# Gout

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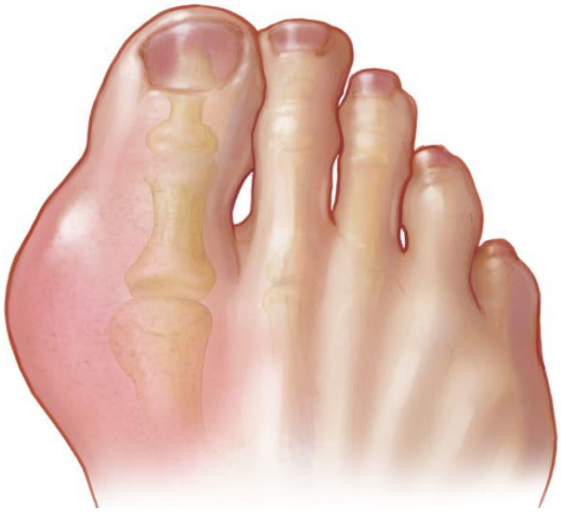
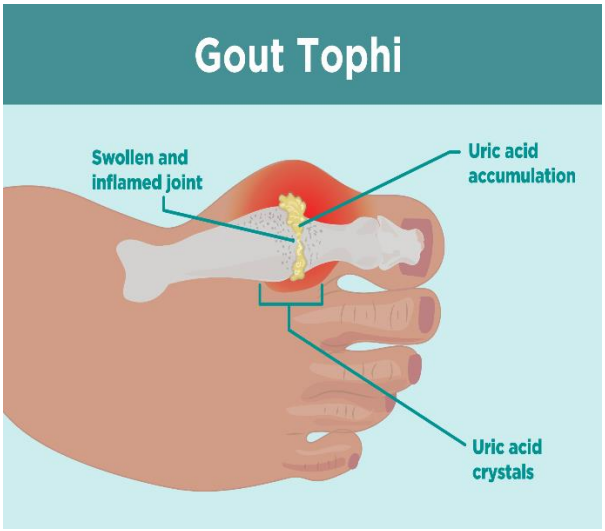
Gout is a common systemic condition caused by the deposition of monosodium urate crystals (MSU) in articular and non-articular structures. Although presenting as an intermittent flaring condition, gout is a chronic disease. It is a painful and debilitating condition with a high prevalence and associated morbidity. [10] Increased serum uric acid (SUA) above a specific threshold is a requirement for the formation of uric acid crystals, and hyperuricaemia is the greatest risk factor for the development of gout. [1, 2] Gout occurs in response to the presence of MSU crystals in joints, soft tissues, and bones. It is characterised by sudden, severe attacks of pain, swelling, redness and tenderness in one or more joints, most often in the big toe, but other commonly affected joints include the ankles, knees, elbows, wrists and fingers. It may result in recurrent flares of inflammatory arthritis, chronic gouty arthropathy, the accumulation of urate crystals in the form of tophaceous deposits, uric acid nephrolithiasis and chronic nephropathy. Long-term complications of gout include joint damage and renal stones. [3, 5, 8, 10]






Serum urate is regulated by urate transporters in the kidney and gut. Activation of the NLRP3 inflammasome by monosodium urate crystals with release of IL-1β plays a major role in the initiation of gout flares, and aggregated neutrophil extracellular traps are important in the resolution phase.[1]

Although hyperuricemia is the main pathogenic defect in gout, many people with hyperuricemia do not develop the condition, or form uric acid crystals. Only 5% of people with hyperuriceamia above 9 mg/dL develop gout, and other factors including genetic predisposition share in its occurrence. [2, 4]

