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In the Clinic®

Gout

Gout is characterized by deposition of monosodium urate (MSU) crystals in or around joints, tendons, bursae, and other tissues, resulting in painful recurrent flares and tissue damage. Gout is the most common form of inflammatory arthritis, with a prevalence of 5.1% in the United States, affecting 12.1 million adults. When urate levels exceed the limit of solubility (6.8 mg/dL [400 μmol/L]), MSU crystals may form or grow. Gout flares are the result of inflammatory responses to MSU crystals. The primary method to prevent and reduce gout flares, tophi, chronic inflammatory arthritis, and joint damage is to reduce urate levels below the saturation threshold. The pathophysiology of gout is well understood, and inexpensive and effective therapies are available. However, outcomes for patients with gout remain poorly optimized.

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Physician Writer
John D. FitzGerald, MD, PhD
University of California, Los Angeles, Los Angeles, California (J.D.F.)

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Gout is the most common inflammatory arthritis, affecting an estimated 12.1 million people (5.1% of the adult U.S. population) (1). Gout flares are intermittent painful inflammatory reactions to monosodium urate (MSU) crystal deposits that can progress to chronic inflammatory arthritis or erosive or tophaceous gout. MSU crystals form when serum urate (SU) levels increase above the saturation threshold.

High SU levels are most commonly due to genetic predisposition affecting urate transporters, resulting in urate underexcretion, with fluctuations in daily levels affected by diet. There may be rare genetic or other predisposing causes of overproduction of urates. Purine nucleotides in the body break down into hypoxanthine and then urate, catalyzed by the enzyme xanthine oxidase. These endogenous purines supply the majority of the urate that is produced, with the rest coming from dietary intake. Two thirds of urate is excreted by the kidneys during normal renal function, and the remainder comes from gastrointestinal excretion.

At normal body temperature and pH, the saturation point of urate is 6.8 mg/dL (400 μmol/L). Above this threshold, urate precipitates as MSU in the joints and other tissues. This threshold may be lower at lower temperatures (such as in the distal extremities) and in more acidic environments.

MSU crystals directly stimulate the innate immune system and lead to gout flares and, in more severe cases, development of tophi and bony erosions.

Risk Factors

What are the risk factors for gout?

Risk factors for gout are summarized in **Appendix Table 1** (available at Annals.org).

Hyperuricemia

Hyperuricemia is the primary risk factor for gout, although not all persons with hyperuricemia develop gout. Although gout affects an estimated 12.1 million (5.1%) adults in the United States (1), hyperuricemia (defined in the National Health and Nutrition Examination Survey [NHANES] as an SU level >7.0 mg/dL in men and >5.7 mg/dL in women) is present in 47.2 million U.S. adults (20.1%) (2). Data from longitudinal cohorts show that the higher the baseline SU level, the more likely people are to progress to incident gout (10 times greater risk with SU level of 8 to 9 mg/dL and 40 times greater risk with SU level >10 mg/dL [3]).

SU level is also predictive of gout flares among patients with prevalent gout.

In a study of 3613 persons with gout from the UK Biobank, baseline SU levels predicted gout flares requiring hospitalization in a dose-dependent manner. For each 1-mg/dL increase in SU level (compared with an SU level <6 mg/dL), the rate ratio for hospitalization for gout increased by an average of 1.7-fold. The rate ratio increased by 10-fold for SU levels of 7 to 10 mg/dL and by 25-fold for SU levels above 10 mg/dL (4).

Genetic predisposition

Genetic variation in urate channel function is the principal risk factor for development of hyperuricemia and incident gout. Genetic variations explain 23.8% of the variability in SU levels (5).

Age and sex

Gout is 2 to 6 times more prevalent in men (approximately 5.2%) than in women (approximately 2.7%) (2), primarily due to estrogen's uricosuric effects. Incidence and prevalence of gout increase with age, affecting fewer than 1% of adults aged 20 to 39 years, 3.4% of those aged 40 to 59 years, and 8.8% of those aged 60 years or older (2). The sex disparity decreases with age; men are more commonly affected during midlife, and women are more commonly affected after menopause.

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Diet

Dietary factors can contribute to incident gout or recurrent gout flares through increased purine and high fructose consumption. Although dietary patterns and individual foods correlate with urate levels, the proportion of urate variation explained by diet or individual foods is small (each <1%) and is log-order lower than the proportion explained by genetic causes (5). Large fructose servings can increase urate levels by 0.2 (5) to 2 mg/dL within 1 hour of consumption (6). Alcohol is rich in purines (particularly beer), increases purine metabolism, and reduces urate excretion (7). A unit of beer or liquor can increase SU levels by 0.16 mg/dL (5).

Obesity

Obesity is an important risk factor for higher SU level and incident gout. Mendelian randomization studies have shown that every 5-kg/m^2 increase in body mass index increases SU level by 0.3 mg/dL and doubles risk for gout (8). In the Health Professionals Follow-up Study, the risk for development of gout over 12 years doubled for men with overweight and tripled for men with obesity compared with men with normal weight (9). In contrast, a loss of more than 10 lb was associated with a 39% reduction in risk for incident gout (10).

Chronic kidney disease

Reduced renal excretion of uric acid from renal insufficiency increases risk for hyperuricemia and gout.

Medications

Medications can have favorable or deleterious effects on SU, incident gout, and recurrent gout flares, most often through effects on kidney excretion or reabsorption (**Appendix Table 2**, available at Annals.org). The list that follows is not exhaustive but highlights the effects of some medications on urate level, particularly those commonly used concurrently due to comorbid metabolic syndrome diseases (11).

Medications that increase urate levels. Loop and thiazide diuretics interact with renal urate transporters to increase SU levels by 1 mg/dL (11). Aspirin in low doses (<1 g/d) increases SU level by 1 mg/dL through biphasic effects on urate reabsorption (12).

Testosterone and insulin also increase SU levels through increases in urate reabsorption. Calcineurin inhibitors increase SU levels through decreased renal clearance by about 1 to 2 mg/dL (11).

The antitubercular drugs pyrazinamide and ethambutol can dramatically increase SU levels. Pyrazinamide, an aromatic organic anion, promotes resorption of uric acid and can increase SU levels by 4.6 mg/dL (13). Ethambutol can increase SU levels by 3.2 mg/dL (14).

Medications that decrease urate levels. Losartan (unlike other angiotensin II–receptor blockers) has a probenecid-like uricosuric effect of increased urinary excretion and may decrease SU levels by 1 mg/dL (15). Dihydropyridines (such as amlodipine) also have uricosuric benefit and may decrease SU levels by 1.1 mg/dL (11).

