ALL ABOUT GOUT

This material describes clinical studies, clinical reviews, patient resources, and other data from the biomedical literature, and contains general recommendations only.

Specific clinical decisions should be made by the treating clinician based on an individual patient's clinical condition.

Principal author

Dr Leslie Jackowski

Reviewers

Professor Debra Rowett

Professor Catherine Hill

Dr Helen Keen

Associate Professor Philip Robinson

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Table 1. G-CAN* endorsed terms and definitions of the basic elements of gout[1]

Term	Definition
Monosodium urate crystals	The pathogenic crystals in gout (chemical formula $C_5H_4N_4O_3Na$)
Urate	The circulating form of the final enzymatic product generated by xanthine oxidase in urine metabolism in humans (chemical formula $C_5H_3N_4O_3$)
Hyperuricaemia	Elevated blood urate concentration over the saturation threshold
Gout flare	A clinically evident episode of acute inflammation induced by monosodium urate crystals
Intercritical gout	The asymptomatic period after or between gout flares, despite the persistence of monosodium urate crystals
Chronic gouty arthritis†	Persistent joint inflammation induced by monosodium urate crystals
Tophus	An ordered structure of monosodium urate crystals and the associated host tissue response
Subcutaneous tophus	A tophus that is detectable by physical examination
Imaging evidence of monosodium urate crystal deposition	Findings that are highly suggestive of monosodium urate crystals on an imaging test
Gouty bone erosion	Evidence of a cortical break in bone suggestive of gout (overhanging edge with sclerotic margin)
Podagra	A gout flare at the 1st metatarsophalangeal joint

* G-CAN = Gout, Hyperuricemia, and Crystal-Associated Disease Network.

† The G-CAN recommendation is that the label "chronic gout" should be avoided

Table adapted from: Bursill D, Taylor WJ, Terkeltaub R, et al. Gout, Hyperuricemia, and Crystal-Associated Disease Network Consensus Statement Regarding Labels and Definitions for Disease Elements in Gout. Arthritis Care Res (Hoboken) 2019;71:427-34.

EPIDEMIOLOGY, PATHOPHYSIOLOGY AND NATURAL HISTORY[2-8]

Gout is the most common form of inflammatory arthritis that affects adults. The prevalence of medically diagnosed gout in adult Australians may be as high as 5.2%.

Gout is caused by the deposition of monosodium urate (MSU) crystals in joints, connective tissue, cartilage, tendons, bursae, bone, and soft tissue. Clinical disease occurs as a result of the inflammatory response of host tissue to deposited MSU crystals. Note that in relation to gout, the terms urate and uric acid are often used interchangeably. Urate is simply a salt derived from uric acid.

Gout typically presents as an acute, self-resolving, inflammatory mono-arthritis that affects a joint of the lower limbs. Sustained elevation of serum urate levels (hyperuricaemia) is the major risk factor for MSU crystal deposition and development of gout.

Subsequent flares of gout can affect any and multiple joint(s) in the body (polyarticular gout) and can mimic the polyarthritis of rheumatoid arthritis. If inadequately treated, gout is a condition that is both chronic and progressive.

If left untreated, gout can lead to tophi formation, which can cause joint erosion and destruction. A tophus is a subcutaneous nodule consisting of deposits of MSU crystals and chronic granulomatous inflammatory tissue. Tophi represent a high burden of monosodium urate (MSU) crystal deposition.

In addition to joint and bone destruction, tophi can also entrap nerves, causing compressive neuropathy, such as carpal tunnel syndrome. Superficial tophi are also susceptible to infection, especially if the overlying skin is ulcerated. Tophi can be surgically removed, but delayed surgical wound healing is not uncommon, particularly in patients with accompanying diabetes mellitus or peripheral vascular disease. Delayed wound healing increases the risk of infection.

In the absence of pharmacotherapy to lower serum urate levels, advanced gout typically occurs more than 10 years after initial presentation with an acute flare. The tophus is the pathognomonic feature of advanced gout.[8]

Gout is associated with a high risk of cardiovascular disease and mortality. Gout is also associated with the metabolic syndrome, hypertension, and chronic kidney disease (CKD).[2-6] It is not known if gout causally contributes to these comorbid disorders.[8] Recent data suggest that hyperuricaemia is likely the effect and not the cause of CKD or CKD progression.[9]

The bottom line

- Gout is a common form of arthritis.
- Gout is cause by an inflammatory response of host tissue to deposited monosodium urate crystals.
- Without pharmacotherapy, advanced gout typically occurs more than 10 years after initial presentation with an acute flare.

PURINES, HYPERURICAEMIA AND GOUT[2-6]

Purines

The story starts with the metabolism of the purine nucleotides (e.g. AMP and GMP, the nucleotides that form part of DNA and RNA), and the formation of uric acid

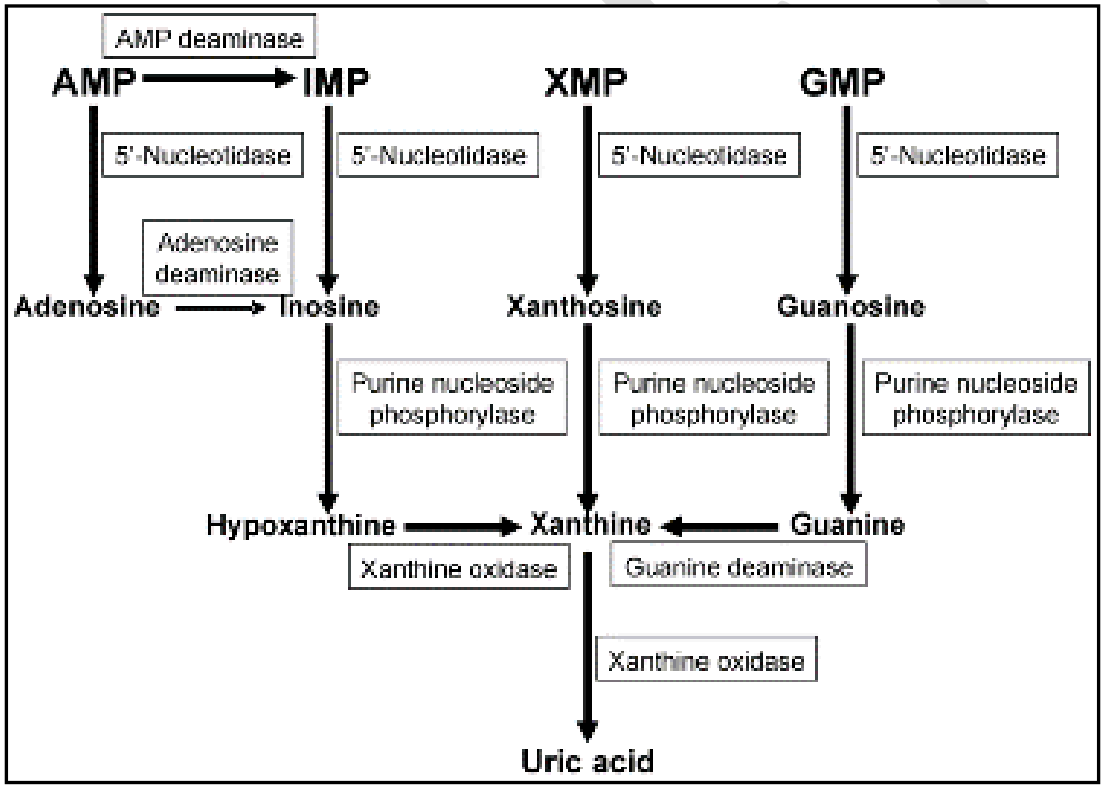

Figure 1. Metabolic pathways of uric acid formation from nucleotide monophosphates
AMP = adenosine monophosphate; IMP = inosine monophosphate; XMP = xanthosine monophosphate, GMP = guanosine monophosphate.

Reproduced from: Toshihisa Ishikawa et al. Metabolic Interactions of Purine Derivatives with Human ABC Transporter ABCG2: Genetic Testing to Assess Gout Risk. Pharmaceuticals 2013, 6(11), 1347-1360

Hyperuricaemia

Gout has traditionally been considered a disorder of purine metabolism. However, urate overproduction is the major cause of hyperuricaemia in only a small

proportion of individuals with gout. Hyperuricemia is due to renal under-excretion of urate in 90% of cases and to overproduction in 10%, although there is often an overlap of both.[10] In the past decade, it has become apparent that reduced urate excretion, both in the gut and the kidneys, has a key role in the pathogenesis of hyperuricaemia and gout (see Figures 3 and 4 below).[2,11-13]

