Crystals of pain: navigating gout and its management

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Abstract

Gout is a form of inflammatory arthritis, caused by the buildup of uric acid crystals in the joints, especially the big toe. If left untreated these tophi, or crystals can become extremely painful, and over time may result in damage to bone and soft tissue. It is important to get a correct diagnosis on gout and to differentiate with other diseases like septic arthritis, rheumatoid arthritis and even stress fractures. Non-pharmacological treatment and prevention strategies include sufficient rest and adequate dietary and lifestyle modifications. The management of gout distinguishes between treatment for acute gout symptoms and the prevention of a gout attack or the lowering of uric acid in the serum. Urate-lowering therapy, like allopurinol and febuxostat, lowers blood urate levels, can prevent gout flare-ups and diminishes tophi over time. Treatment with one or more potent anti-inflammatory medication is necessary for the management of acute flares. Four categories of medicine are available for treatment of acute symptoms of pain and inflammation. They include nonsteroidal anti-inflammatory medicine, corticosteroids, colchicine, and anti-IL-1β biologics. Efficacy between these agents is similar, thus focus should be on minimising individual risks. People with a tendency to develop gout must limit their consumption of red meat, fish, shellfish and alcohol, particularly those that have additional purines such as beer, wine and whiskey.

Keywords: gout, urate-lowering therapy, allopurinol, colchicine

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Introduction

Gout is a common form of inflammatory arthritis that occurs due to a buildup of uric acid in the body over time.[1,2] Since the body cannot easily dissolve and excrete high uric acid levels via urine, the uric acid starts to crystallise and form sharp crystals known as tophi in the joints, usually in the joint of the big toe.[3,4] The tophi initially cause no pain; however, they can become painful over time and may result in damage to the bone and soft tissue, leading to misshapen joints.[2] Although the big toe is more commonly affected, other joints affected by gout are the knees, ankles, feet, hands, wrists, and elbows.[1,5] The presence of high levels of uric acid in these joints causes severe pain and inflammation.[2]

Gout can affect anyone, but it is more prevalent in men, and women usually develop it after menopause.[4] The condition typically begins in middle age, but if it starts at a younger age, the symptoms are usually more severe.[2] Gout is a progressive disease that can go through several stages.[3]

In the first stage, known as hyperuricaemia, elevated urate levels in the blood lead to the formation of crystals in the joints, as shown in Figure 1.[3] Typically, there are no symptoms during this stage.[2] The second stage is characterised by gout flares, which involve periodic attacks of intense joint pain and swelling.[3] Intercritical gout, the third stage, is the period between gout attacks when there are no symptoms.[2] The final stage, chronic gout, involves the accumulation of tophi in the joints, skin, or other parts of the body.[1] Depending on their location, tophi can cause permanent damage to the joints and other internal organs, increasing the risk of developing other conditions or complications, especially related to the heart and kidneys.[2,3] Comorbidities that may increase the prevalence of gout include:[3]

- Hypertension (high blood pressure)
- Chronic kidney disease
- Obesity
- Diabetes
- Nephrolithiasis (kidney stones)
- Myocardial Infarction (heart attack)
- Congestive heart failure
- Sleep apnoea
- Depression

The diagnosis of gout is not always straightforward, and a differential diagnosis may be necessary. Other diseases can

Figure 1: Stages of gout progression[3]

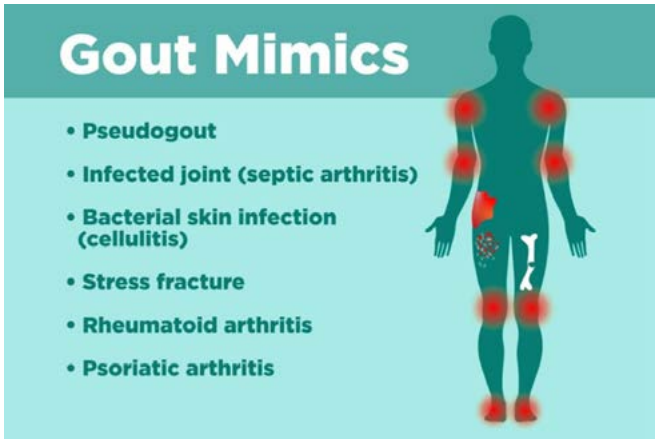

Figure 2: Diseases that mimic gout[6]

present similarly to gout and cause a misdiagnosis as shown in Figure 2.[6]

