

Treating to target in gout

Simple steps towards effective long-term control

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In almost all cases of the common condition gout, treatment options are available to fully control the disease, and yet treatment outcomes are often poor. The following of relatively simple guidelines, especially to achieve and maintain urate levels below target levels, gives the best chance of effective long-term control.

Gout is very common, and indeed the most common inflammatory arthritis, and all doctors dealing with adult patients are likely to be confronted with managing it, at least in the acute phase. In almost all cases, there are treatment options to fully control the disease, and yet studies continue to show poor outcomes.¹ Although it is tempting to attribute failures to patient behaviour, we should first ensure we are following relatively simple guidelines to give our patients the best chance.

Is the diagnosis secure? Have we allowed for the patient's other health problems when deciding on the drugs to use to control and prevent acute flares? Does the patient warrant urate-lowering therapy and if so, which drug is best? Do we know the target serum urate level for this patient? This article will discuss the decisions that need to be made regarding a patient with gout, from initial presentation to lifelong prevention of attacks and of joint damage, focusing on controlling the underlying hyperuricaemia.

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KEY POINTS

- An acutely inflamed joint usually warrants aspiration. Examination of the synovial fluid is the best way to differentiate bacterial infection from crystal-induced arthritis (such as gout) and other less common disorders.
- The treatment of acute gout is determined by the patient's comorbidities. NSAIDs, corticosteroids (oral, intramuscular or intra-articular), intramuscular depot tetracosactrin (off-label use) and colchicine are all reasonable options.
- Confirmation of the diagnosis of gout, by identifying urate crystals using polarised light microscopy is of great value prior to commencing long-term (usually lifelong) urate-lowering drug therapy (ULT).
- When ULT is used, achieving the target serum urate level is of vital importance. The targets are: for nontophaceous gout, <0.36 mmol/L; for tophaceous gout, <0.30 mmol/L.
- Whichever ULT is chosen, in the early phase there is an increased risk of flares, and the risk is higher if the serum urate falls more rapidly. It is wise to introduce ULT at a low dose and to use prophylactic drug therapy (usually colchicine) to avoid flares.
- Allopurinol 300 mg daily is often too low a dose to achieve the target serum urate level. It is safe and effective to progressively increase the dose of allopurinol to 600 mg daily or, if needed, 900 mg daily.



Figure 1. Acute gout attack. Sudden onset of pain, redness, swelling and tenderness in the great toe metatarsophalangeal joint is highly suggestive of gout.



Figure 2. Severe tophaceous gout.

Presentation

The abrupt onset of pain, swelling, redness and warmth in a joint is a diagnostic emergency. It is crucial to confirm or exclude bacterial sepsis, but gout, acute calcium pyrophosphate arthritis and other inflammatory arthritides are more common explanations. Joint aspiration followed by examination of the synovial fluid (polarised light microscopy for urate crystals, white blood cell count, Gram stain and culture) is the key investigation. Sepsis and gout can co-exist; if the progress is not as expected, the joint should be (re)aspirated to look for infection even if urate crystals have been identified. If infection is suspected, oral antibiotics should not be used; they are insufficient to cure septic arthritis, delay the diagnosis and may worsen the outcome.

Clinical features favouring a diagnosis of gout are:²

- recurrent attacks
- involvement of the great metatarsophalangeal, mid-tarsal and ankle joints (Figure 1)
- onset to maximal inflammation within 24 hours, and complete resolution (in less than 14 days) between attacks
- occurring in a man or postmenopausal woman.

Although hyperuricaemia (serum urate level above 0.42 mmol/L) adds support to the diagnosis, only a minority of hyperuricaemic individuals ever develop gout

and of people presenting with proven acute gout, 40% had serum urate levels below 0.42 mmol/L.^{3,4} Pain in the big toe in a patient with hyperuricaemia is not sufficient reason to diagnose gout.

Without treatment gout progresses and more joints become affected, including upper extremity joints, such as the wrist and finger joints (Figure 2).

At the advanced end of the spectrum of gout, persistent joint pain and deformity, sometimes with a lack of marked flares, can lead to misdiagnosis as rheumatoid arthritis (tophi mistaken for nodules), osteoarthritis or neuropathic (mid-foot) arthritis. Aspiration of a lump is technically easy and provides certainty of diagnosis (Figures 3 and 4).