Sodium–glucose cotransporter-2 inhibitors (SGLT2is) promote excretion and decrease SU levels by 0.5 to 1.8 mg/dL depending on which SGLT2i is used and preexisting urate levels, history of gout, and other concurrent medications. Of note, patients starting SGLT2is showed decreases in incident and recurrent flare rates, gout-related emergency department visits (16), and hospitalizations with initiation. Some have postulated that this may be due to concurrent anti-inflammatory effects (17).

Supplemental estrogen decreases urate reabsorption and may decrease SU level by 0.7 to 1.2 mg/dL. Fenofibrate has moderate SU-lowering effects (1.9 mg/dL) (18) but is infrequently used in clinical practice. Statins (particularly atorvastatin) may also decrease SU levels by modest amounts

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(0.1 to 0.6 mg/dL), although the mechanism is unknown (19).

What comorbid diseases are associated with gout?

Gout and hyperuricemia are associated with metabolic syndrome and associated comorbid conditions, hypertension, progression of renal disease, cardiovascular disease (20), and dyslipidemia (21). Fifty percent of patients with gout meet the World Health Organization criteria for metabolic syndrome (22). Compared with patients without gout, patients with gout have 4 times higher odds of hypertension and twice the odds of chronic kidney disease (CKD) (stage 3 or higher), obesity, diabetes, myocardial infarction, heart failure, and stroke (23).

Renal insufficiency leads to hyperuricemia and incident gout. Observational studies suggest that higher SU levels may promote progression of CKD.

A 2022 systematic review and meta-analysis of cohort studies found that higher SU levels (by quartile) were associated with higher incidence of CKD, with 50% to 100% higher risk for the third and fourth quartiles compared with the first quartile and twice the risk for progression (24).

However, data on whether decreasing urate levels slows progression of renal disease have been mixed. In the CKD-FIX randomized controlled trial, 185 patients were treated with allopurinol, but there was no protection of estimated glomerular filtration rate with allopurinol compared with placebo (25).

Patients with gout have roughly double the rates of myocardial infarction, cerebrovascular disease, and heart failure compared with patients without gout (23, 26).

Inflammatory events, such as gout flares, may provoke myocardial infarction (20).

A nested case–control study with an embedded self-controlled case series of 62 574 patients with gout found an increase in cardiovascular events after gout flare that was highest in the first 30 to 60 days and decreased back to baseline cardiovascular risk by 180 days after the flare (20, 27).

Anti-inflammatory medications, such as the interleukin (IL) antagonist canakinumab (28) and colchicine (29, 30), have been found to reduce cardiovascular events. However, there has been little uptake of these medications for management of cardiovascular disease in either the general population or patients with gout.

Gout and hypertension have been associated in several observational studies (31). However, randomized controlled trials have not shown benefit of urate-lowering medications on blood pressure control (32).

Gout is also associated with obesity, type 2 diabetes, and insulin resistance (21, 33). Weight loss has been recommended for patients with gout (34), although effectiveness in preventing gout flares is less clear. Hyperuricemia is also associated with more central adiposity and increased metabolic dysfunction–associated steatotic liver disease (MASLD) (35).

Risk Factors... Hyperuricemia is the most important risk factor for development and management of gout. Hyperuricemia is affected primarily by genetic factors but also by other factors, including age, sex, obesity, renal insufficiency, urate-influencing medications, and dietary factors. Gout frequently requires co-management of (or evaluation for detection of) diabetes, renal impairment, obesity, hyperlipidemia, hypertension, MASLD, and cardiovascular disease.

CLINICAL BOTTOM LINE

What clinical signs suggest a diagnosis of gout?

Classic podagra or presence of tophi are highly suggestive of gout. Synovial fluid analysis is useful to distinguish gout from other similar inflammatory presentations (Table 1). MSU crystals are needle-shaped and have strong negative birefringence on polarized light microscopy (yellow when the crystal is parallel to the axis of the compensator and blue when perpendicular; the colors are reversed for calcium pyrophosphate [CPP] crystals).

Although some patients with gout may have only 1 flare, most have recurrent flares. With ongoing hyperuricemia, intercritical periods may shorten and subsequent flares may last longer and involve more joints.

Among 232 patients who had at least 1 gout flare in the previous year, the risk for having at least 1 recurrent flare in the following year was 69% and the risk for having at least 2 was 57% (36).

With longer disease duration and unabated hyperuricemia, subcutaneous nodules (tophi) may develop, although some patients can present initially with tophi. Typical locations include joints, ears, bursae (for example, olecranon bursa), finger pads, and tendons (for example, Achilles tendon) (37). Tophi are a biologically active, complex, organized, chronic granulomatous inflammatory tissue response to MSU crystals (38).

When should clinicians evaluate synovial fluid?

Synovial fluid analysis provides information on joint inflammation and presence of crystals or bacteria. These data can be helpful in particular settings, such as for a first diagnosis or when evaluating joint infection. Synovial fluid analysis may not be required if the a priori suspicion for gouty (rather than septic) arthritis is high. However, for atypical flares (either joint or duration) or if there is concern about another cause (such as CPP crystals or septic joint), synovial fluid analysis is essential for optimal management.

It is important to emphasize that any suspicion of septic arthritis requires immediate joint aspiration for Gram stain and culture. However, leukocytosis (leukocyte count $>50 \times 10^9$ cells/L) with neutrophil predominance in gout and septic arthritis may overlap. Bloody aspiration may suggest mechanical derangement, such as ligamentous or meniscal tear, or intra-articular fracture (which may also show fat droplets).

What tests can diagnose gout?

The definitive diagnosis of gout requires identification of MSU crystals from synovial fluid (for example, joint or bursa) or tophus aspiration (37). During gout flares, MSU crystals are more likely to be found in intracellular regions. Crystals can be recovered from synovial fluid between gout flares; they are more likely to be extracellular from synovial fluid with a lower leukocyte count.

SU levels are usually elevated in patients with gout, but this may be insufficient for diagnosis. SU levels may be lower during a flare since inflammatory cytokines increase urate excretion (39); thus, a more accurate baseline measure may be obtained 2 weeks after resolution of an acute flare.

What is the role of imaging?

Imaging can be useful in diagnosis of gout by facilitating joint aspiration or by providing evidence of urate deposition in joints or soft tissue or gout-related joint damage, such as bone erosion. Such findings may provide information on severity and thus the need for treatment as well as diagnosis.