Pseudogout

Pseudogout, formerly known as calcium pyrophosphate deposition disease or CPPD, is now commonly referred to as pseudogout due to its similarity to gout.[7] Both gout and pseudogout cause sudden joint pain, swelling, and redness, which makes them difficult to differentiate.[8] It is the type of crystals formed in the two conditions that differ.[7] For gout, it is uric acid, while in pseudogout, it is crystallised calcium pyrophosphate (CPP).[6]

Infected joint (septic arthritis)

Both gout and an infected joint can cause fever and an increase in white blood cells.[4] However, the presence of an offending microorganism in the fluid taken from the affected joint indicates septic arthritis, as it is an infection, unlike gout.[6] Treatment of septic arthritis is directed at eliminating the offending bacteria.

Bacterial skin infection (cellulitis)

Both gout and cellulitis can cause inflammation and pain in the lower leg.[7] The difference is that in gout there is an accumulation of uric acid crystals in a joint, while cellulitis is a bacterial infection in the deep layer of the skin.[6] A blood culture can be used to differentiate the two conditions.

Stress fracture

Gout is often mistaken for injuries to the toes caused by dropping heavy items on the toes or jamming the big toe against a hard surface. Stress fractures can occur without the individual being aware and are frequently confused with gout.[6] An X-ray can assist with identifying the cause of the pain if a stress fracture is suspected.

Rheumatoid arthritis

In individuals with polyarticular gout, which affects several joints, gout is often mistaken for rheumatoid arthritis.[6] The key distinction is that gout typically starts by affecting one or a few joints, while rheumatoid arthritis tends to involve multiple, larger joints symmetrically and can affect many organs in the body.[4] Blood tests, such as anti-CCP, C-reactive protein, erythrocyte sedimentation rate, and rheumatoid factor, can help doctors distinguish between gout and rheumatoid arthritis.[6]

Psoriatic arthritis

As with rheumatoid arthritis, psoriatic arthritis (PsA) can cause swelling around the fingers or toes, which may resemble gout tophi.[6] However, with PsA there is no buildup of uric acid crystals in the joints.[4,6]

Pathophysiology and clinical presentations

Table I: Pathophysiology of gout

Aspect	Details
Pathophysiology	Gout is characterised by elevated serum uric acid levels (hyperuricaemia), typically exceeding 6.8 mg/dL.[9]
Uric acid crystal formation	As blood uric acid levels increase, urate crystals form.
Clinical presentation	**Kidney Stones:** Formation of uric acid crystals can lead to kidney stones
	Tophi: Deposits of urate crystals in joints and tissues can form tophi (chalky nodules).
	Gouty Arthritis: Urate crystal deposition in joints can cause episodes of gouty arthritis, characterised by sudden and severe joint pain.[10]

Hyperuricaemia

Hyperuricaemia is characterised by elevated levels of uric acid in the bloodstream, typically exceeding 6 mg/dL in women and 7 mg/dL in men.[11] Uric acid is produced during the breakdown of purines in the body as shown in Figure 3.[12,13] Research has additionally demonstrated a correlation between elevated uric acid levels and various other health conditions, such as kidney disease, heart disease, hypertension, diabetes, non-alcoholic fatty liver disease, and metabolic syndrome.[14,15,16] Hyperuricaemia causes cardiovascular disease and chronic kidney disease by prompting abnormal growth of vascular smooth muscle cells and impaired endothelial function, which triggers inflammation.[17]

Inflammatory response

Hyperuricaemia gradually progresses and promotes the formation of monosodium urate (MSU) crystals, triggered by various factors such as dehydration, alcohol, hypertension, thereby causing inflammation in the joints.[18,19] Inflammatory cytokines, particularly IL-1β, are the key mediators of gouty inflammation.[20] The NLRP3 inflammasome is the major pathway by which MSU crystals trigger the cellular inflammatory response as shown in Figure 4.[21] Delivery of ingested MSU crystals to the inflammasome in phagocytes subsequently triggers intracellular assembly of the cytosolic NALP3 (cryopyrin) inflammasome protein complex.[21] The MSU crystals cause the inflammasome assembly, which in turn causes caspase-1 activation, phagocyte maturation, and the production of IL-1β.[20]