Pathogenesis

Despite the salvage pathways that allow reutilisation of some of the purine 'building blocks', degradation of purines from cell turnover and from food results in the production of uric acid. Uric acid is the final degradation product of purine breakdown in humans, whereas in most other mammals uric acid is broken down by uricase to allantoin, which is excreted renally.

Uric acid has a pKa of about 5.7 and thus at the serum and synovial pH of 7.4 is mainly dissociated, existing as sodium urate. Excretion is primarily (two-thirds) via the kidney and is dependent on anion transporters in the proximal renal tubule. The genetically

determined efficacy of urate renal clearance is the key factor determining the serum urate concentration and thus the risk of monosodium urate monohydrate (MSU) crystal formation.⁵ In at least 90% of people with hyperuricaemia (and 90% of people with gout), impaired renal clearance is the predominant mechanism; overproduction of urate accounts for less than 10% of cases of hyperuricaemia. Above a concentration of about 0.42 mmol/L, serum and synovial fluid are supersaturated with respect to sodium urate. As the urate concentration rises, the likelihood of developing gout rises, but even at serum urate levels above 0.60 mmol/L, the five-year cumulative incidence is only 70%. In people in whom MSU crystal formation occurs, the process is slow, taking months to years.⁶

An abrupt attack of gout is not due to crystal formation but to a rapid escalation of the interaction between the inflammatory system and the crystals. After the attack settles, the MSU crystals are still in the joint, and are detectable by joint aspiration in more than 95% of patients.

Treatment of the acute attack

In an acute attack of gout, treatment is aimed at pain relief and inflammation reduction. NSAIDs, corticosteroids (oral, parenteral or intra-articular), intramuscular depot tetracosactide (tetracosactrin; synthetic adrenocorticotrophic hormone;



Figure 3. Chronic gout. A tophus on the medial aspect of the left great metatarsophalangeal joint.

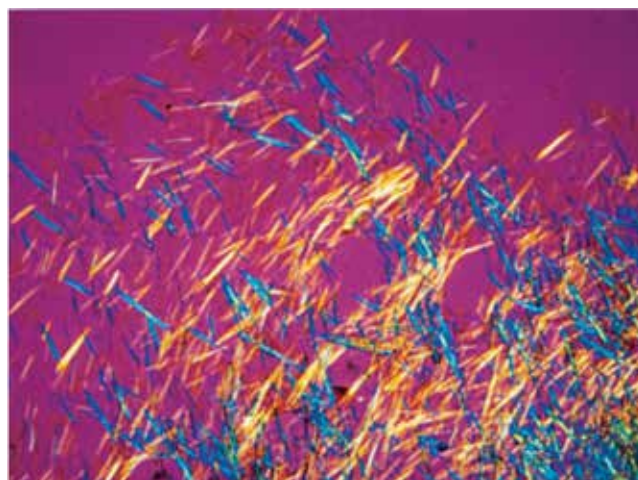


Figure 4. Photomicrograph (polarised light) of aspirate obtained by needle biopsy of a tophus, showing the characteristic needle-shaped and strongly negatively birefringent monosodium urate monohydrate crystals of gout.

off-label use), colchicine and interleukin-1 β inhibitors can be used, the best option being determined by the individual patient's comorbidities, such as hypertension, renal disease or diabetes (Table). Therefore, first consider what else is wrong (or could go wrong) with the patient.

If colchicine is used (i.e. NSAIDs are contraindicated or are not effective), the low-dose schedule (1 mg initially, 0.5 mg one hour later and no more for 24 hours) is appropriate as it is just as effective as the higher-dose regimen stated in the various preparations' prescribing information and much less likely to cause side effects.⁷ It is reasonable to then continue with 0.5 mg twice daily (glomerular filtration rate [GFR], >30 mL/min) or at a lower dose (adjusted for the degree of renal impairment).

Treatment of chronic gout

The long-term management of gout focuses on controlling the underlying hyperuricaemia and preventing flares.