Worldwide, the incidence of gout is increasing gradually due to poor dietary habits such as fast foods, lack of exercise, increased incidence of obesity and metabolic syndrome. Reports

of the prevalence and incidence of gout vary widely according to the population studied and methods employed, but range from a prevalence of < 1% to 6.8% and an incidence of 0.58-2.89 per 1,000 person-years. [3] According to Arthritis Ireland, it is estimated that up to 1 in 40 people are affected by gout.[14] Factors affecting SUA levels include age and gender. It occurs more often in men than women (3–6% in men and 1–2% in women in western countries), however, SUA levels in postmenopausal women can rise to the same levels as in men. Prevalence can rise to 10% in men and 6% in women over the age of 80 years. Rarely, gout can occur in children and young adults who have inborn errors of purine metabolism. [2, 3]

Deficiency of enzymes involved in purine metabolism leads to overproduction of uric acid (UA). Lesch-Nyhan syndrome is an inborn error of metabolism resulting from deficiency of an enzyme (hypoxanthine–guanine phosphoribosyltransferase) involved in UA metabolism. It is a genetic X-linked recessive disorder with varying degrees of severity according to the type of mutation. Lesch-Nyhan syndrome involves neurological abnormalities such as dystonia, chorea, cognitive dysfunction, compulsive injurious behaviour, self-mutilation and articular manifestations (early onset gout), in addition to renal stones. If left untreated, it may lead to tophi formation and renal failure. [3]

Another enzymatic abnormality that causes gout in the young is the super activity of phosphoribosyl pyrophosphate synthetase. It is an X-linked dominant inherited disorder. The syndrome has two clinical forms, a severe early onset form in children, and a mild late juvenile or early adult onset form. It includes neurological abnormalities such as sensorineural hearing loss, hypotonia and ataxia in the severe form. The mild form manifests as uric acid renal stones and arthritis. These enzymatic disorders constitute less than 10% of cases of overproduction of urates. [3]

**Risk Factors**

Hyperuricemia is the leading cause of gout. Factors implicated for gout and/or hyperuricemia include older age, male sex, obesity, purine diet, alcohol, medications, comorbid diseases, and genetics. [5]

Foods rich in purines such as cooked or processed food especially from animal and seafood origin is a key element of increasing uric acid precursors. Alcohol is a well-known risk factor for gout. Certain medications including low dose aspirin, thiazide diuretics, angiotensin-converting enzyme (ACE) inhibitors and beta blockers can increase uric acid levels, as can the use of anti-rejection drugs prescribed for people who have undergone an organ transplant. Increased endogenous production of uric acid occurs in accelerated cellular turnover such as in malignancies, haematological and inflammatory diseases, and increased purine production may also result from chemotherapy and tissue damage. Genome-wide association studies have found several genes associated with gout including SLC2A9, ABCG2, SLC22A12, GCKR, and PDZK1. [5, 8] Increased body weight and obesity leads to enhanced production of uric acid aggravating the risk of hyperuriceamia. Leptin is also found to increase serum levels of urate. [3]

The prevalence of gout is higher among individuals with chronic diseases and comorbidities such as hypertension, chronic kidney disease, diabetes mellitus, obesity, congestive heart failure, and myocardial infarction. Every condition that causes alterations in extracellular urate concentration can trigger a flare-up of gout. These include stress (recent surgery or trauma), dietary factors (e.g., fatty food, beer, wine, and spirits), and medications such as aspirin and diuretics. [5, 8]

**Presentation and Diagnosis**

Patients usually present with acute onset of joint pain. Gout flares are more common at night and in the early morning. The pain is often sudden, waking the person from their sleep or may develop gradually over a few hours, with the maximum intensity of pain at 24 hours. Signs of inflammation usually extend beyond the joint involved. The pain is severe, and even lightly touching the joint can be excruciatingly painful. Gout flare-ups often incite local inflammation, which presents as erythematous, swollen, and a warm joint. Systemic features of joint inflammation may include fever, general malaise, and fatigue. [5, 9]