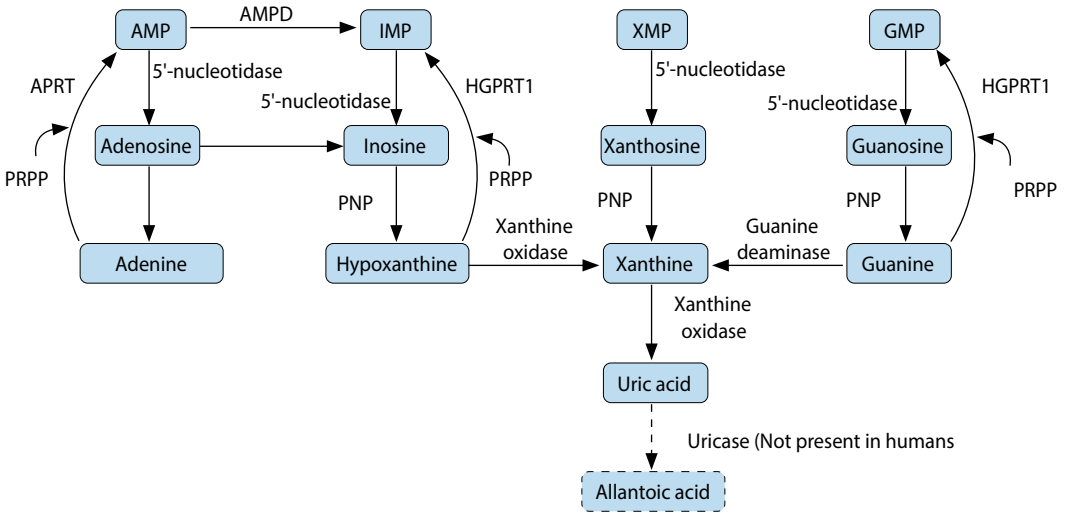

Figure 3: Uric acid synthesis and purine metabolism in gout[13]

Acute gout attacks

Acute gout attacks start suddenly and escalate quickly, with joint pain usually reaching its peak within 24 hours of onset. These attacks often begin to improve within 5–12 days even without treatment, although full recovery may take longer for some individuals.[22]

Chronic gout

Chronic gout develops due to ongoing inflammation that follows repeated gout attacks. It is characterised by persistent synovitis (inflammation of the synovial membrane), erosion of bone, damage to cartilage, and the formation of tophi (deposits of uric acid crystals) in tissue.[23]

Causes and risk factors

The causes of gout typically involve multiple factors, such as genetic predisposition, existing medical conditions, and dietary habits.[4] In uncommon instances, a single genetic anomaly may lead to gout, often linked with other health issues. Regardless of the specific cause, elevated levels of uric acid in the blood can lead to clinical symptoms of gout in susceptible individuals.[25]

Risk factors associated with gout and high uric acid levels include advancing age, male gender, obesity, a diet rich in purines, alcohol consumption, and genetic susceptibility. Medications such as diuretics, low-dose aspirin, ethambutol, pyrazinamide, and cyclosporine are known to potentially raise uric acid levels and contribute to the development of gout.[19] Foods that can increase uric acid levels and contribute to gout include animal products such as seafood (like shrimp and lobster), organ meats (such as liver and kidney), and red meats (like mutton and beef). Additionally, beverages such as alcohol, sweetened drinks, sodas, and those containing high-fructose corn syrup may also play a role in the development of this condition.[25]

Signs and symptoms

Gout attacks are intensely painful and typically occur suddenly, often overnight. Symptoms in the affected joints may include severe pain, redness or discoloration, stiffness, swelling, tenderness (even to light touch, such as from a bedsheet), and a sensation of warmth or intense heat in the joint.[4]

Triggers of symptoms

Factors that can trigger gout flares include consuming foods high in purines and taking medications such as furosemide. Environmental factors such as exposure to lead, particulate matter, temperature changes, and physiological stress have also been identified as triggers for gout flares.[26]

Onset of symptoms

Gout episodes often last a week or two, however, the patient may not exhibit any gout symptoms in between attacks. Nevertheless,

