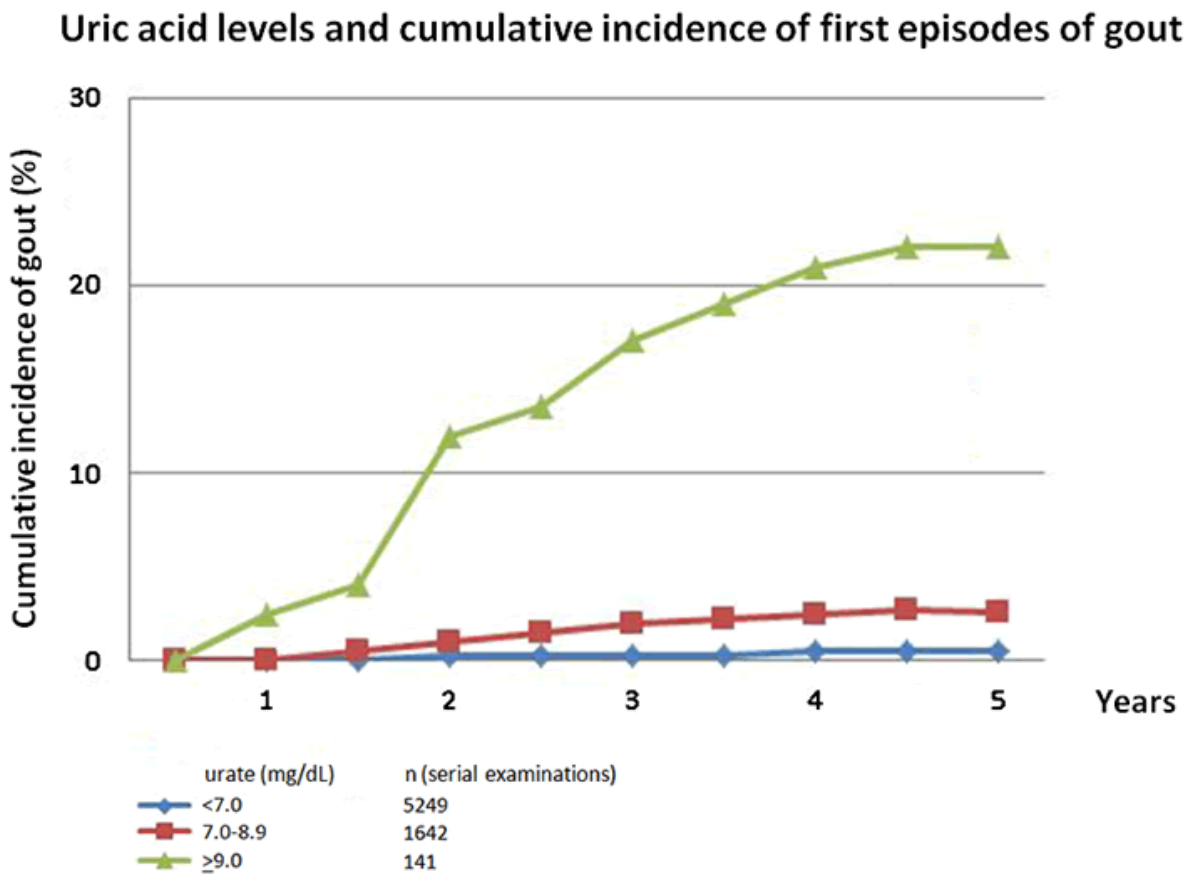

Figure 3: Uric acid levels and cumulative incidence of first episodes of gout

Adapted from Campion EW, Glynn RJ, DeLabry LO. Asymptomatic hyperuricemia. Risks and consequences in the Normative Aging Study. Am J Med. 1987;82:421-426

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Figure 1 – BMJ Best Practice Numeral Style

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