Gout flare is usually mono-articular, often occurring in the lower extremities. The most commonly involved joint is the first metatarsophalangeal joint. In some cases, the talar, subtalar, ankle, and knee can be involved. Other joints, specifically those with underlying osteoarthritis can also be affected. Periarticular structures such as tendons and bursa may also be affected. Gout can occur in axial joints such as sacroiliac joints and the spine, although much less common than peripheral involvement, leading to diagnostic confusion. Polyarticular gout flares are more likely to occur in patients with longstanding disease. Initial presentation of polyarticular gout is more frequent in patients in whom gout and hyperuricemia arise secondary to lymphoproliferative or myeloproliferative disorder, or in organ transplant recipients receiving tacrolimus or cyclosporine. [6, 7]

Physical examination findings usually align with the patient's history. The affected joint is usually red, swollen, warm, and tender. In patients with chronic gout, the flare-up may involve multiple joints. Tophi, which are subcutaneous depositions of urate that form nodules, can also be found in patients with persistent hyperuricemia. Tophi typically occur in the joints, ears, finger pads, tendons, and bursae. [5, 9]

Investigations usually reveal elevations in the white blood cell count (WCC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) during a gout flare-up, however, these features are non-specific and do not confirm the diagnosis. The serum urate level should be repeated in patients with an uncertain gout diagnosis after the resolution of the flare-up. Hyperuricemia is helpful in the clinical diagnosis of gout in symptomatic patients, but hyperuricemia alone does not definitively confirm the diagnosis. Asymptomatic hyperuricemia is not uncommon in the general population. Persistently low serum urate concentrations make the diagnosis of gout less likely. In patients suspected of gout based on clinical features, elevated serum urate level (> 6.8 mg/dL) can support the diagnosis, but is neither diagnostic nor required to establish the diagnosis. The most accurate time for assessing serum urate levels to establish a baseline value is two weeks or more after a gout flare completely subsides.[5]

Monosodium urate crystal identification is the gold standard for gout diagnosis. Gout flare-up is marked by the presence of MSU crystals in synovial fluid obtained from affected joints. Synovial fluid during a gout flare-up is usually yellow in colour and cloudier in appearance, and contains crystals and white blood cells with neutrophil predominance. Synovial fluid in patients with septic arthritis is usually opaque, with a yellow-green appearance. Under microscopic examination, synovial fluid for septic arthritis will have a higher white blood cell count than in gout and a positive gram stain. [5]

Although not routinely used, ultrasonography and dual-energy CT (DECT) can assist in diagnosing gout. Monosodium urate deposition will be apparent on ultrasound as a hyperechoic enhancement over the cartilage. [5]

In 2018, EULAR published updated evidence-based recommendations for the diagnosis of gout, which supersedes the 2006 recommendations. The updated recommendations centre mainly on clinical presentation, imaging tools, and evaluation of comorbidities. They discard recommendations for renal excretion rate and septic arthritis, and reformulate but maintain recommendations for a gold-standard diagnosis based on microscopic synovial fluid analysis, which is mandatory for any acute arthritis. The 2018 EULAR recommendations include a conceptual change from the previous recommendations, reinforcing that gout can be the cause of any kind of acute arthritis, rather than suggesting that typical clinical presentations are highly suggestive of gout. In addition, they outline specific clinical features suggestive of typical gout flares. An interaction between clinical features and imaging findings allowed for formulation of a new staging of gout, known as “subclinical gout” or urate crystal deposition without gout symptoms.[19] There are 8 updated recommendations. [16]