Plain radiography

Plain radiography during a first or early gout flare may show normal findings,

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Table 1. **Conditions That May Be Mistaken for Gout***

Disease	*Mechanism*	*Typical Presentation*	*Co-occurrence or Overlap With Other Arthritis*	*Synovial Fluid Aspirate*	*Radiologic Findings*	*Notes*
Gout	Inflammatory reaction to MSU crystal deposition in or around joints	Exquisitely painful, red, swollen joint; typically the MTP1 of the big toe, but can present in any joint Peaks within 24 h, and self-resolution in 7–14 d	Gout has preference for joints with existing cartilage damage (e.g., osteoarthritis) Gout flare does not rule out septic arthritis CPPD may occur in same joint	Needle-shaped crystal with negative birefringence under polarized light microscopy Leukocyte count may be >50 $\times 10^9$ cells/L with neutrophil predominance	Characteristic erosions on plain radiographs Double-contour sign, MSU aggregates, erosions on ultrasound DECT is specific for MSU deposition but less sensitive in the first 2 y after disease presentation	–
CPPD	Inflammatory reaction to CPP crystals	Acute CPP crystal arthritis may be similar in presentation to an MSU gout flare Preference for knees, wrists, and shoulders, but can occur in any joint (rarely MTP1)	Osteoarthritis	Positive weakly birefringent crystals under polarized light microscopy Elevated leukocyte count	Chondrocalcinosis (calcification within cartilage and fibrocartilage) on radiograph, ultrasound, or CT scan	Osteoarthritis with CPPD includes CPP-induced or accelerated osteoarthritis joint involvement and CPP deposition in an asymptomatic joint
Septic arthritis	–	Presentation (including fever and synovial fluid leukocyte count) may be indistinguishable from MSU or CPP flare Risk factors for hematogenous spread to the joint should be evaluated	Early diagnosis, arthrocentesis, and antimicrobial treatment are important to avoid joint damage Can coexist with gout or other crystal arthritis	Gram stain is specific but not sensitive Culture is specific but requires growth (days) Observation of crystals does not exclude infection	–	Early diagnosis, arthrocentesis, and treatment initiation are important to avoid joint damage
Cellulitis	–	Erythema overlying a joint can be mistaken for gout Typically the joint itself is not tender and no effusion is present, although clinical examination can be difficult if there is soft tissue edema	–	Aspiration may distinguish from MSU or CPP flare if joint is painful to move Avoid aspirating through potentially infected tissue	–	–
Rheumatoid arthritis	–	Typically a polyarticular symmetric inflammatory arthritis Rheumatoid nodules can be mistaken for tophi	Polyarticular gout, particularly involving the hands, can be mistaken for rheumatoid arthritis Tophi can be mistaken for rheumatoid nodules	–	–	Chronic CPP crystal inflammatory arthritis has preference for metacarpal 2 and 3 joints as well as the midcarpal joints, which can also be mistaken for rheumatoid arthritis

Continued on following page

Table 1–**Continued**

Disease	*Mechanism*	*Typical Presentation*	*Co-occurrence or Overlap With Other Arthritis*	*Synovial Fluid Aspirate*	*Radiologic Findings*	*Notes*
Osteoarthritis	–	Hand, knee, hip, and MTP1 joints are commonly affected by osteoarthritis Acute inflammatory pain is not typical	Bone enlargement (hallux valgus) and MTP1 pain can be mistaken for gout Heberden nodes can be mistaken for tophi Gout can occur in joints affected by osteoarthritis	–	–	–
Psoriatic arthritis	–	Dactylitis ("sausage digit") may be similar to gout tenosynovitis	Patients with severe psoriasis can have hyperuricemia due to high cell turnover	–	–	–

CPP = calcium pyrophosphate; CPPD = calcium pyrophosphate deposition; CT = computed tomography; DECT = dual-energy computed tomography; MSU = monosodium urate; MTP1 = first metatarsophalangeal joint.
** Gout can also coexist with other conditions.*

apart from soft tissue swelling of the affected joint. Radiography can evaluate severity of disease when gout-related bone erosion (typically well corticated with overhanging margins [40]) is present. Tophi can be seen as soft tissue opacities. Radiography is helpful to evaluate other concurrent conditions, such as osteoarthritis, rheumatoid arthritis, or CPP deposition.

Ultrasonography

Ultrasonography can identify MSU deposition in or around joints and facilitate joint aspiration. It can also identify subclinical tophi (those that are detectable by ultrasound but not apparent on clinical examination).

The "double-contour sign" is a hyperechoic enhancement resulting from MSU crystal deposition on top of the surface of hyaline articular cartilage (**Appendix Figure**, available at Annals.org). The double-contour sign has good sensitivity (83%) and specificity (76%) for distinguishing gout from other MSU-negative conditions (41). CPP deposition can usually be distinguished from MSU deposition (based on location of the hyperechoic crystal deposition pattern) as CPP crystals more commonly deposit within rather than on top of cartilage.

Point-of-care ultrasound has added benefit as a patient education tool. Visualization of crystal deposits or erosions may affect patients' perception of their disease. Bony erosions can be detected by ultrasound in 27% of patients during the first year after onset of symptoms (42), increasing to 35% at 1 to 5 years and 52% at 5 to 10 years.

Dual-energy computed tomography

Dual-energy computed tomography (DECT) can detect and differentiate urate deposition from calcium but has limitations. Identification of MSU crystal deposition on DECT has sensitivity of 87% and specificity of 84% in established disease (>2 years' duration), but sensitivity rates are lower within the first 2 years after symptom onset (41).

Magnetic resonance imaging

Although not routinely used for gout, magnetic resonance imaging can show joint inflammation, damage, and tophi, but depending on the sequence used, it cannot necessarily distinguish gout from CPP arthritis.

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Diagnosis... Joint pain and hyperuricemia alone cannot establish the diagnosis of gout. The presence of MSU crystals in synovial fluid or tophus confirms the diagnosis. Ultrasound is a helpful diagnostic instrument for identifying findings suggestive of MSU crystal deposition. Clinicians should keep in mind that gout can coexist with or mimic other arthritic conditions. Gout can be differentiated from CPP-related arthritis by radiographic or ultrasound findings and more specifically by examination of the aspirated material under polarizing microscopy. When there is suspicion of infection, synovial fluid examination for cell count and appropriate stains and cultures are necessary.

CLINICAL BOTTOM LINE

Treatment

Treatment of gout should address both inflammatory symptoms and hyperuricemia. Anti-inflammatory medications are the mainstay of treatment of gout flares and can also be used for prophylaxis when patients are at high risk for an acute or recurrent flare. Urate-lowering therapy (ULT) decreases SU levels and can reduce recurrent gout flares, resolve tophi, and prevent progression to severe manifestations of gout (Table 2).

What is the role of anti-inflammatory medications?