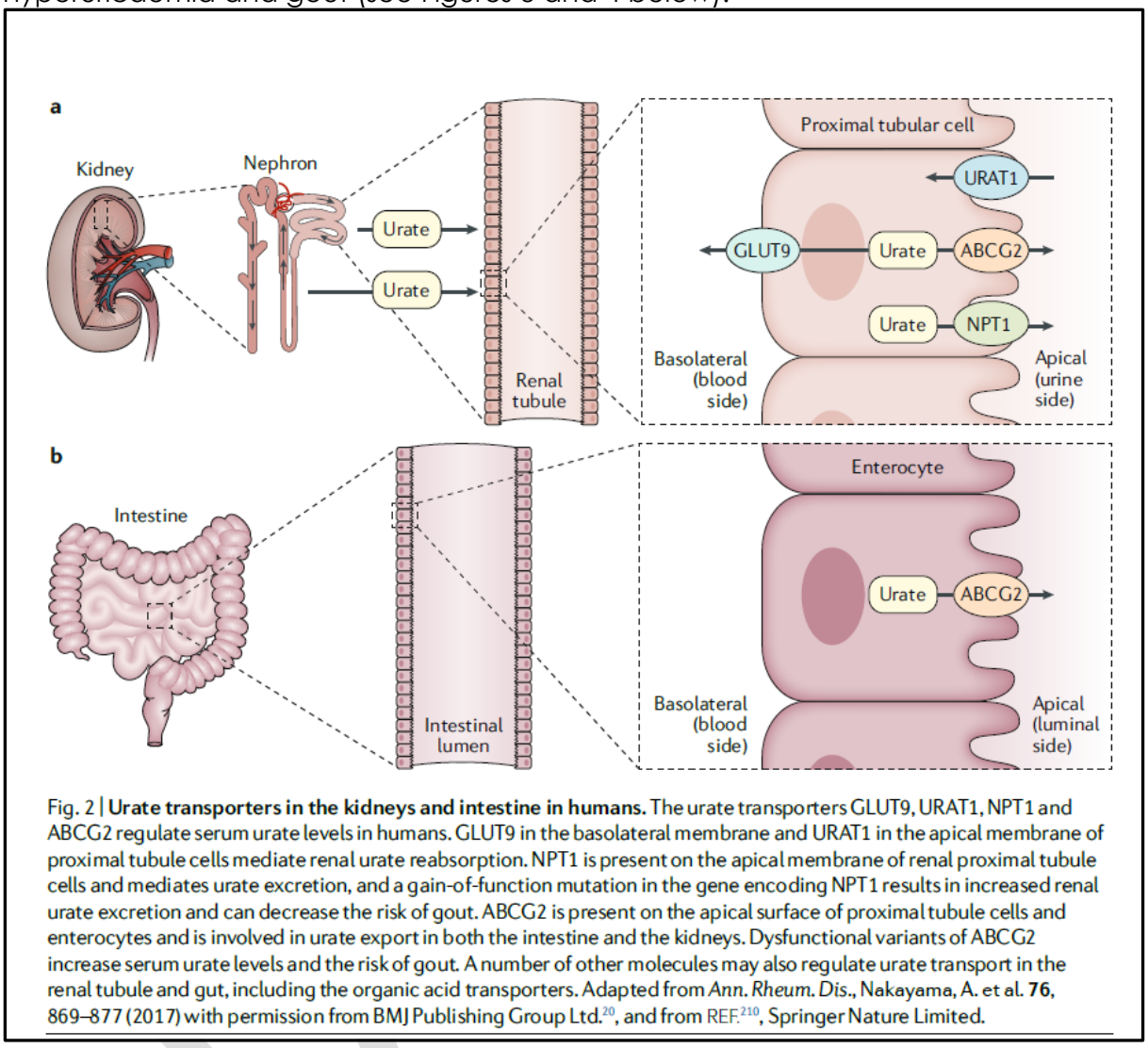

Fig. 2 | **Urate transporters in the kidneys and intestine in humans.** The urate transporters GLUT9, URAT1, NPT1 and ABCG2 regulate serum urate levels in humans. GLUT9 in the basolateral membrane and URAT1 in the apical membrane of proximal tubule cells mediate renal urate reabsorption. NPT1 is present on the apical membrane of renal proximal tubule cells and mediates urate excretion, and a gain-of-function mutation in the gene encoding NPT1 results in increased renal urate excretion and can decrease the risk of gout. ABCG2 is present on the apical surface of proximal tubule cells and enterocytes and is involved in urate export in both the intestine and the kidneys. Dysfunctional variants of ABCG2 increase serum urate levels and the risk of gout. A number of other molecules may also regulate urate transport in the renal tubule and gut, including the organic acid transporters. Adapted from *Ann. Rheum. Dis.*, Nakayama, A. et al. **76**, 869–877 (2017) with permission from BMJ Publishing Group Ltd.[20], and from REF.[210], Springer Nature Limited.

Figure 2. Renal and gastrointestinal urate transport and excretion.
Reproduced from Dalbeth N et al. Gout: Nature Reviews Disease Primers 2019;5:69. Available at: https://www.nature.com/articles/s41572-019-0115-y

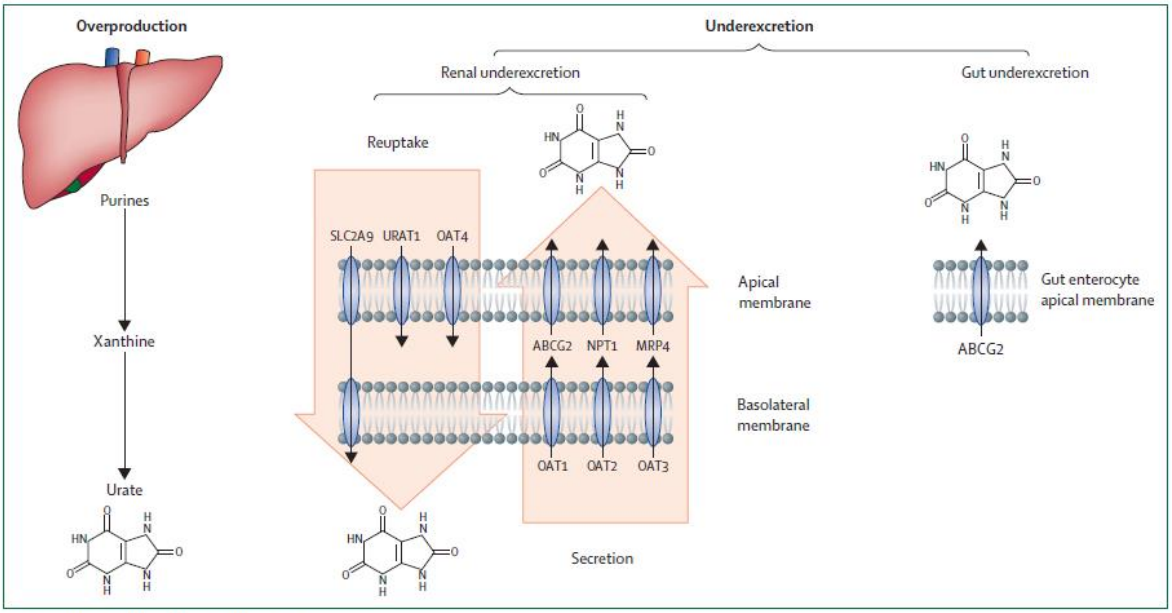

Figure 1: **Mechanisms of hyperuricaemia**
On the left, overproduction of urate through the purine degradation pathway is a minor contributor to serum urate concentrations. Underexcretion of urate is the dominant cause of hyperuricaemia in people with gout. In the centre, major components of the renal proximal tubule urate transportasome are clustered according to their role as reuptake transporters of urate from filtered urine or as secretory transporters. On the right, in the gut, variants in ABCG2 with reduced function block excretion and contribute to under-excretion.

Figure 3. Mechanisms of hyperuricaemia[8]
Reproduced from Dalbeth N et al. Gout. The Lancet 2016;388(10055):2039-2052.

Hyperuricaemia is generally defined as a serum urate level > 0.41mmol/L at 37 degrees C. However, MSU crystals may form at lower urate concentrations, particularly in tissues with a low temperature or acidic pH.

There is a causal relationship between hyperuricaemia and gout. Hyperuricaemia can occur by reduced urate excretion or increased urate formation. Chronic kidney disease (CKD) and diuretics may contribute to hyperuricaemia by decreasing urate excretion. Sudden changes in serum urate levels (up or down) may precipitate or exacerbate acute gout (mechanism uncertain), and gout can occur in patients with a normal serum urate level i.e. without hyperuricaemia

Obesity, and increased consumption of alcohol, fructose, meat, and seafood, have all been shown to be associated with hyperuricemia.[14,15]

Serum urate concentration remains the only proven risk factor for urate crystal formation. Only about 20% of individuals with a serum urate greater than 0.42 mmol/L develop gout, but the incidence of gout increases with increasing urate levels.

Table 1: Relationship between serum urate concentration and cumulative incidence of gout[6]	
Serum urate (mmol/L)	**Five-year cumulative incidence (%)**
<0.36	0.5
0.36-0.41	0.6
0.42-0.47	2.0
0.48-0.53	4.1
0.54-0.59	19.8
>0.60	30.5

Figure 4. Incidence of gout and serum urate concentration
Adapted from Campion et al. Asymptomatic Hyperuricemia. Risks and consequences in the Normative Aging Study. Am J Med 1987;82(3):421-426.

Although serum urate levels are causally associated with gout, there is no definitive evidence that hyperuricaemia causally contributes to comorbid disorders such as atherosclerosis, CKD, hypertension, and metabolic syndrome. There is, however, some evidence that hyperuricaemia might causally contribute to worse outcomes in existing cardiovascular and renal disease.[8]

In asymptomatic individuals, screening for hyperuricaemia is not generally recommended, and asymptomatic hyperuricaemia does not require drug therapy. However, in some individuals with risk factors for gout, such as family history, renal disease, or use of diuretics, serum urate testing may identify hyperuricaemia.

The bottom line

There is a causal relationship between hyperuricaemia and gout, and the incidence of gout increases with increasing urate levels.

The major cause of hyperuricaemia is reduced renal and GI under-excretion rather than urate overproduction.

High urate levels may also increase the risk of kidney stones and are associated with several other comorbidities.

DIET

There are many misconceptions about diet and gout. However, several studies have shown that people with gout are more likely to eat certain foods. These foods contain high levels of substances called purines that can be made into urate in the body.

High-Purine Foods Include:

- Alcoholic beverages (all types)
- Some fish and shellfish, including anchovies, sardines, herring, mussels, mackerel, codfish, scallops, trout and haddock
- Some meats, such as bacon, turkey, veal, venison and organ meats like liver, kidneys, and heart

Moderate-Purine Foods Include:

- Meats, such as beef, chicken, duck, pork and ham
- Shellfish, such as crab, lobster, oysters and shrimp

Consistent with findings that gout is not primarily a disorder of urate overproduction, there is only limited evidence that avoiding purine-rich foods can successfully reduce gout attacks. Not all purine-rich foods are thought to cause gout, and a number of vegetables (asparagus, mushrooms, cauliflower and spinach) are rich in purines but appear less likely to cause gout than diets containing meat and shellfish. Low-fat dairy foods may lower urate levels and help manage gout. For most people with gout, a healthy balanced diet is all that is needed, together with medicines to reduce urate levels.[16]

The bottom line

Dietary management of gout is very restrictive and of limited benefit. A healthy balanced diet and medication is usually enough to manage gout.