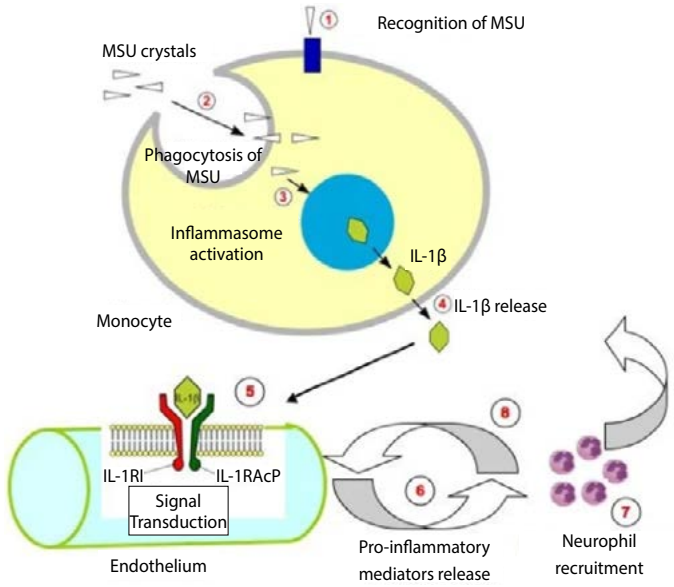

Figure 4: Inflammatory response in gout[21]

some flares continue longer than others and may result in more severe symptoms.[4]

Treatment

Non-pharmacological treatment and prevention strategies

The management of gout involves non-pharmacological measures as adjuncts to managing acute gout attacks.[27] These measures include:

1. Sufficient rest
2. Topical ice application
3. Reduce the intake of sugar-sweetened soft drinks
4. Dietary and lifestyle modifications

It is recommended that people with gout limit their consumption of red meat, fish, shellfish, and alcohol, particularly those that have additional purines such as beer, lager, and whiskey.[27] It has been widely held that diet can reduce the chance of developing gout; in particular, consuming fewer alcoholic beverages and foods high in purines, as these are linked to elevated blood urate levels.[28] A summary of foods one should eat and avoid when they have gout is shown in Figure 5.[29]

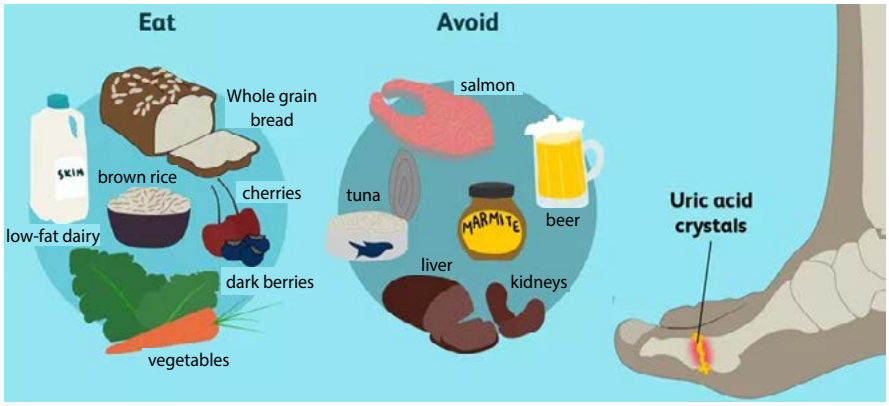

Figure 5: Foods to eat and avoid with gout[29]

Because of its uricosuric effects, which are more pronounced at greater dosages, increasing vitamin C intake above 500 mg/day reduces the incidence of gout, whereas the intake of soy protein, non-soy legumes, and fresh fruit (> 2 portions/day) is negatively correlated with the incidence of gout.[27] Therefore, these dietary and lifestyle modifications can be suggested as supplementary to ULT.[27]

Pharmacological treatment

Urate-lowering therapy (ULT), lowers blood urate levels, stops gout flare-ups, and diminishes tophi over time. ULT comprises of xanthine oxidase inhibitors (allopurinol and febuxostat), uricosuric