Anti-inflammatory medications have dual roles in management of gout. They can be used as abortive (on-demand) therapy to treat acute episodic flares, and they can be used as prophylaxis against an expected increase in flare activity (for example, during ULT initiation).

Abortive management

Anti-inflammatory treatment for pain relief of a gout flare should be started as early as possible. This on-demand strategy, sometimes called "pill-in-pocket," involves patients having anti-inflammatory treatment and instructions on its use available to minimize time from flare onset to initiation of therapy. Topical ice and good hydration can be used as adjuvant therapy for an inflamed joint. The specific agent depends on patient characteristics and comorbid conditions (Table 2).

For mild to moderate pain, particularly flares affecting 1 or few joints, the recommended first-line therapy is nonsteroidal anti-inflammatory drugs (NSAIDs) (including cyclooxygenase-2 [COX-2] inhibitors), colchicine, or glucocorticoids (oral, intra-articular, or parenteral). Monotherapy with an intra-articular glucocorticoid injection may be a good option for flares involving single joints. For more severe flares (such as polyarticular flares or those affecting several large joints), initial combination therapy may be needed (for example, colchicine plus NSAIDs; oral glucocorticoids plus colchicine; or intra-articular glucocorticoids plus NSAIDs, COX-2 inhibitors, or colchicine as oral therapy) (43). Therapy should continue for at least 7 to 10 days for more severe flares; shorter durations can lead to rebound if the inflammation is not adequately reduced.

Prophylaxis

Anti-inflammatory prophylaxis against gout flares is recommended by guidelines from the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) when ULT is being started (34, 44), and the American College of Physicians (ACP) recommends discussing prophylaxis with patients (45). This is particularly important because 20% of patients started on ULT never fill a second prescription (46), and the most common reason reported is a belief that the

43. Zeng L, Qasim A, Neogi T, et al. Efficacy and safety of pharmacologic interventions in patients experiencing a gout flare: a systematic review and network meta-analysis. Arthritis Care Res (Hoboken). 2021;73:755-764. [PMID: 32741131]
44. Richette P, Doherty M, Pascual E, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. Ann Rheum Dis. 2017;76:29-42. [PMID: 27457514]
45. Qaseem A, Harris RP, Forciea MA, et al; Clinical Guidelines Committee of the American College of Physicians. Management of acute and recurrent gout: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2017;166:58-68. [PMID: 27802508]
46. Rashid N, Coburn BW, Wu Y-L, et al. Modifiable factors associated with allopurinol adherence and outcomes among patients with gout in an integrated healthcare system. J Rheumatol. 2015;42:504-512. [PMID: 25512479]

Table 2. **Pharmacologic Therapy for Gout**

Drug (Mechanism of Action)	*Dose*	*Considerations and Precautions*
Anti-inflammatory therapy	–	May be used for treatment of gout flare or for prophylaxis
NSAIDs	Example for abortive treatment: Naproxen, 500 mg twice daily, until flare resolves Example for prophylaxis: Naproxen, 220–250 mg twice daily	Renal, gastrointestinal (may need to consider concomitant proton-pump inhibitor), cardiovascular, congestive heart failure risks
Colchicine	1.2 mg (loading dose) at first sign of flare, followed by 0.6 mg 1 h later, then use prophylaxis dosing until flare resolves For prophylaxis, 0.6 mg daily or twice daily (as comorbid conditions or concurrent medications mandate)	Decrease dose or avoid in patients with renal insufficiency, hepatic dysfunction, or concurrent use of strong CYP3A4 or P-glycoprotein inhibitors Contraindicated with use of strong CYP3A4 inhibitors in setting of renal or hepatic dysfunction Monitor for gastrointestinal symptoms, neuromyotoxicity, and blood dyscrasias
Glucocorticoids	Oral: Prednisone, 0.5 mg/kg daily for 3 d, then reduce to complete 10- to 14-d course Intra-articular injection: Methylprednisolone, 10–60 mg (or equivalent dosing); dose depends on size of joint Not used for prophylaxis unless patient is already receiving low-dose daily prednisone for organ transplant	Caution with oral glucocorticoids in patients with congestive heart failure, systemic infection, or hyperglycemia For patients with congestive heart failure, consider equivalent dosing of dexamethasone
Interleukin-1	Canakinumab, 150 mg once (may repeat every 12 wk as needed) Anakinra (off-label use for gout flare), 100 mg subcutaneously daily for 3 d Not approved for prophylaxis	–
Urate-lowering therapy	Start at low dose and gradually titrate upward every 2–6 wk to achieve serum urate level <6 mg/dL	–
Xanthine oxidase inhibitors (inhibit synthesis of urate)	–	Can be used in patients with urate overexcretion or underexcretion; avoid use or monitor closely in patients receiving azathioprine or 6-mercaptopurine
Allopurinol	Start at 100 mg/d in patients with normal renal function; start at 50 mg/d in patients with chronic kidney disease stage 3b or worse; most patients require doses >300 mg/d to achieve serum urate target; FDA-approved maximum dose is 800 mg/d	About 2%–5% of persons develop mild rash; allopurinol hypersensitivity syndrome is a rare but fatal adverse effect Check for HLA-B*5801 allele in patients of Asian or African descent before starting
Febuxostat	Start at 40 mg/d; no dose adjustment for mild to moderate renal or hepatic insufficiency; FDA-approved maximum dose is 80 mg/d, EMA-approved maximum dose is 120 mg/d	About 2%–5% of persons develop rash; liver enzyme abnormalities can occur; hypersensitivity syndrome also possible
Uricosuric agents (increase renal urate excretion)	–	Avoid in patients with history of nephrolithiasis, CrCl <30 mL/min, or urate overexcretion; adequate hydration is necessary to reduce risk for nephrolithiasis
Probenecid	Start at 250 mg twice daily; patients may require 2–3 g/d in 2 divided doses	Probenecid increases serum concentration of many drugs, including penicillin, NSAIDs, and methotrexate
Uricase (converts urate to soluble allantoin)	–	–
Pegloticase	8-mg intravenous infusion every 2 wk; immunosuppression reduces development of antidrug antibodies	Use for severe gout that is refractory to conventional therapy or if other contraindication or intolerance is present; risk for infusion reaction and anaphylaxis; do not use in patients with G6PD deficiency, and use with caution in patients with congestive heart failure

CrCl = creatinine clearance; CYP3A4 = cytochrome P450 3A4; EMA = European Medicines Agency; FDA = U.S. Food and Drug Administration; G6PD = glucose-6-phosphate dehydrogenase; NSAID = nonsteroidal anti-inflammatory drug.

urate-lowering treatment worsened their gout (47). When prescribed concurrent with initiation of ULT, anti-inflammatories are generally recommended for 3 to 6 months, although recent data suggest an even longer duration may be beneficial (48).