INITIATION AND RESOLUTION OF GOUT FLARES

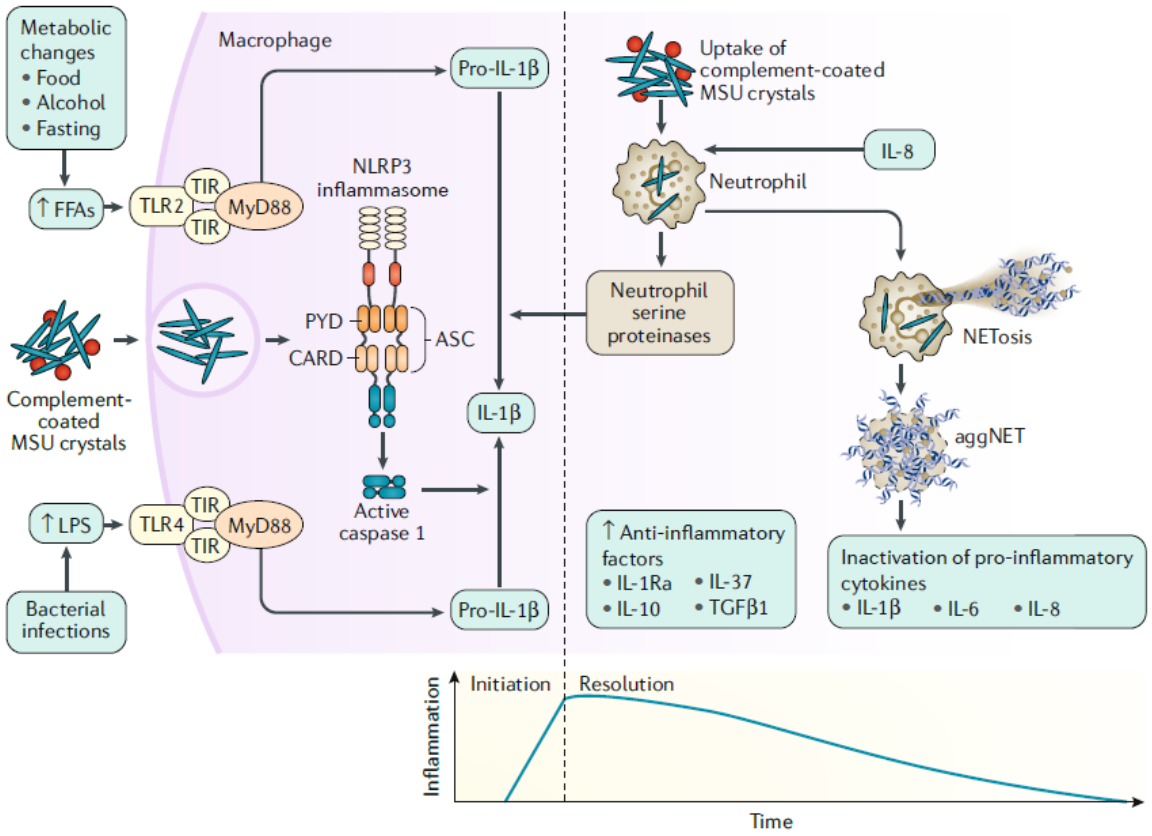

Fig. 4 | **Mechanisms of initiation and resolution of the gout flare.** Acute joint inflammation is initiated by the production of pro-inflammatory cytokines, in particular IL-1β, the production and release of which is a multistep process. IL-1β gene transcription and production of pro-IL-1β is induced by activation of Toll-like receptor 2 (TLR2) or TLR4. Free fatty acids (FFAs; such as palmitic acid (C16:0)) that accumulate due to metabolic alterations or lipopolysaccharide (LPS) released during bacterial infection can trigger TLR2 or TLR4 signalling, respectively, and thereby induce the intracellular accumulation of pro-IL-1β. The uptake of monosodium urate (MSU) crystals activates the NLRP3 inflammasome, resulting in activation of caspase 1, which enzymatically processes pro-IL-1β to bioactive IL-1β. IL-1β signalling initiates the production and secretion of pro-inflammatory mediators, such as IL-6 and IL-8. IL-8 recruits neutrophils to the joint cavity and thereby amplifies the gout flare. After some time, the gout flare self-resolves through the production of anti-inflammatory factors in the joint, such as interleukin-1 receptor antagonist (IL-1Ra), IL-10, IL-37 and transforming growth factor β1 (TGFβ1), which suppress the pro-inflammatory factors. Furthermore, the large numbers of neutrophils in the joint eventually die, either by normal cell turnover or after uptake of MSU crystals. These dying neutrophils release their chromosomal DNA (termed neutrophil extracellular traps (NETs)), a process called NETosis. Aggregated NETs (aggNETs) sequester and thereby inactivate several pro-inflammatory mediators, which leads to resolution of the gout flare. MSU, monosodium urate; TIR, Toll/interleukin-1 (IL-1) receptor domain.

Figure 5. Initiation and resolution of gout flares.
Reproduced from Dalbeth N et al. Gout: Nature Reviews Disease Primers 2019;5:69. Available at: https://www.nature.com/articles/s41572-019-0115-y

The bottom line

- A gout flare represents an acute inflammatory response to deposited MSU crystals. Cytokine IL-1β has a pivotal role in the initiation of the gout flare.
- The gout flare is (usually) a self-limiting inflammation - the redness, joint swelling and severe pain usually disappear after 7–10 days
- A tophus is a chronic inflammatory granulomatous response to deposited crystals.

DISEASE PROGRESSION

As depicted in the following figure, the clinical manifestation of gout progression involves:

- asymptomatic hyperuricaemia;
- recurrent acute flares interspersed between asymptomatic intercritical periods; and
- over time, the development of chronic gouty arthritis and tophaceous gout

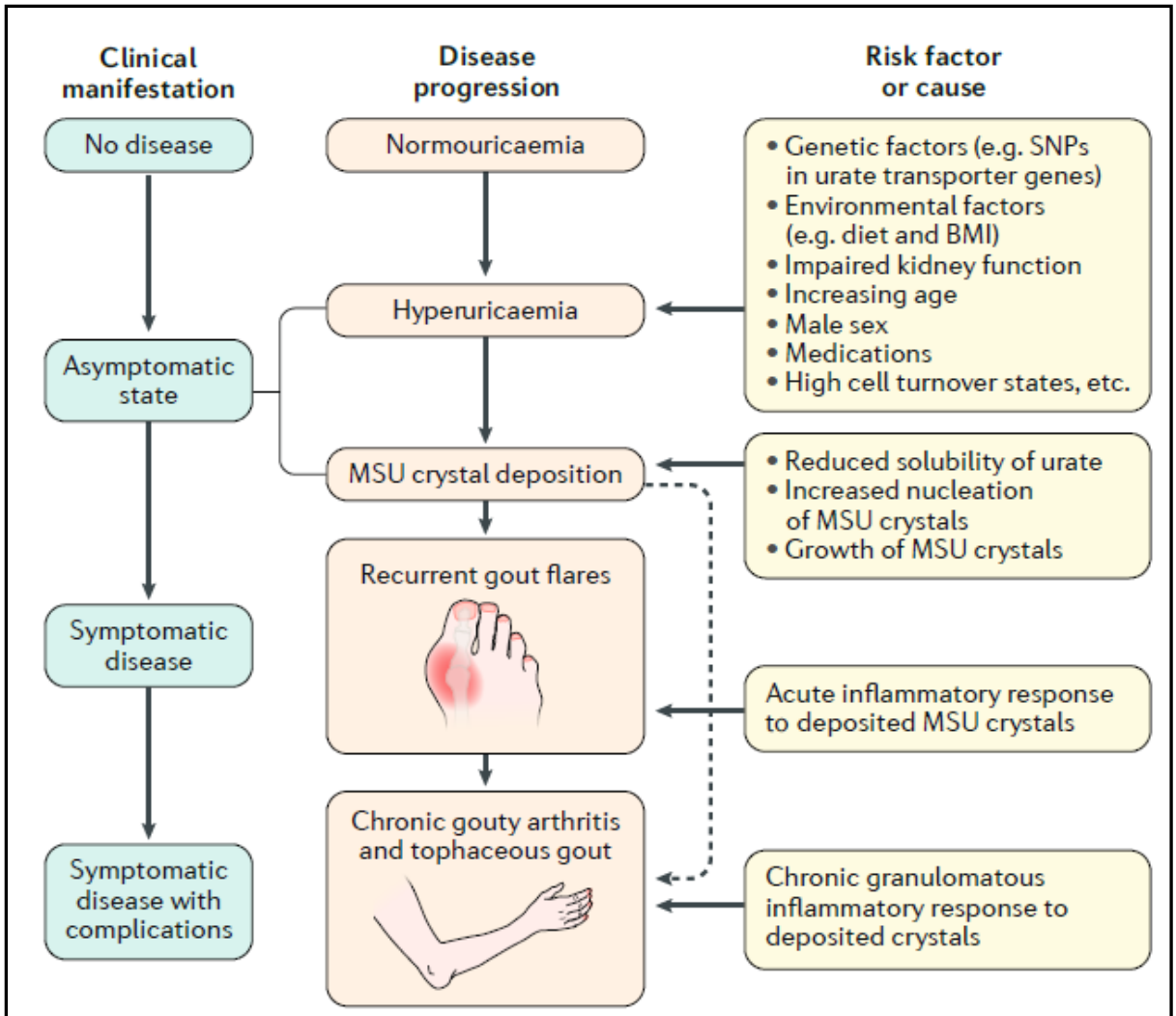

Fig. 1 | **Disease progression in gout.** The transition from normouricaemia to clinically evident gout occurs in a number of steps. The first step is the development of hyperuricaemia, which can be caused by various factors, including genetic variants, chronic kidney disease, high body mass index (BMI), medications and dietary factors. In some individuals with hyperuricaemia, monosodium urate (MSU) crystal deposition occurs, and in some individuals with MSU crystal deposition, the clinical manifestations of gout (gout flares, chronic gouty arthritis and tophaceous gout) occur. Factors that contribute to the transition from hyperuricaemia to clinically evident gout are less well understood. SNP, single-nucleotide polymorphism.

Figure 6. Disease progression in gout.
Reproduced from Dalbeth N et al. Gout: Nature Reviews Disease Primers 2019;5:69. Available at: https://www.nature.com/articles/s41572-019-0115-y

The bottom line

- If inadequately treated, gout is a progressive and chronic disease.
- If gout is not well managed, the time between flares may get shorter, the attacks more severe, and more joints may be affected
- Repeated gout flares can form swollen growths called tophi. Urate crystals and tophi can cause permanent damage to joints over time

DIAGNOSIS[2-7]

Before recommending urate lowering drug therapy, which is almost always required lifelong, the diagnosis of gout should be certain or near certain. A clinical diagnosis can be made with a good degree of certainty in patients with a reliable history of recurrent acute monoarthritis of the first metatarsophalangeal joint (podagra).[4] A definitive diagnosis depends on identification of monosodium urate crystals in a tophus or the synovial fluid of an inflamed joint. Correctly diagnosing gout and differentiating it from other inflammatory arthritides, such as rheumatoid arthritis, septic arthritis, and inflammatory episodes of osteoarthritis is important, because treatment of these conditions differ.[7]

Typical Presentation

An acute episode of inflammation (gout flare) with intense sudden-onset pain, redness, tenderness and swelling involving only one joint of the lower limbs, especially the first metatarsophalangeal (podagra) and tarsal joints, is the paradigm of gout presentation.[17] Gout flares are mostly self-limiting, especially early in the disease. Nodules indicating tophaceous deposits are typically located at the first metatarsophalangeal joint, other joints and tendons of the foot and ankle, including the Achilles tendon, the prepatella bursa, the olecranon bursae and helix of the ear.

Atypical presentation

Atypical presentation may include the development of tophi without accompanying flares, which may be observed in patients who are receiving corticosteroids for other conditions.[2]

A first presentation as a flare involving multiple joints is also atypical. Atypical manifestations of gout occur more frequently in women and elderly individuals. The accuracy of diagnosis in the emergency room falls from 85% in patients with typical (monoarticular) flares to 45% in those with atypical (polyarticular) flares).[2]

Clinical diagnosis and arthrocentesis (joint aspiration)

Relying on clinical features without crystal identification may risk committing someone to lifelong drug therapy for a disease they do not have.[18] Conversely, may

miss less typical presentations. Even when crystals are present, another diagnosis (most importantly septic arthritis) may coexist.