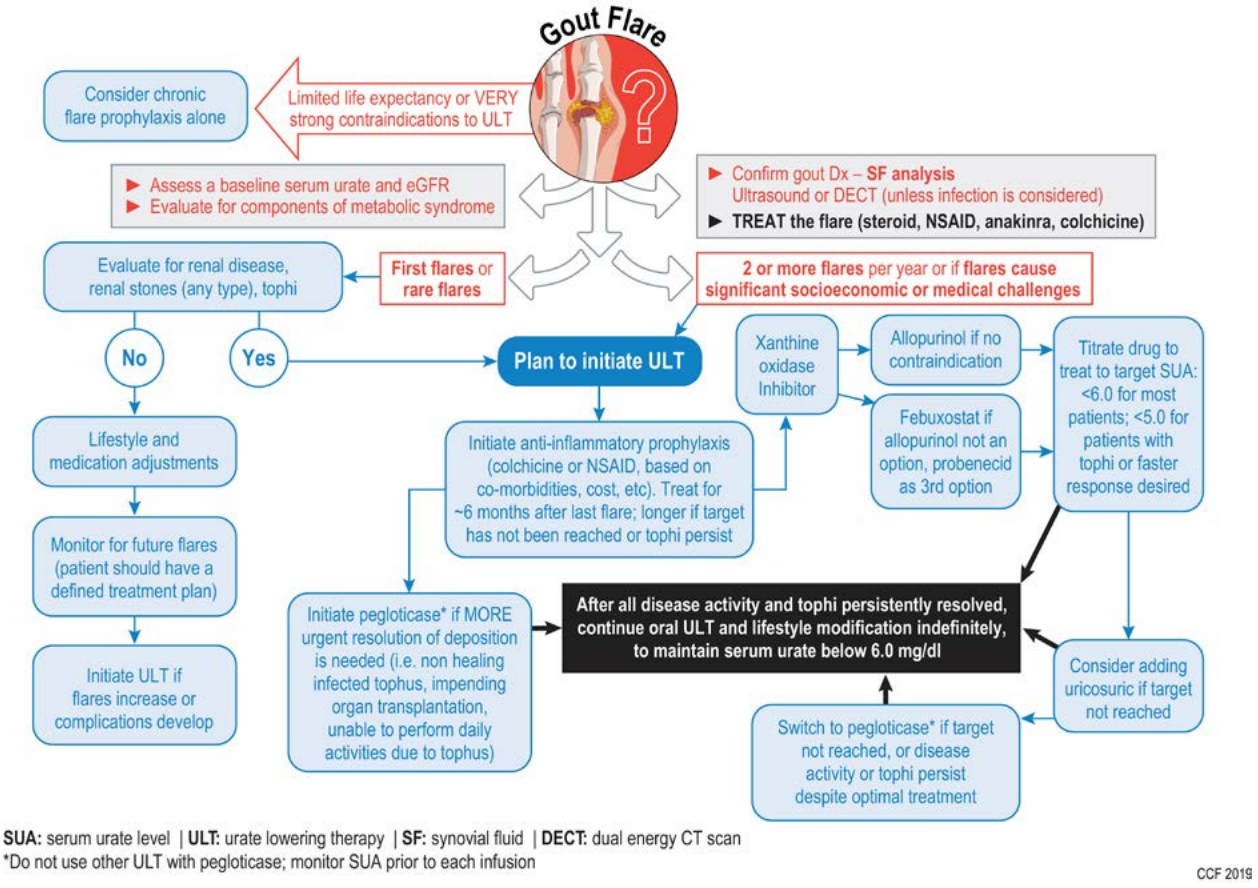

Figure 6: Management of gout: An algorithm[28]

Table II: Treatment of acute gout flares[28]

	Dosing	Duration of treatment
NSAIDs:		
Naproxen	500 mg twice daily	3–5 days
Celecoxib	400 mg twice daily	3–5 days
Indomethacin	50 mg three times a day	5 days
Ibuprofen	800 mg three times a day	5 days
Etoricoxib	120 mg daily	8 days
Corticosteroids:		
Prednisone	0.5 mg/kg or 40 mg daily	2–5 days
Colchicine	0.5–1 mg, followed by 0.5 mg two hours later. Maximum of 6 mg daily.	3 days
Anti-IL-1β biologics:		
Anakinra	100 mg daily	3–5 days
Canakinumab	150 mg SC	1 injection (t =26 days)

Table III: Treatment of established and acute gout[31,32]