What anti–inflammatories are commonly used to treat gout?

The 3 most commonly used anti-inflammatories are nonsteroidals (including COX-2 selective inhibitors), colchicine, and glucocorticoids. All are recommended equally for first-line anti-inflammatory treatment or prophylaxis (34).

A 2021 network meta-analysis found that newer IL-1 antagonists, such as canakinumab, are more effective than traditional agents (43), and these are now approved by the U.S. Food and Drug Administration (FDA) for treatment of gout flares; however, the high cost ($16 000 for each treatment, which may be repeated every 3 months) has limited routine clinical use. Anakinra remains as an alternate (off-label) IL-1 therapy (49).

Nonsteroidal anti-inflammatory drugs

There are no data to recommend one NSAID over another for treating gout flares. NSAIDs should be used with caution in patients with renal insufficiency or gastrointestinal bleeding risk, and these patients may need concomitant proton-pump inhibitor therapy. NSAIDs must also be used with caution or avoided in patients with cardiovascular disease or congestive heart failure. Caution should be used in elderly patients due to increased risk and possible NSAID-induced cognitive confusion.

Colchicine

Colchicine works best when started within 36 hours after flare onset, and ideally within 12 hours. The FDA-approved colchicine regimen (50) for a gout flare is 1.2 mg immediately, followed by 0.6 mg 1 hour later and then a "prophylaxis dose" of 0.6 mg (renally dosed) once or twice daily for up to 14 days.

Colchicine toxicity can result in gastrointestinal symptoms, myelosuppression, transaminitis myopathy, and potentially multiorgan failure and death (51). Thus, clinicians should pay careful attention to drug interactions and dose adjustments for renal and hepatic insufficiency and should err on the side of caution.

Colchicine is metabolized by cytochrome P450 3A4 (CYP3A4) and excreted in the urine and biliary tree largely unchanged. Good hepatic and renal function are necessary for efficient excretion. Drugs that inhibit CYP3A4 may increase colchicine concentrations, increasing the risk for toxicity. Strong CYP3A4 inhibitors include clarithromycin, itraconazole, and all protease inhibitors, including ritonavir. Moderate inhibitors include certain calcium-channel blockers (such as diltiazem, verapamil, and amlodipine), cyclosporine, amiodarone, erythromycin, fluconazole, and grapefruit juice (52).

Colchicine should be avoided in patients receiving concurrent or recently dosed (within the past 14 days) CYP3A4 inhibitors who also have moderate to severe renal or hepatic dysfunction. Colchicine should be held during short courses of strong CYP3A4 inhibitors, such as clarithromycin, ritonavir (as part of nirmatrelvir–ritonavir for treatment of COVID-19), and antifungals, but can be restarted 3 to 5 days after completion of the interacting medication (53).

Older patients have lower excretion rates that are attributable to lower muscle mass and volume of distribution and slower biliary excretion rates (54). Thus, greater attention to dose adjustments is required for elderly patients, even those with good renal function (due to slower nonrenal excretion factors).

Although concomitant statin use can increase risk for neuromyotoxicity, this is clinically rare.

47. Harrold LR, Andrade SE, Briesacher BA, et al. Adherence with urate-lowering therapies for the treatment of gout. Arthritis Res Ther. 2009;11:R46. [PMID: 19327147]
48. Stamp L, Horne A, Mihov B, et al. Is colchicine prophylaxis required with start-low go-slow allopurinol dose escalation in gout? A non-inferiority randomised double-blind placebo-controlled trial. Ann Rheum Dis. 2023;82:1626-1634. [PMID: 37652661]
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51. Stamp LK, Horsley C, Te Karu L, et al. Colchicine: the good, the bad, the ugly and how to minimize the risks. Rheumatology (Oxford). 2024;63:936-944. [PMID: 38019947]
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53. Hansten PD, Tan MS, Horn JR, et al. Colchicine drug interaction errors and misunderstandings: recommendations for improved evidence-based management. Drug Saf. 2023;46:223-242. [PMID: 36522578]
54. Rochdi M, Sabouraud A, Girre C, et al. Pharmacokinetics and absolute bioavailability of colchicine after i.v. and oral administration in healthy human volunteers and elderly subjects. Eur J Clin Pharmacol. 1994;46:351-354. [PMID: 7957521]

In the COLCOT study (30) of 2366 patients assigned to colchicine, severe myopathy was seen once at 3 months after 8 days of colchicine. In the LoDoCo2 (29) trial, none of the 2762 patients receiving colchicine reported severe myopathy despite the majority (94% to 99%) using concurrent statin therapy.

Other interactions have been described that are less common or less severe, with varying recommendations for adjustment (53).

Glucocorticoids

Glucocorticoids are the preferred treatment for gout flares in patients with contraindications to NSAIDs and/or colchicine. For monoarticular gout flares, an intra-articular glucocorticoid injection can be effective. Oral glucocorticoids are preferred for polyarticular gout, often prescribed as a "burst" of prednisone (for example, initial dose of 0.5 mg/kg per day for 5 days followed by a taper).

Patients with diabetes may experience hyperglycemia while receiving glucocorticoids (including intra-articular or intramuscular glucocorticoids) and may require close monitoring and hypoglycemic medication adjustment. Because of its lower mineralocorticoid potency, dexamethasone may be considered for patients with congestive heart failure.

What is the role of lifestyle management?

ACR guidelines recommend weight loss for patients with gout who have overweight or obesity and limiting intake of purine-rich foods, high-fructose corn syrup, and alcohol (34).

A systematic review of 10 longitudinal studies found low- to moderate-quality evidence in favor of weight loss for gout. The effect ranged from a 1.9-mg/dL (168-μmol/L) reduction in SU level to a 0.34-mg/dL (30-μmol/L) increase. Zero percent to 60% of patients achieved the target SU level of less than 4.1 mg/dL (<360 μmol/L). Six of 8 studies found beneficial effects on gout flares (55).

55. Nielsen SM, Bartels EM, Henriksen M, et al. Weight loss for overweight and obese individuals with gout: a systematic review of longitudinal studies. Ann Rheum Dis. 2017;76:1870-1882. [PMID: 28866649]

What are considerations for effectiveness of and adherence to ULT?

ULT is indicated for patients with frequent gout flares (≥2 per year), any clinically apparent tophi, or evidence of erosive disease on imaging. Subsets of patients with high risk for progression of gout (SU level >9 mg/dL) or with comorbid kidney disease (urolithiasis or presence of CKD stage 3 or worse) may also benefit from ULT after onset of their first gout flare (34) (see the **Box:** Indications for Pharmaceutical ULT for Patients With Gout).