A clinical diagnosis is appropriate in situations that are clinically unambiguous and without a significant probability of infection. For example, arthrocentesis would not be essential in a patient with podagra, a history of relevant risk factors, and no sign of an overlying wound. This patient may be considered as having gout and treated appropriately.[7]

When a clinician judges that testing is needed to confirm a presumptive diagnosis of acute gout, the preferred approach is to obtain synovial fluid for white blood cell count and polarised light microscopy to identify urate crystals. It provides a definitive diagnosis.[7] Gram stain and culture can identify septic arthritis, and synovial fluid microscopy can differentiate gout from pseudogout (calcium pyrophosphate deposition disease).[4]

Although identification of MSU crystals in synovial fluid from an inflamed joint provides a definitive diagnosis of gout, most patients are initially seen in primary care or emergency medicine, where synovial fluid analysis is rarely performed. Also, accurate detection of urate crystals requires a polarizing microscope and a trained operator.[7]

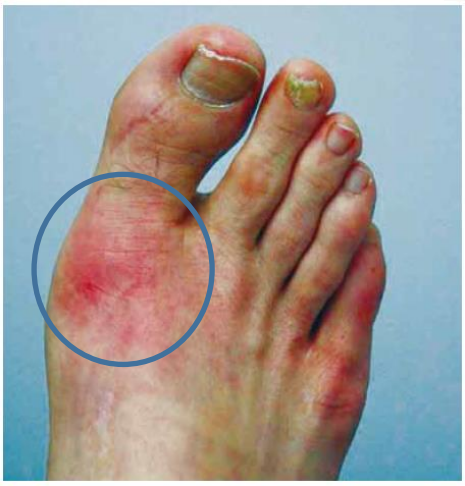

Figure 7. Acute onset of pain, redness and swelling in the great toe MTP joint.
Reproduced from McGill, N. How to Treat: Gout. Australian Doctor February 2015.[18]

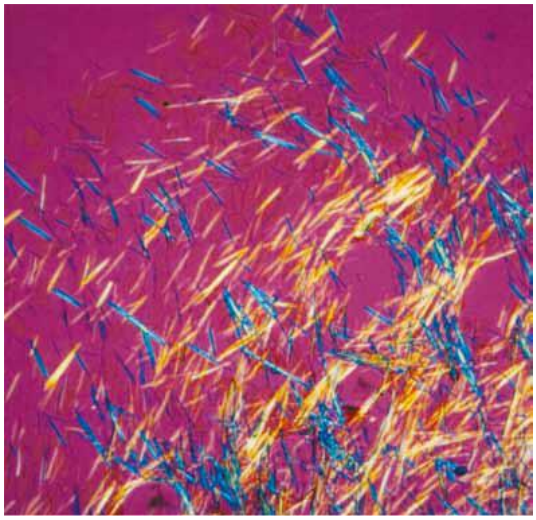

Figure 8. Photomicrograph of monosodium urate monohydrate (urate) crystals.
Viewed under compensated polarised light microscopy collected in an aspirate from a tophus. Monosodium urate crystals are needle shaped and birefringent. Crystals of calcium pyrophosphate (pseudogout) are rhomboid shaped.
Reproduced from McGill, N. How to Treat: Gout. Australian Doctor February 2015.[18]

Imaging

Imaging tools can help establish a diagnosis of gout when histological crystal diagnosis is unable to be established, and also assess the burden of inflammatory and structural disease. Some imaging features can aid diagnostically in differentiating gout from other inflammatory arthritis conditions, but these may be less useful in early disease when the need is often greater. Some imaging modalities can also be used to monitor treatment response. The imaging techniques that currently have a role in the imaging of gout include conventional radiography, ultrasound, computed tomography, dual energy computed tomography, magnetic resonance imaging, and nuclear medicine.[19]

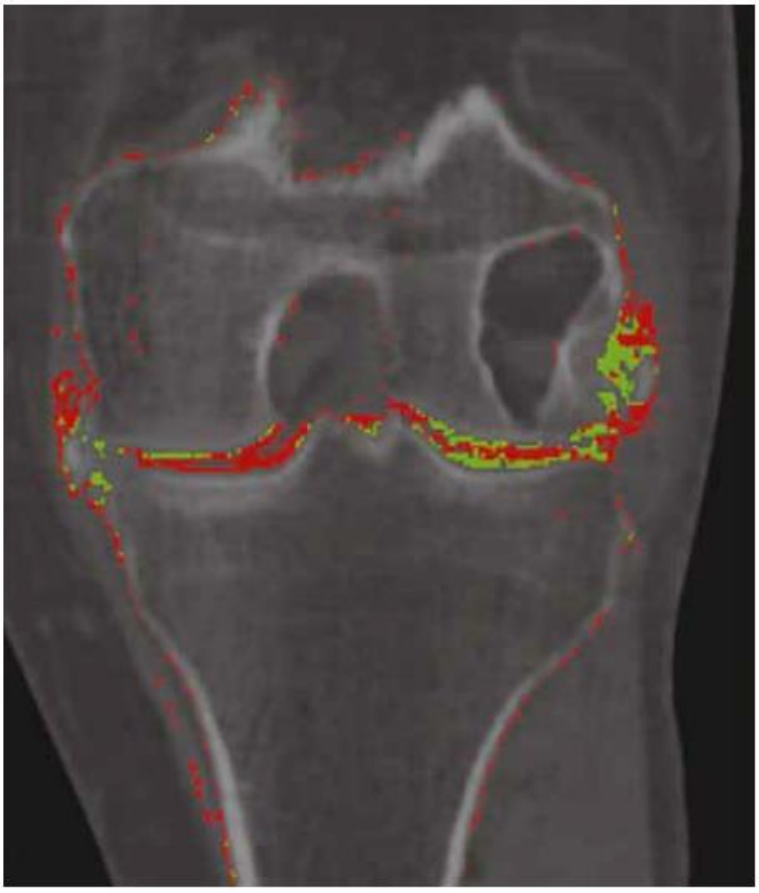

Figure 9. Dual-energy CT of the knee in a patient with crystal-proven gout.
The green pixels represent urate crystals. The patient also had crystal-proven calcium pyrophosphate deposition and osteoarthritis in the same knee.
Reproduced from McGill, N. How to Treat: Gout. Australian Doctor, February 2015.[18]

Differential diagnosis

There are many different forms of arthritis. A list of these conditions along with differentiating signs, symptoms and tests are provided in Appendix 2.

The bottom line

- A definitive diagnosis of gout is made by demonstrating MSU crystals in the synovial fluid of an inflamed joint or in a tophus.
- Gout may present in atypical ways
- Important to exclude other causes of arthritis and/or another co-existing arthritis (such as septic arthritis).

COMPLICATIONS AND COMORBIDITIES

Joint, bone and tendon destruction may occur in severe uncontrolled disease. Gout is associated with the metabolic syndrome, hypertension, atherosclerosis, CKD,

obesity, and nephrolithiasis. Gout is also associated with a high risk of cardiovascular disease and mortality, and traditional CV risk calculators may underestimate the true risk of cardiovascular disease in individuals with gout. A presentation of gout provides an opportunity to assess and treat serious disorders, such as obesity, glucose intolerance, hypertension, dyslipidaemia, renal impairment, and alcohol excess.[2-6,8]

PRACTICE GUIDELINES

A review of clinical guidelines and barriers to the management of gout found considerable inconsistencies in recommendations in current guidelines, contributing to uncertainty in treatment (see also Appendix 1).[6] The review noted that the American College of Physicians guidelines suggest that the absence of high-quality evidence supporting a 'treat-to-target' approach means that a 'treat-to-avoid-symptoms' approach is more supportable. This major discrepancy with other guidelines implies that the absence of strong evidence indicates lack of efficacy. This does not reflect clinical practice realities.[6] Similarly, another review of clinical guidelines and consensus statements found inconsistent recommendations for some aspects of management, including the timing of initiation of urate lowering therapy.[20]

Most guidelines endorse a lower target serum uric acid for severe gout, but there is an absence of a consensus definition of severity encompassing frequency of attacks, number of joints involved, presence of tophi, or comorbidities.[6]

The Australian Therapeutic Guidelines recommend urate lowering therapy for all patients with diagnosed gout, while most evidence based guidelines recommend that urate lowering therapy should be reserved for patients with more severe disease (e.g. tophaceous gout), those with 2 or more flares per year, and those with comorbidities such as CKD).[6] The benefits of earlier initiation of urate lowering therapy, including in individuals with hyperuricaemia and asymptomatic deposition of monosodium urate crystals, are unknown.[8]

MANAGEMENT

Minimise exacerbating factors such as obesity, alcohol, medications (e.g. diuretics) and diet. However, there is little evidence that specific lifestyle changes, such as dietary restrictions, lead to improved outcomes for patients with gout. Nevertheless, many of these lifestyle changes can lead to general health benefits. Most patients with gout will need medication.

THE 6 GENERAL PRINCIPLES OF GOUT MANAGEMENT[2-6,8]

1. Lifestyle modifications;
2. Treat gout flares;
3. Long term urate lowering therapy;

4. Prophylaxis to prevent flares from initiation/titration of urate lowering therapy;
5. Screening and management of comorbidities associated with gout; and
6. Patient and healthcare provider education

Long term success in maintaining sub-saturating serum urate levels results in cessation of gout flares, resolution of tophi, and improvement in patient physical function and quality of life.[21]

Despite the availability of effective urate lowering therapies, gout management remains poor, with very low rates of urate lowering therapy initiation, continuation, and achievement of serum urate targets. The most important question about gout management may be how to improve the long-term use of effective urate lowering therapy. Effective strategies that address both clinician and patient barriers remain an unmet need. Pharmacy-led or nursing-led models of care for people with gout show great promise to ensure understanding of the rationale for urate lowering therapies, adequate dosing, and the need for continuous treatment.[8]

Each of the 6 principles of management are discussed below.

1. Lifestyle modifications

- It's important to maintain a healthy weight.
- Excess alcohol intake (all types, especially beer) and binge drinking can trigger gout.
- People with gout should be safe to eat purine-rich vegetables like spinach or mushrooms.
- Low-fat dairy foods may lower uric acid levels and help manage gout.
- Consuming large amounts of fructose, a type of sugar, can increase urate levels in the blood. It is found in high levels in soft drinks sweetened with corn syrup, processed foods and fruit juices.
- High intake of meat (particularly red meat and offal, such as liver, kidneys and heart) and seafood (particularly shellfish, scallops, mussels, herring, mackerel, sardines and anchovies) are associated with increased uric acid levels.

Because dietary management of gout is so restrictive and of limited benefit, medication is usually the best way to treat gout.

2. Treat acute flares

During an attack, rest the affected joint and apply ice packs or cold compresses (cloth soaked in ice water and wrung out) to the affected spot.[22]

Goal is symptom relief with colchicine, NSAIDs, or intra-articular/systemic steroids. Each agent can be used with either/both of the other two. **These medications relieve symptoms, but they do not reduce serum urate levels or prevent progression of the disease.**

Low dose colchicine commenced within 12 hours of a flare (1.2 mg immediately followed by 0.6 mg after 1 hour) is as effective as high dose (1.2 mg immediately followed by 0.6 mg hourly for 6 hours) and is associated with substantially fewer adverse effects, particularly gastrointestinal. Thus, low dose colchicine is the preferred option.[8] Because of the colchicine formulation in Australia (0.5 mg tablet), that means 1.0 mg immediately followed by 0.5 mg after 1 hour.