Urate-lowering therapy

Although experienced clinicians may feel confident in recognising acute gout and implementing the strategies described in the section above for immediate treatment, a very high level of diagnostic certainty is

warranted before recommending lifelong drug therapy. Crystal identification is ideal for diagnosis confirmation but the web-based calculator accessed at <http://goutclassificationcalculator.auckland.ac.nz> is an excellent alternative.²

Strong indications for urate lowering therapy (ULT) include joint damage due to gout (deformity, erosions on x-ray), tophi, persistent inflammatory joint symptoms, renal impairment (more difficult to clear the MSU burden, probable retardation of renal progression) and uric acid renal calculi. However, for most patients the decision is driven by a desire to avoid the downhill natural history of increasingly frequent and more prolonged attacks and the development of joint damage. If the diagnosis is certain (i.e. urate crystals are identified), it is reasonable to offer ULT after a single attack.

Starting a patient on ULT is easy; achieving a high rate of therapy adherence in the long term is not. Gout has the worst drug adherence rate of the common chronic diseases. In Australia, the USA and the UK, ULT adherence is below 40%.^{1,8,9} Mechanisms that may improve adherence should be at the forefront of considerations when contemplating this therapy.

The use of ULT is summarised in the flowchart.

What is the target?

Target serum urate levels, to be maintained for the remainder of the patient's life, are:^{10,11}

- if no tophi are present, below 0.36 mmol/L
- if tophi are present, below 0.30 mmol/L.

MSU crystal dissolution occurs when the serum urate concentration falls below saturation, but the process is very slow. Thus, if the MSU burden is not large (no tophi present) then the target serum urate level is slightly higher (at below 0.36 mmol/L) than if the burden is greater, as indicated by the presence of tophi (then below 0.30 mmol/L).

These urate targets are well below the reference ranges provided by laboratories. Reference ranges are influenced by sex, age, race and individual laboratory policy, but none of these influences the rate of MSU crystal dissolution.

What role for dietary advice?

Obesity, alcohol excess and other dietary factors (high intake of fructose, meat, seafood; low intake of coffee, low-fat dairy, cherries) are associated with hyperuricaemia and gout and therefore, on a population-wide basis, it is reasonable to conclude that improving these risk factors would reduce the prevalence of gout.

TABLE. TREATMENT OPTIONS FOR AN ACUTE FLARE OF GOUT (THE BEST CHOICE DEPENDS ON THE PATIENT'S COMORBIDITIES)

Therapy option	Reasons to avoid
NSAIDs	Renal impairment; poorly controlled hypertension; unstable coronary disease; peptic ulceration
Corticosteroids	Diabetes; possibility of joint infection (can be masked)
Colchicine	Renal failure; use of clarithromycin, ciclosporin or diltiazem (drug interactions)

But what about a patient who already has gout? Is there a realistic chance of achieving a target urate level through dietary change? No peer-reviewed, published, controlled, dietary trial has demonstrated an improvement in serum urate level through dietary change. Obesity and alcohol excess are bad for many reasons, and regardless of gout it is appropriate to help patients to lose weight and reduce alcohol consumption. Burdening patients with dietary suggestions to fix their gout is misguided and likely to dilute the key messages of knowing their target serum urate level and successfully using drug therapy to achieve it.

How to avoid flares during urate-lowering therapy

Any event, including the introduction of ULT, that quickly reduces the serum urate concentration increases the risk of a flare; and the faster the fall, the higher the risk. All ULT should therefore be introduced at a low dose and increased gradually (e.g. at monthly intervals).

The risk of flares is reduced substantially by the concurrent use with ULT of colchicine (0.5 mg twice daily if normal renal function) continued for six months (prophylactic therapy). NSAIDs or low-dose prednisone (e.g. 5 to 7.5 mg daily) can be used if colchicine is not tolerated or is contraindicated.

Options for urate-lowering drug therapy

Two xanthine oxidase inhibitors (allopurinol and febuxostat) and several relatively weak uricosurics (probenecid, losartan, fenofibrate) are readily available. The xanthine

oxidase inhibitors reduce the production of uric acid and the uricosurics increase renal clearance (by inhibition of anion transport in the proximal renal tubule). Xanthine oxidase inhibitors should not be used with azathioprine or mercaptopurine, both of which require xanthine oxidase for normal metabolism.

Allopurinol

Allopurinol is by far the most frequently prescribed ULT in Australia, and is funded through the PBS. It has been available for many years, is inexpensive and is generally safe and well tolerated.