For patients with indications for ULT, ACR and EULAR recommend a treat-to-target strategy (SU level <6 mg/dL [<5 mg/dL for patients with tophi]). However, any treatment strategy that does not achieve sufficient adherence is likely to be ineffective. Before starting ULT, clinicians should take time to engage patients so that treatment goals and outcomes are aligned with patient expectations. Strategies for

Indications for Pharmaceutical ULT for Patients With Gout

Patient engagement in a long-term pharmaceutical treatment strategy and any of the following:

- Frequent flares (≥2 per year)
- Tophus on clinical examination
- Erosions on imaging study

In addition, if an informed patient values the described benefits of ULT more than the risks, the following factors may be considered as indications for ULT:

- Marked hyperuricemia (SU level >9 mg/dL)
- Chronic kidney disease
- History of nephrolithiasis (any type of stone)
- Concomitant medications or other comorbid conditions that complicate treatment or increase risk for progression of gout

coping with flares should be in place and should be clear to the patient (for example, pill-in-pocket, prophylaxis, slow titration).

The UK Nursing Study found that 151 of 153 patients randomly assigned to an intervention with a strong educational component (8 nurse visits) opted to start ULT, and 95% showed high adherence rates. This resulted in higher mean allopurinol dosing, lower SU values, fewer flares, and greater reduction in tophi (56).

ULT decreases SU levels, but dissolution of MSU crystals may take months to years depending on the burden of crystal deposition (57). Thus, a normal SU level may not reflect the burden of MSU crystals; in fact, initiating ULT may destabilize MSU crystals and precipitate a flare during the first few months of ULT. Twenty percent of patients who start ULT never fill a second prescription (46), and the most common reason reported is their belief that the treatment worsened their gout (47). ACR and EULAR recommend prophylaxis against gout flares when starting ULT (34, 44). ACP also recommends discussing prophylaxis with patients (45). Besides or concurrent with prophylaxis, clinicians should consider a "start low, go slow" uptitration strategy.

The FORTUNE trial (58) randomly assigned patients to 40 mg of febuxostat (with or without colchicine prophylaxis) or to febuxostat increased from 10 to 20 mg at 4 weeks and from 20 to 40 mg 4 weeks later. There was no difference in flare rate between slow titration and febuxostat with prophylaxis. However, patients given febuxostat without prophylaxis had double the flare rate of the other 2 groups. Slow titration has also been successfully done with allopurinol (48).

What urate-lowering agents should clinicians consider?

Xanthine oxidase inhibitors (allopurinol, febuxostat) are first-line treatment options that work by reducing production of urate. Uricosuric agents (probenecid) block reuptake in the proximal tubules of the kidney. Recombinant uricase (pegloticase) converts urate to allantoin.

Allopurinol

Allopurinol is the most commonly used ULT agent (90% of all ULT prescriptions) (59). A "start low, go slow" titration strategy minimizes risk for a gout flare from ULT initiation and risk for allopurinol hypersensitivity (AHS). The recommended starting dose for patients with normal kidney function is 100 mg/d, with an increase of 100 mg every few weeks until the SU target of less than 6 mg/dL is reached. Reduced starting and titration doses of 50 mg/d should be considered for patients with CKD stage 3B. The allopurinol dose required to reach the SU target is best determined by the pre-ULT SU level and the patient's body weight (60). Although an oversimplification, a general rule of thumb may be that for every 100-mg increase in the allopurinol dose, the SU level decreases by about 1 mg/dL (60). The maximum allopurinol dose is 800 mg/d. Allopurinol should not be used with azathioprine or 6-mercaptopurine.

Severe AHS is rare (<1 in 1000 people) but can be life-threatening. Manifestations of AHS include severe cutaneous reactions, such as Stevens–Johnson syndrome; eosinophilia; leukocytosis; fever; hepatitis; or renal failure. AHS is driven by higher starting dose; renal dysfunction; and presence of the HLA-B*5801 allele, which is more common in patients of Asian or African descent. Rash occurs in about 2% to 5% of cases, and physicians should consider stopping allopurinol while assessing the cause of the rash. Risk for a severe cutaneous reaction diminishes with longer duration of therapy; 90% of severe reactions occur within 8 to 9 weeks of initiation (61). The 2020 ACR guidelines conditionally recommend screening all patients of African or Asian descent for the HLA-B*5801 allele because of the high prevalence (4% to 10%) in those

56. Doherty M, Jenkins W, Richardson H, et al. Efficacy and cost-effectiveness of nurse-led care involving education and engagement of patients and a treat-to-target urate-lowering strategy versus usual care for gout: a randomised controlled trial. Lancet. 2018;392:1403-1412. [PMID: 30343856]
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60. Stamp LK, Chapman PT, Barclay M, et al. Relationships between allopurinol dose, oxypurinol concentration and urate-lowering response–in search of a minimum effective oxypurinol concentration. Clin Transl Sci. 2020;13:110-115. [PMID: 31444839]
61. Stamp LK, Barclay ML. How to prevent allopurinol hypersensitivity reactions? Rheumatology (Oxford). 2018;57:i35-i41. [PMID: 29272508]

populations (34). Patients with this allele should receive alternative treatments.

Febuxostat

Febuxostat, 40 to 80 mg/d, is FDA-approved in the United States, and up to 120 mg/d is approved in Europe by the European Medicines Agency. Febuxostat carries a black box warning for an increased cardiovascular risk, based on the CARES trial (62), although more recent data from the FAST trial suggest no increased cardiovascular risk (63). Febuxostat also has a drug–drug contraindication against concurrent 6-mercaptopurine or azathioprine use. Febuxostat is more extensively metabolized by the liver and thus does not require dose adjustment for mild kidney disease, but limiting the dose to 40 mg/d for patients with severe renal impairment (creatinine clearance of 15 to 29 mL/min) is still recommended.

Probenecid

Uricosurics block reuptake of uric acid in the proximal tubule but are rarely used due to limited efficacy, more frequent adverse effects, and drug interactions. Uricosurics may be combined with a xanthine oxidase inhibitor to improve urate lowering.

Probenecid is ineffective in persons with creatinine clearance below 30 mL/min. It increases risk for nephrolithiasis and is contraindicated in patients who have a history of nephrolithiasis or are urate overexcretors. Patients must ensure adequate water intake while receiving probenecid. Probenecid carries risk for a major drug interaction with concurrent use of penicillin, derivatives, or cephalosporins due to its action at the organic anion transport channel. NSAIDs also rely on organic anion transporters for excretion, and concurrent use can result in increased concentrations of the NSAID with associated toxicities.