Use full dose NSAIDs for the shortest possible time, with a PPI for gastroprotection for those at high risk of gastrointestinal complications.[3,8] Avoid NSAIDs in CKD and CHF. Indomethacin is commonly used, although there is no evidence to suggest that it is more effective than other NSAIDs.[23] NSAIDs are equally effective as a class, regardless of choice of the individual drug.[23]

Systemic or intra-articular corticosteroids are also effective agents for management of a gout flare. Corticosteroids have been shown to be as effective as NSAIDs for managing gout, with fewer adverse effects.[23] A randomized double-blinded controlled trial showed that oral prednisone and indomethacin were similarly effective for the management of acute gout in patients presenting to the emergency department.[24] Some, but certainly not all, sources suggest that corticosteroids should be restricted to patients who do not respond to, or cannot tolerate, NSAIDs or colchicine.[3]

Avoid analgesic (high) doses of aspirin during a flare as it may change serum urate concentration and worsen/prolong an attack. Do not stop low-dose aspirin for secondary prevention of cardiovascular events. Aspirin is discussed in more detail later in this document.

A cytokine modulator called anakinra (Kineret) is sometimes used in the US to relieve symptoms of an acute flare. However, this medication is neither FDA nor TGA approved for the treatment of gout. Anakinra is TGA approved for the treatment of rheumatoid arthrirtis.[22]

3. Long term urate lowering therapy (ULT)

Goal is to reduce recurrence, progression and complications of gout.

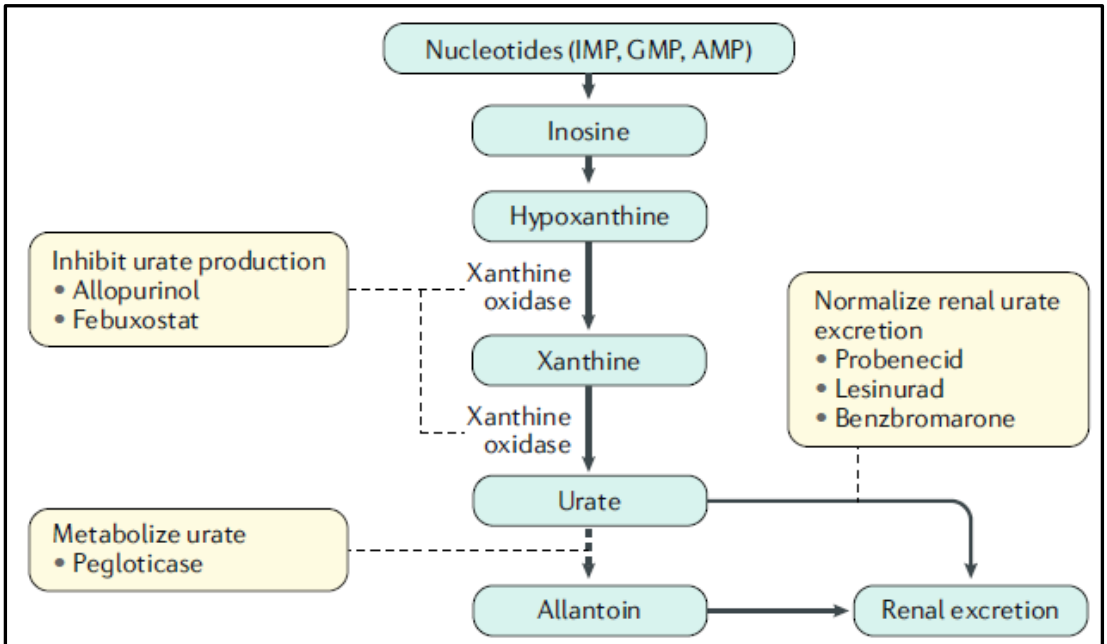

Fig. 8 | **Mechanism of action of urate-lowering drugs currently used for gout treatment.** Various agents can be used to block urate production (xanthine oxidase inhibitors, such as allopurinol and febuxostat), increase the renal excretion of urate (uricosuric agents, such as probenecid, lesinurad and benzbromarone) or metabolize urate to soluble allantoin (for example, the recombinant pegylated uricase pegloticase).

Figure 10. Urate lowering medications in gout.
Reproduced from Dalbeth N et al. Gout: Nature Reviews Disease Primers 2019;5:69. Available at: https://www.nature.com/articles/s41572-019-0115-y

3a. Medications

Allopurinol, probenecid, feboxustat, and lesinurad are all used as urate lowering drugs in Australia. ULT has been traditionally started after a flare has subsided, but a systematic review of three trials showed that initiation of ULT during an acute flare did not prolong the length or severity of the flare.[25] Similarly, a 2021 meta-analysis of the clinical efficacy of urate-lowering therapy in acute gout (6 RCTs with 557 patients) found that: (i) ULT in acute gout may not aggravate the pain; (ii) ULT at the initial stage of an acute gout attack reduces serum uric acid levels and improves medication compliance in patients; and (iii) ULT in acute gout is not associated with an increased risk of gout flares.[26]

ULT should not be stopped during gout flares, and American College of Rheumatology guidance supports starting ULT during a flare.[3,27]

Allopurinol is the recommended first line agent.[27] When initiating allopurinol, patients should be closely monitored for hypersensitivity syndrome (eosinophilia, dermatitis, and multisystem failure).[4] In populations where HLA-B*5801 positive people are at high risk for severe allopurinol hypersensitivity reaction (e.g. Koreans, Han Chinese, Thai, and African Americans), HLA-B*5801 screening should be considered.[27]

Because flares can be triggered by rapid decreases in urate, start urate lowering therapy with a low dose (no more than 100 mg daily) and gradually titrate the dose by 50-100 mg daily at monthly intervals to reduce the risk of gout flares during the initiation phase.

A 2021 meta-analysis found that all urate-lowering medications were effective in achieving target serum urate levels at month 6 compared with placebo in hyperuricaemic patients with gout. Lesinurad in combination with febuxostat or allopurinol was effective in lowering serum urate levels in patients with an inadequate response to xanthine oxidase inhibitor monotherapy, but possibly with a higher risk of adverse events.[28]

3b. Target urate levels

Treat to target urate concentrations:

- < 0.36 mmol/l (6 mg/dl)
- < 0.30 mmol/l (5 mg/dl) for patients with a large urate crystal load, as evidenced by the presence of tophi, erosions, or chronic joint deformity due to gout

All patients taking urate lowering therapy require regular monitoring of renal function and serum urate level to ensure that the dose is appropriate.[3] Monitor renal function at baseline and every 3 months in the first year of urate lowering therapy, and yearly after that.[3] Treatment to prevent gout flares and to lower urate levels is challenging in patients with advanced chronic kidney disease (CKD) and is discussed in detail in Appendix 3.

There is good evidence that achieving a serum urate level to < 0.36 mmol/l results in acute gout attacks becoming less frequent over time (if the serum urate target is maintained).[29]

Measure serum urate:

- at baseline (generally sampled 2–4 weeks after flare resolution, as urate level may be lower during flares)
- every month during dose titration until target reached
- every 6 months during maintenance

3c. Non-adherence/failure to reach target

Adherence may be viewed from the perspective of patient adherence to management, or clinician adherence to best evidence-based practice (which may or may not be present in a particular clinical guideline). In addition to traditional risk factors such as adverse events, adherence should be considered in terms of healthcare disparities and therapeutic inertia.[30]

Non-adherence to pharmacotherapy is an important issue in patients with gout.[31-34]. Treatment is prolonged (perhaps lifelong) and the patient is asymptomatic for the great majority of the time.[21] In a study that assessed use of allopurinol in a managed

care setting, only 18% of patients who initiated treatment complied well with therapy over 24 months of follow-up.[32]

A 2021 review found that adherence to gout treatment continues to be suboptimal as evidenced in multinational meta-analyses. Successful methods of improving adherence include (i) using non-physician providers to coordinate urate lowering therapy titration and monitoring serum urate, and (ii) having more frequent outpatient visits focusing on direct patient care and education.[30]

Urate lowering therapy is usually continuous and indefinite to maintain target urate levels and remain clinically effective.[21] The rationale and importance of ongoing therapy should be emphasised in patient education, initially and over the course of therapy to reduce non-adherence.[21] Patients often understand the analogy of long term treatments required for hypertension or hyperlipidaemia.[6]

If a patient fails to reach or maintain their target serum urate level, consider the following:[18]

- Discuss adherence and adverse events with the patient. If serum urate results fluctuate, adherence may be the problem. Consider use of a dosing device to make it easier for the patient to comply.
- Progressively increase the dose of allopurinol in a stepwise fashion. The serum urate should be measured at each allopurinol dose change (serum urate stabilises within 1-2 weeks of a dosage change) to confirm compliance and to determine the optimal dose. Maximum dose of allopurinol is 900 mg daily, and higher doses rarely further lower urate levels.
- Add a uricosuric medication to the optimal dose of allopurinol.

3d. Duration of urate lowering therapy

Flares may continue even when serum urate is <0.36 mmol/L while urate deposits in tissues, such as tophi, resolve. Once the serum urate is below target, gout flares may continue for up to 12–18 months. They should become less frequent over time if the serum urate target is maintained, and will eventually stop.[5]

If urate lowering therapy is ceased, serum urate levels will increase.[6] Low level evidence suggests that some patients with serum urate levels less than 0.42 mmol/L may be able to stop urate lowering treatment after about 5 years.[23] However, the majority of patients who achieve control of gout with long term urate lowering therapy will have recurrent symptoms and/or tophi if treatment is stopped.[21]

4. Prophylaxis to prevent flares from initiation/titration of urate lowering therapy

Unless contraindicated, flare prophylaxis with colchicine or an NSAID is recommended for at least the first 6 months of urate lowering therapy. 0.5 to 0.6 mg colchicine once or twice a day is first-line option for anti-inflammatory prophylaxis. Although low-dose NSAIDs are frequently used and recommended as second-line agents for prophylaxis, there is a paucity of data.[8] If these anti-inflammatory agents are ineffective/contraindicated/not tolerated, consider low dose corticosteroids, but no clinical trial data support this indication.[2,5,8]

If a flare occurs with NSAID or colchicine prophylaxis, may increase to full dose for the duration of the flare.