1. Search for crystals in synovial fluid or tophus aspirates is recommended in every person with suspected gout, because demonstration of monosodium urate (MSU) crystals allows a definitive diagnosis of gout.
2. Gout should be considered in the diagnosis of any acute arthritis in an adult. When synovial fluid (SF) analysis is not feasible, a clinical diagnosis of gout is supported by the following suggestive features: mono articular involvement of a foot (especially the first metatarsophalangeal, MTP) or ankle joint; previous similar acute arthritis episodes; rapid onset of severe pain and swelling (at its worst in <24 hours); erythema; male gender and associated cardiovascular diseases and hyperurica emia. These features are highly suggestive but not specific for gout.
3. It is strongly recommended that synovial fluid aspiration and examination for crystals is undertaken in any patient with undiagnosed inflammatory arthritis.
4. The diagnosis of gout should not be made on the presence of hyperuricaemia alone.
5. When a clinical diagnosis of gout is uncertain and crystal identification is not possible, patients should be investigated by imaging to search for MSU crystal deposition and features of any alternative diagnosis.
6. Plain radiographs are indicated to search for imaging evidence of MSU crystal deposition but have limited value for the diagnosis of gout flare. Ultrasound scanning can be more helpful in establishing a diagnosis in patients with suspected gout flare or chronic gouty arthritis by detection of tophi not evident on clinical examination, or a double contour sign at cartilage surfaces, which is highly specific for urate deposits in joints.
7. Risk factors for chronic hyperuricaemia should be searched for in every person with gout, specifically: chronic kidney disease; overweight, medications (including diuretics, low-dose aspirin, cyclosporine, tacrolimus); consumption of excess alcohol (particularly beer and spirits), non-diet sodas, meat and shellfish.
8. Systematic assessment for the presence of associated co morbidities in people with gout is recommended including obesity, renal impairment, hypertension, ischaemic heart disease, heart failure, diabetes and dyslipidaemia.

https://www.eular.org/sysModules/obxContent/files/www.eular.2015/1_42291DEB-50E5-49AE-5726D0FAAA83A7D4/pr_gout_final.pdf

**Treatment and Management**

First-line treatment for gout flares are colchicine, NSAIDs, or systemic glucocorticoids. Aspirin is not used to treat gout flare-ups because of the effect salicylic acid has on increasing serum urate. The choice of drug depends on timing, contraindications, the patients previous experience with treatments, and the number and type of joints affected. [12]

The 2016 updated EULAR evidence-based recommendations for the management of gout, generated three overarching principles and 11 key recommendations. [12] "For the treatment of flare, colchicine, non-steroidal anti-inflammatory drugs (NSAIDs), oral or intra-articular steroids or a combination are recommended. In patients with frequent flare and contraindications to colchicine, NSAIDs and corticosteroids, an interleukin-1 blocker should be considered. In addition to education and a non-pharmacological management approach, urate-lowering therapy (ULT) should be considered from the first presentation of the disease, and serum uric acid (SUA) levels should be maintained at < 6 mg/dL (360 µmol/L*)* and < 5 mg/dL (300 µmol/L*)* in those with severe gout. Allopurinol is recommended as first-line ULT and its dosage should be adjusted according to renal function. If the SUA target cannot be achieved with allopurinol, then febuxostat, a uricosuric or combining a xanthine oxidase inhibitor with a uricosuric should be considered. For patients with refractory gout, pegloticase is recommended". Because of the high cost of IL-1 blockers and an increased likelihood of infection, the EULAR task force recommends they be prescribed only for patients who have contraindications to colchicine, NSAIDs and corticosteroids.[12]

A proton-pump inhibitor (PPI) may be required to protect the stomach lining of patients taking NSAIDs. Contraindications for the use of NSAIDs include active duodenal or gastric ulcer, cardiovascular disease, NSAID allergy, and chronic kidney disease. [5] Colchicine should not be given to patients with kidney impairment or those receiving strong P-glycoprotein and/or CYP3A4 inhibitors such as cyclosporin or clarithromycin. [12] Adverse effects of colchicine are abdominal cramping and diarrhoea. [5]