Pegloticase

Pegloticase, a recombinant uricase, is FDA-approved for management of chronic gout that is refractory to conventional treatments. It is reserved for patients with difficult-to-control, severe, and/or tophaceous gout who cannot tolerate or have insufficient response to medically appropriate maximum doses of another ULT. It is administered intravenously every 2 weeks, with premedications and close predose monitoring of SU levels due to risk for infusion reactions and anaphylaxis.

Pegloticase also carries risk for infusion reactions. Prescription should be limited to those with experience or close knowledge of risks and benefits as well as mitigation steps, such as coprescription with methotrexate (64) or another immunosuppressant (65).

When should clinicians consider hospitalizing a patient with gout?

Patients with a severe gout flare may need hospitalization if the intensity of the pain or the extent of the joint involvement limits the patient's ability to care for themselves. If septic arthritis is a concern, the patient may need hospitalization for empirical intravenous antibiotics while awaiting synovial fluid cultures.

Gout flares during hospitalization are common, with annual rates of 10 per 100 000 persons (66). Clinicians and their patients rightly focus on managing the inflammatory symptoms. Patients who are acutely ill in the hospital may add complexity to the choice of anti-inflammatory agents due to concurrent infection, changing renal function, poorly controlled blood glucose, or other acute illness.

There is uncertainty about how best to manage ULT during a hospitalization in the setting of an acute renal injury. Pharmacokinetics can be complicated. Stopping ULT may be overly cautious (if renal injury is not severe) and risks inciting a gout flare. In a single-institution report, the authors reported that stopping allopurinol during a hospitalization resulted in a 14-fold increase in gout flares (67). For mild renal insufficiency, no ULT changes may be required. For severe renal injury, consultation with a

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63. Mackenzie IS, Ford I, Nuki G, et al; FAST Study Group. Long-term cardiovascular safety of febuxostat compared with allopurinol in patients with gout (FAST): a multicentre, prospective, randomised, open-label, non-inferiority trial. Lancet. 2020;396:1745-1757. [PMID: 33181081]
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68. Stamp LK, Chapman PT, Barclay ML, et al. A randomised controlled trial of the efficacy and safety of allopurinol dose escalation to achieve target serum urate in people with gout. Ann Rheum Dis. 2017;76:1522-1528. [PMID: 28314755]

rheumatologist or a nephrologist may help guide decision making.

How should patients with comorbid conditions be managed?

In treating patients with gout and hypertension, when possible, clinicians should consider losartan over diuretics. For patients with gout and an indication for an SGLT2i, there is added benefit of SU lowering.

Patients with renal insufficiency should avoid NSAIDs and use colchicine with caution (particularly in the setting of CYP3A4 inhibitors). Allopurinol can still be the first-line ULT. The allopurinol starting dose may need adjustment, but titration to daily doses above 300 mg may be needed and has been shown to be safe (68).

When should a patient be referred to a specialist?

Most patients (85%) with gout are managed in primary care (46). Referral to a rheumatologist may be warranted for patients with refractory gout flares or intolerance of or lack of response to standard ULT. Patients with progressive tophaceous gout or unstable tophaceous gout (infected tophi, spontaneous drainage, or causing significant disabilities) may also require referral. Patients with solid organ transplants using calcineurin inhibitors may present challenges to management of their gout. Patients receiving dialysis who continue to have inflammatory gout flares or whose SU level remains elevated should be considered for management by a rheumatologist.

Treatment... Gout flares should be treated as soon as possible with NSAIDs, colchicine, or glucocorticoids. ULT is indicated for patients with recurrent gout, tophi, or erosive disease and may be recommended for patients with CKD or very high urate levels (>9 mg/dL). Allopurinol is the preferred ULT. Patients should be educated about the increased risk for a gout flare at the time of ULT initiation as well as prevention or treatment of flares. Comorbid conditions and polypharmacy increase risk for drug–drug interactions and may require dose adjustment or optimal drug selection.

CLINICAL BOTTOM LINE

In the Clinic
Tool Kit

Gout

Patient Information

https://medlineplus.gov/gout.html
https://medlineplus.gov/languages/gout.html
Information on gout in English and other languages from the National Institutes of Health's MedlinePlus.

www.niams.nih.gov/health-topics/gout
Information on gout from the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

https://rheumatology.org/patients/gout
https://rheumatology.org/patients/gota
Patient and caregiver information on gout from the American College of Rheumatology.

www.arthritis.org/about-arthritis/types/gout
Information on gout from the Arthritis Foundation.

Information for Health Professionals

https://rheumatology.org/gout-guideline
Guideline on management of gout from the American College of Rheumatology.

https://ard.bmj.com/content/79/1/31
https://ard.bmj.com/content/76/1/29.long
Evidence-based recommendations for the diagnosis and management of gout from the European League Against Rheumatism.

www.acpjournals.org/doi/10.7326/M16-0570
Clinical practice guideline on management of acute and recurrent gout from the American College of Physicians.

WHAT YOU SHOULD KNOW ABOUT GOUT

What Is Gout?

Gout is a type of arthritis that causes swelling, redness, and severe pain in joints like the big toe. It happens when there is too much uric acid in your body. Uric acid can form painful crystals in the joints. Although anyone can get gout, you are more likely to if you:

- Have high uric acid levels
- Have a genetic predisposition
- Are male
- Are an older adult
- Have obesity
- Have certain health conditions, such as kidney failure, high blood pressure, and diabetes
- Take certain medicines, such as water pills
- Eat certain foods, such as red meat and organ meat (liver)
- Drink alcohol and sugary drinks, such as soda and sugar-sweetened juice

What Are the Warning Signs?

The signs and symptoms of gout usually happen suddenly, without warning, and at night. This is called a "flare." Signs of a flare include:

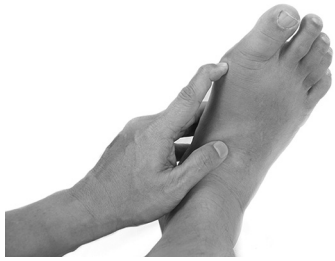
- Severe joint pain, often in the big toe
- Joint pain in other parts of your feet and in your ankles, knees, hands, and wrists
- Swelling, redness, stiffness, and tenderness in the affected joints
- Pain is most severe in the first 24 hours. Gout flares can last 1 to 2 weeks.

How Is It Diagnosed?

- Your doctor will ask you about your symptoms and examine your joints.
- He or she may take a small sample of fluid from an affected joint to look for signs of gout crystals under a microscope.
- Blood tests and imaging tests, such as X-rays or ultrasounds, can also help your doctor learn more about your symptoms.