5. Comorbidity screening and management

Gout is associated with an increased risk of cardiovascular disease and mortality, and traditional CV risk calculators may underestimate the true risk of cardiovascular disease in individuals with gout.[1] People presenting with gout should be assessed for overall cardiovascular risk, cigarette smoking, hypertension, diabetes, dyslipidaemia, obesity, and renal disease.[2,3]

Consistent with their urate lowering effect, calcium-channel blockers and losartan are associated with a lower risk of incident gout in patients with hypertension. By contrast, diuretics, beta-blockers, ACE inhibitors, and non-losartan ARBs are associated with an increased risk of gout.[35]

6. Patient and health-care provider education

Rationale for long-term urate lowering therapy, risk of flares during initiation of urate lowering therapy, action plan for flare management, and advice on healthy lifestyle.[2]

PROGNOSIS

Gout attacks are painful and debilitating, but generally self-limiting. In patients who have not been treated with uric acid-lowering drugs, the risk of recurrence after the first attack is 62%, 78%, and 84% during the first, second, and third year, respectively.[36]

In untreated gout, about 2% of patients develop severe debilitating arthritis typically 20 years after the first attack. Among people with untreated gout, tophi occur in about 50% after 10 years and 72% after 20 years.[4]

Appropriate treatment can reduce the risk of gout flares and their recurrence, and prevent long-term consequences of gout. Treatments for acute and chronic gout have considerable risks and adverse effects.[4]

Data from a general population cohort study suggest that allopurinol initiation modestly reduces risk of death in patients with gout.[37] Another study found no difference in mortality in people with gout who were treated with allopurinol compared with matched controls.[38]

Prospective cohort studies suggest that allopurinol therapy is associated with a reduced incidence of renal disease.[39,40] However, a recent (2020) randomised controlled trial found that in patients with chronic kidney disease and a high risk of progression, and without a history of gout, urate lowering treatment with allopurinol did not slow the decline in eGFR as compared with placebo.[41]

CLINICIAN-PATIENT ISSUES IN GOUT

Nicknamed the disease of kings, inaccurate historical beliefs promulgate the thought that gout is self-inflicted by food and alcohol overindulgence. These beliefs contribute to negative opinions about patients, patient embarrassment, and a focus on unproven dietary solutions.[2]

Although 50% of patients with gout may see a rheumatologist, GPs are usually responsible for ongoing care. Treatment regimens are often insufficient to control acute flares or prevent complications; less than 30% of patients undergo serum urate monitoring and of those, only 33% achieve their target serum urate level.[6]

Typically, patients remain on the starting dose of allopurinol without titration to achieve their target serum urate level. To achieve target, the allopurinol dosage can be increased or a uricosuric agent can be added. However, if adherence is not assessed, this approach may be futile.[6]

Up to 57% of patients with chronic gout are non-adherent to their medication regimen and 70% have interrupted therapy. Long-term adherence is lowest in younger males of lower socioeconomic status without comorbidities and with fewer acute flares. Non-adherence is usually due to clinical/financial factors. Patients cite concerns regarding adverse effects and medication interactions. Acute attacks and pain are the main drivers for adherence, and patients may believe that without acute flares, urate lowering therapy drugs need not be taken continuously.[6]

Patients may also report that the potential complications of gout have not been explained, and they have a poor understanding that gout is an arthritis. Patients typically believe that gout is a self-inflicted consequence of ageing and are reluctant to seek medical advice. Some men hesitate to seek help despite intense pain.[6]

Qualitative studies suggest that physicians believe they have the knowledge and skills to educate patients with gout, but many patients report uncertainty regarding its causes and treatment.[6]

Lack of clinician education is a barrier to optimal care. Compared with other arthritides, gout receives less attention in non-rheumatological training programs.[6]

Many rheumatology societies have published gout management guidelines. These guidelines generally endorse long term urate lowering therapy for patients with recurrent gout flares and/or tophi, using a treat-to-target serum urate concentration approach.[2] However, studies have consistently shown low rates of initiation and continuation of urate lowering therapy in patients with gout, and when urate lowering therapy is prescribed, insufficient dose titration to achieve sub-saturating serum urate targets.[2]

In addition to the burden of severe joint pain and disability, inadequate prescription of urate lowering therapy in patients with poorly controlled gout leads to

unnecessary exposure to the adverse effects of NSAIDs colchicine, and corticosteroids.[2]

Patients and healthcare providers may not understand that urate crystal deposition is present even during asymptomatic periods between flares, providing a rationale for long term urate lowering therapy. Flares soon after initiating urate lowering therapy may lead to negative patient experience of this therapy. Flares are more likely if therapy is initiated with high doses and without anti-inflammatory prophylaxis.[2]

The presence of other serious comorbidities, such as diabetes, cardiovascular disease and CKD, may take priority in healthcare interactions, particularly given the limited time available for patient interactions with a primary care physician.[2]

The development of the 2020 American College of Rheumatology gout treatment guidelines[27] included input from a panel of 8 patients with gout. The patient panel reviewed a number of clinical scenarios and discussed their views and perspectives related to each. They also provided their preference for 1 of the 2 treatment options for each clinical scenario. Patients favoured more active urate-lowering therapy and management of gout flares, resulting in unanimous consensus on choices related to 6 clinical scenarios: (i) ULT initiation in gout; (ii) treat-to-target management strategy; (iii) use of pegloticase for refractory gout; (iv) starting ULT during a gout flare; (v) using injectable treatments (over oral) for acute gout flares; and (vi) use of febuxostat in people with cardiovascular disease.[42]

PATIENT TIPS

In relation to gout, the terms urate and uric acid are often used interchangeably. Your blood test result may use either term, expressed as a concentration in mmol/L e.g. 0.35 mmol/L.

Gout is a type of arthritis and is not an inevitable consequence of ageing.

Most people with gout will need medication.

Some people wrongly think that they only need to take medication during a flare.
Don't stop or decrease your urate lowering therapy during or after a falre

Lowering you urate level usually involves long term therapy, just as long term treatments are needed for hypertension or high cholesterol even if you do not feel unwell.

Some of the medications used to treat a gout flare are the same as those used for flare prevention, but the doses may be different.

When you reach your urate target, ask your doctor to check your urate level every 6 months.

Jackowski January 2021

Visit your GP or specialist immediately if your gout flares become more severe, more frequent, or affect more joints.

THE BOTTOM LINE FOR PHARMACOTHERAPY IN AUSTRALIA

Treat acute flares

- Colchicine
- NSAIDs
- Corticosteroids

Urate-lowering therapy

- Xanthine oxidase inhibitors (allopurinol, febuxostat)
- Uricosurics (probenecid, lesinurad, benzbromarone)

Prophylaxis to prevent flares from initiation of urate-lowering therapy

- Colchicine (1st line)
- NSAIDs
- Low dose corticosteroids (for patients in whom colchicine and NSAIDs cannot be used)

- Medications for flares and prophylaxis do not reduce serum urate levels or prevent progression of the disease.
- Urate lowering therapy is usually required and is used for the long term control of serum urate levels to prevent recurrence and progression of gout.
- Target urate level is < 0.36 mmol/L, or < 0.30 mmol/L in more severe disease.

ASPIRIN AND GOUT

Aspirin appears to have a bimodal dose-dependent effect on serum urate levels. Doses > 2 grams/day reduce serum urate levels, while doses of 1-2 grams/day increase serum urate levels. These are high (analgesic) doses.

A 2014 study showed that low dose aspirin (≤ 325 mg/day) for cardioprotection increased the risk of gout attacks in people with existing gout. However, the concomitant use of allopurinol nullified the detrimental effect of low dose aspirin.[43]

Low-dose aspirin (approximately 100 mg/day) raises serum urate by about 0.02 mmol/L. In patients with chronic gout treated with allopurinol, this small elevation in serum urate is unlikely to negate the clinical efficacy of allopurinol in preventing gout attacks.

The bottom line

- Aspirin may increase the risk of acute gout, but low-dose aspirin used for secondary prevention of adverse cardiovascular events should not be discontinued in patients with gout (benefit greatly outweighs risk).

THE UNKNOWNS AND AREAS OF RESEARCH

- What are the molecular mechanisms of urate control identified by genome-wide association studies?
- In people with asymptomatic hyperuricaemia, does monosodium urate crystal deposition identified on ultrasound or dual energy CT increase the risk of developing symptomatic gout?
- Why do monosodium urate crystals form preferentially at certain sites?
- How do monosodium urate crystals deposit within the joint without inducing an acute flare?
- How do trigger foods precipitate an acute flare?
- Why do gout flares spontaneously resolve?
- Why do tophi form in some individuals?
- Do hyperuricaemia and gout causally contribute to comorbid disorders such as hypertension, chronic kidney disease, atherosclerosis, and metabolic syndrome?
- Should urate-lowering therapy be initiated earlier in the course of the disease (eg, in people with hyperuricaemia and asymptomatic deposits)?
- Does treatment of hyperuricaemia improve outcomes in comorbid disorders such as hypertension, chronic kidney disease, atherosclerosis, and metabolic syndrome?
- Is the serum urate target of 360 µmol/L low enough?
- Once people with gout have cleared monosodium urate crystals (ie, no flares or tophi), can a higher urate concentration be tolerated in the long term (using a remission induction–maintenance model of treatment)?
- Are there risks associated with very low serum urate concentrations?
- Can response be predicted to different urate-lowering therapies—eg, the chance of achieving target, risk of adverse effects?
- What is the role of complementary therapy in the management of gout?
- How can quality of care be improved for people with gout?

Figure 11. Research questions in hyperuricaemia[8]
Reproduced from Dalbeth N et al. Gout. The Lancet 2016;388(10055):2039-2052.

MEDICATION MONOGRAPHS

- To treat acute flares
- Urate lowering therapy
- As prophylaxis to prevent flares from initiation/titration of urate lowering therapy

Acute flares and flare prophylaxis

Table 2. Medications for treatment of gout flares and/or flare prophylaxis when initiating urate lowering therapy.

Medication	Mechanism of action	Use(s)	Adverse effects (not a full list)	Contraindications (not a full list)
NSAIDs e.g. indomethacin **(not aspirin)** Use with PPI for those at high risk of GI complications	COX-1 and/or COX-2 inhibition. No effect on urate production or excretion.	Acute flares and/or prophylaxis to prevent flares from initiation of urate lowering therapy**	dyspepsia peptic ulcers acute renal failure	history of GI bleed; active peptic ulcer; GFR < 30 mls/min; hypertension; heart failure CV disease
Corticosteroids **e.g. prednisolone**	anti-inflammatory	Acute flares (intra-articular or oral)‡‡	hyperglycaemia osteoporosis hypertension	diabetes; osteoporosis; hypertension
Colchicine	Reduces the inflammatory reaction to urate crystals. No effect on urate production or excretion.	Acute flares and/or prophylaxis to prevent flares from initiation of urate lowering therapy**	rash nausea vomiting blood dyscrasias (thrombocytopenia, leucopenia, anaemia)	history of blood dyscrasias; renal impairment (may need to reduce the dose)

***Prophylaxis of acute flare of gout is recommended in patients starting urate lowering therapy. Gout flares at the beginning of urate lowering therapy are very common and prophylaxis aims to prevent them from occurring.*

‡‡*Corticosteroids may be used for flare prophylaxis if colchicine and NSAIDs are ineffective/contraindicated/not tolerated, but no clinical trial data support this indication*

Recognition of the importance of NLRP3 inflammasome activation and bioactive IL-1β release in initiation of the gout flare has led to the development of anti-IL-1β biological therapy for gout flares.
NLRP3 = NOD-LRR and pyrin domain-containing protein 3

Table 3. Anti-IL-1β biological therapy for gout flares.