Long-term urate lowering therapy leads to the dissolution of monosodium urate crystals, ultimately resulting in the prevention of gout flares and tophi and in improved quality of life.[1] There are three main classes of ULT: Xanthine oxidase inhibitors (allopurinol and febuxostat) which inhibit urate production; Uricosurics (probenecid and lesinurad) which increase renal urate excretion; and Recombinant uricases (rasburicase and pegloticase) which catalyse the conversion of urate to allantoin. [20] Xanthine oxidase inhibitors (XOI) allopurinol and febuxostat, work by inhibiting uric acid synthesis.[5] Allopurinol is the recommended first-line pharmacologic ULT in gout. It is not an analgesia, and does not have any effect during a gout attack. It works by lowering the level of uric acid in the blood, and can take 2-3 months to become fully effective. It needs to be taken every day to keep the uric acid level normal to prevent gout attacks.[11] Febuxostat is also effective in preventing gout flares by keeping uric acid levels low, however, it has side-effects, and is usually reserved for people who are unable

to take allopurinol. [11] British guidelines advise waiting one-to-two weeks after a gout flare-up to start ULT, however, the American guidelines support an immediate start.[20] Two studies have shown that starting ULT during a flare does not prolong it, provided the flare is being adequately treated. Up-titrating ULT slowly reduces the risk of it triggering a flare. It is important that ULT is not discontinued at the onset of and during a flare, while a patient is receiving ULT.[20]

Urate-lowering therapy (ULT) is started at a low dose to monitor the side effects and response to treatment. Titration of the dose is every 2 to 6 weeks to achieve serum urate levels of less than 6 mg/dl, or 5 mg/dl in patients with tophi. During ULT initiation, there is an increased risk of gout flare-ups, so anti-inflammatory medications or colchicine prophylaxis is recommended for two to three months after achieving serum urate levels, to reduce the risk.[5]

**EULAR 2016 Gout Management Recommendations [13]**

https://www.rheumatologyadvisor.com/home/topics/gout/eular-releases-updated-gout-management-guidelines/

1. Acute gout flares should be treated as soon as diagnosed.
2. First line options identified for acute flare include: colchicine, loading dose of 1 mg, 0.5 mg on day 1, or a nonsteroidal anti-inflammatory drug (NSAID), oral corticosteroids (equivalent prednisolone dose of 30–35 mg/day for 3–5 days), or joint aspiration with intraarticular injection of corticosteroids. Avoid colchicine and NSAID administration in patients with renal impairment.
3. Interleukin (IL)-1 blockers should be considered in patients with both frequent disease flares and contraindications to receiving colchicine, NSAIDs, or corticosteroids.
4. Urate-lowering therapy (ULT) should be accompanied by prophylaxis in the first 6 months of treatment. Colchicine, is recommended at a dose of 0.5–1 mg/day, with adjustments for renal impairment. When colchicine is not tolerated well or is contraindicated, prophylaxis with NSAIDs at a low dosage can be considered.
5. Patients with definitive gout diagnosis and ≥2 gout flares/year, tophi, urate arthropathy, or recurrent kidney stones should be considered for ULT. Patients who are < 40 years old or who have SUA levels > 8 mg/dL (480 µmol/L), or other comorbidities should receive early ULT.
6. SUA targets of < 6 mg/dL (360 µmol/L) should be targeted with ULT therapy, SUA targets of <5 mg/dL (300 µmol/L) may be appropriate in patients with severe gout. Long-term SUA levels of < 3 mg/dL are generally not recommended.
7. Initiation of low-dose ULTs are recommended, with upward titration until SUA goal is attained.
8. Allopurinol is recommended by the task force as first-line ULT, beginning with 100 mg/day and increasing by 100 mg increments every 2–4 weeks if needed to attain SUA goal. Febuxostat or a uricosuric should be started if allopurinol alone cannot be used to attain target SUA, or if it is not well tolerated.
9. Creatinine clearance should be used to adjust allopurinol maximum daily doses for patients with renal impairment.
10. When target SUA levels cannot be attained in patients with debilitating chronic tophaceous gout and crystal-proven disease, pegloticase is indicated.
11. If a patient presents with gout and is on loop or thiazide diuretics, it is recommended that the diuretic be switched. Losartan or calcium channel blockers should be considered to replace diuretic indicated for hypertension and a statin should be considered for hyperlipidemia.