The use of allopurinol in Australia, however, remains suboptimal with respect to both minimising risk and optimising benefit. Although 300 mg daily remains (inappropriately) the most frequently prescribed dose of allopurinol, this dose is insufficient in most patients to achieve target serum urate levels. The dose can and should be increased progressively (monthly) until the target urate level is reached or no further fall in the urate level occurs. Occasionally, doses as high as 900 mg daily may be required. Fluctuating urate levels indicate suboptimal adherence and should prompt efforts to improve adherence (e.g. further education of the patient and family regarding the importance of maintaining the target urate level to enable crystal dissolution, use of a dosette pack, more frequent measurement of serum urate levels). The percentage of patients achieving target rises dramatically as a result of up-titration (from as few as 20% of patients at a dose of 300 mg daily up to 88% as a result of up-titration).¹² Although the starting dose

should be lower in patients with renal insufficiency (see below), the principle of up-titration is even more important in this group because higher maintenance doses of allopurinol are required in the setting of renal insufficiency.

Like most other drugs, allopurinol has risks associated with its use. Rash occurs in about 2% of recipients and is generally mild. Severe hypersensitivity syndrome occurs in fewer than 1 in 1000 people taking allopurinol but has a 20% mortality rate and is more frequent in the presence of renal impairment, when a higher initial dose of allopurinol is used and in certain racial groups (i.e. Han Chinese, Thai and Korean). Testing for the presence of the human leukocyte antigen allele *HLA-B58:01* (not Medicare-funded) is recommended in these high-risk racial groups; detection renders allopurinol use inappropriate and an alternative ULT should be prescribed.

Starting allopurinol at a low dose and increasing slowly reduces the risk of allergy and the risk of a flare. If the patient's renal function is normal, the starting dose is 100 mg daily; in renal impairment, the daily starting dose is 25 to 50 mg. A useful guide is that the initial daily dose in mg is approximately 1.5 times the estimated GFR (eGFR); for example, if eGFR is 30 mL/min/1.73 m², the starting dose will be 30 x 1.5, which is approximately 50 mg daily.

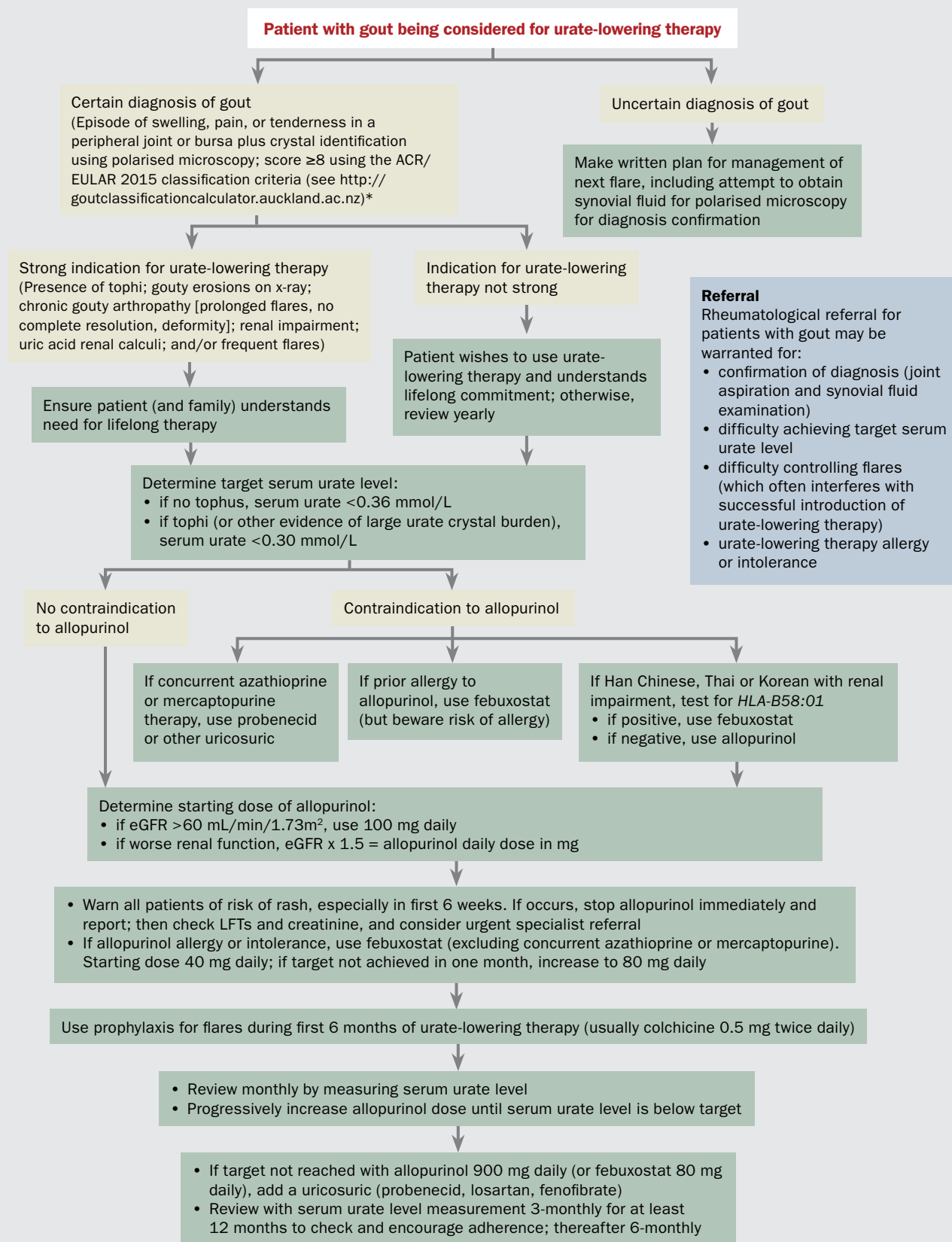
When allopurinol hypersensitivity syndrome occurs, it usually does so within six weeks of commencing therapy and is associated with rash. Patients should be warned of the possibility of rash, and to immediately stop taking allopurinol and report the rash if it occurs.