Medication	Mechanism of action	Use(s)	Adverse effects (not a full list)	Contraindications (not a full list)
Canakinumab	IL-1β inhibitor (human anti-IL-1β monoclonal antibody)	Acute flares	serious infections immunosuppression	severe hepatic impairment. pregnant women and females of reproductive potential not using effective contraception. co-administration with leflunomide.
Canakinumab is approved by the European Medicines Agency for the treatment of adults with frequent attacks of gouty arthritis refractory to NSAIDs, colchicine, and corticosteroids. It is FDA and TGA approved for several indications, but NOT for gout. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5935617/ Effectiveness of canakinumab for acute flares of gout is marginal according to a Cochrane review.[44]				

Urate lowering therapy

Table 4. Medications for long term urate lowering therapy.

Medication	Mechanism of action	Use(s)	Adverse effects (not a full list)	Contraindications (not a full list)
Allopurinol (first line)	Inhibits xanthine oxidase leading to reduced uric acid synthesis.	Long-term reduction in serum urate levels‡‡	rash blood dyscrasias (thrombocytopenia, leucopenia, anaemia)	history of blood dyscrasias; renal impairment (may need to reduce the starting dose) Allopurinol hypersensitivity

			allopurinol hypersensitivity syndrome	
Probenecid (second line)	Increases renal excretion of uric acid by reducing tubular reabsorption.	Long-term reduction in serum urate levels##	rash blood dyscrasias (thrombocytopenia, leucopenia, anaemia)	history of blood dyscrasias; renal impairment
Febuxostat **(PBS listed in patients with contraindication to allopurinol)**	Inhibits xanthine oxidase leading to reduced uric acid synthesis.	Long-term reduction in serum urate levels##	rash blood dyscrasias (thrombocytopenia, leucopenia, anaemia)	history of blood dyscrasias; renal impairment (may need to use a lower dose)
Medication	**Mechanism of action**	**Use(s)**	**Adverse effects (not a full list)**	**Contraindications (not a full list)**
Lesinurad	Increases renal excretion of uric acid by reducing tubular reabsorption.	Long-term reduction in serum urate levels##	headache Influenza blood creatinine increase GORD	Severe renal impairment, ESRD, kidney transplant recipients, or patients on dialysis; Tumor lysis syndrome or Lesch-Nyhan syndrome
Lesinurad is TGA approved for use in combination with a xanthine oxidase inhibitor for the treatment of hyperuricaemia associated with gout in patients who have not achieved target serum uric acid levels with an adequate dose of a xanthine oxidase inhibitor alone.				

Benzbromarone	Increases renal excretion of uric acid by reducing tubular reabsorption.	Long-term reduction in serum urate levels‡‡	GI effects Severe hepatotoxicity	Moderate or severe renal impairment.
Benzbromarone is not marketed in Australia, but is available via the SAS and may be used by specialists when serum urate is >0.36 mmol/L despite treatment with a xanthine oxidase inhibitor and probenecid.				

Medication	Mechanism of action	Use(s)	Adverse effects (not a full list)	Contraindications (not a full list)
Pegloticase (recombinant pegylated uricase)	Enzyme that metabolizes urate to soluble allantoin.	Long-term reduction in serum urate levels‡‡	infusion reactions nausea contusion or ecchymosis nasopharyngitis constipation chest pain anaphylaxis vomiting	Glucose-6-phosphate dehydrogenase (G6PD) deficiency
Pegloticase is FDA approved in the US for the treatment of severe, treatment-refractory, chronic gout. Given by intravenous infusion. Not TGA approved for use in Australia.				

‡‡*The aim of long-term treatment is to reduce the serum urate level to ≤ 0.36 mmol/l, (below the saturation point of sodium urate), so that new crystals cannot form and existing crystals are dissolved. Target urate level is < 0.30 mmol/L in severe gout e.g.tophaceous disease*

The **adverse effects and contraindications** shown in the above tables are not an exhaustive list. Note that rash and blood dyscrasias are adverse effects shared across the most commonly used urate lowering medications (allopurinol, probenecid, febuxostat).

A contraindication for a medication may be relative or absolute. For example, recommendations for the use of Drug X might include:

- Use with caution in mild-moderate renal impairment (GFR 30–90 mls/min) – may cause an increased risk of adverse effects. Monitor GFR; dose reduction or cessation may be necessary if renal function worsens; and
- Do not use in severe renal impairment (GFR < 30 mls/min).

The first of these is a relative contraindication (sometimes called a precaution); the second is an absolute contraindication.

CASE STUDY[45]

This case study is adapted from: *Neogi T. Clinical practice. Gout. N Engl J Med 2011;364:443-52.*

Medical history

A 54-year-old man with crystal-proven gout has a history of 4 flares during the previous year. Despite receiving 300 mg of allopurinol daily, his serum urate level is 0.43 mmol/L. He is obese and has hypertension, for which he receives hydrochlorothiazide. His renal function (eGFR) is normal, and he is compliant with allopurinol. How should this patient be managed?

Management

The patient described in this vignette has crystal proven gout, with multiple flares and a serum urate level > 0.36 mmol/L despite receiving allopurinol at a dose of 300 mg per day.

Since his renal function is normal, the allopurinol dose should be increased (e.g. by 50-100 mg increments monthly to a maximum of 900 mg daily) until the target urate level is reached, with monitoring of renal function, serum urate levels, and potential adverse effects. Colchicine prophylaxis (0.5 mg once or twice daily) is reasonable while the dose of allopurinol is escalated.

The patient should understand that the intake of alcohol and an excessive amount of meat/seafood/sugar-sweetened drinks may contribute to elevated urate levels and should be minimized. He should be advised to keep well hydrated and to lose weight. Associated cardiovascular risk factors should be identified and treated.

Although the use of hydrochlorothiazide may contribute to the elevated urate level, cessation at this stage is not necessarily needed if it is effectively controlling his blood pressure. Advise him to take the diuretic consistently, since intermittent use may precipitate flares. The addition of losartan or a calcium channel blocker might be considered if blood pressure is inadequately controlled. He should be advised to maintain his urate lowering regimen during flares, which can be managed with colchicine, an NSAID, or a corticosteroid

Follow-up is essential to ensure that target serum urate level is achieved and maintained and to monitor the patient for adverse effects. If the target serum urate

level cannot be achieved, or if the patient has serious side effects at higher allopurinol doses, the use of either febuxostat or a uricosuric agent is another option, given his normal renal function.

PATIENT RESOURCES

a) Arthritis Information Sheet: Gout and Diet. Arthritis Australia and Australian Rheumatology Association 2017. Available at: https://arthritisaustralia.com.au/wordpress/wp-content/uploads/2018/02/ArthAus_GoutDiet_1805.pdf

b) Patient Fact Sheet: Gout. American College of Rheumatology 2019. Available at https://www.rheumatology.org/Portals/0/Files/Gout-Fact-Sheet.pdf

c) Arthritis Information Sheet: Gout. Arthritis Australia and Australian Rheumatology Association 2017. Available at: https://arthritisaustralia.com.au/wordpress/wp-content/uploads/2017/09/ArthAus_Gout_1705.pdf

d) Taking Control of Your Gout. Arthritis Australia 2019. Available at https://arthritisaustralia.com.au/get-support/resources/booklets/

e) Patient education: Gout (Beyond the Basics). UpToDate. Available at: https://www.uptodate.com/contents/gout-beyond-the-basics

f) Musculoskeletal Australia: Gout. Available at: https://www.msk.org.au/wp-content/uploads/2020/02/Gout.pdf

FURTHER READING

1. Patient Education: Gout (The Basics). UpToDate.
2. Lifestyle modifications and other strategies to reduce the risk of gout flares and progression of gout. UpToDate.

APPENDIX 1. SUMMARY OF GOUT GUIDELINES[6]

Table 1. Comparison of published gout guidelines

	ACP	EULAR	Aust & NZ	3e Initiative	ACR	BSR
SUA target						
General	–	<6 mg/dL (0.36 mmol/L)	<0.36 mmol/L	<0.36 mmol/L (6 mg/dL)	<6 mg/dL	<300 µmol/L
Specified	–	<5 mg/dL (0.30 mmol/L) severe gout	<0.30 mmol/L tophaceous gout	<0.30 mmol/L (5 mg/dL) tophaceous gout	<5 mg/dL severe gout	–
ULT indications						
Tophi	✓	✓	✓	–	✓	✓
Attacks	≥2/year	Recurrent	–	–	>2/year	>2/year
Arthropathy	–	✓	–	–	–	–
Radiographic evidence	–	✓	–	–	✓	–
Comorbidities	✓	✓	–	–	✓	✓
ULT initiation	–	Near time of diagnosis	–	–	During attack	1–2 weeks after attack
First-line ULT	Allopurinol, febuxostat	Allopurinol	Allopurinol	Allopurinol	Allopurinol, febuxostat	Allopurinol
Starting dose (mg/day)	–	100	–	50–100	100	50–100
Titration to target SUA	–	100 mg every 2–4 weeks	Gradual increases	Slow increases	Every 2–5 weeks	50–100 mg every few weeks

ACP, American College of Physicians (2016) guidelines[13]; EULAR, European League Against Rheumatism (2016) guidelines[15]; Aust & NZ, Australian and New Zealand (2015) recommendations[19]; 3e Initiative, Multinational Evidence, Expertise, Exchange Initiative (2013) guidelines[16]; ACR, American College of Rheumatology (2012) guidelines[17]; BSR, British Society of Rheumatology (2007) guidelines[18]; – Not specified in guideline; ✓ Specified in guideline; SUA, serum uric acid; ULT, urate-lowering therapy

Reproduced from: Rogenmoser S, Arnold MH. Chronic gout: Barriers to effective management. Aust J Gen Pract 2018;47:351-6.[6]

***Aust & NZ** = Graf SW, Whittle SL, Wechalekar MD, et al. Australian and New Zealand recommendations for the diagnosis and management of gout: Integrating systematic literature review and expert opinion in the 3e Initiative. Int J Rheum Dis 2015;18(3):341–51.[46]*

Note that the ACR guidelines in this table are from 2012. The updated (2020) guidelines provide similar recommendations for the parameters assessed in this table.