How Is It Treated?

Treatment for a gout flare starts with medicines that decrease your pain and stop the flare. This can include anti-inflammatory medicines such as ibuprofen.



Some people may need more treatment. If you have a history of repeated gout flares, nodules from gout crystals, a history of kidney stones, or kidney problems, your doctor may prescribe medicines that help decrease uric acid levels. This will help prevent future flares and complications, such as joint damage. These medicines may temporarily increase risk for a flare, so your doctor may recommend taking medicines to prevent the flare for the first few months.

Lifestyle changes can also help. These include losing weight if you have overweight, avoiding certain foods, limiting alcoholic drinks, and drinking lots of water.

Your doctor may recommend periodic blood tests to check uric acid levels. He or she may also refer you to a specialist if you need more treatment.

Questions for My Doctor

- What treatment is best for me?
- When will my symptoms go away?
- Will gout damage my joints?
- Should I avoid certain foods and drinks?
- Do any of my medicines increase my uric acid levels?
- Can I take a painkiller?
- When I have a flare, are there any activities I should avoid?
- What can happen if my gout is not treated?
- How can I reduce my future risk for flares?

For More Information

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American College of Rheumatology
https://rheumatology.org/patients/gout
https://rheumatology.org/patients/gota

Arthritis Foundation
www.arthritis.org/about-arthritis/types/gout

MedlinePlus
https://medlineplus.gov/gout.html
https://medlineplus.gov/languages/gout.html

National Institute of Arthritis and Musculoskeletal and Skin Diseases
www.niams.nih.gov/health-topics/gout

Patient Information

Appendix Table 1. **Risk Factors for Hyperuricemia and Gout**

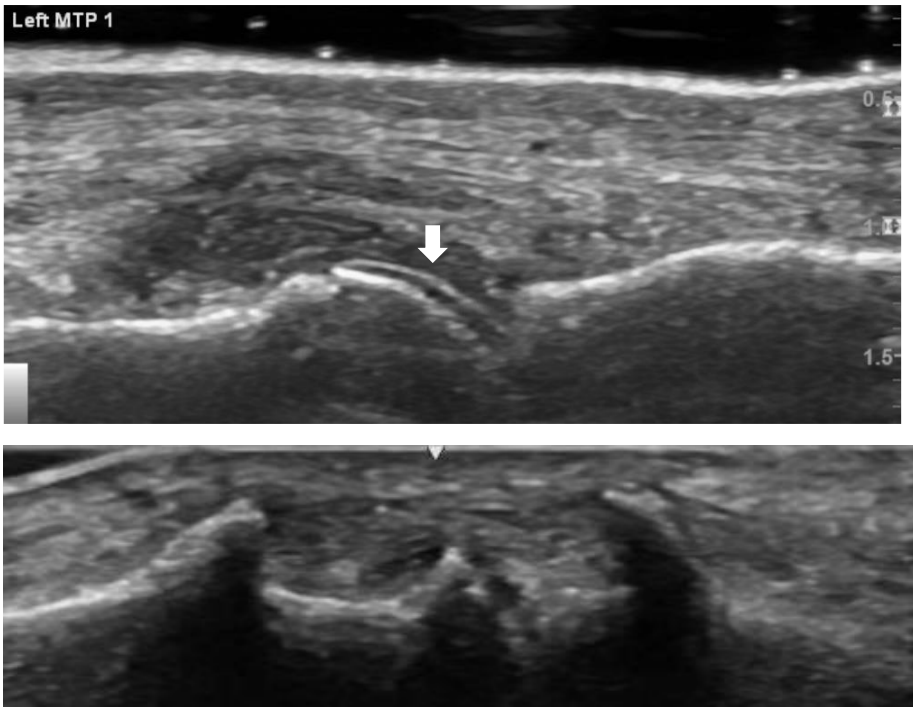
Genetic risk factors
Male sex
Older age
Renal insufficiency
Medications (e.g., thiazide or loop diuretics, cyclosporine)
Diet high in animal sources of purines (e.g., red meat, shellfish)
Consumption of alcohol and high-fructose corn syrup–sweetened drinks (e.g., soda)
Obesity

Appendix Table 2. **Medications That Can Secondarily Affect Serum Urate Levels**

Medication Class	*Approximate Mean Change in Serum Urate Level*	*Mechanism of Action*
Medications that can increase serum urate level		
Loop and thiazide diuretics	1-mg/dL increase	Increased resorption of uric acid (11)
Low-dose (<1 g/d) aspirin	1-mg/dL increase	Increased resorption of uric acid (12)
Calcineurin inhibitors	1- to 2-mg/dL increase	Decreased renal clearance (11)
Pyrazinamide and ethambutol	4- to 5-mg/dL increase	Increased resorption of uric acid (13, 14, 69)
Medications that can decrease serum urate level		
Sodium–glucose cotransporter-2 inhibitors	0.5- to 2-mg/dL decrease	Glucosuria-dependent uricosuric effect (17)
Losartan	0.5-mg/dL decrease	Uricosuric effect (15, 34, 70)
Dihydropyridines (e.g., amlodipine)	1-mg/dL decrease	Uricosuric effect (11)
Statins (particularly atorvastatin) and fenofibrate	0.5-mg/dL decrease (statins) 2-mg/dL decrease (fenofibrate)	Unknown (18, 19) Uricosuric effect
Estrogen	1-mg/dL decrease	Decreases urate reabsorption

69. Louthrenoo W, Hongsongkiat S, Kasitanon N, et al. Effect of antituberculous drugs on serum uric acid and urine uric acid excretion. J Clin Rheumatol. 2015;21:346-348. [PMID: 26398460]
70. Miao Y, Ottenbros SA, Laverman GD, et al. Effect of a reduction in uric acid on renal outcomes during losartan treatment: a post hoc analysis of the reduction of endpoints in non-insulin-dependent diabetes mellitus with the Angiotensin II Antagonist Losartan Trial. Hypertension. 2011;58:2-7. [PMID: 21632472]

Appendix Figure. **Ultrasonographic view of MTP1.**



MTP1 = first metatarsophalangeal joint. **Top.** Dorsal longitudinal view of MTP1 showing double-contour sign (*arrow*), joint capsule distention filled with mixed echogenic signal ("snowstorm") and some hyperechoic signal (*bright spots*), and aggregates of monosodium urate crystals. **Bottom.** Medial longitudinal view of MTP1 showing 0.7-mm erosion on the metatarsal side of the joint. Mixed echogenic material with bright hyperechoic aggregates are noted to fill the erosive space.