	Allopurinol	Colchicine Houdé
Dosing	**Prophylactic treatment of gout and hyperuricaemia**: • 50 mg, 12 hourly; Increase dose as required up to 200–400 mg. • **Treatment of hyperuricaemia**: Initial: 200 mg, 8 hourly. Maintenance: 300–400 mg daily.	**Acute attacks of gout**: • Initial: 0.5–1 mg immediately, followed by 0.5 mg every 2 hours until pain relief is obtained or until vomiting or diarrhoea occurs. • Maximum: 6 mg for a minimum of 3 days, but preferably 7 days, should elapse between courses of gout treatment with colchicine.
Drug interactions	• **Warfarin:** increased risk of bleeding and bruising • **Azathioprine:** increased risk of bone marrow toxicity • **Theophylline:** increases effects by slowing drug metabolism. • **Enalapril (ACE-I):** increased risk for anaphylaxis(rash) and Stevens-Johnson syndrome.	• **Quinidine:** increase the effect of colchicine by affecting elimination • **Itraconazole:** increased effects with fatal side effects in kidney and hepatic dysfunction. • **Verapamil, ketoconazole, clarithromycin, erythromycin, atazanavir, ritonavir, cyclosporine:** increase effects. • **Digoxin and statins** increase the risk of toxicity of the other, rhabdomyolysis including fatality.
Contraindications	• Hypersensitivity to allopurinol or to any of the excipients • Severe renal disorder • Severe hepatic disorder • An acute gout attack • Patients who have exhibited serious adverse effects from the medicine • In children, except those with malignancy • Pregnancy • Lactation	• Hypersensitivity to colchicine or any of its excipients • Patients undergoing haemodialysis • Severe renal impairment (CrCl < 10ml/min) • Severe hepatic impairment • Blood disorders - Myelosuppression - Leukopenia - Granulocytopenia - Thrombocytopenia - Aplastic anaemia • Coadministration with P-glycoprotein inhibitors such as ciclosporin, verapamil, or quinidine in patients with renal or hepatic impairment • Coadministration with strong CYP3A4 inhibitors such as ritonavir, atazanavir, indinavir, clarithromycin, telithromycin, itraconazole, or ketoconazole in patients with renal or hepatic impairment • Pregnancy and lactation
Adverse effects	• Stevens-Johnson syndrome (rash) • Angioedema • Thrombocytopenia • Agitation • Ammonia-like breath odour • Bleeding gums • Joint or muscle pain • Bloody or black, tarry stools • Cloudy urine	• Peripheral neuritis • Neuropathy • Rhabdomyolysis • Hepatic impairment • Rash • Alopecia • Bone marrow depression with agranulocytosis • Aplastic anaemia • Thrombocytopenia • Burning, "crawling", or tingling feeling in the skin • Muscle weakness • Numbness in the fingers or toes (usually mild)

agents (probenecid and lesinurad), and uricases (rasburicase and pegloticase). ULT is normally started several weeks after the resolution of a gout flare, as it is believed that commencing during a flare will exacerbate the current flare. When ULT is started the flare becomes worse, which leads to patients discontinuing treatment.[30]

Treatment of acute gout flares

Treatment with one or more potent anti-inflammatory medications is necessary for the management of acute flares. There are four categories accessible: nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, colchicine, and anti-IL-1β biologics. Since they are all efficient, selecting one should focus on minimising individual risks.[28]

Treatment of established gout

Urate-lowering therapy (ULT)

Guidelines published by the Rheumatologic Society support the idea that urate-lowering is essential for the treatment of established gout.[28] Allopurinol is the oldest available and most used xanthine oxidase inhibitor.[28]

Flare prophylaxis during urate lowering

Patients with gout frequently had more flare-ups during the early stages of urate reduction, most likely because of crystals being released from dissolving urate collections.[28] When feasible, prophylactic anti-inflammatory medication should be supplied to patients in addition to the initial ULT. Low doses of colchicine (0.6 mg once or twice daily) are frequently used, even if other anti-inflammatories may be appropriate for treating acute flares. This may be because colchicine is most likely to be tolerated during the three to nine months following the initial ULT, which is necessary to lower the risk of gout flares below pre-treatment levels.[28]

Conclusion

Gout is a common form of inflammatory arthritis that occurs due to a buildup of uric acid, forming urate crystals in the joints over a long period. The management involves non-pharmacological measures to prevent flareups, that include sufficient rest, reduced intake of sugar-sweetened drinks and general dietary and lifestyle modifications. ULT is essential for the treatment of established gout, with the aim to reduce flare-ups. Acute symptoms can be treated with colchicine, or in severe cases with NSAIDs in combination with glucocorticoids like prednisone.

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