APPENDIX 2. DIFFERENTIAL DIAGNOSES[4]

Condition	Differentiating signs / symptoms	Differentiating tests
Pseudogout (calcium pyrophosphate deposition disease)	• Presentation may be identical to that of gout.[48] • Pseudogout is more likely to affect wrist and knee joints.	• Chondrocalcinosis (radiographic calcification of cartilage in certain joints) is usually present. • Ultrasound may help to differentiate calcium pyrophosphate deposition disease (CPPD) from gout. Calcium pyrophosphate deposits are found deeper in the cartilage and are less homogenous (lumpy-bumpy) than the superficial double contour sign seen in gout. • The definitive diagnosis is finding calcium pyrophosphate crystals in the synovial fluid. These are rhomboid-shaped, weakly positively birefringent crystals.
Septic arthritis	• Presentation may be identical to that of gout.[48] • Occurs in both sexes and at any age. • Risk factors for infection, such as intravenous drug use and immunocompromise, may be present.	• Synovial fluid microscopy and culture may be Gram positive and show growth. • Blood cultures may grow the causal bacteria. • Coexistence of crystals and infection in the joint is not uncommon.
Trauma	• A positive history is present. • Usually, there are fewer inflammatory signs, such as erythema or warmth, on joint examination than with gout.	• Synovial fluid is usually bloody and has no monosodium urate crystals.
Rheumatoid arthritis (RA)	• Chronic tophaceous and polyarticular gout may present like RA, and tophi can be misdiagnosed as rheumatoid nodules. • History of intermittent, acute, self-limited attacks of arthritis and podagra suggests gout. • RA and gout appear to be negatively correlated, as very few cases of coexistence have been reported.	• Associated with positive rheumatoid factor (RF) in 70% to 78% of cases; however, 30% of patients with gout have a positive RF.[64] • Anti-cyclic citrullinated peptide (anti-CCP) has high specificity, but low sensitivity, for RA. It may be useful in the early detection of patients who will have severe RA.[65]

Condition	Differentiating signs / symptoms	Differentiating tests
		• Synovial fluid is inflammatory (WBC count >2000/mm³), but no monosodium urate crystals are found.
Reactive arthritis	• Recent infection with appropriate organism. • Oligoarthritis present. • Commonly affects weight-bearing joints. • May have tendon insertion inflammation and dactylitis (whole digit inflammation). • Conjunctivitis, urethritis, and stomatitis may be present.	• X-rays may show soft-tissue swelling.
Psoriatic arthritis	• Patients usually have a history of psoriasis. • Asymmetrical joint distribution. • Commonly affects the distal interphalangeal joints. • Presence of dactylitis.	• Typical radiographic findings include joint erosions, joint space narrowing, bony proliferation including periarticular and shaft periostitis, osteolysis including "pencil in cup" deformity and acro-osteolysis, ankylosis, spur formation, and spondylitis.[66]

Table reproduced from Badlissi F. BMJ Best Practice Gout https://bestpractice.bmj.com/topics/en-us/13. 2020

APPENDIX 3. MANAGEMENT IN ADVANCED CHRONIC KIDNEY DISEASE

The following material has been reproduced from "Perez-Ruiz F, Dalbeth N, Romain P. Pharmacologic urate-lowering therapy and treatment of tophi in patients with gout. UpToDate 2020".[21]

Treatment to prevent gout flares and to reduce the size of tophi is challenging in patients with advanced chronic kidney disease (CKD). The choice of agents and drug dosing for the prophylaxis of gout flares and for urate-lowering therapy are influenced by significant impairment of renal function, and nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided; treatment of hyperphosphatemia caused by kidney disease can also affect serum urate levels. (See 'Prophylactic therapy' below and 'Urate-lowering therapy in chronic kidney disease' below.)

Prophylactic therapy — Particular caution should be taken in patients with CKD treated prophylactically with colchicine. The clearance of colchicine is reduced in patients with CKD, increasing the risk of neuromyopathy. If given for prophylaxis, the recommended colchicine dose is 0.6 mg once daily at a creatinine clearance (CrCl) of 35 to 49 mL/minute and 0.6 mg every two to three days at a CrCl of 10 to 34 mL/minute. Colchicine is not dialyzable and is contraindicated at a CrCl below 10 mL/minute.

Drug interactions involving colchicine are more problematic in patients with CKD. Among patients with CKD, drugs that inhibit CYP3A4 or P-glycoprotein may further reduce clearance of colchicine by interfering with colchicine metabolism. These agents include some commonly used antibiotics such as clarithromycin, azithromycin, and ketoconazole; antiretroviral drugs; and antihypertensive agents, including verapamil and diltiazem. Concurrent use of these medications with colchicine may thus increase the risk of myelosuppression, and fatal pancytopenia may ensue.

Low doses of glucocorticoids may reduce the frequency of gout flares, but a prophylactic benefit for glucocorticoids is not supported by adequate evidence. Adverse effects of chronic glucocorticoid use should be anticipated with long-term therapy. If used for prophylaxis, the glucocorticoid dose should be the minimum necessary to prevent recurrent flares.

Urate lowering therapy in chronic kidney disease — The half-lives of allopurinol and its active metabolite, oxypurinol, are prolonged in renal failure; we thus reduce the starting dose of allopurinol in patients with CKD, depending upon the severity of the reduction in the estimated glomerular filtration rate (eGFR). The initial daily dose of allopurinol should not exceed 1.5 mg per mL/minute of eGFR. As an example, for an eGFR of 50 mL/minute, the initial daily dose of allopurinol should not exceed 75 mg daily, and for such a patient, half of a 100 mg pill daily could be used as a starting dose.

The desired serum urate concentration is often not achieved if treatment is limited to the dose used to initiate therapy. In such patients, cautious up-titration of the dose of allopurinol is warranted (in 100 mg increments every two to five weeks in patients

with eGFR ≥60 mL/minute and in 50 mg increments in patients with CKD stage 3 or with more severe disease); this approach to dose adjustment, with careful observation for adverse effects, has been successful without increased toxicity. We advise continued and careful dose titration and monitoring of serum urate and eGFR in this clinical setting.

Febuxostat has also been effective in safely reducing the serum urate in patients with moderate to severe renal impairment (eGFR 15 to 50 mL/minute/1.73 m^2), as shown in a randomized 12-month trial involving 96 such patients who were treated with febuxostat 30 mg twice daily, febuxostat 40 mg once daily (increased after one month to 80 mg once daily if serum urate was ≥6 mg/dL after 14 days of therapy), or placebo. The mean serum urate decreased from baseline to month 12 in both groups receiving febuxostat (difference from placebo -4.8 mg/dL, 95% CI -5.7 to -3.9 mg/dL, and -4.0 mg/dL, 95% CI -4.9 to -3.1 mg/dL). There was no notable imbalance in renal adverse events or renal function between the febuxostat and placebo treatment groups.

Uricosuric drugs, such as probenecid, may be less effective in patients with moderately impaired kidney function and are relatively ineffective, except for benzbromarone, when the eGFR is more substantially reduced. Uricosurics should not be used in patients with severe CKD (stages 4 to 5).

A modest lowering of serum urate is a potentially beneficial side effect of treatment of hyperphosphatemic CKD patients with phosphate-binding agents (e.g., calcium-containing antacids or sevelamer). However, it is uncertain if serum urate lowering with these drugs results in fewer gout flares or reduction in the size of tophi, and phosphate-lowering therapy should not be used in patients with normal serum phosphate because hypophosphatemia may ensue. The management of hyperphosphatemia in CKD is described in detail separately. (See "Management of hyperphosphatemia in adults with chronic kidney disease".)

Organ transplant recipients — Patients with gout and impaired renal function due to organ transplantation have additional issues including interactions between urate-lowering therapy with xanthine oxidase inhibitors (XOIs; allopurinol, febuxostat) and immunosuppressive agents, particularly azathioprine and mercaptopurine. Treatment of gout in patients following renal transplantation is discussed separately. (See "Kidney transplantation in adults: Hyperuricemia and gout in kidney transplant recipients".)

APPENDIX 4. GOUT TRUE/FALSE QUIZ

1. Asymptomatic hyperuricaemia should be aggressively treated with medications to reduce the risk of developing gout. **T/F**

2. Allopurinol reduces serum urate levels by inhibiting the enzyme xanthine oxidase. **T/F**

3. First presentation of gout is often in one joint. **T/F**

4. NSAIDs and corticosteroids are useful agents for continuous long-term management of gout. **T/F**

5. Gout occurs more commonly in men than women. **T/F**

6. A clinical diagnosis of gout can be confirmed by demonstrating the presence of monosodium urate crystals in the synovial fluid of an affected joint. **T/F**

7. Even if poorly controlled, gout rarely affects multiple joints. **T/F**

8. Elevated serum urate is diagnostic of gout. **T/F**

9. Colchicine can be used to prevent flares of gout. **T/F**

10. Patients with gout should avoid excessive alcohol intake, especially beer. **T/F**

11. Pseudo-gout involves the deposition of monosodium urate crystals in synovial fluid. **T/F**

12. Bacteria are commonly present in the synovial fluid of joints affected by gout. **T/F**

13. Gout is associated with an increased risk of cardiovascular disease. **T/F**

14. A diet high in purines may exacerbate gout. **T/F**

15. A number of medications used for long term lowering of urate levels can cause blood disorders such as anaemia and thrombocytopenia. **T/F**

16. Thiazide diuretics can increase serum urate levels. **T/F**

17. Patient with gout should be treated to a target serum urate target of < 0.36 mmol/L or < 0.30 mmol/L if tophi present. **T/F**

18. Colchicine should not be used in conjunction with urate lowering medications such as allopurinol. **T/F**

19. An acute fall in serum urate levels may precipitate a flare of gout. **T/F**

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20. Dietary management of gout is very restrictive and of limited benefit. **T/F**

21. Most people with hyperuricaemia will develop gout. **T/F**

22. Urate lowering therapy is only needed during an acute flare of gout. **T/F**

23. There is a causal relationship between hyperuricaemia and gout, and the incidence of gout increases with increasing urate levels. **T/F**

24. Few patients with gout will need medication. **T/F**

25. The major cause of hyperuricaemia is urate overproduction rather than reduced renal and GI excretion. **T/F**

26. Repeated gout flares can form swollen growths called tophi. Urate crystals and tophi can cause permanent damage to joints over time. **T/F**

27. Medications are available to manage gout flares, to lower serum urate levels, and for prophylaxis against gout flares. **T/F**

28. Medications used for gout have very few serious adverse effects. **T/F**

29. Low-dose aspirin used for the secondary prevention of adverse cardiovascular events should be discontinued in patients with gout. **T/F**

30. Differentiating gout from septic arthritis is not important because management is the same. **T/F**

1. F	**2. T**	**3. T**	**4. F**
5. T	**6. T**	**7. F**	**8. F**
9. T	**10. T**	**11. F**	**12. F**
13. T	**14. T**	**15. T**	**16. T**
17. T	**18. F**	**19. T**	**20. T**
21. F	**22. F**	**23. T**	**24. F**
25. F	**26. T**	**27. T**	**28. F**
29. F	**30. F**		

Q 1. No need to treat asymptomatic hyperuricaemia

Q 4. Adverse effects prevent long term use.

Q 8. Most people with hyperuricaemia do not develop gout.

Q11. Pseudogout = calcium pyrophosphate crystals (rhomboid shaped) in synovial fluid (not monosodium urate crystals)

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Suggested reading: References 2-6, 8, 16, 18, 27 (PDFs available on request)

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