As mentioned earlier, allopurinol should not be used with azathioprine or mercaptopurine because it increases the toxicity of these drugs.

Febuxostat

Febuxostat is a selective non-purine xanthine oxidase inhibitor that is now funded through the PBS (authority required) for patients with gout who are hypersensitive to or intolerant of allopurinol or for whom

AN APPROACH TO THE USE OF URATE-LOWERING DRUG THERAPY



Abbreviations: ACR/EULAR = American College of Rheumatology/European League Against Rheumatism.

* Neogi T, Jansen TL, Dalbeth N, et al. 2015 Gout classification criteria. An American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheumatol* 2015; 67: 2557-2568.

allopurinol is contraindicated. It is effective and does not require dosage modification in patients with renal insufficiency down to GFR 30 mL/min (insufficient published data for more severe renal impairment). It is available as an 80-mg scored tablet that can be broken. Patients who have had allopurinol allergy have about a 10% chance of febuxostat allergy.

Febuxostat 40 mg/80 mg daily is more potent than allopurinol 100 mg/300 mg daily, and when starting therapy, even half a tablet daily results in a rapid fall in the serum urate level and a significant risk of a gout flare; prophylaxis against this effect, such as with low-dose colchicine (0.5 mg twice daily), is important. There are no published data to determine whether febuxostat 80 mg daily (the maximal approved dose in Australia) is more effective than optimal dose allopurinol, and there is no PBS funding on the basis of insufficient response to allopurinol.

As mentioned earlier, febuxostat should not be used with azathioprine or mercaptopurine because it increases the toxicity of these drugs.

Probenecid, losartan and fenofibrate

Probenecid is a reasonable choice if allopurinol and febuxostat are inappropriate (e.g. in the setting of azathioprine therapy). It requires twice daily dosing and reasonable renal function (GFR greater than 30 to 40 mL/min).

Losartan and fenofibrate, which are not TGA-indicated for gout, are relatively weak uricosurics (and probably less potent than probenecid) but if the patient has another indication for one of these, the uricosuric effect may be sufficient to achieve the target urate level.

As uricosuric agents initially increase the concentration of uric acid in the urine, prophylaxis against uric acid calculi is required (good fluid intake, urinary alkalinisation).