The American College of Rheumatology (ACR) published an updated set of guidelines for the management of gout in 2020. Strong recommendations included initiation of ULT for all patients with tophaceous gout, radiographic damage due to gout, or frequent gout flares; allopurinol as the preferred first-line ULT, including for those with moderate-to-severe chronic kidney disease (CKD; stage ≥3); using a low starting dose of allopurinol (≤100 mg/day, and lower in CKD) or febuxostat (≤40 mg/day); and a treat-to-target management strategy with ULT dose titration guided by serial serum urate (SU) measurements, with an SU target of <6 mg/dl. When initiating ULT, concomitant anti-inflammatory prophylaxis therapy for a duration of at least 3–6 months was strongly recommended. For management of gout flares, colchicine, nonsteroidal anti-inflammatory drugs, or glucocorticoids (oral, intraarticular, or intramuscular) were strongly recommended. [17, 18]

Non-pharmacological management such as rest with topical application of ice packs combined with medications can help reduce inflammation. [5] Most people continue to have further flares. These can be prevented by a combination of lifestyle modification such as losing weight, changing diet, reducing/eliminating alcohol and medicines to reduce urate levels. [10]

The EULAR evidence-based recommendations for the management of gout recommend that every person with gout should be systematically screened for associated comorbidities and cardiovascular risk factors, including renal impairment, coronary heart disease, heart failure, stroke, peripheral arterial disease, obesity, hyperlipidaemia, hypertension, diabetes and smoking, which should be addressed as an integral part of the management of gout. [12, 13]

Patient education is a key aspect of gout management, and patients must be kept informed and involved in the management of their condition. All patients with gout should receive advice regarding lifestyle management; weight loss if appropriate and avoidance of alcohol especially beer and spirits and sugar-sweetened drinks, heavy meals and excessive intake of meat and seafood. Low-fat dairy products should be encouraged and regular exercise should be advised. [12] Patients should receive information regarding gout pathophysiology, triggers, treatment options, burden of comorbidities, general medical management of acute attack management, and the lifelong need to reduce serum uric acid (SUA) to target levels. [13, 14]

For detailed information about Gout and sleep and fatigue, exercise, work and lifestyle information, patients can download the *Living with Gout* booklet or contact the Arthritis Ireland Helpline at 0818252846 or email: helpline@arthritisireland.ie. [14]

**Outlook**

Although gout is a treatable disease, its management is still not optimal in a large proportion of patients. Studies report that less than half of patients with gout receive urate lowering therapy (ULT), and that when prescribed, it is often at an insufficient dose to effectively lower the SUA levels to target.[3, 12] Studies also suggest that fewer than half of patients adhere to

treatment.[3] Many gout risk factors exist, including obesity, dietary factors and comorbid conditions. As well as a firmly established increased risk of cardiovascular disease and chronic kidney disease, associations of gout with other comorbidities have been reported, including erectile dysfunction, atrial fibrillation, obstructive sleep apnoea, osteoporosis and venous thromboembolism. Increasing prevalence and incidence of obesity and comorbidities are likely to contribute substantially to the rising burden of gout.[3]

Published in the journal *Cellular and Molecular Immunology*, researchers at Washington State University and elsewhere recently identified a new therapeutic target for the treatment of gout. The study suggests that blocking a signalling molecule known as TAK1 can suppress inflammation caused by gout. The discovery has opened the door towards the development of new treatment strategies for gout. This research lays the foundation for the development of potential new treatment strategies that could significantly improve the quality of life of millions of people around the world. [15]

Continued emphasis on patient and clinician education, and attempts to standardise international medical approaches regarding gout, outcome measures, staging and its management are important strategies. Investigating the possible role of the microbiome in gout parallel to its metabolic counterparts, and intensive studies in genomics and proteomics may also lead to a better understanding of disease predisposition and susceptibility to drug adverse effects, and offer potential therapeutic breakthroughs for the future treatment and management of gout.[1]

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