When to refer to a rheumatologist?

A GP should consider referral of a patient with gout to a rheumatologist in the following circumstances:

- in the acute setting, when sepsis is possible or to confirm the diagnosis with certainty by aspiration of synovial fluid
- if ULT is being considered but the diagnosis is not certain and confirmation is needed (crystal identification or the meeting of criteria at <http://goutclassificationcalculator.auckland.ac.nz>)
- if target urate level is not being achieved
- if there are complex comorbidities (e.g. renal failure, azathioprine or mercaptopurine therapy, allopurinol allergy)
- if there is severe tophaceous gout.

Conclusion

As drug therapy to cure gout is required lifelong, certainty of diagnosis (crystal identification) is warranted. Maintaining the serum urate level below target (0.36 mmol/L for nontophaceous gout, 0.30 mmol/L for tophaceous gout) is required and can be achieved in most patients provided ULT is uptitrated. For allopurinol, a dose of 600 mg daily or more is often required. MT

References

1. Robinson PC, Taylor WJ, Dalbeth N. An observational study of gout prevalence and quality of care in a national Australian general practice population. *J Rheumatol* 2015; 42: 1702-1707.
2. Neogi T, Jansen TL, Dalbeth N, et al. 2015 Gout classification criteria. An American College of Rheumatology / European League Against Rheumatism collaborative initiative. *Arthritis Rheumatol* 2015; 67: 2557-2568.
3. Schlesinger N, Baker DG, Schumacher HR. Serum uric acid during bouts of acute gouty arthritis. *J Rheumatol* 1997; 24: 2265-2266.
4. Logan JA, Morrison E, McGill PK. Serum uric acid in acute gout. *Ann Rheum Dis* 1997; 56: 696-697.
5. Merriman TR, Dalbeth N. The genetic basis of hyperuricaemia and gout. *Joint Bone Spine* 2011; 78: 35-40.
6. Pascual E, Doherty M. Aspiration of normal or asymptomatic pathological joints for diagnosis and research: indications, technique and success rate. *Ann Rheum Dis* 2009; 68: 3-7.

7. Terkeltaub RA, Furst DE, Bennett K, Kook KA, Crockett RS, Davis MW. High versus low dosing of oral colchicine for early acute gout flare: twenty-four-hour outcome of the first multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-comparison colchicine study. *Arthritis Rheum* 2010; 62: 1060-1068.
8. De Vera MA, Marcotte G, Rai S, Galo JS, Bhole V. Medication adherence in gout: a systematic review. *Arthritis Care Res* 2014; 66: 1551-1559.
9. Kuo C-F, Grainge MJ, Mallen C, Zhang W, Doherty M. Rising burden of gout in the UK but continuing suboptimal management: a nationwide population study. *Ann Rheum Dis* 2015; 74: 661-667.
10. Khanna D, Fitzgerald JD, Khanna PP, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care Res* 2012; 64: 1431-1446.
11. Sivera F, Andres M, Carmona L, et al. Multinational evidence-based recommendations for the diagnosis and management of gout: integrating systematic literature review and expert opinion of a broad panel of rheumatologists in the 3e initiative. *Ann Rheum Dis* 2014; 73: 328-335.
12. Stamp L, O'Donnell JL, Zhang M, et al. Using allopurinol above the dose based on creatinine clearance is effective and safe in chronic gout, including in those with renal impairment. *Arthritis Rheum* 2011; 63: 412-421.

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ONLINE CPD JOURNAL PROGRAM

The long-term management of gout focuses on controlling serum levels of which purine degradation product?



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Managing your gout: simple steps to long-term control

Prepared by Associate Professor Neil McGill, Clinical Associate Professor of Medicine at The University of Sydney; and a Rheumatologist at the Institute of Rheumatology and Orthopaedics, Royal Prince Alfred Hospital, Sydney, NSW.

Gout is a type of arthritis that causes attacks of painful swelling in one or more joints. It is very common and can be fully controlled by medication. Men are more commonly affected than women, and the first attack can occur even before 30 years of age.

What causes gout?

Gout occurs as a result of the formation of crystals of monosodium urate in and around joints. The crystals form very slowly (over months) without causing pain or any other symptoms. They form in some but not all people who have a higher than normal amount of urate (uric acid) in their blood. For most people with a high level of urate in their blood, the main reason is that their kidneys, despite otherwise working well, are less effective at moving urate from the blood into the urine; this is mainly determined by inheritance. Obesity, alcohol excess and other dietary factors also play a role in determining the blood urate level.

Acute attacks of gout

A flare of gout typically starts abruptly, usually in the big toe, foot or ankle, and within 24 hours is so painful that walking is almost impossible. The joint usually becomes red, swollen and warm.

The flare is caused by the body's defence system 'attacking' the urate crystals in the joint. The attack does not get rid of the crystals but the inflammation it causes is painful. Treatment is aimed at suppressing this inflammation.

Other diseases, including bacterial infection, can mimic gout. It is therefore important that the diagnosis of gout is confirmed (and other possibilities excluded), preferably by examination of a small sample of joint fluid under the microscope.

Dealing with an acute attack

Treatment of a flare of gout is by medication, usually taken by mouth but sometimes by injection. Nonsteroidal anti-inflammatory drugs (NSAIDs), cortisone-type drugs or colchicine can be used, and the best choice depends on your other health issues (such as high blood pressure, kidney problems or diabetes).

This handout provides some information about gout and its treatment.



Figure. Gout at the base of the big toe of the right foot.



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Ongoing management of gout

Without treatment, gout progressively gets worse over the years. More frequent and longer flares, more days off work, permanent joint damage and disfigured feet and hands are all part of the expected outcome.

Treatment targets

To prevent the problems gout causes, further crystal formation must be prevented and the existing crystals must be dissolved. This will occur if the amount of urate in the blood is kept below the ‘target’ level.

The blood (serum) target urate level depends on how many crystals have already formed in your body.

- If no lumps of crystals (tophi) are present, the target is a blood urate level below 0.36 mmol/L
- If lumps of crystals (tophi) are present, the target is a blood urate level below 0.30 mmol/L.

You will need regular blood tests to determine if treatment has reduced the amount of urate in your blood to your target level and then to check that the level is remaining at target.

Unfortunately, changes in diet are rarely enough to reduce the urate amount to the target level. Medication by mouth is required, and needs to be continued lifelong, or the crystals will form again. You should, however, aim to have a healthy lifestyle, including maintaining a healthy body weight and only drinking alcohol in moderation.

Medications

Allopurinol is the usual medication used to lower urate levels, and for most people is well tolerated and safe. A small dose (usually 100 mg daily) is used initially and the dose is increased gradually until the urate concentration is below the target level. A dose of 600 mg or more daily is often needed.

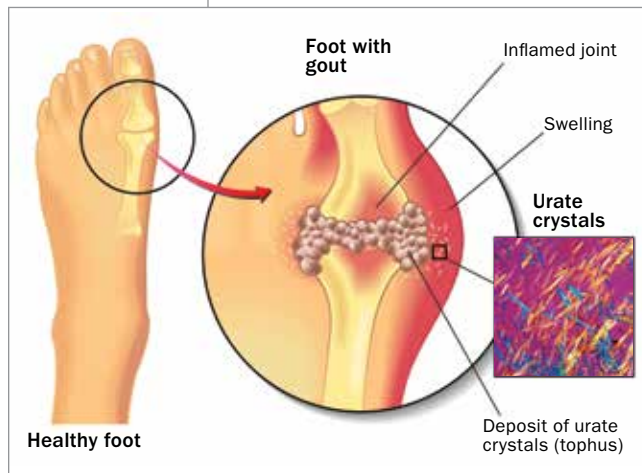
A few people are allergic to allopurinol, and will develop a rash, usually within the first six weeks of taking it. If you develop a rash when taking allopurinol, you must stop taking it immediately and notify your doctor.

For people who do not tolerate allopurinol, several other drug options are available, including febuxostat and probenecid.

Whichever drug is used, even after reaching target, there is a risk of flares of gout until the crystals have dissolved. The time taken for the crystals to dissolve depends on the quantity present, but is always months to years. In the first six months of therapy, another medication (usually a low dose of colchicine) is used to reduce the risk of flares.

MT

Gout is curable but requires lifelong medication. Know your target blood urate level, keep your level below it and you are on your way to being cured!



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